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- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

GlaxoSmithKline Biologicals

Study title

Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.

Study detailed title

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Note: This report presents the results of the analyses performed at Year 1.

Clinical Study Report for Study 110080 (Tdap 0.3-009 Ext: 007 Year 1)

(Development Phase IIIb)

IND Number: BB-IND-8461

Indication Studied: Healthy adults aged 19 years and older, who received a single dose study vaccination in the 106316 study.

Study initiation date (Year 1):	28 June 2007
Study completion date (Year 1):	20 September 2007
Date of report:	09 July 2008

Sponsor Signatory: [redacted] MD
Director, Clinical Research and Development and Medical Affairs, Vaccines
GlaxoSmithKline Biologicals

This study was performed in compliance with Good Clinical Practice including the archiving of essential documents.

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SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Principal investigators and study centers: This was a multicentre study conducted across 38 centers in the United States by multiple investigators.

Publication (reference): Not published as of 09 July 2008

Study period: Study initiation date (Year 1): 28 June 2007 Study completion date (Year 1): 20 September 2007	**Clinical phase:** IIIb

Objectives:

Primary:

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Secondary:

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Note: This report presents only the results of the analyses performed at Year 1.

Study design: A phase IIIb, controlled, non-interventional, observational multicenter study in United States with two parallel groups, Boostrix and Adacel.

- Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
- Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.

Blood samples were collected from all subjects at Year 1 (Visit 3) for evaluation of antibody persistence. This report presents the results of the analyses performed at Year 1.

Number of subjects	**Boostrix group**	**Adacel group**	**Total**
Subjects vaccinated in the 106316 study	1522	762	2284
Subjects who returned for Year 1 follow-up (Year 1 cohort)	1069	523	1592
According-to-Protocol Year 1 cohort for analysis of immunogenicity	1015	506	1521

Diagnosis and criteria for inclusion: All subjects who received a single dose of the study vaccination (*Boostrix* or *Adacel*) in the 106316 study and gave written informed consent prior to Year 1 (Visit 3) were enrolled.

Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule/site: Subjects received GSK Biologicals' *Boostrix* vaccine as an intramuscular (IM) injection administered at the non-dominant side of the upper deltoid in the 106316 study.

Vaccine composition/ dose/ lot number: One single dose vial (0.5 mL) of GSK Biologicals' *Boostrix* (Lot No.: AC52B009BA) vaccine contained: D toxoid: minimum 2.5 limit of flocculation (Lf), T toxoid: 5 Lf, PT: 8 µg, FHA: 8 µg, PRN: 2.5 µg and ≤0.39 mg aluminum as salts.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Reference vaccine /Comparator, dose and mode of administration, lot no.:
Vaccination schedule /site: Subjects received Sanofi Pasteur's *Adacel* vaccine as an IM injection administered at the non-dominant side of the upper deltoid in the 106316 study.
Vaccine composition /dose /lot number: One single dose vial (0.5 mL) of Sanofi Pasteur's *Adacel* (Lot No: C2457AA) vaccine contained: minimum D toxoid: 2 Lf, T toxoid: 5 Lf, PT: 2.5 µg, FHA: 5 µg, PRN: 3 µg, Fimbriae types 2 (FIM2): 5 µg, FIM3: 5 µg, formaldehyde: ≤ 5 µg, glutaraldehyde ≤5 nanogram (ng), 2-phenoxyethanol: 3.3 mg and 0.33 mg aluminum salts.

Duration of the study: The duration of the study up to Visit 3 was approximately one year per subject.

Criteria for evaluation:
Immunogenicity:

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel groups at 1 year following vaccination.
- Subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups at 1 year following vaccination.
- Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN GMCs for each subject in the Boostrix and Adacel groups at 1 year following vaccination.

Statistical methods: Three cohorts were defined for the purpose of analysis:

- The Year 1 cohort was a subset of the total vaccinated cohort in the primary study and was the cohort of subjects for whom serological results for at least one antigen was available after a blood sample was taken 1 year after vaccination.
- The ATP Year 1 cohort included all subjects from the Year 1 cohort who were in the ATP cohort for analysis of immunogenicity in the 106316 study and who have not met the protocol-specified elimination criteria.
- The ATP Complete Year 1 cohort included all subjects who belong to the ATP Year 1 and all previously defined yearly ATP cohorts. For the Year 1 analysis, the ATP Complete Year 1 cohort was the same as the ATP Year 1 cohort.

Analysis of demography: Demographic characteristics (age at Year 1 blood sampling and sex) of the ATP Year 1 cohort and the Year 1 cohort were tabulated.

Analysis of Immunogenicity: The primary analysis of immunogenicity was performed on the ATP Year 1 cohort. As the percentage of subjects eliminated from the ATP Year 1 cohort in the Boostrix group differed from the Year 1 cohort by more than 5%, a complementary immunogenicity analysis based on the Year 1 cohort was performed. The following analyses were performed:
Within group assessment:
For each group, at the Year 1 time point:

- Seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA) and overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI were calculated by group.
- Seroprotection rates for anti-T (percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI were calculated by group.
- Seropositivity rates (percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U) with exact 95% CI were calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated by group.

In addition, the distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves by group.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Comparability between Groups (Exploratory Analyses):

- For anti-D and anti-T antibody response:
  - The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 1 year after vaccination was calculated.
  - The two-sided 95% CI for the adjusted GMC ratio (Boostrix group divided by Adacel group) 1 year after vaccination was calculated. The GMC ratio was obtained using an ANCOVA model on the logarithm-transformed concentrations. The ANCOVA model included the group as fixed effect, the age at Year 1 blood sampling in years and baseline (pre vaccine) antibody concentration as regressors.
- The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the overall seroprotection rates for D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), 1 year after vaccination was calculated.

Analysis of Safety: No safety analysis was performed for this persistence study.

Summary:

Demography Results: The demographic profile of subjects in the ATP Year 1 cohort was similar in both groups.

Immunogenicity Results: Immunogenicity analyses were performed on the ATP Year 1 cohort and on the Year 1 cohort.

Within group assessment (Based on the ATP Year 1 cohort):

One year after the single-dose of Tdap booster vaccination:

- The percentage of subjects seroprotected for D and T (antibody concentrations ≥ 0.1 IU/mL by ELISA) at Year 1 (at least 95.7% and 98.6 %, respectively) were not noticeably decreased from that observed one month after vaccination and appeared to be similar in both groups.
- The overall anti-D seroprotection rates (antibody concentrations ≥ 0.1IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay) were at least 98.2% in both groups and this was seen to be similar to results at Month 1.
- The percentages of subjects with anti-D ≥ 1.0 IU/mL at Year 1 (at least 66.6%) appeared to be decreased from that at Month 1, while there was no noticeable decrease in percentage of subjects with anti-T ≥ 1.0 IU/mL (at least 93.9%) as compared to Month 1. This was seen to be similar in both groups.
- The seropositivity rate for anti-PT at Year 1 (90.5% and 86% in the Boostrix and Adacel groups, respectively) appeared to be slightly decreased from Month 1, while those for anti-FHA (99.8%) and anti-PRN antibodies (at least 96%) showed similar results as Month 1 in both groups.
- The GMCs for all the antibodies at Year 1 were seen to have decreased from the Month 1 results but remained higher than the pre-vaccination GMCs.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Synopsis table 1: Seropositivity rates and GMCs with 95% CI for anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies at Year 1 (ATP Year 1 cohort)

Endpoints	Timing	Boostrix group					Adacel group				
		N	%	GMC	LL	UL	N	%	GMC	LL	UL
Anti-D (≥ 0.1 IU/mL)	PI(M1)	1012	98.1	4.6	4.3	5.0	505	98.4	4.9	4.4	5.5
	PI(Y1)	1010	95.7	1.4	1.3	1.6	504	97.0	1.4	1.3	1.6
Anti-T (≥ 0.1 IU/mL)	PI(M1)	1013	99.5	8.5	8.0	9.0	506	100	13.2	12.3	14.2
	PI(Y1)	1014	98.6	3.4	3.2	3.6	506	99.6	4.4	4.1	4.7
Anti-PT (≥ 5 EL.U)	PI(M1)	1001	97.0	62.3	58.3	66.7	501	94.2	32.7	29.6	36.2
	PI(Y1)	1013	90.5	22.4	21.0	24.0	506	86.0	15.6	14.2	17.2
Anti-FHA (≥ 5 EL.U)	PI(M1)	1012	100	617.8	582.5	655.2	502	100	363.6	334.2	395.5
	PI(Y1)	1014	99.8	190.1	178.5	202.6	502	99.8	118.8	108.7	129.9
Anti-PRN (≥ 5 EL.U)	PI(M1)	1011	98.9	399.4	360.7	442.3	505	99.4	334.9	293.7	381.9
	PI(Y1)	1011	96.0	152.2	137.2	168.8	501	97.6	132.5	115.6	151.8

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects seropositive for the given antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one year after the vaccination

Between group assessment (Based on ATP Year 1 cohort):

- There was no statistically significant difference between both groups in the anti-D (≥0.1 IU/mL by ELISA) and anti-T (≥0.1 IU/mL) seroprotection rates at Year 1 evidenced by the fact that the 95% CI for the difference between the two groups included 0.
- The overall seroprotection rates for D (anti-D ≥ 0.1 IU/mL by ELISA or ≥0.016 IU/mL by VERO) 1 year following *Boostrix* vaccination were similar to the results following *Adacel* vaccination (98.3%, with 95% CI: 97.3-99.0%; and 98.2%, with 95% CI: 96.6-99.2%, respectively).
- The adjusted GMCs for anti-D were similar in both groups (95% CI included 1) while the anti-T GMC was seen to be higher in the Adacel group than the Boostrix group (95% CI excluded 1).

Conclusions:

- Evaluation of persistence of anti-D and anti-T elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus one year after vaccination.
- Levels of all antibodies elicited by a single dose of *Boostrix* decreased one year after vaccination as compared to levels observed one month after vaccination, but remained higher than the pre-vaccination levels.

Date of report: 09 July 2008

TABLE OF CONTENTS

PAGE

MODULAR APPENDICES

LIST OF TABLES

PAGE

LIST OF SUPPLEMENTS

PAGE

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ANCOVA	Analysis of Co-variance
ATP	According-to-protocol
CDC	Center for Disease Control and Prevention
CI	Confidence interval
D	Diphtheria Toxoid
eCRF	Electronic Case Report Form
EL.U	ELISA Units
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food And Drug Administration, United States
FHA	Filamentous Hemagglutinin
GMC	Geometric mean concentration
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
Lf	Limits of Flocculation Unit(s)
LL	Lower Limit
MA	Medically Attended visit
MedDRA	Medical Directory for Regulatory Activities
mL	milliliter
PRN	Pertactin

PT	Pertussis Toxoid
RDE	Remote Data Entry
SAE	Serious adverse event
SBIR	GSK Biologicals' Internet Randomization System
SOP	Standard Operating Procedure
T	Tetanus Toxoid
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed
UL	Upper Limit

GLOSSARY OF TERMS

Active phase (106316 study)	The active phase of the study refers to the time point when the subjects received *Boostrix* and *Adacel* vaccination and were evaluated for booster response [Day 0 (Visit1) to 1 month post-vaccination (Visit 2).
ATP Year 1 cohort	The ATP Year 1 cohort included all subjects from the Year 1 cohort who were in the ATP cohort for analysis of immunogenicity in the 106316 study and who have not met the protocol-specified elimination criteria.
ATP Complete Year 1 cohort	The ATP Complete Year 1 cohort included all subjects who belonged to the ATP Year 1 and all previously defined yearly cohorts. For the Year 1 analysis, the ATP complete Year 1 cohort was the same as the ATP Year 1 cohort.
Completed:	Subjects who completed Visit 3.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion /exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the analysis.
Subject(s):	Term used throughout the protocol to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Year 1 cohort	The Year 1 cohort was a subset of the total vaccinated cohort in 106316 study and was the cohort of subjects for whom serological results for at least one antigen was available from the blood sample taken 1 year after vaccination.

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the CSR (including the synopsis), the names of the vaccines and/or medications will be written without the subscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	generic description
Infanrix®	Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine
Boostrix®	Tetanus toxoid, reduced diphtheria toxoid and Acellular pertussis adsorbed vaccine (Tdap).

Trademarks not owned by the GlaxoSmithKline group of companies	generic description
Adacel™	Tetanus toxoid, reduced diphtheria toxoid and Acellular pertussis adsorbed vaccine.

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, the informed consent, and other information that required pre-approval were reviewed and approved by a national IRB.

1.2. Ethical conduct of the study

This study was conducted in accordance with "Good Clinical Practice" (GCP), the October 1996 Declaration of Helsinki, US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.

1.3. Subject information and consent

Written informed consent was obtained from each subject, in accordance with 21 CFR 50.25 prior to the performance of any study-specific procedures.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted by 35 investigators across 38 centers in the United States (US). GSK Biologicals, King of Prussia, PA, US was responsible for administration of the study including clinical trial supply management and laboratory facilities. There was a reduction in the number of participating centers in the Year 1 phase of the study (38 centers) as compared to the primary study 106316 (45 centers) since several investigators declined to participate in this phase of the study. The non-participating centers will still be invited to participate in the Year 3, 5 and 10 phases of the study.

3. INTRODUCTION

Since the early 1940s, routine childhood vaccination programs against diphtheria, tetanus and pertussis have substantially helped to reduce the incidence of each of these highly infectious diseases. Even though the rates of diphtheria and tetanus cases are extremely uncommon in countries where these programs have been implemented, pertussis continues to be prevalent despite the wide vaccine coverage [Greenberg, 2005], [Frampton, 2006].

Despite high coverage with pertussis-containing vaccines in the US, the reported pertussis rate per 100,000 population increased from 1.8 to 8.9 during 1994 to 2004 [CDC, 2006a]. In 2004, the number of pertussis cases peaked with 25,827 cases reported

to the national passive reporting system at the Centers for Disease Control and Prevention (CDC) [CDC, 2006a]. The number of pertussis cases remained stable in 2005 with 25,616 reported cases [CDC, 2007a], and decreased to 15,632 cases in 2006 [CDC, 2007b].

On October 26, 2005, the Advisory Committee on Immunization Practices (ACIP) issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.

GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap), (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age. This vaccine is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti, 2002; Greco, 1996; Schmitt, 1996a; Schmitt, 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in *Boostrix* are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. As of December 2007, over 14 million doses of *Boostrix* have been distributed worldwide.

The 106316 study (primary study) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age [GlaxoSmithKline Biologicals Clinical Report 106316]. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, *Adacel* vaccine, which is licensed in the US for individuals 11-64 years of age.

Data on persistence of antibodies and long-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study would provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 years following vaccination with a single dose of *Boostrix*. This report presents immunogenicity analyses performed at Year 1 after vaccination.

4. STUDY OBJECTIVES

See Section 5.9 for details of the study endpoints. This report presents only the results for the evaluation of antibody persistence at the Year 1 time point.

4.1. Primary objective

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥0.016 IU/mL (VERO, for subjects with an

ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

4.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

- A phase IIIb, controlled, non-interventional, observational multicenter study with two parallel groups, Boostrix and Adacel as in the active phase (Day 0 to 1 month post-vaccination) of the 106316 study.
- Subjects who received *Boostrix* or *Adacel* in the 106316 study were analyzed as separate groups.
- Treatment allocation: No vaccine was administered during this study. Subjects in the 106316 study were randomized into groups, Boostrix or Adacel (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blinding: This study was an open study since there was no vaccination in this study.
- Blood samples were collected at the Year 1 time point following the dose of vaccination.
- Duration of the study: The duration of the study up to Visit 3 was approximately one year per subject.
- Data collection: Remote Data Entry (RDE).

5.2. Study procedures

5.2.1. Outline of study procedures

The list of study procedures are outlined in Table 1.

Table 1 Outline of study procedures

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 Year 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
The grey shaded area represents the time point for which analyses are presented in this report.

5.2.2. Intervals between study visits

The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits

Visit*	Length of interval
Visit 3 (Tdap vaccination in the 106316 study→Visit 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in the 106316 study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in the 106316 study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in the 106316 study →Visit 6)	10 years ± 5 weeks

*The date of the previous visit served as reference date.
The grey shaded area represents the time point for which analyses are presented in this report.

5.3. Selection of study population

The study was conducted at 38 centers in the US. The total number of subjects enrolled in the 106316 study was 2284 subjects, randomized into Boostrix or Adacel groups in the ratio 2:1.

At Year 1, assuming a 15% attrition rate per year, it was estimated that 1942 subjects (1294 subjects in the Boostrix group and 648 subjects in the Adacel group) would return for blood sampling.

5.3.1. Inclusion criteria

All subjects were to have satisfied the following criteria at study entry:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in the 106316 study were considered eligible to participate in this study.
- Written informed consent obtained from the subject.

5.3.2. Exclusion criteria

Not applicable for this phase of the study.

5.3.3. Elimination criteria

The following criteria were checked at Visit 3 (Year 1). If any became applicable during the study, it did not require withdrawal of the subject from the study but was considered in determining a subject's evaluability in the according-to-protocol (ATP) analysis.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in the 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in the 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators deferred the blood draw for these subjects until the time the criterion no longer applied.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to Visit 3. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

5.3.4. Contraindications to subsequent doses of vaccine

Not applicable for this phase of the study.

5.3.5. Warnings and precautions

Not applicable for this phase of the study.

5.3.6. Subject completion and withdrawal from study

5.3.6.1. Subject completion

A subject who returned for Visit 3 as specified in the protocol was considered to have completed the study phase (Year 1) pertaining to that study visit.

5.3.6.2. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study was any subject who was not available for the contact foreseen in the protocol at a given persistence time point.

Subjects could participate in each persistence time point independent of other persistence time points. For example, a subject who did not participate in the Year 1 antibody persistence analysis could be approached for participation in the 3, 5, and 10 year persistence analyses.

A subject qualified as a withdrawal from the study when no study procedure had occurred, no follow-up had been performed, and no further information had been collected for the subject since the last contact.

Information relative to the withdrawal of a subject was documented on the study continuation/conclusion screens of the eCRF. The investigator documented whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (included receipt of prohibited vaccine or medication; was to be specified)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (was to be specified).

5.3.6.3. Subject withdrawal from administration of the investigational product

Since subjects were not administered a vaccine in this antibody persistence study, subjects were not withdrawn from receipt of investigational product, but could have been withdrawn from other study procedures.

5.4. Composition and administration of vaccines

Refer to the 106316 study report for details of the composition and administration of vaccines in the 106316 study.

5.5. Prior and concomitant medication/vaccinations

At Visit 3, the investigator questioned the subject about any medications taken.

Any treatments and/or medications specifically contraindicated (e.g. any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling were to be recorded in the eCRF with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, was to be recorded in the eCRF with the trade name, route of administration, and date of administration.

5.6. Assessment of Immunogenicity variables

5.6.1. Laboratory assays and time points

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum was obtained at the Year 1 time point following study vaccination in the 106316 study. After blood centrifugation and serum separation, serum samples were stored at approximately –20°C until sent to the sponsor. Sera were sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Belgium for storage prior to analysis.

Serological assays for anti-D toxoid and anti-T toxoid antibodies were performed at GSK Biologicals' laboratory in Laval, QC, Canada. The assays for anti-D VERO cell neutralization, anti-PT, anti- FHA and anti-PRN antibodies were conducted in GSK Biologicals' laboratory in Rixensart, Belgium. All serological assays were performed using standardized, validated procedures with adequate controls.

5.6.2. Antibodies against diphtheria and tetanus

Antibody concentrations against diphtheria and tetanus were measured by enzyme-linked immunosorbent assay (ELISA). The cut-off of both assays was 0.1 IU/mL [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL were to be re-tested using the neutralization assay on VERO cells, which was more sensitive for low antibody concentrations and had a cut-off of 0.016 IU/mL [Melville-Smith, 1988].

5.6.3. Antibodies against PT, FHA and PRN

Antibody concentrations against the pertussis components (PT, FHA and PRN) contained in Boostrix were measured by ELISA technique. The cut-off for the assays was 5 EL.U/mL for each antigen tested [Sato, 1982; Granström, 1987].

Table 3 presents the details of laboratory assays.

Table 3 Laboratory assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory*
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-D	Neutralization test on VERO cell**	In-house assay	IU/mL	0.016	Rixensart
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-PT	ELISA	In-house assay	EL.U./mL	5	Rixensart
Serological	anti-FHA	ELISA	In-house assay	EL.U./mL	5	Rixensart
Serological	anti-PRN	ELISA	In-house assay	EL.U./mL	5	Rixensart

*All serological assays were performed using standardized, validated procedures with adequate controls
ELISA = enzyme-linked immunosorbent assay
** VERO cell testing was performed in subjects with an ELISA result of < 0.1 IU/mL
IU/mL = International Units per milliliter
Laval = GSK Biological laboratories in Laval, Quebec, Canada
EL.U/mL = ELISA units per milliliter
Rixensart = GSK Biologicals laboratories, Rixensart, Belgium

Table 4 presents the immunological read-outs.

Table 4 Immunological read-outs

Blood sampling time point Timing	Visit no.	Marker
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 10	6	D
		T
		PT
		FHA
		PRN

The grey shaded area represents the time point whose analyses are presented in this report.

5.7. Assessment of safety variables

5.7.1. Serious adverse events

Because subjects were not being vaccinated as part of the study protocol, investigators were not required to specifically solicit SAEs in this phase of the study. However, if an investigator became aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in the 106316 study, he/she was to do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations, SAEs that were considered to be related to study participation (e.g. blood draws) were to be collected and recorded from the time the subject consented to participate in the study until she/he was discharged.

A serious adverse event (SAE) was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occurred during hospitalization were considered AEs. If a complication prolonged hospitalization or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE was to be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

NOTE: The term disability meant a substantial disruption of a person's ability to conduct normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which could interfere or prevent everyday life functions but did not constitute a substantial disruption.

e. was a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgment was exercised in deciding whether reporting was appropriate in other situations, such as important medical events that could not be immediately life-threatening or resulted in death or hospitalization but could jeopardize the subject or could require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These would also be

considered serious. Examples of such events would be invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization.

5.7.2. Clinical laboratory parameters and other abnormal assessments qualifying as serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology and urinalysis) or other abnormal assessments (e.g. vital signs) that were judged by the investigator to be clinically significant were to be recorded as SAEs if they met the definition of an SAE, as defined in Section 5.7.1. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were to be reported as SAEs. The investigator was to exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

5.7.3. Time period, frequency, and method of detecting serious adverse events

When an SAE occurred, it was to be the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator was then to record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It would not be considered acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases would be requested by GSK Biologicals. In this instance, all subject identifiers were to be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator was to attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was to be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF was to be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs did not work, or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system were to be used to report SAEs.

5.7.4. Evaluating serious adverse events

This section is only applicable if an investigator became aware of an SAE that warranted notification of the sponsor.

5.7.4.1. Assessment of intensity

The investigator was to make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment was to be based on the investigator's clinical judgment.

The intensity of each SAE recorded in the eCRF or SAE Report Form, as applicable, was to be assigned to one of the following categories:

1 (mild)	=	An SAE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An SAE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevented normal, everyday activities. (In adults, such an SAE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

Grade 3 was a category utilized for rating the intensity of an event; and SAEs could be assessed as Grade 3. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in Section 5.7.1.

5.7.4.2. Assessment of causality

The investigator was obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator was to use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product were to be considered and investigated. The investigator was also to consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

In situations when a SAE occurred and the investigator had minimal information to include in the initial report to GSK Biologicals, it was very important that the investigator was always to make an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. If the investigator changed his/her opinion of causality in light of follow-up information, he was to amend the SAE information accordingly. The causality assessment was to be one of the criteria used when determining regulatory reporting requirements.

If an event met the criteria to be determined "serious" (see Section 5.7.1 for definition of serious adverse event), it was to be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccines, if applicable
- Erroneous administration
- Other cause (was to be specified).

5.7.5. Pregnancy

Since subjects were not being vaccinated as part of the study protocol, investigators were not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who were pregnant at the time of a study visit were not excluded from the visit on the basis of their pregnancy.

A spontaneous abortion was always to be considered an SAE and was to be reported as an SAE. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, was to be reported to GSK Biologicals. While the investigator was not obligated to actively seek this information from former study participants, he/she might have learnt of a pregnancy through spontaneous reporting.

5.8. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, eCRF and RDE system, and safety reporting were reviewed with the investigators and their personnel responsible for the conduct of the study by the Company representative(s) prior to study start. Two multi-investigator meetings were held prior to the start of the study.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

A Contract Research Organization (CRO) [ICON Clinical Research, North Wales, PA] was employed to conduct site monitoring activities, collection of regulatory documents and issue and negotiation of site contracts for this study. The CRO responsibilities were conducted according to their own SOPs.

No study specific audits were performed for this study.

5.9. Statistical methods

All analyses were performed as specified in the protocol.

The statistical analyses were performed using the Statistical Analysis System (SAS) version 9.1.3 on Windows XP Professional and StatXact-8.0 procedure on SAS.

5.9.1. Primary endpoint

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel groups, 1 year, 3 years, 5 years and 10 years following vaccination.

For this report, the primary endpoint corresponds to Year 1.

5.9.2. Secondary endpoints

- Subjects with anti-pertussis toxoid, anti-filamentous hemagglutinin, and anti-pertactin antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-T concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PT concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-FHA concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PRN concentration for each subject at the time of analysis in the Boostrix and Adacel groups.

For this report, the time of analysis corresponds to Year 1.

5.9.3. Determination of sample size

All subjects who had received vaccination in the 106316 study were eligible for enrolment in this study. Refer to the 106316 study report for sample size estimation.

5.9.4. Study cohorts/data sets analyzed

Three cohorts were defined for the purpose of analysis and are described here:

Year 1 cohort

The Year 1 cohort was a subset of the total vaccinated cohort in the 106316 study and was the cohort of subjects for whom serological results for at least one antigen was available after a blood sample taken 1 year after vaccination.

According-To-Protocol (ATP) Year 1 cohort

The ATP Year 1 cohort included all subjects from the Year 1 cohort who were in the ATP cohort for analysis of immunogenicity in the 106316 study and who did not meet the following elimination criteria:

- Without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in the 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in the 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this meant prednisone, or equivalent, ≥0.5 mg/kg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

This cohort was the primary cohort for the analysis.

ATP Complete Year 1 cohort

The ATP Complete Year 1 cohort included all subjects who belonged to the ATP Year 1 cohort and all previously defined yearly ATP cohorts.

For the Year 1 analysis, the ATP complete Year 1 cohort was the same as the ATP Year 1 cohort.

5.9.5. Derived and transformed data

Immunogenicity

- The cut-off value was defined by the laboratory before the analysis and was described in Section 5.6.1.
- A seronegative subject was a subject whose antibody concentration was below the assay cut-off value.
- A seropositive subject was a subject whose antibody concentration was greater than or equal to the assay cut-off value.
- Seroprotection rate was defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody.

- The percentage of subjects with antibody concentrations ≥0.1 IU/mL (ELISA) or ≥0.016 IU/mL (VERO) and anti-T antibody concentrations ≥0.1 IU/mL in both groups (Boostrix and the Adacel groups) at 1 year following vaccination was derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups at 1 year following vaccination was derived to evaluate the first secondary objective.
- The geometric mean concentration (GMC) calculations were performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay would be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies at 1 year after vaccination with *Boostrix* were derived to evaluate the other secondary objectives.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

5.9.6. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at Year 1 blood sampling and sex) of the ATP Year 1 cohort and the Year 1 cohort were tabulated.

The number of subjects included in the Total Vaccinated Cohort in the 106316 study, in the ATP Year 1 cohort and in the ATP complete Year 1 cohort was tabulated.

The time from vaccination in the 106316 study to blood sampling at Year 1 (in years) was summarized using descriptive statistics.

5.9.7. Analysis of immunogenicity

The primary analysis was based on the ATP Year 1 cohort. As the percentage of subjects eliminated from the ATP Year 1 cohort in the Boostrix group differed from the Year 1 cohort by more than 5%, a complementary immunogenicity analysis based on the Year 1 cohort was performed.

The following analyses were performed:

Within group assessment:

For each group, at the Year 1 time point:

- Seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA) and overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or

≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI were calculated by group.

- Seroprotection rates for anti-T (percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI were calculated by group.
- Seropositivity rates (percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U) with exact 95% CI were calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated by group.

In addition:

- The distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves by group.

Comparability between Groups:

Exploratory analyses

- For anti-D and anti-T antibody response:
  - The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 1 year after vaccination was calculated.
  - The two-sided 95% CI for the adjusted GMC ratio (Boostrix group divided by Adacel group) 1 year after vaccination was calculated. The GMC ratio was obtained using an ANCOVA model on the logarithm-transformed concentrations. The ANCOVA model included the group as fixed effect, the age at Year 1 blood sampling in years and baseline (pre vaccine) antibody concentration as regressors.
- The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the overall seroprotection rates for D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), 1 year after vaccination was calculated.

5.9.8. Analysis of safety

No safety analysis was performed for this persistence study. If GSK received information by an investigator of an SAE that in his/her medical judgment was reasonably related to the study vaccine administered in the 106316 study, or to participation in this persistence study, the pertinent clinical details were to be summarized in the study report.

5.9.9. Interim analysis

No interim analysis was planned, nor performed for this persistence study.

5.10. Changes in the conduct of the study or planned analyses

5.10.1. Protocol amendments

There were no amendments to the protocol of this study.

5.10.2. Other changes

Analyses were performed as planned in the protocol.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject visit for collection of Year 1 samples (Visit 3) was on 28 June 2007 and the last subject visit was on 20 September 2007.

6.2. Subject eligibility and attrition from the study

6.2.1. Study completion and withdrawal from study

Subjects were enrolled at 38 centers in the United States. The number of subjects enrolled at Year 1 visit and the number included into the ATP Year 1 cohort is presented in Table 5.

Table 5 Number of subjects included in Year 1 follow-up period

Title	Boostrix group	Adacel group	Total
	n	n	n
Number of subjects vaccinated in the 106316 study (Tdap 0.3-007)	1522	762	2284
Year 1 follow-up (Year 1 cohort)	1069	523	1592
Year 1 follow-up (ATP Year 1 cohort)	1015	506	1521

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
n = number of subjects included in each group or in total for a defined cohort.

A total of 2284 subjects (1522 subjects in the Boostrix group and 762 subjects in the Adacel group) were vaccinated in the 106316 study. Out of the 2284, 1592 subjects (1069 subjects in the Boostrix group and 523 subjects in the Adacel group) returned for the Year 1 blood sampling visit (Visit 3).

The number of enrolled subjects by center for the Year 1 cohort is presented in Supplement 1.

6.2.2. Protocol deviations

A summary of the subjects enrolled into the study as well as the number eliminated from ATP analyses with reasons for elimination is presented in Table 6.

Table 6 Number of subjects enrolled into the study as well as the number eliminated from ATP analyses with reasons for elimination

	Total			Boostrix group		Adacel group	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total vaccinated cohort in the 106316 study	**2284**			**1522**		**762**	
Number of subjects returning for blood sampling at Year 1	**1592**			**1069**		**523**	
Administration of vaccines forbidden in the protocol (code 1040)	8	8		6	6	2	2
Protocol violation (inclusion/exclusion criteria) (code 2010)	2	2		2	2	0	0
Non compliance with blood sampling schedule [including wrong and unknown dates (code 2090)]	31	31		22	22	9	9
Essential serological data missing (code 2100)	4	5		4	5	0	0
Number of subjects who returned at Year 1 visit but were previously eliminated from ATP Immunogenicity cohort	26			20		6	
ATP Year 1 immunogenicity cohort	**1521**		**95.5**	**1015**		**506**	

Note: Subjects may have more than one elimination code assigned
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number (The numbers in bold represent the total number of subjects in each group)
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the number of subjects returning for blood sampling at Year 1

Out of 2284 vaccinated subjects (Total Vaccinated cohort in the 106316 study), 1592 subjects entered the Year 1 cohort. A total of 71 subjects were eliminated from the ATP Year 1 cohort as a result of having met protocol-defined elimination criteria. Of these 71 subjects eliminated from the ATP Year 1 cohort, twenty-six subjects (20 in the Boostrix group and 6 in the Adacel group) were eliminated from the ATP Year 1 cohort as they were eliminated from the primary ATP immunogenicity cohort of the 106316 study.

Thus, a total of 1521 subjects (1015 subjects in the Boostrix group and 506 subjects in the Adacel group) were included in the ATP Year 1 cohort.

6.3. Demographic characteristics

6.3.1. ATP Year 1 cohort

The summary of demographic characteristics for the ATP Year 1 cohort is presented in Table 7.

Table 7 Summary of demographic characteristics (ATP Year 1 cohort)

		Boostrix group N = 1015		Adacel group N = 506		Total N = 1521	
Characteristics	**Parameters**	**Value**		**Value**		**Value**	
Age (years)	Mean	41.8		42.6		42.1	
	SD	13.35		13.24		13.31	
	Median	43.0		44.0		44.0	
	Minimum	19		19		19	
	Maximum	65		65		65	
	Categories	**n**	**%**	**n**	**%**	**n**	**%**
Age stratum	19-29 (Y)	301	29.6	141	27.9	442	29.1
	30-49 (Y)	350	34.5	177	35.0	527	34.6
	50-64 (Y)	364	35.9	188	37.1	552	36.3
Sex	Female	648	63.8	345	68.2	993	65.3
	Male	367	36.2	161	31.8	528	34.7

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = total number of subjects
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Age(Y)= age at Year 1 blood sampling, expressed in years
Age stratum: based on the age at vaccination in 106316 study

For the ATP Year 1 cohort, the groups appeared to be similar to each other with respect to mean age (42.1 years) and sex (65.3% female). The percentages of females and males were similar to that seen in the ATP cohort for immunogenicity at the Month 1 time point. The older age groups (30-49 years of age and 50-64 years of age strata) appeared to be represented more (34.6% and 36.3% of subjects, respectively) than the 19-29 years of age stratum (29.1% of subjects) at the Year 1 time point as compared to Month 1. All 3 groups were equally represented in the primary ATP cohort for immunogenicity of the 106316 study due to stratification of enrollment according to age groups. [GlaxoSmithKline Biologicals Clinical Report 106316]

6.3.2. Year 1 cohort

The summary of demographic characteristics for the Year 1 cohort is presented in Supplement 2. The demographic profile of the Year 1 cohort was similar to the ATP Year 1 cohort.

7. IMMUNOGENICITY RESULTS

7.1. Data sets analyzed

The primary analysis of immunogenicity was performed on the ATP Year 1 cohort. A complementary analysis based on the Year 1 cohort was performed as more than 5% of the vaccinated subjects who returned for blood sampling at Year 1 were eliminated from the ATP Year 1 cohort in the Boostrix group. See Section 5.9.4 for the definition of the cohorts identified for analyses and Section 6.2 for eligibility for analyses.

7.2. According-to-protocol analysis

A total of 1521 subjects (1015 subjects in the Boostrix group and 506 subjects in the Adacel group) were included into the ATP Year 1 cohort.

7.2.1. Evaluation of persistence of antibodies to diphtheria and tetanus toxoids

The percentages of subjects with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1 according to group for the ATP Year 1 cohort are presented in Table 8.

Table 8 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1, according to group (ATP Year 1 cohort)

				≥0.1 IU/mL				≥1 IU/mL				GMC (IU/mL)		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	PRE	1007	855	84.9	82.5	87.1	251	24.9	22.3	27.7	0.4	0.4	0.5
		PI(M1)	1012	993	98.1	97.1	98.9	888	87.7	85.6	89.7	4.6	4.3	5.0
		PI(Y1)	1010	967	95.7	94.3	96.9	673	66.6	63.6	69.5	1.4	1.3	1.6
	Adacel	PRE	500	443	88.6	85.5	91.3	127	25.4	21.6	29.5	0.4	0.4	0.5
		PI(M1)	505	497	98.4	96.9	99.3	464	91.9	89.1	94.1	4.9	4.4	5.5
		PI(Y1)	504	489	97.0	95.1	98.3	351	69.6	65.4	73.6	1.4	1.3	1.6
Anti-T	Boostrix	PRE	1014	978	96.4	95.1	97.5	729	71.9	69.0	74.6	1.6	1.5	1.7
		PI(M1)	1013	1008	99.5	98.9	99.8	995	98.2	97.2	98.9	8.5	8.0	9.0
		PI(Y1)	1014	1000	98.6	97.7	99.2	952	93.9	92.2	95.3	3.4	3.2	3.6
	Adacel	PRE	505	494	97.8	96.1	98.9	382	75.6	71.7	79.3	1.7	1.5	1.9
		PI(M1)	506	506	100	99.3	100	502	99.2	98.0	99.8	13.2	12.3	14.2
		PI(Y1)	506	504	99.6	98.6	100	487	96.2	94.2	97.7	4.4	4.1	4.7

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration ≥ specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

One year after vaccination, the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL was at least 95.7% in both groups, while that of anti-T antibodies was at least 98.6% in both groups. Anti-D antibody concentrations ≥ 1.0 IU/mL were observed in at least 66.6% of subjects in both groups, and at least 93.9% of subjects in both groups had anti-T antibody concentrations ≥ 1.0 IU/mL.

Percentages of subjects with anti-D ≥ 0.1 IU/mL, anti-T ≥ 0.1 IU/mL or anti-T ≥ 1.0 IU/mL were not noticeably decreased from those observed 1 month following vaccination. The percentage of subjects with anti-D ≥ 1.0 IU/mL appeared to have decreased from those observed at 1 month following vaccination and appeared to be

similar between groups. GMCs for both anti-D and anti-T were low in both groups relative to one month following vaccination but remained above pre-vaccination levels (Table 8).

Subjects with anti-D concentrations < 0.1 IU/mL were retested using the more sensitive VERO cell assay. Seroprotection for D was defined in this assay by an antibody concentration ≥ 0.016 IU/mL. The overall anti-D seroprotection rates in the ATP Year 1 cohort were then shown by the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay with exact 95% CI. This information is presented in Table 9.

Table 9 Overall seroprotection status for anti-D antibody concentration by ELISA and VERO at Year 1 according to groups (ATP Year 1 cohort)

			Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for Anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
Timing	Group	N	n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
PRE	Boostrix	1007	152/1007	15.1	72/152	47.4	152/1007 x 72/152	7.1	92.9	91.1	94.4
	Adacel	500	57/500	11.4	21/56	37.5	57/500 x 21/56	4.3	95.7	93.7	97.3
PI(M1)	Boostrix	1012	19/1012	1.9	7/19	36.8	19/1012 x 7/19	0.7	99.3	98.6	99.7
	Adacel	505	8/505	1.6	5/8	62.5	8/505 x 5/8	1.0	99.0	97.7	99.7
PI(Y1)	Boostrix	1012	45/1012	4.4	17/45	37.8	45/1012 x 17/45	1.7	98.3	97.3	99.0
	Adacel	505	16/505	3.2	9/16	56.3	16/505 x 9/16	1.8	98.2	96.6	99.2

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralization test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = exact 95% confidence interval for group(s); LL = Lower Limit, UL = Upper Limit
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.

After retesting with VERO cell assay, the overall anti-D seroprotection rates were at least 98.2% in both groups. These results were similar to those observed one month following vaccination.

The percentage of subjects with anti-D and anti-T antibody concentrations ≥0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1 according to group, stratified by age and sex for the ATP Year 1 cohort are presented in Supplement 3 and Supplement 4, respectively.

Supplement 5 and Supplement 6 present the overall D seroprotective rates for the ATP Year 1 cohort with respect to age group and sex, respectively.

The reverse cumulative curves for anti-D and anti-T antibody concentrations in the Boostrix and Adacel groups one year after vaccination for the ATP Year 1 cohort are presented in Supplement 7 and Supplement 8, respectively.

7.2.2. Evaluation of the persistence of antibodies to acellular pertussis antigens

Table 10 presents the percentages of subjects with seropositivity rates for anti-PT, anti-FHA and anti-PRN (≥5 EL.U/mL) and their respective GMCs according to group for the ATP Year 1 cohort.

Table 10 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at Year 1 (ATP Year 1 cohort)

				≥ 5 EL.U/mL				GMC (EL.U/mL)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	PRE	1005	569	56.6	53.5	59.7	7.1	6.6	7.6
		PI(M1)	1001	971	97.0	95.7	98.0	62.3	58.3	66.7
		PI(Y1)	1013	917	90.5	88.6	92.3	22.4	21.0	24.0
	Adacel	PRE	502	320	63.7	59.4	68.0	8.3	7.5	9.1
		PI(M1)	501	472	94.2	91.8	96.1	32.7	29.6	36.2
		PI(Y1)	506	435	86.0	82.6	88.9	15.6	14.2	17.2
Anti-FHA	Boostrix	PRE	1008	975	96.7	95.4	97.7	30.9	28.9	33.1
		PI(M1)	1012	1012	100	99.6	100	617.8	582.5	655.2
		PI(Y1)	1014	1012	99.8	99.3	100	190.1	178.5	202.6
	Adacel	PRE	497	479	96.4	94.3	97.8	34.4	31.1	37.9
		PI(M1)	502	502	100	99.3	100	363.6	334.2	395.5
		PI(Y1)	502	501	99.8	98.9	100	118.8	108.7	129.9
Anti-PRN	Boostrix	PRE	1012	769	76.0	73.2	78.6	13.7	12.6	14.8
		PI(M1)	1011	1000	98.9	98.1	99.5	399.4	360.7	442.3
		PI(Y1)	1011	971	96.0	94.7	97.2	152.2	137.2	168.8
	Adacel	PRE	505	376	74.5	70.4	78.2	14.4	12.7	16.4
		PI(M1)	505	502	99.4	98.3	99.9	334.9	293.7	381.9
		PI(Y1)	501	489	97.6	95.9	98.8	132.5	115.6	151.8

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Overall, the seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies were similar for both groups. The percentages of subjects seropositive for FHA (99.8%) and PRN antibodies (at least 96.0%) at Year 1 in each group did not appear to be decreased relative to one month after vaccination, while the seropositivity rate for anti-PT at Year 1

(90.5% and 86.0% in the Boostrix and Adacel groups, respectively) appeared to be slightly decreased from that observed one month after vaccination.

GMCs for anti-pertussis antibodies were low as compared to those observed one month after vaccination but remained higher than pre-vaccination GMCs (Table 10).

The seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies stratified by age and sex are presented in Supplement 9 and Supplement 10, respectively.

The reverse cumulative curves for anti-PT, anti-FHA and anti-PRN antibody concentrations in Boostrix and Adacel groups one year after vaccination for the ATP Year 1 cohort are presented in Supplement 11 to Supplement 13, respectively.

7.3. Year 1 cohort analysis

The results of the Year 1 cohort analyses are presented in Supplement 14 to Supplement 19. The results for all antibodies showed similar results as the ATP Year 1 cohort for both groups.

7.4. Exploratory analyses

7.4.1. Between-group differences in percentages of subjects seroprotected for D and T

The differences between the Boostrix group and the Adacel group in the anti-D seroprotection rate (percentage of subjects with anti-D ≥ 0.1 IU/mL by ELISA) and anti-T seroprotection rate (percentage of subjects with anti-T ≥ 0.1 IU/mL) for the ATP Year 1 cohort are presented in Table 11.

Table 11 Difference between groups in anti-D, anti-T seroprotection rates at Year 1 (ATP Year 1 cohort)

							Difference in seroprotection rate (Boostrix group minus Adacel group)			
									95 % CI	
Antibody	Group	N	%	Group	N	%	Difference	%	LL	UL
Anti-D	Adacel	504	97.0	Boostrix	1010	95.7	Boostrix group - Adacel group	-1.28	-3.15	0.87
Anti-T	Adacel	506	99.6	Boostrix	1014	98.6	Boostrix group- Adacel group	-0.99	-1.98	0.14

N = number of subjects with available results
% = percentage of subjects with anti-D, T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.

There was no statistically significant difference between the Boostrix group and the Adacel group with respect to percentages of subjects with anti-D or anti-T ≥ 0.1 IU/mL, evidenced by the fact that 95% CI for between-group difference included 0.

Supplement 20 and Supplement 21 present the differences in the D and T seroprotection rates at Year 1 between the Boostrix and Adacel groups for the ATP Year 1 cohort, stratified by age and sex, respectively.

7.4.2. Between-group differences in overall D seroprotection

The difference between the Boostrix group and the Adacel group in the overall D seroprotection rate (percentages of subjects with anti-D ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO) at Year 1 for the ATP Year 1 cohort is presented in Table 12.

Table 12 Difference between groups in the percentage of subjects with anti-D antibody concentration greater than or equal to 0.1 IU/mL by ELISA or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations less than 0.1 IU/mL by ELISA) at Year 1 (ATP Year 1 cohort)

						Difference in seroprotection rate (Boostrix minus Adacel)			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Adacel	505	98.2	Boostrix	1012	98.3	Boostrix group – Adacel group	0.10	-1.21	1.79

N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or at least 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.

There was no statistically significant difference between the Boostrix group and the Adacel group with respect to overall anti-D seroprotection rate, evidenced by the fact that 95% CI for between-group difference included 0.

The differences in the overall D seroprotection rates between the Boostrix group and the Adacel group for the ATP Year 1 cohort according to age group and sex are presented in Supplement 22 and Supplement 23, respectively.

7.4.3. Between-group differences in anti-D and anti-T GMCs

Table 13 presents the adjusted ratios of anti-D and anti-T GMCs at Year 1 for the ATP Year 1 cohort.

Table 13 Adjusted ratios of anti-D, anti-T GMCs at Year 1 (ATP Year 1 cohort)

					Adjusted GMC ratio (Boostrix group / Adacel group)		
	Boostrix group		Adacel group			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D (IU/mL)	1004	1.4	500	1.4	1.02	0.92	1.12
Anti-T (IU/mL)	1013	3.4	505	4.3	0.78	0.72	0.84

Adjusted GMC = geometric mean antibody concentration adjusted for Age (Y), baseline concentration
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

One year after vaccination, the adjusted GMCs for anti-D were the same in the Boostrix and Adacel groups (1.4 IU/ml; 95% CI for adjusted GMC ratio included 1). The anti-T GMC was higher in the Adacel group (4.3 IU/mL) than in the Boostrix group (3.4 IU/mL) one year after vaccination (95% CI for GMC ratio excluded 1) and this was similar to the results observed at Month 1 of the 106316 study [GlaxoSmithKline Biologicals Clinical Report 106316]. Since the seroprotection rates and percentages of subjects with anti-T ≥ 1.0 IU/mL were similar between the groups, the difference in anti-T GMC is thought to be not clinically relevant.

The adjusted ratios of anti-D and anti-T GMCs at Year 1 for the ATP Year 1 cohort according to age and sex strata are presented in Supplement 24 and Supplement 25, respectively.

8. SAFETY RESULTS

There were no pregnancies or other SAEs reported in this phase of the study.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1. Discussion

The objective of this study was to assess antibody persistence of GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine adsorbed, *Boostrix*, one year after vaccination in adults aged 19-64 years.

Subjects had been vaccinated with either *Boostrix* or *Adacel* in the primary study (106316, Tdap 0.3-007). A total of 2284 subjects were vaccinated in that study, 1522 subjects with *Boostrix* and 762 subjects with *Adacel*. Of these, a total of 1592 subjects returned for blood sampling for antibody assessment at Year 1, and 1521 subjects (1015 subjects in the Boostrix group and 506 subjects in the Adacel group) met the criteria for inclusion in the ATP Year 1 cohort. The 2:1 ratio for subjects vaccinated with *Boostrix* and *Adacel* was maintained at the Year 1 assessment. The groups remained similar with respect to mean age and male/female ratio. Racial/ethnic makeup of the Year 1 cohorts was not examined but was assumed to be similar to that of the primary study. Enrollment

in the primary study had been stratified by age, with equal representation of subjects aged 19-29, 30-49, and 50-64. In the Year 1 cohort, there was a tendency for greater representation of the older age strata in both groups.

As expected, antibody levels to all vaccine antigens were observed to decrease from the peaks seen one month after vaccination, but remained higher than the pre-vaccination levels. Anti-D seroprotection rates, as shown by ELISA and VERO cell assays were at least 98% in both groups one year after vaccination. Seroprotection rates for tetanus remained high as well, with > 98% of subjects with anti-T ≥ 0.1 IU/mL and > 93% with anti-T ≥ 1.0 IU/mL in both groups. Anti-D GMCs were similar between groups, while the anti-T GMC was greater in the Adacel group than in the Boostrix group. This difference was noted at one month following vaccination as well. Since the seroprotection rates for tetanus were similar between groups, the difference in anti-T GMCs is not thought to be of clinical significance.

Seropositivity rates for antibodies to acellular pertussis antigens remained relatively high one year after vaccination (at least 86%, 99.8% and 96%, respectively for anti-PT, anti-FHA and anti-PRN antibodies) and appeared to be similar in both groups. GMCs for anti-PT and anti-FHA were approximately 2-fold higher in the Boostrix group than in the Adacel group one month after vaccination. These differences remained apparent one year after vaccination, although the magnitude appears less.

The results of this US adult antibody persistence study were found to be consistent with antibody persistence data three years following vaccination of the non-US formulation of *Boostrix* in adults [McIntyre, 2004], and 5-year antibody persistence data following vaccination of the non-US formulation of *Boostrix* in adolescents [Edelman, 2007].

9.2. Overall conclusion

- Evaluation of persistence of anti-D and anti-T elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus one year after vaccination.
- Levels of all antibodies elicited by a single dose of *Boostrix* decreased one year after vaccination as compared to levels observed one month after vaccination, but remained higher than the pre-vaccination levels.

10. SUPPLEMENTS

Supplement 1 Number of subjects by center (Year 1 cohort)

	Boostrix	Adacel	Total	
Center*	n	n	n	%
[redacted]	21	12	33	2.1
	15	8	23	1.4
	16	9	25	1.6
	10	4	14	0.9
	12	7	19	1.2
	56	23	79	5.0
	49	18	67	4.2
	24	11	35	2.2
	11	6	17	1.1
	7	2	9	0.6
	50	21	71	4.5
	17	8	25	1.6
	7	4	11	0.7
	12	5	17	1.1
	21	11	32	2.0
	32	22	54	3.4
	50	28	78	4.9
	18	12	30	1.9
	18	9	27	1.7
	33	14	47	3.0
	71	34	105	6.6
	78	37	115	7.2
	27	13	40	2.5
	26	12	38	2.4
	12	8	20	1.3
	12	6	18	1.1
	50	25	75	4.7
	7	3	10	0.6
	65	30	95	6.0
	33	18	51	3.2
	15	6	21	1.3
	22	13	35	2.2
	26	14	40	2.5
	27	15	42	2.6
	45	18	63	4.0
	43	22	65	4.1
	18	9	27	1.7
	13	6	19	1.2
All	1069	523	1592	100

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number
* = Centers [redacted] of the 106316 study did not participate in the Year 1 phase of the study.

Supplement 2 Summary of demographic characteristics (Year 1 cohort)

		Boostrix N = 1069		Adacel N = 523		Total N = 1592	
Characteristics	**Parameters**	**Value**		**Value**		**Value**	
Age (years)	Mean	41.7		42.5		42.0	
	Sd	13.39		13.27		13.35	
	Median	43.0		44.0		44.0	
	Minimum	19		19		19	
	Maximum	65		65		65	
	Unknown	4		0		4	
	Categories	**n**	**%**	**n**	**%**	**n**	**%**
Age stratum	19-29 (Y)	324	30.3	147	28.1	471	29.6
	30-49 (Y)	365	34.1	183	35.0	548	34.4
	50-64 (Y)	380	35.6	193	36.9	573	36.0
Sex	Female	680	63.6	357	68.3	1037	65.1
	Male	389	36.4	166	31.7	555	34.9

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = total number of subjects
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Age(Y) = age at Year 1 blood sampling, expressed in years
Age stratum: based on the age at vaccination in 106316 study

Supplement 3 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1, stratified by age group (ATP Year 1 cohort)

					≥ 0.1 IU/mL				≥ 1 IU/mL				GMC (IU/mL)		
0							95% CI				95% CI			95% CI	
Antibody	**Sub-group**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-D	19-29	Boostrix	PRE	300	274	91.3	87.6	94.3	85	28.3	23.3	33.8	0.5	0.4	0.6
			PI(M1)	301	300	99.7	98.2	100	295	98.0	95.7	99.3	7.8	7.0	8.7
			PI(Y1)	301	300	99.7	98.2	100	250	83.1	78.3	87.1	2.4	2.1	2.7
		Adacel	PRE	141	128	90.8	84.7	95.0	39	27.7	20.5	35.8	0.5	0.4	0.6
			PI(M1)	141	140	99.3	96.1	100	137	97.2	92.9	99.2	6.6	5.7	7.7
			PI(Y1)	141	140	99.3	96.1	100	119	84.4	77.3	90.0	2.0	1.7	2.3
	30-49	Boostrix	PRE	346	310	89.6	85.9	92.6	94	27.2	22.5	32.2	0.5	0.4	0.5
			PI(M1)	349	345	98.9	97.1	99.7	321	92.0	88.6	94.6	5.4	4.8	6.2
			PI(Y1)	349	341	97.7	95.5	99.0	247	70.8	65.7	75.5	1.6	1.4	1.8
		Adacel	PRE	173	159	91.9	86.8	95.5	43	24.9	18.6	32.0	0.5	0.4	0.6
			PI(M1)	177	174	98.3	95.1	99.6	167	94.4	89.9	97.3	5.7	4.8	6.7
			PI(Y1)	176	173	98.3	95.1	99.6	128	72.7	65.5	79.2	1.7	1.4	2.0
	50-64	Boostrix	PRE	361	271	75.1	70.3	79.4	72	19.9	15.9	24.4	0.3	0.3	0.4
			PI(M1)	362	348	96.1	93.6	97.9	272	75.1	70.4	79.5	2.6	2.2	3.0
			PI(Y1)	360	326	90.6	87.1	93.4	176	48.9	43.6	54.2	0.8	0.7	1.0
		Adacel	PRE	186	156	83.9	77.8	88.8	45	24.2	18.2	31.0	0.4	0.3	0.4
			PI(M1)	187	183	97.9	94.6	99.4	160	85.6	79.7	90.3	3.4	2.8	4.2
			PI(Y1)	187	176	94.1	89.7	97.0	104	55.6	48.2	62.9	1.0	0.8	1.2
Anti-T	19-29	Boostrix	PRE	301	292	97.0	94.4	98.6	216	71.8	66.3	76.8	1.7	1.5	1.9
			PI(M1)	301	300	99.7	98.2	100	298	99.0	97.1	99.8	9.9	9.0	10.8
			PI(Y1)	301	301	100	98.8	100	297	98.7	96.6	99.6	4.3	4.0	4.6
		Adacel	PRE	141	139	98.6	95.0	99.8	108	76.6	68.7	83.3	1.8	1.5	2.2
			PI(M1)	141	141	100	97.4	100	141	100	97.4	100	14.6	12.7	16.8
			PI(Y1)	141	141	100	97.4	100	139	98.6	95.0	99.8	5.1	4.4	5.8
	30-49	Boostrix	PRE	349	343	98.3	96.3	99.4	266	76.2	71.4	80.6	1.7	1.6	1.9
			PI(M1)	350	350	100	99.0	100	350	100	99.0	100	9.0	8.3	9.7
			PI(Y1)	350	348	99.4	98.0	99.9	335	95.7	93.0	97.6	3.5	3.3	3.8
		Adacel	PRE	176	173	98.3	95.1	99.6	135	76.7	69.8	82.7	1.8	1.5	2.1
			PI(M1)	177	177	100	97.9	100	175	98.9	96.0	99.9	14.0	12.4	16.0
			PI(Y1)	177	176	99.4	96.9	100	172	97.2	93.5	99.1	4.9	4.4	5.5
	50-64	Boostrix	PRE	364	343	94.2	91.3	96.4	247	67.9	62.8	72.6	1.4	1.2	1.6
			PI(M1)	362	358	98.9	97.2	99.7	347	95.9	93.3	97.7	7.1	6.4	7.9
			PI(Y1)	363	351	96.7	94.3	98.3	320	88.2	84.4	91.3	2.7	2.4	3.0
		Adacel	PRE	188	182	96.8	93.2	98.8	139	73.9	67.0	80.1	1.5	1.3	1.8
			PI(M1)	188	188	100	98.1	100	186	98.9	96.2	99.9	11.6	10.3	13.1
			PI(Y1)	188	187	99.5	97.1	100	176	93.6	89.1	96.7	3.6	3.2	4.1

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
19-29 = 19-29Years
30-49 = 30-49Years
50-64 = 50-64Years
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Supplement 4 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1, stratified by sex (ATP Year 1 cohort)

					≥ 0.1 IU/mL				≥ 1 IU/mL				GMC (IU/mL)		
							95% CI				95% CI			95% CI	
Antibody	**Sub-group**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-D	Male	Boostrix	PRE	364	312	85.7	81.7	89.1	109	29.9	25.3	34.9	0.5	0.4	0.5
			PI(M1)	365	360	98.6	96.8	99.6	321	87.9	84.2	91.1	4.7	4.1	5.4
			PI(Y1)	364	349	95.9	93.3	97.7	241	66.2	61.1	71.1	1.4	1.3	1.6
		Adacel	PRE	159	150	94.3	89.5	97.4	44	27.7	20.9	35.3	0.5	0.4	0.6
			PI(M1)	160	160	100	97.7	100	151	94.4	89.6	97.4	5.3	4.6	6.2
			PI(Y1)	160	159	99.4	96.6	100	115	71.9	64.2	78.7	1.6	1.3	1.9
	Female	Boostrix	PRE	643	543	84.4	81.4	87.2	142	22.1	18.9	25.5	0.4	0.4	0.4
			PI(M1)	647	633	97.8	96.4	98.8	567	87.6	84.8	90.1	4.6	4.1	5.1
			PI(Y1)	646	618	95.7	93.8	97.1	432	66.9	63.1	70.5	1.4	1.3	1.6
		Adacel	PRE	341	293	85.9	81.8	89.4	83	24.3	19.9	29.3	0.4	0.4	0.5
			PI(M1)	345	337	97.7	95.5	99.0	313	90.7	87.2	93.6	4.7	4.2	5.4
			PI(Y1)	344	330	95.9	93.3	97.8	236	68.6	63.4	73.5	1.4	1.2	1.6
Anti-T	Male	Boostrix	PRE	366	356	97.3	95.0	98.7	286	78.1	73.6	82.3	1.9	1.7	2.1
			PI(M1)	365	365	100	99.0	100	359	98.4	96.5	99.4	8.0	7.4	8.6
			PI(Y1)	366	362	98.9	97.2	99.7	345	94.3	91.4	96.4	3.4	3.1	3.7
		Adacel	PRE	161	161	100	97.7	100	128	79.5	72.4	85.5	2.1	1.8	2.5
			PI(M1)	161	161	100	97.7	100	160	99.4	96.6	100	13.1	11.6	14.8
			PI(Y1)	161	161	100	97.7	100	156	96.9	92.9	99.0	4.9	4.3	5.5
	Female	Boostrix	PRE	648	622	96.0	94.2	97.4	443	68.4	64.6	71.9	1.4	1.3	1.6
			PI(M1)	648	643	99.2	98.2	99.7	636	98.1	96.8	99.0	8.8	8.2	9.5
			PI(Y1)	648	638	98.5	97.2	99.3	607	93.7	91.5	95.4	3.4	3.1	3.6
		Adacel	PRE	344	333	96.8	94.4	98.4	254	73.8	68.9	78.4	1.5	1.4	1.8
			PI(M1)	345	345	100	98.9	100	342	99.1	97.5	99.8	13.3	12.1	14.6
			PI(Y1)	345	343	99.4	97.9	99.9	331	95.9	93.3	97.8	4.2	3.8	4.6

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 5 Overall seroprotection status for anti-D antibody concentration by ELISA and VERO at Year 1, stratified by age group (ATP Year 1 cohort)

				Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
Timing	**Sub-group**	**Group**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
PRE	19-29	Boostrix	300	26/300	8.7	12/26	46.2	26/300 x 12/26	4.0	96.0	93.1	97.9
		Adacel	141	13/141	9.2	4/13	30.8	13/141 x 4/13	2.8	97.2	92.9	99.2
	30-49	Boostrix	346	36/346	10.4	14/36	38.9	36/346 x 14/36	4.0	96.0	93.3	97.8
		Adacel	173	14/173	8.1	4/13	30.8	14/173 x 4/13	2.5	97.5	94.2	99.2
	50-64	Boostrix	361	90/361	24.9	46/90	51.1	90/361 x 46/90	12.7	87.3	83.4	90.5
		Adacel	186	30/186	16.1	13/30	43.3	30/186 x 13/30	7.0	93.0	88.3	96.2
PI(M1)	19-29	Boostrix	301	1/301	0.3	1/1	100	1/301 x 1/1	0.3	99.7	98.2	100
		Adacel	141	1/141	0.7	0/1	0.0	1/141 x 0/1	0.0	100	97.4	100
	30-49	Boostrix	349	4/349	1.1	0/4	0.0	4/349 x 0/4	0.0	100	98.9	100
		Adacel	177	3/177	1.7	2/3	66.7	3/177 x 2/3	1.1	98.9	96.0	99.9
	50-64	Boostrix	362	14/362	3.9	6/14	42.9	14/362 x 6/14	1.7	98.3	96.4	99.4
		Adacel	187	4/187	2.1	3/4	75.0	4/187 x 3/4	1.6	98.4	95.4	99.7
PI(Y1)	19-29	Boostrix	301	1/301	0.3	0/1	0.0	1/301 x 0/1	0.0	100	98.8	100
		Adacel	141	1/141	0.7	1/1	100	1/141 x 1/1	0.7	99.3	96.1	100
	30-49	Boostrix	350	9/350	2.6	7/9	77.8	9/350 x 7/9	2.0	98.0	95.9	99.2
		Adacel	176	3/176	1.7	2/3	66.7	3/176 x 2/3	1.1	98.9	96.0	99.9
	50-64	Boostrix	361	35/361	9.7	10/35	28.6	35/361 x 10/35	2.8	97.2	95.0	98.7
		Adacel	188	12/188	6.4	6/12	50.0	12/188 x 6/12	3.2	96.8	93.2	98.8

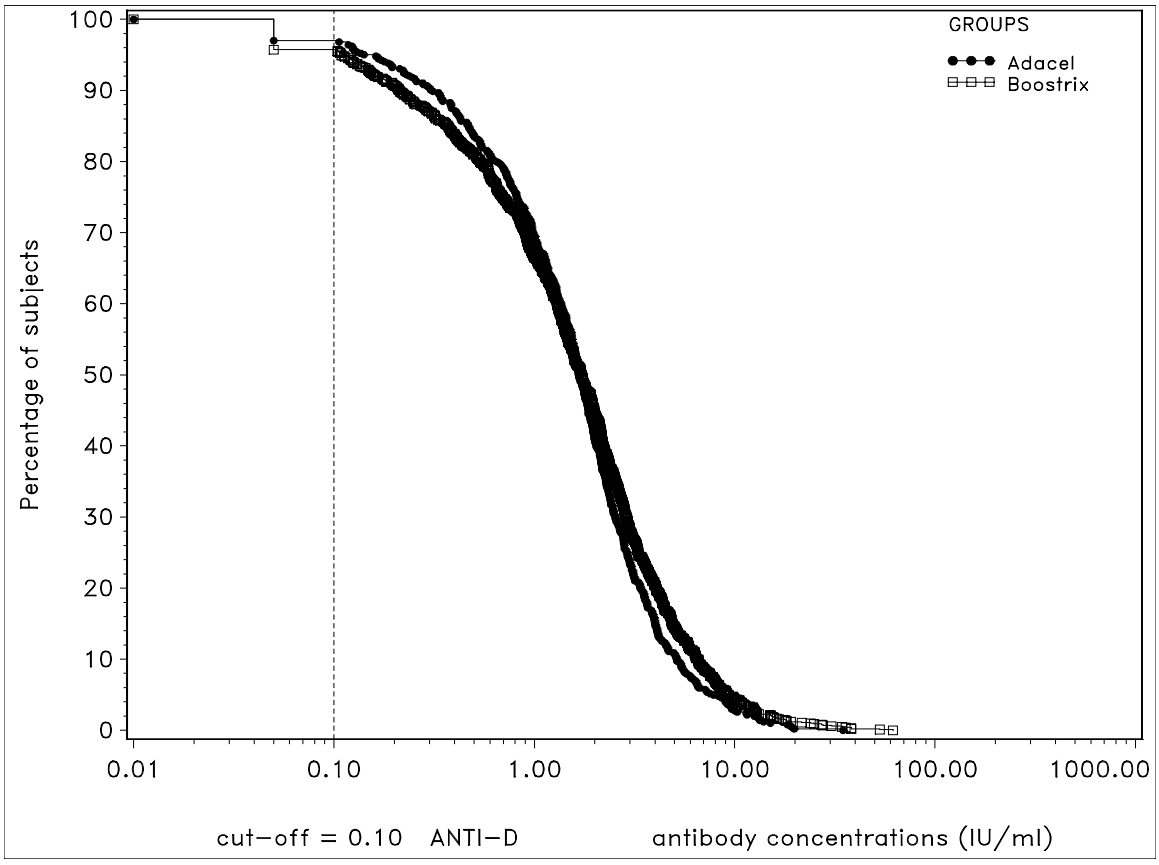
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination
19-29 = 19-29Years
30-49 = 30-49Years
50-64 = 50-64Years
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralization test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for group(s); LL = Lower Limit, UL = Upper Limit

Supplement 6 Overall seroprotection status for anti-D antibody concentration by ELISA and VERO at Year 1, stratified by sex (ATP Year 1 cohort)

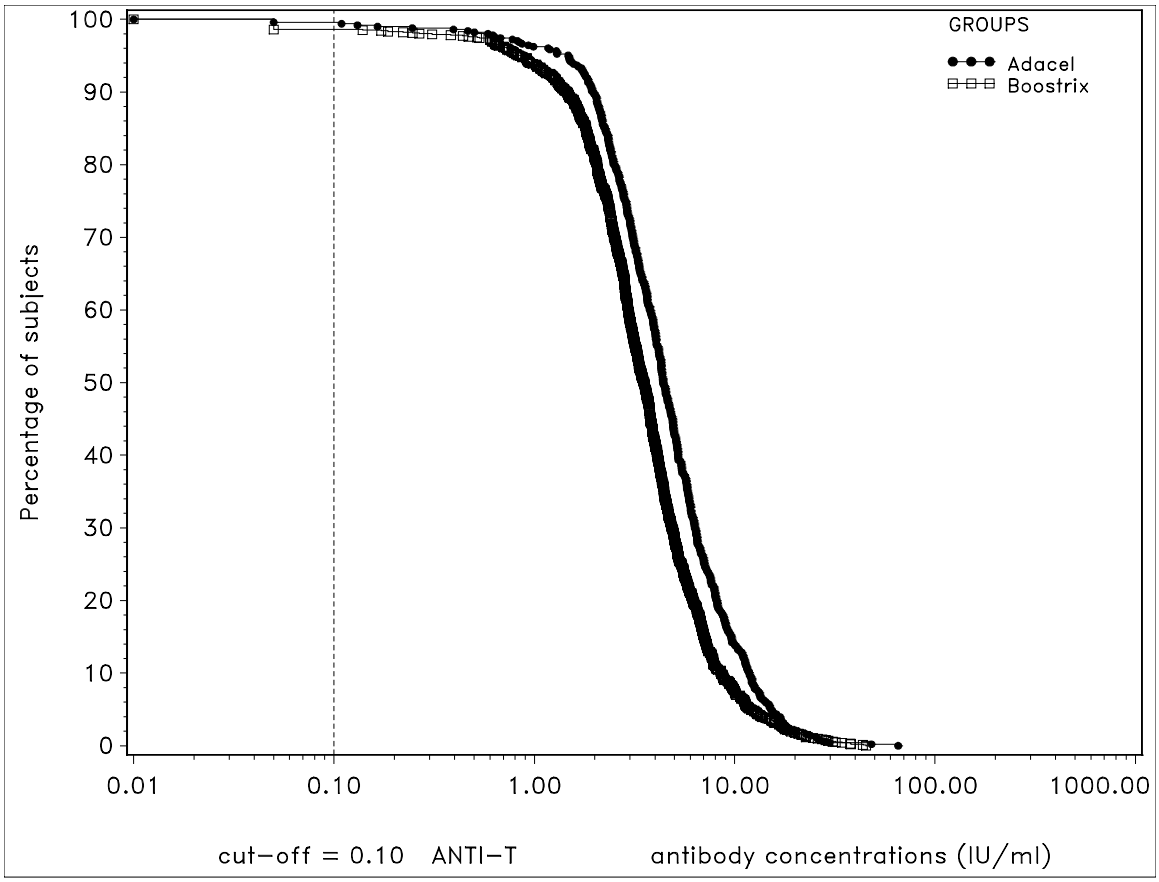
				Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
Timing	**Sub-group**	**Group**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
PRE	Male	Boostrix	364	52/364	14.3	20/52	38.5	52/364 x 20/52	5.5	94.5	91.6	96.6
		Adacel	159	9/159	5.7	2/9	22.2	9/159 x 2/9	1.3	98.7	95.5	99.8
	Female	Boostrix	643	100/643	15.6	52/100	52.0	100/643 x 52/100	8.1	91.9	89.5	93.9
		Adacel	341	48/341	14.1	19/47	40.4	48/341 x 19/47	5.7	94.3	91.5	96.4
PI(M1)	Male	Boostrix	365	5/365	1.4	1/5	20.0	5/365 x 1/5	0.3	99.7	98.5	100
		Adacel	160	0/160	0.0	0/0	.	-	.	.	.	.
	Female	Boostrix	647	14/647	2.2	6/14	42.9	14/647 x 6/14	0.9	99.1	98.0	99.7
		Adacel	345	8/345	2.3	5/8	62.5	8/345 x 5/8	1.4	98.6	96.7	99.5
PI(Y1)	Male	Boostrix	365	16/365	4.4	3/16	18.8	16/365 x 3/16	0.8	99.2	97.6	99.8
		Adacel	161	2/161	1.2	2/2	100	2/161 x 2/2	1.2	98.8	95.6	99.8
	Female	Boostrix	647	29/647	4.5	14/29	48.3	29/647 x 14/29	2.2	97.8	96.4	98.8
		Adacel	344	14/344	4.1	7/14	50.0	14/344 x 7/14	2.0	98.0	95.9	99.2

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = exact 95% confidence interval for group(s); LL = Lower Limit, UL = Upper Limit
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralisation test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing

Supplement 7 **Reverse cumulative curves for anti-D antibody concentrations in Boostrix and Adacel groups one year after vaccination (ATP Year 1 cohort)**



Supplement 8 **Reverse cumulative curves for anti-T antibody concentrations in Boostrix and Adacel groups one year after vaccination (ATP Year 1 cohort)**



Supplement 9 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at Year 1, stratified by age group (ATP Year 1 cohort)

					≥ 5 EL.U/mL				GMC (EL.U/mL)		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	19-29	Boostrix	PRE	299	186	62.2	56.4	67.7	7.6	6.8	8.6
			PI(M1)	297	289	97.3	94.8	98.8	70.9	63.0	79.8
			PI(Y1)	300	280	93.3	89.9	95.9	25.2	22.4	28.4
		Adacel	PRE	141	92	65.2	56.8	73.1	8.8	7.3	10.7
			PI(M1)	139	133	95.7	90.8	98.4	38.6	32.4	46.0
			PI(Y1)	141	121	85.8	78.9	91.1	16.6	13.8	20.0
	30-49	Boostrix	PRE	344	189	54.9	49.5	60.3	7.1	6.3	7.9
			PI(M1)	346	341	98.6	96.7	99.5	68.7	61.8	76.4
			PI(Y1)	349	325	93.1	89.9	95.5	25.5	22.8	28.6
		Adacel	PRE	174	113	64.9	57.4	72.0	8.3	7.0	9.8
			PI(M1)	176	168	95.5	91.2	98.0	32.0	27.3	37.7
			PI(Y1)	177	154	87.0	81.1	91.6	15.4	13.2	17.9
	50-64	Boostrix	PRE	362	194	53.6	48.3	58.8	6.7	6.0	7.5
			PI(M1)	358	341	95.3	92.5	97.2	50.9	45.1	57.5
			PI(Y1)	364	312	85.7	81.7	89.1	18.0	16.0	20.2
		Adacel	PRE	187	115	61.5	54.1	68.5	7.8	6.7	9.1
			PI(M1)	186	171	91.9	87.0	95.4	29.4	24.5	35.4
			PI(Y1)	188	160	85.1	79.2	89.9	15.1	12.8	17.7
Anti-FHA	19-29	Boostrix	PRE	298	290	97.3	94.8	98.8	29.8	26.4	33.7
			PI(M1)	301	301	100	98.8	100	662.9	601.9	730.1
			PI(Y1)	301	300	99.7	98.2	100	211.0	189.3	235.1
		Adacel	PRE	140	135	96.4	91.9	98.8	35.6	29.4	43.2
			PI(M1)	141	141	100	97.4	100	412.3	356.5	477.0
			PI(Y1)	140	140	100	97.4	100	142.9	121.2	168.5
	30-49	Boostrix	PRE	347	341	98.3	96.3	99.4	31.7	28.5	35.1
			PI(M1)	350	350	100	99.0	100	668.1	605.9	736.5
			PI(Y1)	350	349	99.7	98.4	100	203.8	183.1	226.8
		Adacel	PRE	172	166	96.5	92.6	98.7	34.8	29.2	41.4
			PI(M1)	177	177	100	97.9	100	370.6	321.7	426.9
			PI(Y1)	176	176	100	97.9	100	117.6	100.8	137.0
	50-64	Boostrix	PRE	363	344	94.8	91.9	96.8	31.1	27.5	35.2
			PI(M1)	361	361	100	99.0	100	539.9	484.9	601.3
			PI(Y1)	363	363	100	99.0	100	163.1	145.9	182.4
		Adacel	PRE	185	178	96.2	92.4	98.5	33.0	28.2	38.6
			PI(M1)	184	184	100	98.0	100	324.1	279.3	376.0
			PI(Y1)	186	185	99.5	97.0	100	104.4	90.3	120.9
Anti-PRN	19-29	Boostrix	PRE	301	227	75.4	70.1	80.2	12.6	10.9	14.7
			PI(M1)	301	299	99.3	97.6	99.9	462.2	392.1	544.9
			PI(Y1)	301	294	97.7	95.3	99.1	180.9	152.7	214.3
		Adacel	PRE	141	114	80.9	73.4	87.0	16.9	13.3	21.4
			PI(M1)	141	140	99.3	96.1	100	436.4	350.1	544.1
			PI(Y1)	139	136	97.8	93.8	99.6	185.1	145.4	235.8
	30-49	Boostrix	PRE	347	281	81.0	76.4	85.0	16.5	14.4	18.9
			PI(M1)	348	345	99.1	97.5	99.8	543.9	459.8	643.3
			PI(Y1)	350	342	97.7	95.5	99.0	213.1	180.3	251.8
		Adacel	PRE	176	135	76.7	69.8	82.7	15.6	12.6	19.4
			PI(M1)	177	177	100	97.9	100	393.1	321.1	481.2
			PI(Y1)	175	172	98.3	95.1	99.6	151.5	121.9	188.2
	50-64	Boostrix	PRE	364	261	71.7	66.8	76.3	12.2	10.6	13.9

					≥ 5 EL.U/mL				GMC (EL.U/mL)		
							95% CI			95% CI	
Antibody	**Sub-group**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
			PI(M1)	362	356	98.3	96.4	99.4	262.9	218.8	316.0
			PI(Y1)	360	335	93.1	89.9	95.5	95.0	78.8	114.4
		Adacel	PRE	188	127	67.6	60.4	74.2	11.9	9.8	14.6
			PI(M1)	187	185	98.9	96.2	99.9	235.7	184.9	300.6
			PI(Y1)	187	181	96.8	93.1	98.8	91.2	71.9	115.5

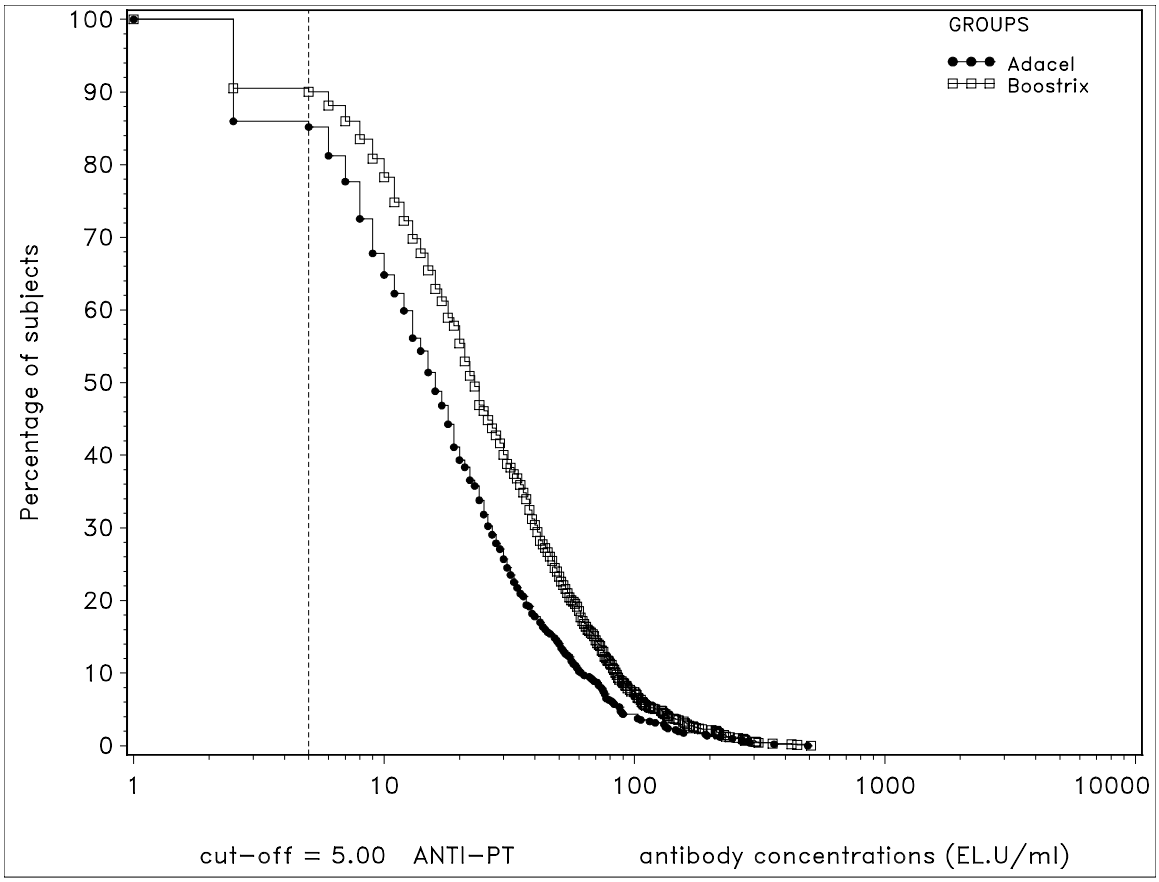
Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
19-29 = 19-29Years
30-49 = 30-49Years
50-64 = 50-64Years
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Supplement 10 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at Year 1, stratified by sex (ATP Year 1 cohort)

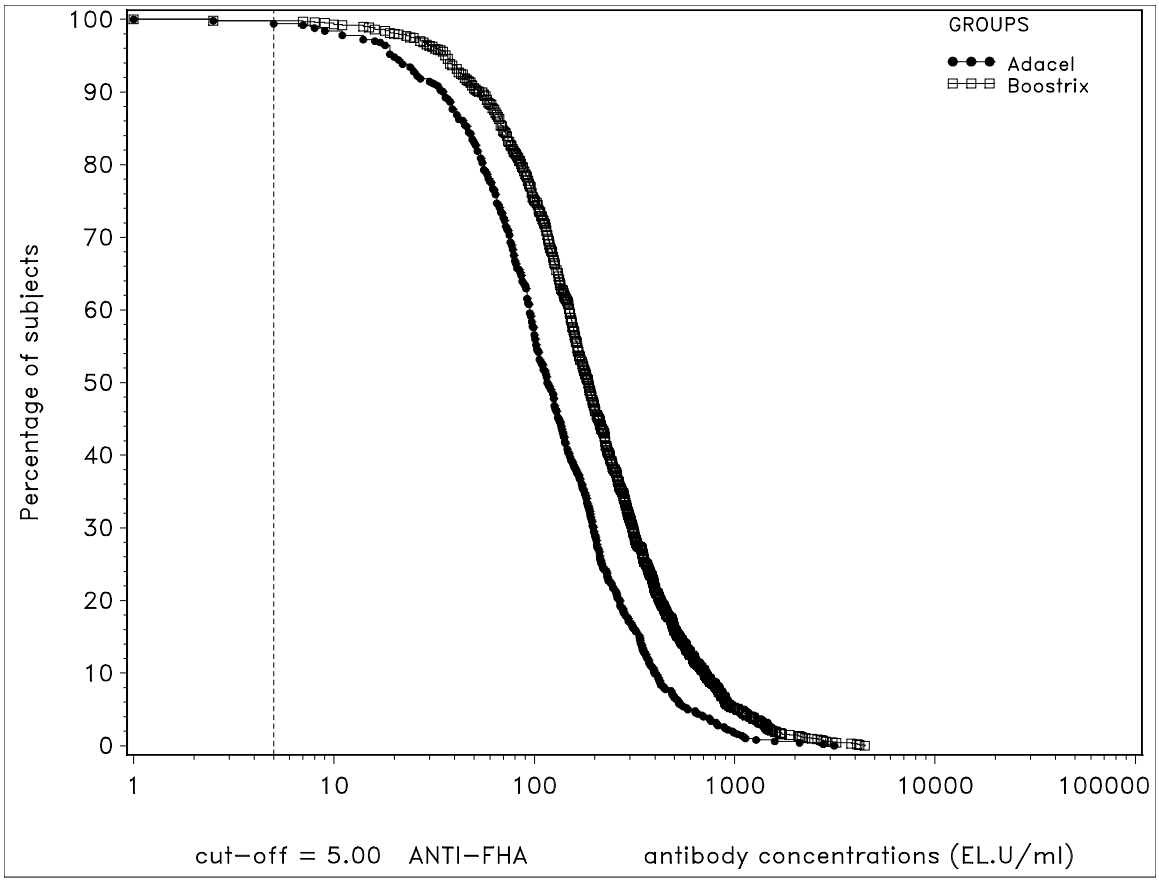
					≥ 5 EL.U/mL				GMC (EL.U/mL)		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Male	Boostrix	PRE	363	227	62.5	57.3	67.5	7.9	7.1	8.9
			PI(M1)	359	352	98.1	96.0	99.2	71.2	63.7	79.6
			PI(Y1)	366	339	92.6	89.4	95.1	26.4	23.5	29.6
		Adacel	PRE	159	106	66.7	58.8	73.9	8.6	7.2	10.2
			PI(M1)	158	149	94.3	89.5	97.4	32.5	27.1	39.1
			PI(Y1)	161	140	87.0	80.8	91.7	16.7	14.0	19.9
	Female	Boostrix	PRE	642	342	53.3	49.3	57.2	6.7	6.1	7.2
			PI(M1)	642	619	96.4	94.7	97.7	57.8	53.2	62.9
			PI(Y1)	647	578	89.3	86.7	91.6	20.5	18.8	22.3
		Adacel	PRE	343	214	62.4	57.0	67.5	8.1	7.2	9.1
			PI(M1)	343	323	94.2	91.1	96.4	32.8	29.0	37.0
			PI(Y1)	345	295	85.5	81.3	89.0	15.1	13.5	16.9
Anti-FHA	Male	Boostrix	PRE	363	360	99.2	97.6	99.8	39.4	35.3	44.0
			PI(M1)	365	365	100	99.0	100	695.1	633.2	763.0
			PI(Y1)	366	366	100	99.0	100	220.7	200.0	243.7
		Adacel	PRE	158	153	96.8	92.8	99.0	38.3	32.3	45.6
			PI(M1)	159	159	100	97.7	100	402.5	348.8	464.4
			PI(Y1)	160	159	99.4	96.6	100	138.8	119.2	161.7
	Female	Boostrix	PRE	645	615	95.3	93.4	96.8	27.0	24.8	29.3
			PI(M1)	647	647	100	99.4	100	578.0	536.3	623.1
			PI(Y1)	648	646	99.7	98.9	100	174.8	161.1	189.6
		Adacel	PRE	339	326	96.2	93.5	97.9	32.6	28.9	36.9
			PI(M1)	343	343	100	98.9	100	346.8	312.5	384.9
			PI(Y1)	342	342	100	98.9	100	110.5	99.0	123.2
Anti-PRN	Male	Boostrix	PRE	365	302	82.7	78.5	86.5	16.7	14.6	19.1
			PI(M1)	364	362	99.5	98.0	99.9	519.2	443.1	608.4
			PI(Y1)	366	355	97.0	94.7	98.5	199.9	169.6	235.7
		Adacel	PRE	161	127	78.9	71.8	84.9	17.2	13.6	21.7
			PI(M1)	160	159	99.4	96.6	100	391.5	312.9	489.9
			PI(Y1)	159	158	99.4	96.5	100	162.5	127.9	206.3
	Female	Boostrix	PRE	647	467	72.2	68.6	75.6	12.2	11.0	13.5
			PI(M1)	647	638	98.6	97.4	99.4	344.7	302.4	392.9
			PI(Y1)	645	616	95.5	93.6	97.0	130.4	114.3	148.6
		Adacel	PRE	344	249	72.4	67.3	77.0	13.3	11.5	15.4
			PI(M1)	345	343	99.4	97.9	99.9	311.5	264.9	366.3
			PI(Y1)	342	331	96.8	94.3	98.4	120.5	102.1	142.2

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

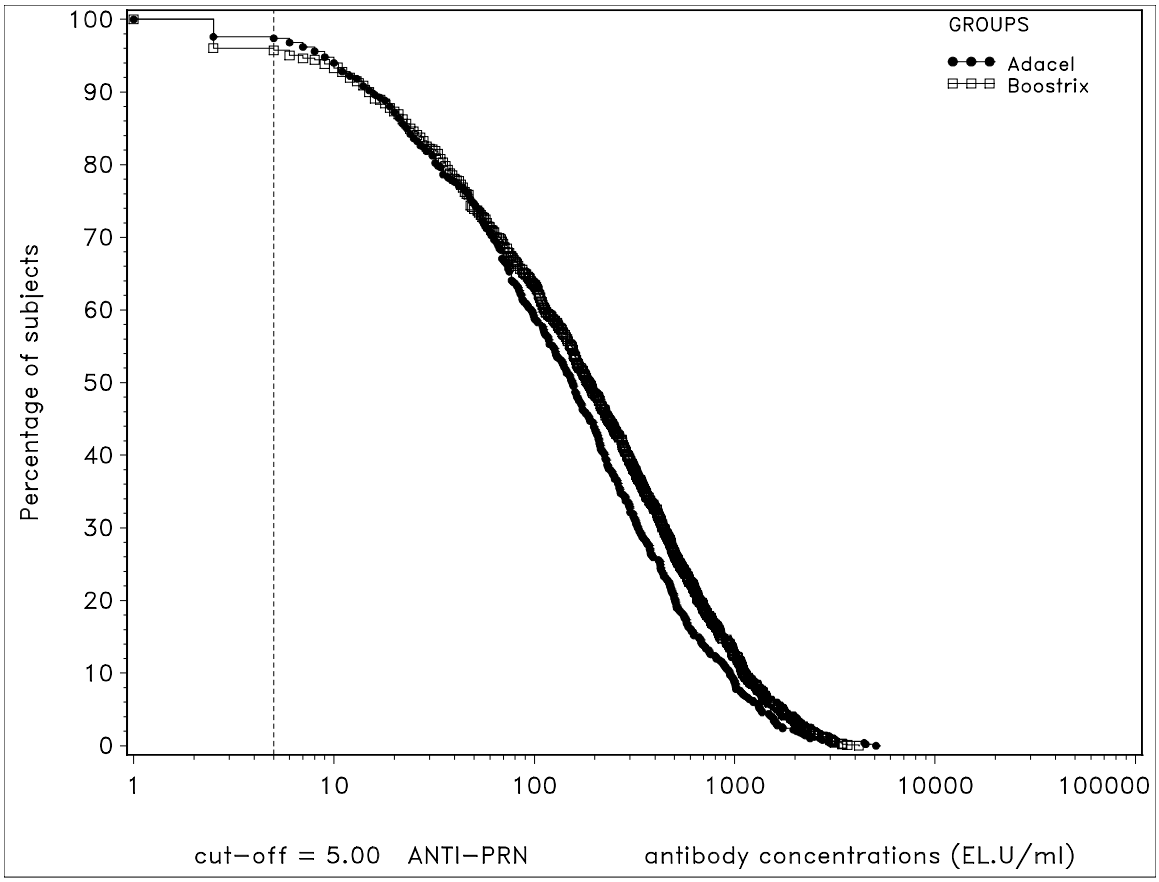
Supplement 11 **Reverse cumulative curves for anti-PT antibody concentrations in Boostrix and Adacel groups one year after vaccination (ATP Year 1 cohort)**



Supplement 12 **Reverse cumulative curves for anti-FHA antibody concentrations in Boostrix and Adacel groups one year after vaccination (ATP Year 1 cohort)**



Supplement 13 **Reverse cumulative curves for anti-PRN antibody concentrations in Boostrix and Adacel groups one year after vaccination (ATP Year 1 cohort)**



Supplement 14 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU/mL or 1.0 IU/mL and anti-D and anti-T GMCs at Year 1 according to treatment group (Year 1 cohort)

				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC (IU/mL)		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-D	Boostrix	PRE	1061	902	85.0	82.7	87.1	264	24.9	22.3	27.6	0.4	0.4	0.5
		PI(M1)	1056	1036	98.1	97.1	98.8	926	87.7	85.6	89.6	4.6	4.2	5.0
		PI(Y1)	1059	1014	95.8	94.4	96.9	707	66.8	63.8	69.6	1.4	1.3	1.6
	Adacel	PRE	517	459	88.8	85.7	91.4	133	25.7	22.0	29.7	0.4	0.4	0.5
		PI(M1)	517	508	98.3	96.7	99.2	474	91.7	89.0	93.9	4.9	4.4	5.4
		PI(Y1)	521	504	96.7	94.8	98.1	361	69.3	65.1	73.2	1.4	1.3	1.6
Anti-T	Boostrix	PRE	1068	1030	96.4	95.1	97.5	772	72.3	69.5	75.0	1.6	1.5	1.7
		PI(M1)	1058	1053	99.5	98.9	99.8	1040	98.3	97.3	99.0	8.5	8.1	9.0
		PI(Y1)	1063	1049	98.7	97.8	99.3	999	94.0	92.4	95.3	3.4	3.2	3.6
	Adacel	PRE	522	511	97.9	96.3	98.9	397	76.1	72.2	79.7	1.7	1.6	1.9
		PI(M1)	518	518	100	99.3	100	514	99.2	98.0	99.8	13.2	12.3	14.2
		PI(Y1)	523	521	99.6	98.6	100	503	96.2	94.2	97.6	4.4	4.1	4.7

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Blood sample taken before the vaccination PI(Y1)
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Supplement 15 Overall seroprotection status for anti-D antibody concentration by ELISA and VERO at Year 1 according to group (Year 1 cohort)

			Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
Timing	**Group**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
PRE	Boostrix	1061	159/1061	15.0	76/159	47.8	159/1061 x 76/159	7.2	92.8	91.1	94.3
	Adacel	517	58/517	11.2	22/57	38.6	58/517 x 22/57	4.3	95.7	93.7	97.2
PI(M1)	Boostrix	1056	20/1056	1.9	7/20	35.0	20/1056x 7/20	0.7	99.3	98.6	99.7
	Adacel	517	9/517	1.7	6/9	66.7	9/517 x 6/9	1.2	98.8	97.5	99.6
PI(Y1)	Boostrix	1061	47/1061	4.4	17/47	36.2	47/1061 x 17/47	1.6	98.4	97.4	99.1
	Adacel	522	18/522	3.4	11/18	61.1	18/522 x 11/18	2.1	97.9	96.3	98.9

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralisation test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for group(s); LL = Lower Limit, UL = Upper Limit
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Supplement 16 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at Year 1 (Year 1 cohort)

				≥ 5 EL.U/mL				GMC (EL.U/mL)		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PT	Boostrix	PRE	1059	604	57.0	54.0	60.0	7.1	6.7	7.6
		PI(M1)	1046	1016	97.1	95.9	98.1	62.2	58.2	66.3
		PI(Y1)	1062	964	90.8	88.9	92.4	22.6	21.1	24.1
	Adacel	PRE	519	333	64.2	59.9	68.3	8.4	7.7	9.3
		PI(M1)	512	482	94.1	91.7	96.0	32.6	29.5	36.1
		PI(Y1)	523	449	85.9	82.6	88.7	15.6	14.2	17.2
Anti-FHA	Boostrix	PRE	1062	1029	96.9	95.7	97.9	31.5	29.4	33.6
		PI(M1)	1057	1057	100	99.7	100	615.7	581.3	652.0
		PI(Y1)	1063	1061	99.8	99.3	100	191.3	179.8	203.4
	Adacel	PRE	514	496	96.5	94.5	97.9	34.6	31.4	38.1
		PI(M1)	514	514	100	99.3	100	364.9	335.9	396.4
		PI(Y1)	519	518	99.8	98.9	100	118.8	109.0	129.6
Anti-PRN	Boostrix	PRE	1066	813	76.3	73.6	78.8	13.8	12.7	14.9
		PI(M1)	1056	1045	99.0	98.1	99.5	401.9	364.0	443.8
		PI(Y1)	1060	1020	96.2	94.9	97.3	154.3	139.6	170.6
	Adacel	PRE	522	389	74.5	70.6	78.2	14.5	12.8	16.4
		PI(M1)	517	514	99.4	98.3	99.9	335.9	294.8	382.9
		PI(Y1)	518	506	97.7	96.0	98.8	131.7	115.1	150.5

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Blood sample taken before the vaccination
PI(M1) = Blood sample taken one month after the vaccination
PI(Y1) = Blood sample taken one Year after the vaccination

Supplement 17 Difference between groups in anti-D, anti-T seroprotection rates at Year 1 (Year 1 cohort)

							Difference in seroprotection rate (Boostrix group minus Adacel group)			
									95 % CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-D	Adacel	521	96.7	Boostrix	1059	95.8	Boostrix group - Adacel group	-0.99	-2.85	1.18
Anti-T	Adacel	523	99.6	Boostrix	1063	98.7	Boostrix group - Adacel group	-0.93	-1.88	0.16

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.N = number of subjects with available results

% = percentage of subjects with anti-D, T concentration ≥ 0.1 IU/mL

95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 18 Difference in the percentage of subjects with antibody concentration greater than or equal to 0.1 IU/mL by ELISA or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations less than 0.1 IU/mL by ELISA) between groups at Year 1 after vaccination (Year 1 cohort)

						Difference in seroprotection rate (Boostrix minus Adacel)			
								95 % CI	
Group	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Adacel	522	97.9	Boostrix	1061	98.4	Boostrix group - Adacel group	0.51	-0.82	2.24

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or at least 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 19 Adjusted ratios of anti-D, anti-T GMCs at Year 1 (Year 1 cohort)

					Adjusted GMC ratio (Boostrix group / Adacel group)		
	Boostrix group		Adacel group			95% CI	
Antibody	**N**	**Adjusted GMC**	**N**	**Adjusted GMC**	**Value**	**LL**	**UL**
Anti-D (IU/mL)	1053	1.5	517	1.4	1.03	0.94	1.14
Anti-T (IU/mL)	1062	3.4	522	4.4	0.78	0.72	0.85

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
Adjusted GMC = geometric mean antibody concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Supplement 20 Difference between groups in anti-D, anti-T seroprotection rate at Year 1 by age group (ATP Year 1 cohort)

							Difference in seroprotection rate (Boostrix minus Adacel)			
									95 % CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-D	19-29/Adacel	141	99.3	19-29/Boostrix	301	99.7	19-29/Boostrix - 19-29/Adacel	0.38	-1.24	3.60
	30-49/Adacel	176	98.3	30-49/Boostrix	349	97.7	30-49/Boostrix - 30-49/Adacel	-0.59	-3.08	2.77
	50-64/Adacel	187	94.1	50-64/Boostrix	360	90.6	50-64/Boostrix - 50-64/Adacel	-3.56	-7.96	1.46
Anti-T	19-29/Adacel	141	100	19-29/Boostrix	301	100	19-29/Boostrix - 19-29/Adacel	0.00	-1.26	2.66
	30-49/Adacel	177	99.4	30-49/Boostrix	350	99.4	30-49/Boostrix - 30-49/Adacel	-0.01	-1.58	2.59
	50-64/Adacel	188	99.5	50-64/Boostrix	363	96.7	50-64/Boostrix - 50-64/Adacel	-2.77	-5.25	-0.14

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
19-29 = 19-29Years
30-49 = 30-49Years
50-64 = 50-64Years
N = number of subjects with available results
% = percentage of subjects with anti-D, T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 21 Difference between groups in anti-D, anti-T seroprotection rate at Year 1 by sex (ATP Year 1 cohort)

						Difference in seroprotection rate (Boostrix minus Adacel)				
									95 % CI	
Antibody	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-D	Male/Adacel	160	99.4	Male/Boostrix	364	95.9	Male/Boostrix - Male/Adacel	-3.50	-6.19	-0.43
	Female/Adacel	344	95.9	Female/Boostrix	646	95.7	Female/Boostrix - Female/Adacel	-0.26	-2.76	2.68
Anti-T	Male/Adacel	161	100	Male/Boostrix	366	98.9	Male/Boostrix - Male/Adacel	-1.09	-2.78	1.25
	Female/Adacel	345	99.4	Female/Boostrix	648	98.5	Female/Boostrix - Female/Adacel	-0.96	-2.34	0.66

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D, T concentration ≥ 0.1 IU/mL
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 22 Difference in the percentage of subjects with antibody concentration greater than or equal to 0.1 IU/mL by ELISA or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations less than 0.1 IU/mL by ELISA) between groups at Year 1, stratified by age group (ATP Year 1 cohort)

							Difference in seroprotection rate (Boostrix minus Adacel)			
									95 % CI	
Subgroup	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
19-29 Years	Adacel	141	99.3	Boostrix	301	100	19-29/ Boostrix - 19-29/Adacel	0.71	-0.56	3.91
30-49Years	Adacel	176	98.9	Boostrix	350	98.0	30-49/ Boostrix - 30-49/Adacel	-0.86	-3.15	2.19
50-64Years	Adacel	188	96.8	Boostrix	361	97.2	50-64/ Boostrix - 50-64/Adacel	0.42	-2.44	4.24

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or at least 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 23 Difference in the percentage of subjects with antibody concentration greater than or equal to 0.1 IU/mL by ELISA or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations less than 0.1 IU/mL by ELISA) between groups at Year 1, stratified by sex (ATP Year 1 cohort)

							Difference in seroprotection rate (Boostrix minus Adacel)			
									95 % CI	
Subgroup	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Male	Adacel	161	98.8	Boostrix	365	99.2	Male/ Boostrix - Male/Adacel	0.42	-1.39	3.65
Female	Adacel	344	98.0	Boostrix	647	97.8	Female/ Boostrix - Female/Adacel	-0.13	-1.92	2.14

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or at least 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 24 Adjusted ratios of anti-D, anti-T GMCs at Year 1, stratified by age group (ATP Year 1 cohort)

						Adjusted GMC ratio (Boostrix group/Adacel group)		
		Boostrix group		Adacel group			95% CI	
Subgroup	Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
19-29 years	Anti-D (IU/mL)	300	2.4	141	2.0	1.17	0.98	1.40
	Anti-T (IU/mL)	301	4.3	141	5.1	0.85	0.73	0.98
30-49 years	Anti-D (IU/mL)	346	1.6	173	1.6	1.00	0.85	1.17
	Anti-T (IU/mL)	349	3.5	176	4.8	0.73	0.65	0.83
50-64 years	Anti-D (IU/mL)	358	0.9	186	0.9	0.95	0.81	1.11
	Anti-T (IU/mL)	363	2.7	188	3.5	0.77	0.68	0.88

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
Adjusted GMC = geometric mean antibody concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Supplement 25 Adjusted ratios of anti-D, anti-T GMCs at Year 1, stratified by sex (ATP Year 1 cohort)

						Adjusted GMC ratio (Boostrix group/Adacel group)		
		Boostrix group		Adacel group			95% CI	
Subgroup	Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Male	Anti-D (IU/mL)	363	1.4	159	1.6	0.92	0.78	1.08
	Anti-T (IU/mL)	366	3.4	161	4.8	0.70	0.62	0.80
Female	Anti-D (IU/mL)	641	1.4	341	1.3	1.08	0.95	1.22
	Anti-T (IU/mL)	647	3.4	344	4.1	0.82	0.74	0.91

Boostrix group: Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
Adjusted GMC = geometric mean antibody concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
PI(Y1) = Blood sample taken one Year after the vaccination
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

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12. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

Scientific Writer: [redacted]

Project Statistician: [redacted]

Central Study Coordinator: [redacted]

Study Manager: [redacted]

Central Safety Contact: [redacted] [redacted]

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13. SERIOUS ADVERSE EVENTS /PREGNANCY

There were no pregnancy or SAEs reported in this phase of the study.

Modular Appendices

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Sponsor information	-
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs (plus name of committee chair if required by regulatory authority)	16.1.3
Representative written information for patient and sample consent forms.	16.1.3
List of investigators and other important participants in the study	16.1.4
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
Randomization list (patient identification and treatment assigned).	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods.	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used.	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report.	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Sponsor Information

eTrack study number(s) and abbreviated title(s)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of document	04 Jun 2008
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

1. (Principal) Investigator

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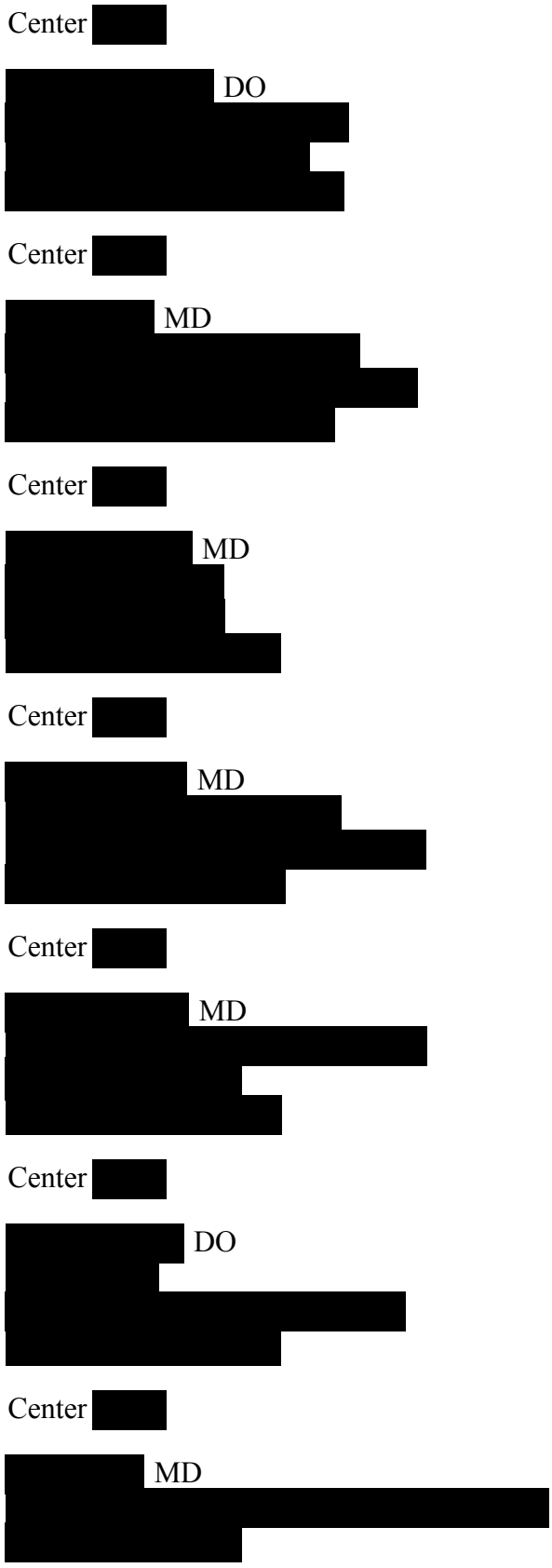
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Fax: [redacted]

GSK Biologicals Clinical Safety Physician: [redacted] MD
Office: [redacted]
Cell: [redacted]

5. Study Contact for Emergency Code Break

Not applicable as there is no vaccine administered in this study.

6. Study Centres

38 Study Centers as listed in item #1

Protocol and Protocol Amendments

Sponsor
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772

Study vaccine number	776423
Study vaccine	GlaxoSmithKline (GSK) Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, containing 0.3 mg aluminum [776423/Tdap, (Boostrix®)] Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap) vaccine (Adacel™)
eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
Investigational New Drug (IND) number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Title	Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Co-ordinating author	[redacted] Scientific writer
Contributing authors	[redacted] Clinical Development Manager, Vaccine (US) [redacted] Director, Vaccines (US) [redacted] Biostatistician (US) [redacted] Project statistician, Boostrix (US) [redacted] Study Manager (US) [redacted], Director, Clinical R&D, World-Wide Clinical Development, Life-cycle Vaccines [redacted] Central Study Coordinator

GSK Biologicals' Protocol DS V 12.4

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	[redacted] MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.
Signature:	_____
Date:	_____

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Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: _____

_____ _____

Investigator signature **Date**

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Synopsis

Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Indication/Study population	Healthy adults, 19 years of age and older, who received a single dose study vaccination in study 106316.
Rationale	This study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, up to 10 years following vaccination with GlaxoSmithKline's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).
Objectives	**Primary** To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination. **Secondary** • To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose *of Boostrix*. • To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix.*
Study design	• Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study. • Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be

maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.

- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

Number of subjects

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points. For example, if the subject did not want to participate in the Year 1 evaluation, he can participate at Years 3, 5 and 10.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel*

vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

TABLE OF CONTENTS

PAGE

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
DTPw	Diphtheria, Tetanus Whole Cell Pertussis Vaccine
DTaP	Diphtheria, Tetanus Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FDA	Food And Drug Administration, United States
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter
PRN	Pertactin
PT	Pertussis Toxoid
RDE	Remote Data Entry

SAE	Serious Adverse Event
SBIR	GSK Biologicals' Internet Randomization System
SOP	Standard Operating Procedure
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

Glossary of Terms

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.3 and 10.4 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain

	further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

1. INTRODUCTION

1.1. Background

Diphtheria, tetanus (toxoids) and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Reported pertussis incidence in the United States increased from 1010 cases in 1976 to 25,827 cases in 2004 [CDC, 2004; CDC, 2002]. On October 26, 2005, ACIP issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.

Recently, GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age. This vaccine is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti , 2002; Greco , 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in Boostrix are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. A total of 6,173,696 doses have been distributed since launch until 02 August 2006.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of *Boostrix*.

1.2. Rationale for the study

Recently a study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by sanofi pasteur's *Adacel* vaccine.

Data on persistence of antibodies and longer-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 years following vaccination with GlaxoSmithKline Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).

2. OBJECTIVES

2.1. Primary objective

To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW

- Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study.
- Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

4. STUDY COHORT

4.1. Number of subjects / centres

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

4.2. Inclusion criteria

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

4.3. Elimination criteria during the study

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

4.4. Contraindications to subsequent vaccination

Not applicable.

4.5. Warnings and Precautions

Not applicable.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 Declaration of Helsinki (Protocol Appendix A), US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.
Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator. A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favorable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favorable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favorable opinion of the IRB/IEC will be transmitted by investigator to CRA prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favorable opinion of an appropriate amendment or administrative change, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].)

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,
- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the October 1996 Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects face to face. The Informed Consent Form may be read to the subjects but, in any event, the investigator or designate shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subjects and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The subjects should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects for participating in the trial.

l. The anticipated expenses, if any, to subjects for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject is authorising such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects will be informed in a timely manner if information becomes available that may be relevant to the subjects' willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be

followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. Subject identification

Subjects will retain their subject numbers as in the 106316 study.

5.3. Outline of study procedures

The summary of study procedures is summarized in Table 1.

Table 1 List of study procedures

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 Year 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. Table 2 presents the intervals between the study visits.

Table 2 Intervals between study visits

Visit	Length of interval
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks

5.4. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Obtain written informed consent from all subjects at all long-term time points.
- Check inclusion criteria at all study visits.
- Check elimination criteria at all study visits.
- Record concomitant medication/vaccination as described in Section 6.3.
- Collect approximately 5 mL of whole venous blood to provide a minimum of 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Study continuation at Years 3, 5 and 10.
- Study conclusion at Year 10 visit (Visit 6).

5.5. Sample handling and analysis

5.5.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

5.5.2. Laboratory assays

Table 3 presents the details of laboratory assays.

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and ten years following study vaccination in 106316 study. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C until sent to the sponsor. Sera will be sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Belgium for the laboratory assays.

All serological assays will be performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off of both assays is 0.1 IU/mL [Camargo , 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL.

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA or multiplex (Luminex) techniques. The cut-off of the three assays is 5 EL.U/mL [Sato, 1982].

Table 3 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
** VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL

All serological assays will be performed at GSK Biologicals using standardized, validated procedures with adequate controls.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.5.3. Immunological read-outs

Table 4 presents the immunological read-outs.

Table 4 Immunological read-outs for all

Blood sampling time point		Marker
Timing	Visit no.	
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 10	6	D
		T
		PT
		FHA
		PRN

All: All subjects enrolled at the long-term time point.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

It may be that any findings in the present or in other studies necessitate further investigation by GSK Biologicals into the efficacy or immunogenicity of the *Boostrix* vaccines and its constituents under study or further research in the disease(s) under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.Any sample testing will be done in line with the consent of the individual subject.

Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to protocol Appendix B, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking above may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.5.4. Activities at study conclusion

All subjects will be offered a booster dose of Td vaccine following the blood draw at the 10 year visit. A booster dose of Tdap may be offered instead if a second dose of Tdap is recommended at that time.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Study vaccines in study 106316 were *Boostrix* and *Adacel*. No additional vaccination will be given as part of this study.

6.1. Treatment allocation and randomisation

Not applicable.

6.2. Method of blinding and breaking the study blind

The study is an open study, since there is no administration of vaccination is this study.

6.3. Concomitant medication/treatment

At each study visit, the investigator should question the subject about any medications taken.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Section 4.3.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration. Refer to Section 4.3.

7. HEALTH ECONOMICS

Not applicable.

8. SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting SAEs, as detailed in this section of the protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.2. Clinical laboratory parameters and other abnormal assessments qualifying as serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as SAEs if they meet the definition of a SAE, as defined in Section 8.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as SAEs. The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.3. Time period, frequency, and method of detecting serious adverse events

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2 for details of the back-up reporting system.

8.4. Evaluating serious adverse events

This section is only applicable if an investigator becomes aware of an SAE that warrants notification of the sponsor.

8.4.1. Assessment of intensity

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevents normal, everyday activities. (In adults, such an SAE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

Grade 3 is a category utilised for rating the intensity of an event; and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.

8.4.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If an event meets the criteria to be determined "serious" (see Section 8.1 for definition of serious adverse event), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.5. Follow-up of serious adverse events and assessment of outcome

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits.

Investigators will follow-up subjects:

- with SAEs, until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.6.1.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2. for details of the back-up reporting system.

Outcome of any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.6. Prompt reporting of serious adverse events to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

8.6.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

8.6.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within

24 hours as outlined in Section 8.6.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received WITHIN 24 HOURS as outlined in Section 8.6.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.4.2.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 8.6.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.6.1.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.6.1.

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF / sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

Please see Sponsor Information Sheet for contact details.

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: [redacted] Tel: [redacted] **US Study Contacts for Concerns Relating to an SAE** GSK Biologicals Medical Monitor: [redacted] MD Office: [redacted] Cell: [redacted] GSK Biologicals Clinical Safety Physician: [redacted] MD Office: [redacted] Cell: [redacted]
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at [redacted] and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.

8.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.6. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will

file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.8. Post-study adverse events and serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.3. Investigators are not obligated to actively seek SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.

8.9. Pregnancy

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.6. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to GSK Biologicals as described in Section 8.8. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for a study visit as specified in the protocol is considered to have completed the study phase (time point) pertaining to that study visit.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE until resolution of the event (see Section 8.1).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

9.2.2. Subject withdrawal from investigational product

Since subjects will not be administered vaccine in this antibody persistence study, subjects will not be withdrawn from receipt of investigational product, but may be withdrawn from other study procedures.

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

10.2. Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

10.3. Estimated sample size

No sample size is calculated for this study. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study.

With a total of 2284 enrolled subjects in primary study 106316, it is expected approximately 1941 subjects will be present for the 1 year time point, 1402 subjects for the 3 year time point, 1013 subjects for the 5 year time point, and 449 subjects for the 10-year time point, assuming a 15% attrition rate per year.

10.4. Study cohorts to be evaluated

Year X (1, 3, 5, 10) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

According-To-Protocol (ATP) Year X (1, 3, 5, 10) cohort

The ATP Year X (1, 3, 5, 10) cohort will include all subjects from Year X (1, 3, 5, 10) cohort who is in the ATP cohort for analysis of immunogenicity in 106316 study and who have not met the following elimination criteria.

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.

- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

ATP Complete Year X (1, 3, 5, 10) cohort

The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.

10.5. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.5.2.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 10.6.2 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the first secondary objective.
- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

- The geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

10.6. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 10) on cleaned data obtained through Year X. A clinical study report (CSR) will also be written following each analysis.

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year 10) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 10) cohort, in the ATP Year X (1, 3, 5 or 10) cohort and in the ATP complete Year X (1, 3, 5 and 10) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 10) (in years) will be summarized using descriptive statistics.

10.6.2. Analysis of immunogenicity

The primary analysis will be based on the ATP Year X cohort.

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 10) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves by group.

Comparability between Groups:

Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), Year X (1, 3, 5, 10) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 10) after vaccination will be calculated.

10.6.3. Analysis of safety

No safety analysis will be performed for this persistence study. If GSK is informed by an investigator of an SAE that in his/her medical judgement could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

10.7. Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5, and Year 10) as available and reported separately.

10.8. Planned interim analysis

No interim analysis is planned for this persistence study.

11. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

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Appendix A World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the

study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments/administrative changes is required prior to implementation.
- Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory

authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is

anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF/ RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability
- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of CRF data

- Reports to the IRB/IEC and the sponsor
    - Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed

Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

Appendix C Overview of the Recruitment Plan

- All subjects who received vaccination in the study 106316 will be invited to participate in this long-term study.
- As part of the visit activities at the study conclusion visit in the 106316 study, subjects were asked to state their interest in participating in an extension study. Subjects who responded positively to this question will be contacted by the site as the sampling time point approaches in order to schedule the study visit.
- Subjects who do not provide samples at earlier long-term time points may still be considered eligible to provide samples at later long-term time points.
- The study will take place at multiple centers in the US.
- The Site Monitor will perform monitoring of actual enrolment against target enrolment on a continuous basis.
- Enrolment will be monitored through RDE.
- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date subject received vaccination in study 106316. A window of ± 5 weeks around the actual time point for each subject will be permitted. Visits for the year 1, 3, 5, and 10 samplings are therefore expected to take place between 8 June – 17 August 2007, 2009, 2011, and 2016.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used to minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimising the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".
- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate label provided by GSK Biologicals (see point 3).

3. Labelling

- The standard labels provided by Quest should be used to label each serum sample.
- If necessary, any hand-written additions to the labels should be made using indelible ink.

4. Sorting and storage

- The tubes of serum should be stored in a vertical position at approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to Quest Diagnostics. Wherever possible, a backup facility for storage of serum samples should be available.
- Detailed instructions concerning the collection, Quest labelling and storage of all serum specimens are provided in the Quest Diagnostics Clinical Trials Investigator Manual for Protocol Number 110080, 110082, 110084 and 110086.

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, Van Nuys, California.

Refer to the separate Quest Diagnostics Clinical Trials Investigator Manual for Protocol Numbers 110080, 110082, 110084 and 110086 for shipping details.

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	[redacted] MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.
Signature:	[redacted]
Date:	5/10/07

For internal use only
----------Checksum----------!Ver.!Created On
2881058bc73398a193fcb56b179fc02d 1.3 16/05/2007

Sample Case Report Form

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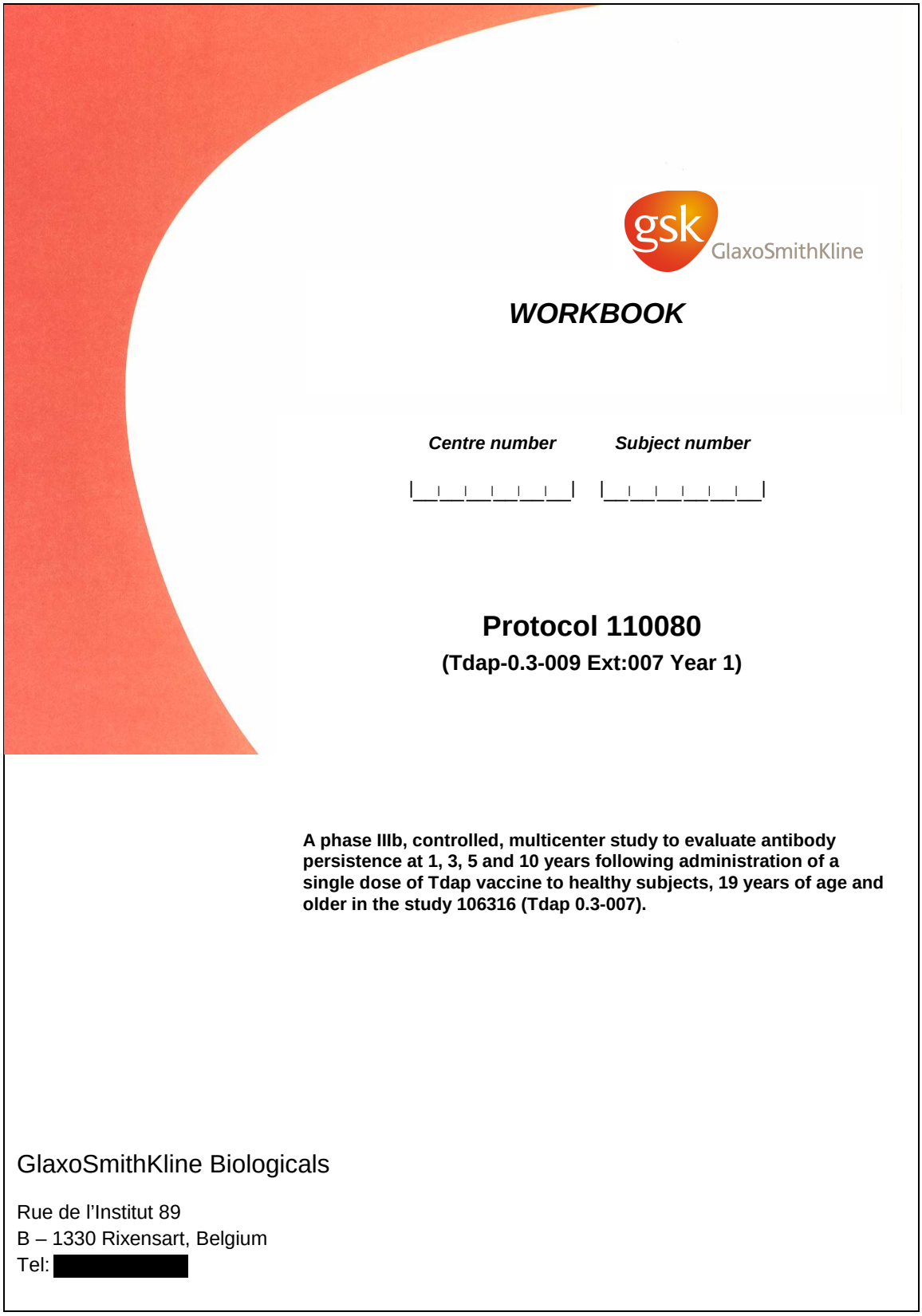

WORKBOOK

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Protocol 110080

(Tdap-0.3-009 Ext:007 Year 1)

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

GlaxoSmithKline Biologicals

Rue de l'Institut 89
B – 1330 Rixensart, Belgium
Tel: [redacted]

GENERAL INSTRUCTIONS

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

DATES

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example: | 0 1 | | J A N | | 2 0 0 6 | = 1st January 2006
day month year

The **Medication** and the **Concomitant Vaccination** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at each long-term follow-up study.

For all subjects enrolled, please complete the **Study Continuation** form**.**

ADVERSE EVENT DEFINITIONS

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.

3: Severe: An adverse event which prevents normal, everyday activities
(In adults/ adolescents, such an adverse event would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO: The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1: Recovered / resolved.

2: Recovering / resolving: If the subject is recovering at the time the subject completes the study or at the time the subject dropped out.

3: Not recovered / not resolved: This means an AE ongoing at the time the subject completes the study or becomes lost to follow-up; if AE/SAE was ongoing at the time of death, but was not the cause of death.

4: Recovered with sequelae / Resolved with sequelae.

5: Fatal: AE is the cause of death (only applicable for SAE reports).

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death.
- is life threatening.
- results in persistent or significant disability / incapacity.
- requires in-patient hospitalization.
- prolongation of existing hospitalization.
- is a congenital anomaly / birth defect in the offspring of a study subject.
- In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

For each serious adverse event related to study participation or related to vaccination in the primary study the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

In case of pregnancy the investigator becomes aware of, please complete and submit a **Pregnancy Notification** form to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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FLOW SHEET

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 Year 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

Intervals between study visits

Visit	Length of interval
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks

VISIT 3

YEAR 1

Informed Consent has to be obtained prior to any study procedure

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. (See section 10.4 for definition of study cohorts to be evaluated.)

[A] Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.

[B] Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.

[C] Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

[D] Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).

[E] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book	Visit	Date of visit	Subject Number
110080		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__| day month year

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study? ☐ Yes ☐ No ☐ NA

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender: [M] ☐ Male
[F] ☐ Female

LONG-TERM FOLLOW-UP

PREVIOUS STUDY

106316 (Tdap 0.3-007)

Subject number will be the same as in the previous study.

1.

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book	Visit		Subject Number
110080		**VISIT 3**		|__|__|__|__|__|__|__|

ELIGIBILITY CHECK

Did the subject meet all the entry criteria?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed

[1] ☐ All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.

[2] ☐ Written informed consent must be obtained from the subject prior to each study time point.

2.

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book	Visit		Subject Number
110080		**VISIT 3**		|__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample for antibodies determination been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

3.

CONCOMITANT VACCINATION

At each study visit/contact, the investigator should question the subject or subject's parents/guardians about any vaccination(s) administered.

- Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration.

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book			Subject Number
110080				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any Td or Tdap Vaccine, or any registered or investigational vaccine utilizing a Diphtheria toxoïd or tetanus toxoïd vaccines been administered at any time after the vaccination in the 106316 study?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** **day month year**
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

Route:

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

4.

Template CRF version 12.4 – May 30, 2007 15:30

MEDICATION

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Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
IN	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject or subject's parents/guardians about any medication(s) taken.

- Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment

110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book			Subject Number
110080				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments specifically contraindicated in the protocol been administered?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

5.

STUDY CONTINUATION

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book			Subject Number
110080				|__|__|__|__|__|__|

FOLLOW-UP STUDIES

If a booster study or a follow-up study is offered in the future, would the subject or parents/guardians be willing to be contacted and learn more about it?

☐ Yes

☐ No, please specify the most appropriate reason:

→ ☐ Adverse Events, or Serious Adverse Events:

please specify: _____

→ ☐ Other:

please specify: _____

OCCURRENCE OF SERIOUS ADVERSE EVENT

Because subjects are not vaccinated as part of the study protocol, investigators are not required to specifically solicit SAE's.

However if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in 106316 study, he/she should do so within 24hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

Did the subject experience any Serious Adverse Event during the study?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

6.

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110080 (Tdap-0.3-009 EXT: 007 Year 1)

Protocol	Book			Subject Number
110080				|_|_|_|_|_|_|

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____

Date: |_\|_\| |_\|_\|_\| |_\|_\|_\|_\|
day month year

Printed Investigator's name: _____

7.

GlaxoSmithKline

110080 (Tdap-.-0.3-009 EXT:007 Year 1)

<table>
<tr><th>Protocol</th><th>Previous study</th><th rowspan="2">Tracking Document
Reason for non participation</th><th>Center Number</th></tr>
<tr><td>110080</td><td>106316
(Tdap 0.3-007)</td><td>|__|__|__|__|__|__|</td></tr>
</table>

<table>
<tr><th>Previous Subject Number</th><th>Date of Birth
<i>(day month year)</i></th><th>Reason for non participation</th><th>Date of Contact
<i>(day month year)</i></th></tr>
<tr><td>|__|__|__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td><td>[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________
[2] ☐ Subject lost to follow-up or not reached.
[3] ☐ Subject eligible but not willing to participate due to:
☐ Adverse event(s), or serious adverse event; Please specify: ___________________
☐ Other;
Please specify: ____________________
[4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td></tr>
<tr><td>|__|__|__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td><td>[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________
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☐ Adverse event(s), or serious adverse event; Please specify: ___________________
☐ Other;
Please specify: ____________________
[4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td></tr>
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[2] ☐ Subject lost to follow-up or not reached.
[3] ☐ Subject eligible but not willing to participate due to:
☐ Adverse event(s), or serious adverse event; Please specify: ___________________
☐ Other;
Please specify: ____________________
[4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td></tr>
<tr><td>|__|__|__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td><td>[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________
[2] ☐ Subject lost to follow-up or not reached.
[3] ☐ Subject eligible but not willing to participate due to:
☐ Adverse event(s), or serious adverse event; Please specify: ___________________
☐ Other;
Please specify: ____________________
[4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|</td><td>|__|__||__|__|__||__|__|__|__|</td></tr>
</table>

<table>
<tr><th>Investigator name: (PRINT name)</th><th>Signature:</th><th>Date: <i>(day month year)</i></th></tr>
<tr><td></td><td></td><td>|__|__| |__|__|__| |__|__|__|__|</td></tr>
</table>

GlaxoSmithKline

110080 (Tdap 0.3-009 EXT:007 Year 1)

Protocol	Centre	
110080	|_|_|_|_|_|_|	

USE OF HUMAN SAMPLES BY GSK

In addition to the use of samples for the tests described in the protocol, samples might be used for other research by GSK (see protocol). Please tick what is also covered by the subject Informed Consent form of your center.

[2] ☐ **Quality Assurance of tests described in the protocol**

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in the protocol as well as making sure that new tests are comparable to previous methods and work reliably.

[3a] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study (Diphtheria Tetanus Pertussis). These investigations excludes genetics and HIV testing.**

[3b] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study(Diphtheria Tetanus Pertussis). These investigations excludes genetic and HIV testing. Investigator will always ask in advance the permission of the independent Ethics Committee/Institutional Review Board linked to the institution where this research is performed.**

[4] ☐ **Further research by GSK Biologicals that is NOT RELATED to Boostrix (Tdap,776423)or the diseases under study (Diphtheria Tetanus Pertussis) done on an anonymous basis (meaning that any identification linking the subject to the sample is destroyed). This research excludes genetic and HIV testing and does not affect subject participation in the study.**

Please tick below box if a 15 years GSK storage period is covered by the subject's Informed Consent form of your center.

☐ **At least 15 years storage period by GSK Biologicals**

☐ **Other, specify:** _____

ICF Effective date: |__|__| |__|__|__| |__|__|__|__|
day month year

! Complete and submit a new form for each change during the study.

INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

1.

List of Independent Ethics Committees/Institutional Review Boards

Independent Ethics Committees/Institutional Review Boards

Center Numbers *	Ethics Review Body	Location
[redacted]	[redacted]	[redacted]

* GSK Biologicals assigned center number

Representative written information for patient and sample consent forms

INFORMED CONSENT FORM

Study Identification: 110080 (Tdap-0.3-009 Ext:007 Year 1)
110082 (Tdap-0.3-009 Ext:007 Year 3)
110084 (Tdap-0.3-009 Ext:007 Year 5)
110086 (Tdap-0.3-009 Ext:007 Year 10)

Study Title: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Version Number: 1 Date: 24 April 2007

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification:

This document should be presented to the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the subject.

What does giving consent for this study mean?

Consent means agreeing to take part in this clinical research study. You have the right to decide if you want to take part in the study or not. Please take time to read the following information carefully and discuss it if you wish with friends, relatives and your personal doctor. Ask us if there is anything that is not clear or if you would like more information.

Why is this study being carried out?

You were vaccinated with a Tdap (tetanus toxoid, diphtheria toxoid and acellular pertussis) vaccine in study 106316. Vaccines work by stimulating antibodies (substances that protect against diseases). This study is being conducted to find out how long information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens remain elevated following a single dose vaccination with GlaxoSmithKline Biologicals's Tdap vaccine (*Boostrix*).

What does this study involve?

In order to be included in this study, the following requirements must be met:

- You have signed this informed consent form.
- You have received a dose of Tdap vaccine (*Boostrix* or *Adacel*) as part of the 106316 study.

If you take part in the study, you will have the following tests and procedures:

- A blood sample of 5 ml will be taken from you.

- You should contact the health care provider immediately should you have any signs or symptoms you think may be serious, or if you are hospitalized during the study period.

How many other subjects are there in the study?

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*.

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, you decline to participate in the study, your refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.

Do you have to stay in the study?

You may decide to stop participating in this study at any time without giving a reason. If you decide to stop participating in the study, you must notify the study doctor immediately. Your leaving the study will not have any effect on future medical care.

Your doctor for this study or GlaxoSmithKline Biologicals may also stop the study at any time before it is completed. If GlaxoSmithKline stops the study, the reason for that decision will be given to you.

If, during the time you are participating in the study, any new information becomes available that might affect whether you are willing to stay in the study, that information will be shared with you in a timely manner.

If you decide the stop participating in the study before it is completed, GlaxoSmithKline will still use the information and data they have collected about you up until that point, as part of the results of their research.

What are the foreseeable risks for taking part in the study?

Blood sampling may cause momentary discomfort, minor bruising or bleeding. The amount to be taken will not be harmful to your health.

Are there any benefits for taking part in the study?

Information from this study may help researchers understand more about protecting adults against tetanus, diphtheria and pertussis diseases in the future.

What payments will be made for the study?

You will receive the following payment for your participation in the study:

$ XXX for each completed scheduled visit, if you do not complete the entire study.

If you have to withdraw from the study for medical reasons related to the study, you will receive full payment.

Will you have to meet any cost/expenses for taking part in the study?

There will be no costs to you to participate in this study.

Who should you contact to answer any questions on the study?

You have the right to ask [**name**] at [**contact details**] any questions concerning this study at any time. This includes questions about your rights, study-related injuries, and the research study itself.

You may ask the study doctor questions about the study. If you have any questions, please contact:

Name of investigator:

Address of investigator:

Telephone number of investigator: _____Fax number _____:

In the event that you are injured in the study what compensation will be available?

If you are injured by any procedure that is done to you as specified by the study, GlaxoSmithKline will pay for reasonable and necessary medical expenses to treat the injury - as long as those expenses are not covered by your medical insurance or an alternative source such as the National Vaccine Injury Compensation Fund. GlaxoSmithKline is not offering to compensate you for any other expenses, but you keep all of your legal rights when you sign this form.

Who will have access to medical and personal information about you that is collected in this study?

If you decide to participate in the study, the study doctor and staff will collect medical and personal information about you as part of doing the study. People who work for or with GSK, and others like the independent ethics committee or the institutional review board (IEC/IRB) for the study or regulatory authorities responsible for approving medicines, will have access to this information at the site in order to check that the study is done properly. GSK staff who see this information at the site will keep it confidential.

The study site will also transfer to GSK some of the information it collects, in a coded form. The information transferred will not include your name, initials, address, or other direct identifiers. It will be assigned a code number that only the site can connect back to your name.

Your permission to the study doctor and staff to use this information or share it with GSK and others as described below for the study doesn't automatically end at a particular time.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

Medical information about you may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your medical care it will be given to the study doctor who will be encouraged to share it with you or your doctor. While you are in the study, however, the study site will not share certain new medical information about you that is created as part of the study (such as whether or not you are getting study drug, or the results of certain tests) unless the study doctor decides it is medically important to do so. This is done to stop the study results from being distorted. Once the study is over, you will be given access to medical information about you that you are entitled to see. You will be told if any of this medical information requires confirmation using a clinical test. This is important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment. At any time, you may ask your study doctor to let you see your personal information, e.g. name and address and to correct it if necessary

What will GlaxoSmithKline do with the information it gets?

- GSK may use the information that the study doctor gives it (i.e. the coded information):
- By storing and analyzing it electronically to find out what this study is telling us.
- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study (this will not include any information that directly identifies you)
- By sharing it as part of research with other companies or universities for the purpose of further understanding or developing this vaccine and with other GlaxoSmithKline offices in this country and in other countries. If the information is sent to another country, GSK will apply the same level of protection to your information, to the extent permitted by local law
- By using it to plan new studies or other types of research or other medical purposes related to the development of the vaccine.

What will happen to blood samples from this study?

- Samples will not be labelled with information that directly identifies you but will be coded with your study identification number.
- Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.
- By agreeing to take part in this study you will be allowing GSK Biologicals to use your samples for the following purposes:
- Testing to measure the immune response (e.g. amount of antibodies) to the vaccine(s) you received during the Study

- Testing to assure that the results from your sample are of good quality, for improvements of those tests or development of new test methods.
- If any findings from related studies require further investigation into the ability of the Boostrix vaccine to protect people or for further research in the diseases under study (diphtheria, tetanus and pertussis), additional testing on your collected samples may be performed by GSK Biologicals. This will, however, exclude testing related to your genes and HIV.

Collected samples will be stored for up to 15 years.

How is GlaxoSmithKline involved?

The study doctor and the institution are paid to conduct this research study by GSK.

The information and the materials that are given to you in relation to the study are confidential information belonging to GlaxoSmithKline and should be kept private. You can discuss this information in confidence with your doctor or friends and family to decide about taking part in this study and talking about your healthcare.

Informed Consent Form **CONFIDENTIAL**
Study Identification Tdap-0.3-009 Ext 007

Consent statement

I, (Printed name of Subject)

confirm that I have read the written information (or have had the information read to me) for studies 110080 (Tdap0.3-009 Ext: 007 Year 1, 110082 (Tdap-0.3-009 Ext: 007 Year 3, 110084 (Tdap-0.3-009 Ext-007 Year 5 and 110086 (Tdap-0.3-009 Ext: 007 Year 10), Version 1, dated 24 April 2007, 6 pages and the study procedures have been explained to me by study staff during the consent process for this study.

- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data to authorised persons described in the information sheet
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my primary health care physician will be notified of my participation in this study.

Yes **No**

Tick as appropriate

I agree that my biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study. This will be done on an anonymous basis (meaning that any identification linking me to the sample is destroyed). Testing on my genes or testing for HIV will not be done. I understand that if I select "No", it will not affect my participation in the study.

Yes No

I agree to take part in this study.

Subject's Signature _____ **Date:** _____

Signature of Person conducting Consent _____ **Date:**

Printed Name of Person conducting Consent _____

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Center number*	Number of subjects enrolled per center (% of enrollment)	Investigational site	Location	Phone number	Ext	Fax number
[redacted]	[redacted]	33 (2.1)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	23 (1.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	25 (1.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	20 (1.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	18 (1.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	14 (0.9)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	19 (1.2)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	63 (4.0)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	79 (5.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	67 (4.2)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	30 (1.9)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	35 (2.2)	[redacted] MD, PC	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	17 (1.1)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	9 (0.6)	[redacted]	[redacted]	[redacted]		[redacted]

Investigator's name	Center number*	Number of subjects enrolled per center (% of enrollment)	Investigational site	Location	Phone number	Ext	Fax number
[redacted]	[redacted]	71 (4.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	25 (1.6)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	11 (0.7)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	17 (1.1)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	32 (2.0)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	54 (3.4)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	78 (4.9)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	27 (1.7)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	65 (4.1)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	51 (3.2)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	47 (3.0)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	105 (6.6)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	115 (7.2)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	40 (2.5)	[redacted]	[redacted]	[redacted]		[redacted]

Investigator's name	Center number*	Number of subjects enrolled per center (% of enrollment)	Investigational site	Location	Phone number	Ext	Fax number
[redacted]	[redacted]	38 (2.4)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	75 (4.7)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	10 (0.6)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	95 (6.0)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	21 (1.3)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	35 (2.2)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	40 (2.5)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	42 (2.6)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	27 (1.7)	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	19 (1.2)	[redacted]	[redacted]	[redacted]		[redacted]

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals
Global Clinical Research and Development

Investigator Approval Page

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110080 (Tdap 0.3-009 Ext: 007 Y1) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:

Affiliation:

Signature of Investigator: _____

Date: _____

For internal use only
----------Checksum----------!Ver.!Created On
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GlaxoSmithKline Biologicals
Global Clinical Research and Development

Sponsor Signatory Approval Page

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110080 (Tdap 0.3-009 Ext: 007 Y1) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] MD.

Title of Sponsor Signatory: Director, Clinical Research and Development and Medical Affairs, Vaccines, GlaxoSmithKline Biologicals

Signature: _____

Date: _____

For internal use only
----------Checksum----------!Ver.!Created On
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c4c971be5cafac63410fc1aa287ebc66 1.2 24/07/2008

Listings of patients receiving test drug(s) /investigational product(s) from specific batches

Not applicable.

Randomisation list (patient identification and treatment assigned)

Not applicable.

Audit certificates

None

Documentation of statistical methods

Not applicable.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable.

Publications based on the study

None as of 09 July 2008.

Important Publications Referenced in the Report

This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.

Individual Listings

NOTES TO INDIVIDUAL LISTINGS

Clintrial Eligibility Codes

Elimination from ATP cohort for immunogenicity in Study 110080 (Tdap 0.3-009 Ext: 007 Y1)

- **Elimination from ATP cohort for safety and immunogenicity**

1040 Administration of vaccine not specified, or forbidden, in the protocol
Administration of a vaccine different from the trial vaccine

- **Elimination from ATP cohort for immunogenicity**

2010 Demographics protocol violation
Too young
Too old
Unknown age, sex
2040 Medication forbidden by the protocol
Any medication forbidden
2050 Underlying medical condition
2060 Concomitant infection related to the vaccine
Infection with any of the vaccine components
2070 Concomitant infection not related to the vaccine
Any viral infection
2090 Non compliance with blood sampling schedule (including wrong and unknown dates)
2100 Blood sample lost or unable to test (haemolysis, insufficient volume, etc.)
Absence of parallelism
Essential serological data missing
2120 Obvious incoherence or abnormality or error in data
Wrong labelling in body system
Abnormal serology evolution
2500 Others

Elimination applied to Study 106316 (Tdap 0.3-007)

- **Elimination from ATP cohort for safety and immunogenicity**

1030 Study vaccine dose not administered
Vaccine dose not given but not a withdrawal
1040 Administration of vaccine not specified, or forbidden, in the protocol
Administration of a vaccine different from the trial vaccine
1050 Randomization failure
Wrong vaccine vial given
1060 Randomization code broken
Code open for any reason
1070 Site of study vaccine administration incorrect or unknown
1500 Other (specify): subjects not meet Inclusion/Exclusion/Elimination criteria

- **Elimination from ATP cohort for immunogenicity**

2010 Demographics protocol violation

Too young
Too old
Unknown age, sex

2040 Medication forbidden by the protocol
Any medication forbidden

2050 Underlying medical condition

2060 Concomitant infection related to the vaccine
Infection with any of the vaccine components

2070 Concomitant infection not related to the vaccine
Any viral infection

2090 Non compliance with blood sampling schedule (including wrong and unknown dates)

2100 Blood sample lost or unable to test (haemolysis, insufficient volume, etc.)
Absence of parallelism
Essential serological data missing

2120 Obvious incoherence or abnormality or error in data
Wrong labelling in body system
Abnormal serology evolution

Notes To Individual Listings (continued)

The following abbreviations are common throughout the Appendix tables:
Sub. No. : subject number
Eli. (Y1) : eligibility at Year 1
E : eliminated from reactogenicity and immunogenicity analyses
I : eliminated from immunogenicity analysis
Ctr. : Study centre
Abbreviations which are unique to a particular appendix are presented below.

Appendix tables IIDi
Prev. dose : previous vaccine dose
Rel. day of onset: day of onset of medication, relative to day of previous vaccination
Start date : date medication administration started
End date : date of end of medication
Dur (day) : duration (days)
Trade-Generic name : trade and/or generic name of medication
Medical indic. : medical indication for which medication was used
Proph : Prophylactic medication Y (Yes) or blank

Appendix table IIDii
Trade name : trade name of vaccine administered
Admin Date : date of administration of concomitant vaccine
Prev. dose : previous vaccine dose
Rel. day of onset: day of onset of concomitant vaccination, relative to day of previous vaccination
Prev. Vaccination date: date of administration of previous study vaccine

Appendix table IIIA
cut : Cut-off of the laboratory assay
AP : Absence of parallelism
BS ND : Blood sampling not done
IR : Invalid result
QNS : Quantity of serum not sufficient

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

CRFs/eCRFs for deaths, other SAEs and withdrawals due to adverse events.

Not applicable.

GlaxoSmithKline

Study Reporting and Analysis Plan Approval

Title:	A Phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007)
eTrack study number	110080 110082 110084 110086
eTrack abbreviated title	Tdap-0.3-009 Ext:007 Year 1 Tdap-0.3-009 Ext:007 Year 3 Tdap-0.3-009 Ext:007 Year 5 Tdap-0.3-009 Ext:007 Year 10
Scope:	All data pertaining to the above study
Date:	20-Feb-08
Co-ordinating author:	[redacted]
Other author(s):	

Approved by:

Clinical Development Manager/Epidemiologist			
	Name	Signature	dd-mmm-yyyy
Project Statistician			
	Name	Signature	dd-mmm-yyyy
Franchise Stat	Name	Signature	dd-mmm-yyyy

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

CI	Confidence Interval
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FHA	Filamentous Hemagglutinin
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
IU	International Units
mL	Milliliter
PRN	Pertactin
PT	Pertussis Toxoid
SAE	Serious Adverse Event
SBIR	GSK Biologicals' Internet Randomization System
SOP	Standard Operating Procedure
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

1. LIST OF AMENDMENTS TO THE RAP

Date	Description
20-Feb-08	First version

2. INTRODUCTION

This document summarizes the planned statistical analyses based on the study features as per protocol/amendment dated 17APR2007. The document will be used to guide the analyses on Year 1, 3, 5, and 10**.** The changes in the analyses as compared to the protocol/amendment are provided in section 4. The list of tables/listings to be produced in the statistical report is available in section 5.

3. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

3.1. Primary Endpoints

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

3.2. Secondary Endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

3.3. Study cohorts to be evaluated

Year X (1, 3, 5, 10) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

According-To-Protocol (ATP) Year X (1, 3, 5, 10) cohort

The ATP Year X (1, 3, 5, 10) cohort will include all subjects from Year X (1, 3, 5, 10) cohort who is in the ATP cohort for analysis of immunogenicity in 106316 study and who have not met the following elimination criteria.

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

ATP Complete Year X (1, 3, 5, 10) cohort

The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.

For Year 1 analysis, the ATP complete Year 1 cohort is the same as the ATP Year 1 cohort.

The list of applicable elimination codes for each cohort can be found in section 6.

Cohort	**Elimination codes**	**Eli Type**
ATP Year X cohort for analysis for immunogenicity	1000-2500	Y(x) (x=1,3,5,10)

3.4. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5 (Table 3) of the protocol.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody.
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the first secondary objective.
- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- The geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

3.5. Data presentation description

The following decimal description will be used for the demography and immunogenicity analyses.

Display Table	**Parameters**	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
Demographic characteristics	Mean, median age	1

Demographic characteristics	SD (age)	2
anti-Diphtheria	GMC	1
anti-Tetanus	GMC	1
anti-PT	GMC	1
anti-FHA	GMC	1
anti-PRN	GMC	1
Immunogenicity	GMC ratio	2

3.6. Group description

The following groups will be used for the statistical analyses.

Study	Group order in tables	Group label in tables	Group definition for footnote
eTrack #/Tdap0.3-009 Ext:007 Year X	1	Boostrix	None
	2	Adacel	None

All analyses will be performed per treatment actually administered according to Study Tdap 0.3-007.

3.7. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 10) on cleaned data obtained through Year X. A clinical study report (CSR) will also be written following each analysis.

3.7.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at blood sample taken at Year X and gender) for Year X cohort and ATP Year X cohort (Year 1, Year 3, Year 5 and Year 10) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 10) cohort, in the ATP Year X (1, 3, 5 or 10) cohort and in the ATP complete Year X (1, 3, 5 and 10) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 10) (in years) by vaccine group will be summarized using descriptive statistics.

3.7.2. Analysis of immunogenicity/persistency

Persistence (immunogencitiy) data will be analyzed at Year 1, Year 3, and Year 5 as soon as results are available.

For each Year X, the primary analysis for persistency will be based on the ATP Year X cohort. If, for any vaccine group, the percentage of subjects who come back for the Year X follow-up with serological results excluded from the ATP Year X cohort is more than

5%, a second analysis based on the Year X cohort will be performed to complement the ATP analysis.

All the persistency date will be re-analyzed by based on ATP complete Year cohort for Year 3, 5 and 10.

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 10) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves by group.

Comparability between Groups (exploratory analyses):

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), Year X (1, 3, 5, 10) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 10) after vaccination will be calculated.
- For anti-D and anti-T antibody response, the two-sided 95% CIs of the GMC ratio between subjects in the *Boostrix* vaccine group and (divided by) the *Adacel* group will in computed using an ANCOVA model on the logarithm_{10} transformation of the concentrations for Year X (1, 3, 5, 10) after vaccination.

All the persistency data summary and exploratory analysis will be repeated for subgroup of age strata (19-29Y, 30-49Y and 50-64Y) and gender (male and female) defined in the primary study.

To investigate a potential bias due to the drop out of ATP cohort, the primary objectives defined in the primary study will be re-evaluated using Year X cohort.

An additional analysis may be performed at Year 5 and 10 to examine how the immune response changes over time. This will be analyzed using repeated mixed model to include immune response at different time point as a response variable, baseline antibody concentration, time and vaccine group will be included as dependent variables in the model.

3.7.3. Analysis of Safety

Subjects with any SAE reporting will be listed in a listing. Subjects who take any concomitant medication or vaccine will be listed in a listing as well.

No analysis for other safety parameters will be performed for this study.

If GSK is informed by an investigator of an SAE that in his/her medical judgement could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the clinical study report.

3.7.4. Methodology for computing CI

All CI will be 2 sided 95% CI.

- The exact 95% CIs for a proportion within a group will be calculated from Proc StatXact [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika.* 1934;26:404-413].
- Proc StatXact will be used to derive the standardized asymptotic 95% CI for the group difference in proportions [ROBERT G. NEWCOMBE , INTERVAL ESTIMATION FOR THE DIFFERENCE BETWEEN INDEPENDENT PROPORTIONS: COMPARISON OF ELEVEN METHODS, *Statist. Med.* 17, 873-890 (1998): the standardized asymptotic method used within GSK Bio is method 6].
- The 95% CI for geometric mean concentrations (GMCs) will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer/concentration.
- The group GMC ratio was obtained using an ANCOVA model on the logarithm- transformed concentrations. The ANCOVA model included the vaccine group as fixed effect, the age in years and pre vaccine antibody concentration as regressors. The GMC ratio and its 95% CI will be derived as exponential-transformation of the corresponding group contrast in the model.
- The 95% CI for the adjusted GMC was obtained by exponential-transformation of the 95% CI for the group least square mean of the above ANCOVA model.

3.8. Reporting of final analyses

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5, and Year 10), and the summary presentation will include all the persistence data up to Year X and reported separately at each time point accordingly.

3.9. Interim analysis

No interim analysis is planned for this persistence study.

4. CHANGE FROM PROTOCOL

None.

5. ANNEX 1: INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES

5.1. Individual listings for the final analysis on Year X

Appendix Table I.A - Elimination codes

Appendix Table I.B - Demography

Appendix Table I.Ci - Dates of birth, Informed consent, Vaccination and blood sampling, Contact

Appendix Table I.Ei - Conclusion of study Year 10 (for Year 10 analysis only)

Appendix Table I.F – Eligibility

Appendix Table II.Di - Concomitant medications

Appendix Table II.Dii - Concomitant vaccinations

Appendix Table III.A – Immunogenicity

5.2. List of tables for the final analysis

5.2.1. Demographics Analysis

TABLE # in reference of section 5.3	Table Title	Final Analysis	Macro
Table D 1	Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion	ST	%ELIMLIST
Table D 2	Number of subjects included in each follow-up period up to 10 Years	CR	
Table D 3	Number of subjects by center (Year X cohort)	ST	%CENTER
Table D 4	Minimum and maximum activity dates (Year X cohort)	WT	%DATE
Table D 5	REF _Ref188166674 \h Duration (in weeks) from the vaccination in primary study to Year X blood sampling for each group (Year X cohort)	WT	
Table D 6	Summary of demographic characteristics (Year X cohort)	CR	%DEMOGRA
Table D 7	Summary of demographic characteristics (ATP Year X cohort)	CR	%DEMOGRA
Table CTRS 1	Demography for CTRS	CTRS	%CTR_DEMOG

CR = Within the clinical study report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure

5.2.2. For Safety Analysis

TABLE # in reference of section 5.3	Table Title	Final Analysis	Macro
Table R 1	Listing of SAEs (Year X cohort)	CR	%SAE

CR = Within the clinical report

5.2.3. For Immunogenicity Analysis:

TABLE # in reference of section 5.3	Abbreviated Title (see annex 1 for the proposed wording in the stat report)	Final Analysis	Macro
Table I 1	Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups at Year X after vaccination (ATP Year X cohort)	CR*	%GMT
Table I 2	Seronegativity status for ANTI-D antibody concentration by ELISA and VERO at Year X after vaccination (ATP Year X cohort)	CR*	%SP_VERO
Table **I 3**	Seropositivity and GMCs for ANTI-PT, ANTI-FHA and ANTI-PRN antibodies (ATP Year X cohort)	CR*	%GMT
Table I 4	Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL to D and T between the Boostrix and Adacel at Year X after vaccination (ATP Year X cohort)	ST*	%SP_CI
Table I 5	Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL by ELISA to D or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year X after vaccination (ATP Year X cohort)	ST*	%SP_CI
Table I 6	Adjusted ratios of ANTI-D, ANTI-T GMCs at Year X after vaccination (ATP Year X cohort)	ST*	%BIOGMT
Table I 7	Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL to D and T between the Boostrix and Adacel one-month after vaccination (Year X cohort)	ST	%SP_CI
Table I 8	Difference in the Percentage of Subjects with antibody concentration ≥1.0 IU/mL to T between the Boostrix and Adacel one-month after vaccination (Year X cohort)	ST	%SP_CI
Table I 9	Comparison of ANTI-PT, ANTI-FHA, ANTI-PRN antibody GMTs in Study 776423/007 (one-month after vaccination) and Study APV-039 (Year X cohort)	ST	%BIOGMT
Figure I 1	Reverse cumulative curves for anti-D concentration at Year X (ATP Year X cohort)	ST*	%REVCUM ps:logscale=10
Figure I 2	Reverse cumulative curves for anti-T concentration at	ST*	%REVCUM ps:logscale=10

	Year X (ATP Year X cohort)		
Figure I 3	Reverse cumulative curves for anti-PT concentration at Year X (ATP Year X cohort)	ST*	%REVCUM ps:logscale=10
Figure I 4	Reverse cumulative curves for anti-FHA concentration at Year X (ATP Year X cohort)	ST*	%REVCUM ps:logscale=10
Figure I 5	Reverse cumulative curves for anti-PRN concentration at Year X (ATP Year X cohort)	ST*	%REVCUM ps:logscale=10

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
*: a complementary analysis based on the Year X cohort will be provided if more than 5% of the subjects in ATP Year X cohort are excluded from that cohort. The resulting tables will appear as supplemental tables.

5.3. Template of tables

Table D 1 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total			Boostrix		Adacel	
Title	n	s	%	n	s	n	s
Number of subjects vaccinated in Primary study (Tdap 0.3-007)							
Number of subjects returning for blood sampling at Year X (Year X cohort)							
Number of subjects in ATP Year X cohort							
Number of subjects in ATP Complete Year X cohort							
Number of subjects with protocol violation linked to the inclusion/exclusion criteria including age and excluding codes (2010)							
Number of subject with other Elim codes…							

Percent = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort.
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned
Codes are listed based on a ranking order

Table D 2 Number of subjects included in each follow-up period up to 10 Years

	Boostrix	Adacel	Total
Title	n	n	n
Number of subjects vaccinated in Primary study (Tdap 0.3-007)			
Year 1 follow-up (Year 1 cohort)			
Year 1 follow-up (ATP Year 1 cohort)			
Year 3 follow-up (Year 3 cohort)			
Year 3 follow-up (ATP Year 3 cohort)			
Year 3 follow-up (ATP Year 3 complete cohort)			
Year 5 follow-up (Year 5 cohort)			
Year 5 follow-up (ATP Year 5 cohort)			
Year 5 follow-up (ATP Year 5 complete cohort)			
Year 10 follow-up (Year 10 cohort)			
Year 10 follow-up (ATP Year 10 cohort)			
Year 10 follow-up (ATP Year 10 complete cohort)			

n = number of subjects included in each group or in total for a defined cohort.

Table D 3 Number of subjects by center (Year X cohort)

	Boostrix	Adacel	Total	
Center	n	n	n	%
[redacted]				
[redacted]				
[redacted]				
…..				
All				

n = number of subjects included in each group or in total for a given center or for all centers.
All = sum of all subjects in each group or in total (sum of all groups).
% = n/All*100
Center = GSK assigned center number.

Table D 4 Minimum and maximum activity dates (Year X cohort)

Activity number	Minimum date	Maximum date
30 …		

Table D 5 Duration (in weeks) from the vaccination in primary study to Year X blood sampling for each group (Year X cohort)

Vaccine Group	N	Mean	SD	Median	Minmum	Maximum
Boostrix						
Adacel						

N = number of subjects in Year X cohort

Table D 6 Summary of demographic characteristics (Year X cohort)

Characteristics	Parameters or Categories	Boostrix N= XXX		Adacel N= XXX		Total N= XXX	
		Value or n	%	Value or n	%	Value or n	%
Age(Y)*	Mean SD Median Minimum Maximum						
Age stratum**	19-29 (Y)						
	30-49 (Y)						
	50-64 (Y)						
Gender	Female Male						

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD= standard deviation
Age(Y)= age at Year X blood sampling, expressed in years
Age stratum: based on the age at vaccination in primary study

Table D 7 Summary of demographic characteristics (ATP Year X cohort)

See table template D 6

Table R 1 Listing of SAEs (Year X cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
Boostrix													
Adacel													

Table I 1 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups at Year X after vaccination (ATP Year X cohort)

Antibody	Group	Timing	N	≥0.100 IU/mL				GMC			
				n	%	95% CI		n	%	95% CI	
						LL	UL			LL	UL
ANTI-D	Boostrix	Pre									
		1 month post									
		1 Year post									
		....									
		X- Year post									
	Adacel	Pre									
		1 month post									
		1 Year post									
		....									
		X- Year post									
ANTI-T	Boostrix	Pre									
		1 month post									
		1 Year post									
		....									
		X- Year post									
	Adacel	Pre									
		1 month post									
		1 Year post									
		....									
		X- Year post									

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table I 2 Seronegativity status for ANTI-D antibody concentration by ELISA and VERO at Year X after vaccination (ATP Year X cohort)

			Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for ANTI-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
Group	Timing	N	n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Boostrix	Pre										
	1 month post										
	1 Year post										
	....										
	X- Year post										
Adacel	Pre										
	1 month post										
	1 Year post										
	....										
	X- Year post										

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ML / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ML / number of subjects tested by NEUTRA neutralisation test
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for NEUTRA)
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for ANTI-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for group(s); LL = lower limit, UL = upper limit

Table I 3 Seropositivity and GMCs for ANTI-PT, ANTI-FHA and ANTI-PRN antibodies (ATP Year X cohort)

				>= 5 ELU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-PT	Boostrix	Pre								
		1 month post								
		1 Year post								
		....								
		X- Year post								
	Adacel	Pre								
		1 month post								
		1 Year post								
		....								
		X- Year post								
ANTI-FHA	Boostrix	Pre								
		...								
	Adacel	Pre								
		...								
ANTI-PRN	Boostrix	Pre								
		...								

				>= 5 ELU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
	Adacel	Pre								
		...								

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table I 4 Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL to D and T between the Boostrix and Adacel at Year X after vaccination (ATP Year X cohort)

							Difference in seroprotection rate (Group 2 minus Group 1)			
									95 % CI	
Anti body	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
ANTI-D (IU/mL)	Adacel			Boostrix						
ANTI-T (IU/mL)	Adacel			Boostrix						

N = number of subjects with available results
% = percentage of subjects with ANTI-D and ANTI-T concentration >= 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table I 5 Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL by ELISA to D or at least 0.016 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year X after vaccination (ATP Year X cohort)

							Difference in seroprotection rate (Group 2 minus Group 1)			
									95 % CI	
Anti body	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
ANTI-D (IU/mL)	Adacel			Boostrix						

N = number of subjects with available results
% = percentage of subjects with ANTI-D and ANTI-T concentration >= 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table I 6 Adjusted ratios of ANTI-D, ANTI-T GMCs at Year X after vaccination (ATP Year X cohort)

					Adjusted GMC ratio (Boostrix / Adacel)		
	Boostrix		Adacel			95% CI	
Anti body	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
ANTI-D (IU/ML)							
ANTI-T (IU/ML)							

Adjusted GMC = geometric mean antibody concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y) and baseline concentration); LL = lower limit, UL = upper limit

Table I 7 Difference in the Percentage of Subjects with antibody concentration ≥0.1 IU/mL to D and T between the Boostrix and Adacel one-month after vaccination (Year X cohort)

See Template Table I4

Table I 8 Difference in the Percentage of Subjects with antibody concentration ≥1.0 IU/mL to T between the Boostrix and Adacel one-month after vaccination (Year X cohort)

See Template Table I4

Table I 9 Comparison of ANTI-PT, ANTI-FHA, ANTI-PRN antibody GMTs in Study 776423/007 (one-month after vaccination) and Study APV-039 (Year X cohort)

					GMT ratio (Boostrix / DTaP-APV039)		
	Boostrix		DTaP-APV039			95% CI	
Anti body	N	GMT	N	GMT	Value	LL	UL
ANTI-PT (ELU/ML)							
ANTI-FHA (ELU/ML)							
ANTI-PRN (ELU/ML)							

Boostrix = Boostrix 776423/007(Blood sample taken one month after the vaccination with Boostrix)
DTaP-APV039 = Pooled DTaP from APV039
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Figure I 1 Reverse cumulative curves for anti-D concentration at Year X (ATP Year X cohort)

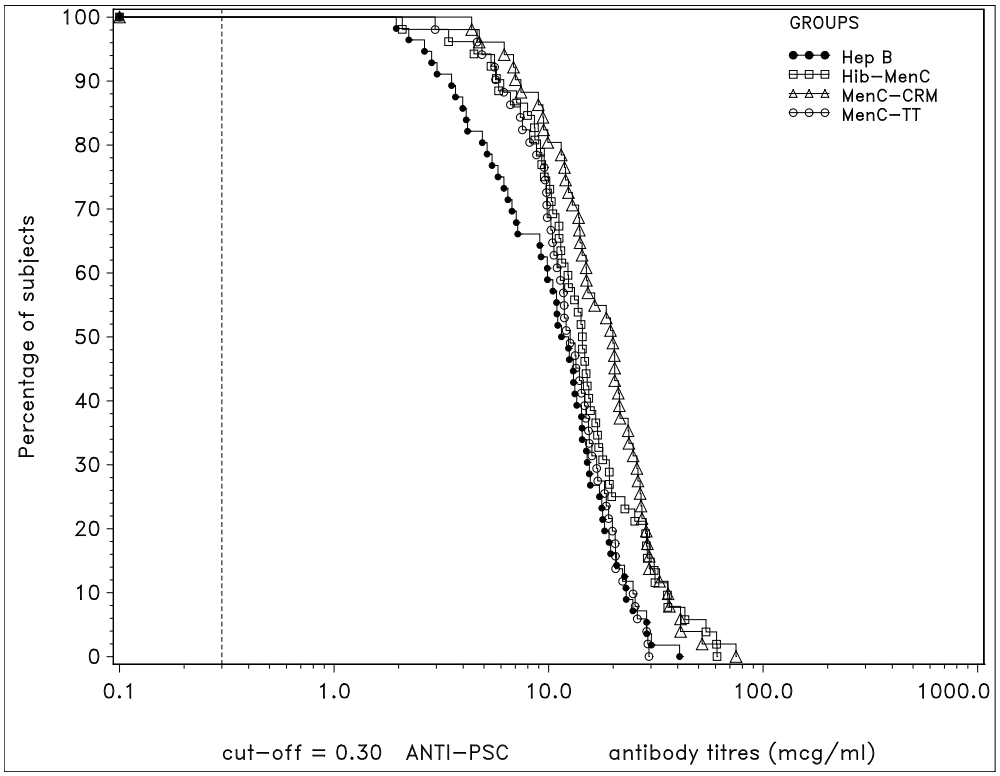

Figure I 2 Reverse cumulative curves for anti-T concentration at Year X (ATP Year X cohort)

See template for Figure I 1

Figure I 3 Reverse cumulative curves for anti-PT concentration at Year X (ATP Year X cohort)

See template for Figure I 1

Figure I 4 Reverse cumulative curves for anti-FHA concentration at Year X (ATP Year X cohort)

See template for Figure I 1

Figure I 5 Reverse cumulative curves for anti-PRN concentration at Year X (ATP Year X cohort)

See template for Figure I 1

Table CTRS 1 Demography for CTRS

Number of subjects	Boostrix	Adacel
Planned, N		
Randomised, N (Total Vaccinated Cohort)		
Year X cohort, n (%)		
Total Number Subjects Withdrawn, n (%)		
Withdrawn due to Adverse Events, n (%)		
Withdrawn due to Lack of Efficacy, n (%)		
Withdrawn for other reasons, n (%)		
Demographics	Boostrix	Adacel
N (Year X Cohort)		
Females:Males		
Mean Age, months (SD)		
White/caucasian, n (%)		

Table CTRS 2 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups at Year X after vaccination (ATP Year X cohort)

See table template I 1

Table CTRS 3 Seronegativity status for ANTI-D antibody concentration by ELISA and VERO at Year X after vaccination (ATP Year X cohort)

See table template I 2

Table CTRS 4 Seropositivity and GMCs for ANTI-PT, ANTI-FHA and ANTI-PRN antibodies (ATP Year X cohort)

See table template I 3

6. ANNEX 2: CRITERIA FOR ELIMINATING SUBJECTS FROM STAT ANALYSES

Cleaning Scope*:*	**Cleaning Level***:*
☐ Interim analysis	☒ Full cleaning
☒ Active phase (all subjects, all data)	☐ Abridged cleaning
☐ Safety follow-up	☐ Automatic
☐ Immunology	☐ Manual
☐ Other, specify:	☐ Only SAE cleaned

Cleaning site: ☐ Rixensart ☒ CDMCI ☐ Other:

CDR:	
CLC:	
CDA:	
CSC:	
CDM:	
STAT:	
Safety:	

6.1. SUMMARY

Nr of subjects enrolled:	
Nr of subjects completed:	
Nr of subjects drop-outs:	(attach study conclusion listing for reasons of drop out)

6.2. SERIOUS ADVERSE EVENTS: (final version not available before analysis)

Total Nr of subjects with SAEs:	
Nr of SAEs related and possibly related to vaccination:	
	(subject number:)
Nr of SAEs leading to withdrawal from the study:	
	(subject number:)
Nr of SAEs still ongoing at the end of the study:	
	(subjets numbers:)
Comment s:	

6.3. PREGNANCIES:

Nr of pregnancies:
Comments, data not available in the unsolicited AE section:

6.4. INTERVALS CONSIDERED:

Schedule	DM	From	DM	To	DM	Adapted interval (days/weeks/months)
Age (days/weeks/months/years) – code 2010: NA						
Time between vaccinations (days/weeks/months/years) – code 2080: NA						
Time between vaccination and blood sample (days/weeks/months/years) – code 2090						
		From Tdap vaccination in parent study to		Visit 3		1 year ± 5 weeks (47-57 wks)
				Visit 4		3 year ± 5 weeks (151-161 wks)
				Visit 5		5 year ± 5 weeks (255-265 wks)
				Visit 6		10 year ± 5 weeks (515-525 wks)

DOB=date of birth; VAC=vaccination; BL=Blood sample

6.5. ELIM CODES ALLOCATED and POINTS TO BE DISCUSSED

(Please annex the Elimination Codes listing)

Elimination from safety and immunology analysis

	Code	Description
☐	1010	Subject or vaccine number not allocated
		Vaccine not administered at all
		No subject allocated to the randomised number
Subject No.:		
Comments:		
☐	1030	Study vaccine dose not administered AT ALL but subject number allocated
	Subj.	
Comments:		
☒	1040	Administration of concomitant vaccine(s) forbidden in the protocol (**see also eligibility criteria)**
Subject No.:		
Comments:		
☐	1050	Randomisation failure (subject not randomized in the correct group) **TO BE ATTRIBUTED ONLY BY STAT**: (Check SBIR, replacement, vaccine administration)
Subject No.:		
Comments:		
☐	1060	Randomisation code broken at the investigator site OR at GSK Safety department (**ONLY for DOUBLE-BLIND or OBSERVER-BLIND studies**)

Subject number	***Date of unblinding***	***Reason for unblinding***

Comments:

☐	1070	Study vaccine dose not administered according to protocol (attach CL_14):
		- One of planned injections not administered and NOT due to drop out
		- Side, site or route of study vaccine administration wrong or unknown
		- Replacement vial used NOT corresponding to the correct randomization group
		- Subject number not in the randomization list and not requested by the sponsor
		- Extra PID

Elimination from safety and immunology analysis

	Code	Description
		- Wrong vaccine vials given
Subject No.:		
Comments:		
☒	1500	Other (specify): subjects not meet eligibility criteria (e.g., other D, T related vaccines)
	Subj.	
Comments:		

Elimination from immunology analysis

	Code	Description
☒	2010	Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.
Subject No.:		
Comments:		Assign to subject without informed consent
☐	2020	Initially seropositive OR initially unknown antibody status (pre BS missing or unable to test because of hemolysis, insufficient volume, AP). Please specify the applicable rule: ☐ elimination code if all values are positive or unknown ☐ elimination code if at least one value is positive or unknown

Schedule	DM	Blood sample	DM	Antigen	DM

Subject No.:		
Comments:		
☐	2030	Biochemistry, haematology and other laboratory values outside range before any vaccination. Please specify the applicable rule: ☐ elimination code if all values are out of range ☐ elimination code if at least one value is out of range

Schedule	DM	Blood sample	DM	Antigen	DM

Subject No.:		
Comments:		
☒	2040	Administration of any medication forbidden by the protocol (responsibility of CDM following review of individual data listings)

Elimination from immunology analysis

	Code	Description
	Subj.	
☒	2050	Underlying medical condition forbidden by the protocol (responsibility of CDM following review of individual data listings)
Subject No.:		
Comments:		
☒	2060	Concomitant infection related to the vaccine which may influence immune response (responsibility of CDM following review of individual data listings)
		Infection related to any of the vaccine component(e.g. lyme infection in a lyme study) (responsibility of CDM following review of individual data listings)
Subject No.:		
Comments:		
☒	2070	Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study) (responsibility of CDM following review of individual data listings)
Subject No.:		
Comments:		
☐	2080	Non compliance with vaccination schedules (dates of vaccination not corresponding to adapted protocol intervals or unknown vaccination dates)
Subject No.:		
Comments:		
☒	2090	Non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS dates)
	Subj.	
Comments:		

Important remark: When a visit and/or a vaccination is Not Done, only the code 2100 is attributed to the subject but codes 2080 and/or 2090 should not be assigned to the same subject

☒ 2100 Serological results not available for antigens POST vaccination (including BS lost, Not Done, unable to test, absence of parallelism,). Please specify the applicable rule:

☒ elimination code if all are missing (or QNS/BS ND)

☐ elimination code if at least one is missing

Schedule	DM	Blood sample	DM	Antigen	DM
1		Per visit		All antigen	

Subject No.:

Comments:

☐ 2110 Essential serological temporarily missing because of not yet tested (interim analysis only)

Antig.

Subject No.:

Comments:

☒ 2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results, wrong labeling in BS)

Subject No.:

Comments:

☐ 2130 Subjects not planned in the protocol to be bled for their all blood sampling visits

Subject No.:

Comments:

☐ 2500 Other (specify):

Subject No.:

Comments:

Extra Elimination from analysis

	Code	**Description**
☐		

Extra Elimination from analysis
Code Description
Subject No.:
Comments:

6.6. OTHER POINTS TO CONSIDER

Inform Consent procedure not respected:		
Subject Number	Problem	Oral IC date if available
Comments:		

Subjects who did not perform their last visit at least 30 days after last vaccination, specify subject numbers:

Subjects with numbered replacements or wrong vials (version < 12.1):	
Subject Number	Replacement Treatment Number
Comments:	

Pending Queries not to be resolved:		
Subject Number	Query Id	Reason for not sending
Comments:		

Subjects unblinded during the study period **(ONLY for PARTIALLY-BLIND / SINGLE-BLIND / OPEN studies)**		
Subject Number	Date of unblinding	Reason for unblinding
Comments:		

Others:

6.7. **DRAFT VERSION** (When FINAL Post-cleaning meeting completed)

CDR signature: (mandatory)	
CLC \ CSC signature: (mandatory)	
Date of meeting:	

6.8. **FINAL VERSION** (When FINAL Pre-analysis meeting completed)

CLC \ CSC signature: (mandatory)	
Date of meeting:	

7. ANNEX 3: EXAMPLES OF HANDLING OF MISSING DAILY RECORDING

N/A

GlaxoSmithKline Biologicals
Global Clinical Research and Development

Sponsor Signatory Approval Page

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110080 (Tdap 0.3-009 Ext: 007 Y1) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted] MD.

Title of Sponsor Signatory: Director, Clinical Research and Development and Medical Affairs, Vaccines, GlaxoSmithKline Biologicals

Signature: [redacted]

Date: 7/29/08

For internal use only
----------Checksum----------!Ver.!Created On
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c4c971be5cafac63410fc1aa287ebc66 1.2 24/07/2008

In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

GlaxoSmithKline Biologicals

Study title

Persistence study of GSK Biologicals Tdap vaccine 776423 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.

Study detailed title

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Note: This report presents the results of the analyses performed at Year 3.

Clinical Study Report for Study 110082 (Tdap 0.3-009 Ext: 007 Year 3)

(Development Phase IIIb)

IND Number: BB-IND-8461

Indication Studied: Healthy adults aged 19 years and older, who received a single dose study vaccination in the 106316 study.

Study initiation date (Year 3):	18 June 2009
Study completion date (Year 3):	22 September 2009
Data lock point (Date of database freeze):	30 March 2010
Date of report:	13 December 2010
Earlier Study Reports:	
Clinical study report 106316 (Tdap 0.3-007):	13 December 2007
Clinical study report 110080 (Tdap 0.3 Ext: 007 Year 1):	09 July 2008

Sponsor Signatories: Karin Hardt, PhD, Director, Clinical Development,
Lead DTP Combination Vaccines,
Global Vaccine Development,
GlaxoSmithKline Biologicals.

Francesca Ceddia,
MD, Vice President and Vaccine Development Leader
(DTP Portfolio, Neisseria), Global Vaccine Development,
GlaxoSmithKline Biologicals.

This study was performed in compliance with Good Clinical Practice including the archiving of essential documents.

GSK Biologicals' Study Report INS-BIO-CLIN-1010 v02

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SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance**: Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Principal investigators and study centers: This was a multicenter study conducted across 39 centers in the United States (US) by multiple investigators.

Publication (reference): Blatter M, Friedland LR, Weston WM et al. Immunogenicity and safety of a tetanus toxoids, reduced diphtheria toxoids and three component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine* 2009; 27:765-72.

Study period:	Study initiation date (Year 3): 18 June 2009 Study completion date (Year 3): 22 September 2009 Data lock point (Date of database freeze): 30 March 2010	**Clinical phase:** IIIb

Objectives:

Primary:

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (Vero, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Secondary:

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Note: This report presents the results of the analyses performed up to Year 3.

Study design: Open-label, controlled, non-interventional, long-term follow-up study in the US with 2 parallel groups:

- **Boostrix group:** Subjects who received a single dose of GSK Biologicals' *Boostrix* in the 106316 study.
- **Adacel group**: Subjects who received a single dose of Sanofi Pasteur's *Adacel* in the 106316 study.

Blood samples were collected at Year 3 for evaluation of antibody persistence.

Number of subjects:	Boostrix group	Adacel group	Total
Number of subjects vaccinated in the 106316 study (Tdap 0.3-007)	1522	762	2284
Subjects who returned at Year 3 (Year 3 cohort)	976	465	1441
According-to-Protocol (ATP) Year 3 cohort for immunogenicity	937	449	1386
ATP Complete Year 3 cohort for immunogenicity	776	367	1143

Diagnosis and criteria for inclusion: All subjects who received a single dose of the study vaccination (Boostrix or Adacel) in the 106316 study and who gave written informed consent prior to enrollment into the Year 3 follow-up study were eligible.

Study vaccine, dose, mode of administration, lot no: Refer to the 106316 study report for details of the composition and administration of vaccines.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance**: Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Reference vaccine/Comparator, dose and mode of administration, lot no:
Refer to the 106316 study report for details of the composition and administration of vaccines.

Duration of the study: The duration of the study from vaccination in the 106316 study up to Year 3 (Visit 4) was approximately 3 years per subject.

Criteria for evaluation:

Immunogenicity:

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (Vero) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel groups at 1 year, 3 years, 5 years and 10 years following vaccination.
- Subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups at 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN GMCs in the Boostrix and Adacel groups at 1 year, 3 years, 5 years and 10 years following vaccination.

Statistical methods: Three cohorts were defined for the purpose of analysis:

- The Year 3 cohort was a subset of the Total Vaccinated cohort in the 106316 study. This cohort included subjects for whom serological results for at least 1 antigen were available after a blood sample was taken 3 years after vaccination.
- The ATP Year 3 cohort for immunogenicity included all subjects from the Year 3 cohort who were in the ATP cohort for immunogenicity in the 106316 study and who did not meet the protocol-specified elimination criteria. This cohort was the primary cohort for the immunogenicity persistence analysis.
- The ATP Complete Year 3 cohort for immunogenicity included all subjects who belonged to the ATP Year 3 cohort for immunogenicity and the previously defined Year 1 ATP cohorts.

Analysis of demography: Demographic characteristics (age in years at Year 3 and gender) for the Year 3 cohort and the ATP Year 3 cohort for immunogenicity were tabulated. The number of subjects vaccinated in the 106316 study, in the ATP Year 3 cohort and in the ATP Complete Year 3 cohort for immunogenicity was tabulated.

Analysis of immunogenicity: The analysis of antibody persistence at Year 3 was performed on the ATP Year 3 cohort for immunogenicity. Since the percentage of subjects eliminated from the ATP Year 3 cohort for immunogenicity was more than 5%, a complementary persistence analysis based on the Year 3 cohort was performed. An analysis on the ATP Complete Year 3 cohort for immunogenicity was also performed. The following analyses were performed:

Within group assessment:

For each vaccine group, at Year 3:

Seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA) and overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by Vero cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) for anti-D with exact 95% confidence interval (CI) were calculated per group.

- Seroprotection rates for anti-T (percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI were calculated per group.
- Seropositivity rates (percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U) with exact 95% CI were calculated per group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated per group.

In addition, the distribution of antibody concentrations for each antigen was displayed using reverse cumulative curves (RCCs) per group.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance**: Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Comparability between groups (Exploratory analyses):

- For anti-D and anti-T antibody response:
  - The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 3 years after vaccination was calculated.
  - The two-sided 95% CI for the adjusted GMC ratio (Boostrix group divided by Adacel group) 3 years after vaccination was calculated. The GMC ratio was obtained using an Analysis of Co-variance (ANCOVA) model on the logarithm-transformed concentrations. The ANCOVA model included the group as fixed effect, the age at Year 3 blood sampling in years and baseline (pre vaccine) antibody concentration as regressors.
- The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group-Adacel group) in the overall seroprotection rates for D, 3 years after vaccination was calculated.

If the 95% CI on the group differences in seroprotection rates excluded 0, or if the 95% CI on the between-group GMC ratio excluded 1, then this was taken as an indication of potential differences between groups. The exploratory comparisons are to be interpreted with caution since there was no adjustment for multiplicity of endpoints. The persistence and exploratory analyses were also stratified by age (19-29 years, 30-49 years and 50-64 years) and gender (male and female) as defined in the 106316 study.

Analysis of Safety: No safety analyses were performed in this persistence study since no SAE or pregnancy was reported. If GSK received information from an investigator of an SAE that in his/her medical judgment was reasonably related to the study vaccine administered in the 106316 study or to participation in this persistence study, the pertinent clinical details were to be summarized in the study report.

Summary:

Demography Results: The mean age of the subjects at the time of Year 3 blood draw in the ATP Year 3 cohort for immunogenicity was 44.9 years with a standard deviation of 13.3 years. The groups appeared to be similar to each other with respect to mean age and gender (66.2% female). The percentages of females and males were similar to that seen in the ATP Year 1 cohort at Year 1.

Immunogenicity Results: Analyses of immunogenicity were performed on the ATP Year 3 cohort for immunogenicity (primary analyses) and on the Year 3 cohort (secondary analyses).

Three years after the single-dose of Tdap booster vaccination:

- The percentage of subjects with seroprotective anti-D antibody concentrations (≥ 0.1 IU/mL) was slightly decreased from that observed at Month 1 following vaccination, and was comparable to that observed at Year 1. The percentage of subjects with seroprotective anti-T antibody concentrations (≥ 0.1 IU/mL) was comparable to those observed at Month 1 and Year 1 following vaccination.
- The percentages of subjects with anti-D or anti-T antibody concentrations ≥ 1.0 IU/mL were decreased from that observed at Month 1 and Year 1 after vaccination in both groups.
- GMCs for anti-D and anti-T antibodies decreased from Year 1 to Year 3 in both groups and remained higher than the pre-vaccination levels.
- The overall anti-D seroprotection rates were at least 96.9% in both groups, decreasing slightly compared to Month 1 following vaccination and comparable to Year 1.
- The seropositivity rate for anti-PT antibodies at Year 3 appeared to have decreased from the values observed at Month 1 and Year 1, while those for anti-FHA and anti-PRN antibodies at Year 3 did not appear to have decreased from Month 1 and Year 1 in both groups. The seropositivity rates for the anti-PT, anti-FHA and anti-PRN antibodies remained higher than the pre-vaccination levels. GMCs for anti-pertussis antibodies decreased at Year 3 compared to Month 1 and Year 1 and remained higher than pre-vaccination GMCs.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance**: Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Table 1: Seroprotection/seropositivity rates and GMCs with 95% CI for anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies at Year 3 (ATP Year 3 cohort for immunogenicity).

Endpoints	Timing	Boostrix group					Adacel group				
		N	%	GMC	95%CI		N	%	GMC	95%CI	
					LL	UL				LL	UL
Anti-D (≥ 0.1 IU/mL)	PRE	930	84.8	0.4	0.4	0.4	443	89.6	0.5	0.4	0.5
	PI(M1)	926	97.8	4.6	4.2	5.0	444	98.6	4.9	4.4	5.4
	PI(Y1)	802	95.8	1.4	1.3	1.6	375	97.1	1.4	1.3	1.6
	PI(Y3)	934	93.8	0.9	0.8	1.0	449	96.2	1.0	0.9	1.1
Anti-T (≥ 0.1 IU/mL)	PRE	936	95.8	1.5	1.4	1.7	448	97.1	1.7	1.6	1.9
	PI(M1)	927	99.4	8.3	7.9	8.8	445	100	12.8	11.8	13.8
	PI(Y1)	806	98.5	3.3	3.1	3.5	377	99.7	4.4	4.0	4.7
	PI(Y3)	937	98.1	2.2	2.1	2.3	449	99.6	2.9	2.7	3.1
Anti-PT (≥ 5 EL.U)	PRE	927	55.9	7.1	6.6	7.6	445	63.8	8.5	7.7	9.5
	PI(M1)	922	97.1	62.7	58.5	67.2	439	93.4	32.7	29.3	36.6
	PI(Y1)	805	91.1	22.7	21.1	24.5	377	86.5	15.8	14.2	17.7
	PI(Y3)	934	82.1	14.1	13.1	15.1	449	71.9	10.0	9.1	11.1
Anti-FHA (≥ 5 EL.U)	PRE	930	96.5	31.0	28.8	33.3	441	96.8	35.2	31.6	39.1
	PI(M1)	928	100	597.6	561.0	636.7	443	100	365.8	335.8	398.5
	PI(Y1)	806	99.8	183.7	171.0	197.4	375	100	119.4	107.8	132.1
	PI(Y3)	936	99.7	115.0	108.0	122.4	446	99.6	81.5	74.6	89.1
Anti-PRN (≥ 5 EL.U)	PRE	934	76.2	13.6	12.5	14.8	448	75.2	14.8	13.0	16.9
	PI(M1)	926	98.8	393.7	354.3	437.4	445	99.3	329.0	285.4	379.4
	PI(Y1)	803	96.0	151.7	135.2	170.3	374	98.4	130.6	111.4	153.0
	PI(Y3)	935	94.3	83.1	75.1	92.1	449	96.4	70.2	61.2	80.4

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results; % = percentage of subjects with concentration within a specified range; GMC = geometric mean concentration calculated on all subjects; 95% CI = 95% confidence interval;
LL = Lower Limit; UL = Upper Limit; PRE = blood sample taken before vaccination;
PI (M1) = blood sample taken 1 month after vaccination; PI (Y1) = blood sample taken 1 year after vaccination;
PI (Y3) = blood sample taken 3 years after vaccination.

Exploratory analyses:

- Exploratory analysis did not indicate a difference between the Boostrix group and the Adacel group with respect to the percentages of subjects with anti-D antibodies ≥ 0.1 IU/mL, since the 95% CI for between-group difference included the value 0.
- The exploratory analysis suggested a higher percentage of subjects with anti-T antibodies ≥ 0.1 IU/mL in the Adacel group than in the Boostrix group (95 % CI for the group difference excluded the value 0). This was a change from the previous time points, for which no apparent differences in percentages of subjects with anti-T antibodies ≥ 0.1 IU/mL were noted. Seroprotection rates for anti-T antibodies were very high in both groups (99.6% for Adacel, 98.1% for Boostrix). The clinical relevance of this observation is unclear.

Safety results: There were no pregnancies or SAEs reported in this phase of the study.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance**: Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Conclusions:

- Evaluation of anti-D and anti-T antibodies elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus 3 years after vaccination.
- Antibody concentrations to all antigens elicited by a single dose of *Boostrix* were lower compared to the antibody concentrations observed 1 month and 1 year after vaccination and remained higher than the pre-vaccination levels.
- There were no pregnancies or SAEs reported in this study.

Date of report: 13 December 2010

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF SUPPLEMENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Co-variance
ATP	According-to-protocol
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	Confidence Interval
CRO	Contract Research Organization
D	Diphtheria
DTaP	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed vaccine
eCRF	electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EL.U	ELISA Units
FHA	Filamentous hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
kg	Kilogram
Lf	Limits of Flocculation Unit(s)
LL	Lower Limit

mg	Milligram
mL	Milliliter
PRN	Pertactin
PT	Pertussis Toxoid
RAP	Reporting and Analysis Plan
RCC	Reverse Cumulative Curve
RDE	Remote Data Entry
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
SP	Seroprotected
T	Tetanus
Td	Tetanus and diphtheria toxoids vaccine
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
UL	Upper Limit
US	United States
Vero	Verdana Reno (African green monkey kidney cells)

GLOSSARY OF TERMS

106316 study:	The 106316 study refers to the active phase of the study when subjects received either *Boostrix* or *Adacel* vaccination and were evaluated for booster response.
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
ATP Year 3 cohort for immunogenicity:	The ATP Year 3 cohort for immunogenicity included all subjects from the Year 3 cohort who were in the ATP cohort of immunogenicity in the 106316 study and who did not meet the protocol-defined elimination criteria.
ATP Complete Year 3 cohort for immunogenicity:	The ATP Complete Year 3 cohort for immunogenicity included all subjects who belonged to the ATP Year 3 and the previously defined Year 1 ATP cohorts.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes.
Completed:	Subjects who completed Visit 4.
Diary card:	Cards given to the subjects by the investigator to record adverse events following vaccination.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the analysis.

Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Seronegative subject:	A subject whose antibody concentration was below the cut-off value.
Seropositive subject:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Seroprotected subject:	A seroprotected subject was a subject with antibody concentrations greater than or equal to the seroprotection cut-off value defined for that antibody.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Year 3 cohort:	The Year 3 cohort was a subset of the Total Vaccinated cohort in the 106316 study and was the cohort of subjects for whom serological results for at least 1 antigen was available from the blood sample taken 3 years after vaccination.

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines will be written without the superscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Infanrix®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed (DTaP) vaccine.
Boostrix®	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap).

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Adacel® (Sanofi Pasteur)	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, the informed consent, and other information that required pre-approval were reviewed and approved by the central IRB (Quorum Review IRB).

1.2. Ethical conduct of the study

This study was conducted in accordance with "Good Clinical Practice" (GCP), the Declaration of Helsinki, Title 21 of the United States (US) Code of Federal Regulations (CFR) Part 50-Protection of Human Subjects, and Part 56 –IRBs and local rules and regulations of the country.

1.3. Subject information and consent

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures, in accordance with 21 CFR 50.25. Data collection was done by Remote Data Entry (RDE) using individual electronic case report forms (eCRFs).

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted by 36 investigators across multiple centers in the US. GSK Biologicals, King of Prussia, PA, US was responsible for administration of the study including clinical trial supply management and laboratory facilities. There was a reduction in the number of participating centers at Year 3 (39 centers) when compared to the 106316 study (45 centers) since several investigators declined to participate in this phase of the study. Samples collected from 57 subjects enrolled at 3 participating centers were lost in transit from the study center. Subjects whose samples were lost were still considered as participating in the study. The non-participating centers will be invited to participate in the Year 5 and Year 10 phase of the study.

3. INTRODUCTION

Since the early 1940s, routine childhood vaccination programs against diphtheria, tetanus and pertussis have substantially helped to reduce the incidence of each of these highly infectious diseases. Even though the rates of diphtheria and tetanus cases are extremely uncommon in countries where these programs have been implemented, pertussis continues to be prevalent despite the wide vaccine coverage [Greenberg, 2005, Frampton, , 2006].

In 2004, 25,827 cases of pertussis were reported in the US to the national passive reporting system—the highest number since the 1950s [COID, 2006]. Case reporting for pertussis in the US decreased to 10,454 cases in 2007 [CDC, 2008a] but increased again

in 2008 (13,278 cases reported) and in 2009 (16, 858 cases were reported [CDC, 2009]. However, pertussis in adults is believed to be underreported and the true incidence is estimated to be as high as 600,000 cases annually [Cortese, 2007]. Data from earlier studies suggest that approximately 1 million cases of pertussis occur annually in the US in the adult and adolescent population aged 15 years and above [COID, 2006].

GSK Biologicals' *Boostrix* vaccine, a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, was licensed in the US in May 2005, as a single-dose booster for adolescents 10–18 years of age for combined protection against pertussis, diphtheria and tetanus. In December 2008, the approved age range for use of *Boostrix* was extended to include adolescents and adults 10–64 years of age. This vaccine is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti, 2002; Greco, 1996; Schmitt, 1996a; Schmitt, 1996b]. The tetanus and diphtheria toxoid content of *Boostrix* is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared to *Infanrix*. The quantities of the pertussis antigens in *Boostrix* are approximately one-third of those in *Infanrix*. In the US, *Boostrix* is formulated to contain approximately 0.3 mg aluminum (as aluminum hydroxide) per 0.5 milliliter (mL) dose and is preservative-free while outside the US, *Boostrix* contains approximately 0.5 mg aluminum per dose. As of December 2009, over 5 million doses of *Boostrix* have been distributed in the US.

The 106316 study was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age [Blatter, 2009]. The immunogenicity and reactogenicity of *Boostrix* was compared to that elicited by Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, *Adacel* vaccine, which is licensed in the US for individuals 11-64 years of age.

Data on persistence of antibodies and long-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study provides information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 years following vaccination with a single dose of *Boostrix*.

Immunogenicity results from Year 1 showed that concentrations of antibodies to *Boostrix* antigens were lower than those observed 1 month after vaccination but remained elevated relative to pre-vaccination levels.

This report presents results of immunogenicity analyses for subjects in the 106316 study, 3 years following vaccination in that study.

4. STUDY OBJECTIVES

4.1. Primary objective

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (Vero, for subjects with an

ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

4.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

See Sections 5.10.1 and 5.10.2 for details of the study endpoints.

This report presents the results of the analyses performed up to Year 3.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

- A phase IIIb, controlled, non-interventional, multicenter, long-term follow-up study in the US with 2 parallel groups:
  - **Boostrix group:** Subjects who received a single dose of GSK Biologicals' *Boostrix* in the 106316 study.
  - **Adacel group**: Subjects who received a single dose of Sanofi Pasteur's *Adacel* in the 106316 study.
- Treatment allocation: No vaccine was administered during this study. Subjects in the 106316 study were randomized into groups, Boostrix or Adacel (2:1 ratio), with stratified age groups of 19-29, 30-49 and 50-64 years).
- Blinding: This was an open-label study since no vaccines were administered.
- Blood samples were collected at Year 3 for evaluation of antibody persistence.
- Duration of the study: The duration of the study from vaccination in the 106316 study up to Year 3 (Visit 4) was approximately 3 years per subject.
- Data collection: RDE using eCRFs.

5.2. Study procedures

5.2.1. Outline of study procedures

The list of study procedures are outlined in Table 1.

Table 1 Outline of study procedures

Visit	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Timing	Year 1	Year 3	Year 5	Year 10
Sampling time point	1 year following *Boostrix*/ *Adacel* vaccination	3 years following *Boostrix*/ *Adacel* vaccination	5 years following *Boostrix*/ *Adacel* vaccination	10 years following *Boostrix*/ *Adacel* vaccination
Informed consent	●	●	●	●
Check of inclusion criteria	●	●	●	●
Check of elimination criteria	●	●	●	●
Recording of concomitant medication/vaccination	●	●	●	●
Blood sampling				
for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● Study procedure that required documentation in the individual eCRF.
The gray shaded area represents the time point for which the analyses are presented in this report.

5.2.2. Intervals between study visits

The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits

Visit*	Length of interval
Visit 3 (Tdap vaccination in the 106316 study→Visit 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in the 106316 study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in the 106316 study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in the 106316 study →Visit 6)	10 years ± 5 weeks

*The date of the previous visit served as the reference date.
The gray shaded area represents the time point for which the analyses are presented in this report.

5.3. Selection of study population

A total of 39 centers in the US participated in the blood sample collection at Year 3. The total number of subjects enrolled in the 106316 study was 2284, randomized into Boostrix or Adacel groups in the ratio 2:1. All subjects who received vaccination in the 106316 study were considered eligible to participate at Year 3. A total of 1441 subjects provided blood samples at Year 3; of these, 1386 subjects (937 in the Boostrix group and 449 in the Adacel group) were included in the ATP Year 3 cohort for immunogenicity.

5.3.1. Inclusion criteria

All subjects were to have satisfied the following criteria at study entry:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in the 106316 study were considered eligible to participate in this study.
- Written informed consent was obtained from the subject prior to enrollment in the Year 3 follow-up study.

5.3.2. Exclusion criteria

Not applicable for this phase of the study.

5.3.3. Elimination criteria

The following criteria were checked at Year 3 (Visit 4). If any became applicable during the study, it did not require withdrawal of the subject from the study but were considered in determining a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 5.10.4 for definition of study cohorts that were evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in the 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in the 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators deferred the blood draw for these subjects until the time the criterion no longer applied.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to Visit 4. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

5.3.4. Contraindications to subsequent doses of vaccine

Not applicable for this phase of the study.

5.3.4.1. Warnings and precautions

Not applicable for this phase of the study.

5.3.5. Subject completion and withdrawal from study

5.3.5.1. Subject completion

A subject who returned for Visit 4 as specified in the protocol was considered to have completed the Year 3 follow-up time point.

5.3.5.2. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study was any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects could participate in each persistence time point independent of other persistence time points. For example, a subject who did not participate in the Year 3 antibody persistence analysis could be approached for participation in the 5 and 10 year persistence analyses.

A subject qualified as a 'withdrawal' from the study when no study procedure had occurred, no follow-up had been performed, and no further information had been collected for the subject since the last contact.

Information relative to the withdrawal of a subject was documented on the study continuation/conclusion screens of the eCRF. The investigator documented whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event (SAE)
- Non-serious adverse event (AE)
- Protocol violation (included receipt of prohibited vaccine or medication; was to be specified)
- Consent withdrawal, not due to an AE
- Moved from the study area
- Lost to follow-up
- Other (was specified).

5.3.5.3. Subject withdrawal from administration of the investigational product

Not applicable for this phase of the study.

5.4. Composition and administration of vaccines

Refer to the 106316 study report for details of the composition of vaccines administered in the 106316 study.

5.5. Prior and concomitant medication/vaccinations

At Visit 4, the investigator questioned the subject about any medications taken.

Any treatments and/or medications specifically contraindicated (e.g. any immunoglobulins, other blood products and any immune modifying drugs) administered within 90 days prior to any study blood sampling were to be recorded in the eCRF with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, was to be recorded in the eCRF with the trade name, route of administration, and date of administration.

5.6. Laboratory assays and time points

- Antibody concentrations against diphtheria and tetanus were measured by ELISA. The cut-off of both assays was 0.1 IU/mL. All samples with anti-D antibody concentrations < 0.1 IU/mL were retested using the neutralization assay on Vero cells, which was more sensitive for low antibody concentrations and had a cut-off of 0.016 IU/mL.
- Antibody concentrations against the pertussis components (PT, FHA and PRN) contained in *Boostrix* or *Adacel* were measured by the ELISA technique. The cut-off for the assays was 5 EL.U/mL for each antigen tested.

The details of laboratory assays that were performed are presented in Table 3.

Table 3 Laboratory assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory*
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-D	Neutralization test on Vero cell**	In-house assay	IU/mL	0.016	Rixensart
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-PT	ELISA	In-house assay	EL.U./mL	5	Laval
Serological	anti-FHA	ELISA	In-house assay	EL.U./mL	5	Laval
Serological	anti-PRN	ELISA	In-house assay	EL.U./mL	5	Laval

*All serological assays were performed using standardized, validated procedures with adequate controls
ELISA = enzyme-linked immunosorbent assay
** Vero cell testing was performed in subjects with an ELISA result of < 0.1 IU/mL
IU/mL = International Units per milliliter
Laval = GSK Biological laboratories in Laval, Quebec, Canada
EL.U/mL = ELISA units per milliliter
Rixensart = GSK Biologicals laboratories, Rixensart, Belgium

5.7. Assessment of immunogenicity variables

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum was obtained at Year 3 following study vaccination in the 106316 study. After blood centrifugation and serum separation, serum samples were stored at approximately –20°C until they were sent to the sponsor. Sera were sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Laval for storage prior to analysis.

Serological assays for anti-D toxoid, anti-T toxoid, anti-PT, anti-FHA and anti-PRN antibodies were performed at GSK Biologicals' laboratory in Laval, QC, Canada. The assays for anti-D Vero cell neutralization were conducted in GSK Biologicals' laboratory in Rixensart, Belgium. All serological assays were performed using standardized, validated procedures with adequate controls.

The priority listing for antibody testing was as shown in Table 4.

Table 4 Immunological read-outs

Blood sampling time point		Marker
Timing	Visit no.	
Year 3	4	D (ELISA and Vero)
		T
		PT
		FHA
		PRN

ELISA = enzyme-linked immunosorbent assay
Vero cell testing was performed in subjects with an ELISA result of < 0.1 IU/mL

5.7.1. Immunological correlates of protection

- The assay cut-offs for antibodies against diphtheria and tetanus toxoids was set at 0.1 IU/mL (ELISA), which provided a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983]. The cut-off of the Vero-cell assay (performed for serum samples with ELISA anti-diphtheria antibody concentrations < 0.1 IU/mL) was 0.016 IU/mL. Antibody concentrations greater than or equal to this value was considered as protective [Camargo, 1984].
- No correlate of protection was defined for the immune response to pertussis antigens [Sato, 1982; Granström, 1987; Karpinsky, 1987].

5.8. Assessment of safety variables

5.8.1. Serious adverse events

Because subjects were not being vaccinated as part of the study protocol, investigators were not required to specifically solicit SAEs in this phase of the study. However, if an investigator became aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in the 106316 study, he/she was to report to GSK Biologicals within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations, SAEs that were considered to be related to study participation (e.g. blood draws) were to be collected and recorded from the time the subject consented to participate in the study until she/he was discharged.

An SAE was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

c. required hospitalization or prolongation of existing hospitalization,

d. resulted in disability/incapacity, or

e. was a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgment was to be exercised in deciding whether reporting was appropriate in other situations, such as important medical events that might not have been immediately life-threatening or resulted in death or hospitalization but might have jeopardized the subject or might have required medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization.

5.8.2. Evaluating serious adverse events

This section was only applicable if an investigator became aware of an SAE that warranted notification to the sponsor.

5.8.2.1. Assessment of intensity

The investigator was to make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment was to be based on the investigator's clinical judgment.

The intensity of each SAE recorded in the eCRF, as applicable, was to be assigned to 1 of the following categories:

1 (mild)	=	An SAE which was easily tolerated by the subject, caused minimal discomfort and did not interfere with everyday activities.
2 (moderate)	=	An SAE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevented normal, everyday activities. (In adults, such an SAE, for example, prevented attendance at work and necessitated the administration of corrective therapy.)

5.8.2.2. Assessment of causality

The investigator was obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator was to use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product was considered and investigated. The investigator also consulted the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

In situations when an SAE occurred and the investigator had minimal information to include in the initial report to GSK Biologicals, it was very important that the investigator

always made an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. If the investigator changed his/her opinion of causality in light of follow-up information, he was to amend the SAE information accordingly. The causality assessment was to be 1 of the criteria used when determining regulatory reporting requirements.

If an event met the criteria to be determined as "serious" (see Section 5.8.1 for definition of SAE), it was to be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE.

Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccines, if applicable
- Erroneous administration
- Other cause (was to be specified).

5.8.3. Pregnancy

Since subjects were not being vaccinated as part of the study protocol, investigators were not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who were pregnant at the time of a study visit were not excluded from the visit on the basis of their pregnancy.

A spontaneous abortion was always to be considered an SAE and was to be reported as an SAE. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, was to be reported to GSK Biologicals. While the investigator was not obligated to actively seek this information from former study participants, he/she might have learnt of a pregnancy through spontaneous reporting.

5.9. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, eCRF and RDE system and safety reporting were reviewed with the investigators and their personnel responsible for the conduct of the study by the Company representative(s) prior to study start. A multi-investigator meeting was held on 09 June 2009, prior to the study start.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF

completion. All procedures were performed according to methodologies detailed in GSK Standard Operating Procedures (SOPs).

A Contract Research Organization (CRO) [ICON Clinical Research, North Wales, PA] was employed to perform site monitoring activities, collection and maintenance of regulatory documents and issues. The CRO's responsibilities were conducted according to their own SOPs.

Independent Audit statement:

No study specific audits were performed for this study.

5.10. Statistical methods

All analyses were performed as specified in the protocol and in the reporting and analysis plan (RAP).

The statistical analyses were performed using the Statistical Analysis System (SAS) version 9.1 on Windows XP Professional and StatXact-8.0 procedure on SAS.

5.10.1. Primary endpoint

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (Vero) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel groups at 1 year, 3 years, 5 years and 10 years following vaccination.

5.10.2. Secondary endpoints

- Subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups at 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration at the time of analysis in the Boostrix and Adacel groups.
- Anti-T concentration at the time of analysis in the Boostrix and Adacel groups.
- Anti-PT concentration at the time of analysis in the Boostrix and Adacel groups.
- Anti-FHA concentration at the time of analysis in the Boostrix and Adacel groups.
- Anti-PRN concentration at the time of analysis in the Boostrix and Adacel groups.

For this report, the time of analysis corresponds to Year 3.

5.10.3. Determination of sample size

All subjects who had received vaccination in the 106316 study were eligible for enrollment in this study. Refer to the 106316 study report for sample size estimation.

5.10.4. Study cohorts/data sets analyzed

Three cohorts were defined for the purpose of analysis and are described here:

Year 3 cohort

The Year 3 cohort was a subset of the Total Vaccinated cohort in the 106316 study. This cohort included subjects for whom serological results for at least 1 antigen were available after a blood sample was taken 3 years after vaccination in the 106316 study.

ATP Year 3 cohort for immunogenicity

The ATP Year 3 cohort for immunogenicity included all subjects from the Year 3 cohort who were in the ATP cohort for immunogenicity in the 106316 study and who did not meet the protocol-defined elimination criteria (See Section 5.3.3). This cohort was the primary cohort for the immunogenicity persistence analysis.

ATP Complete Year 3 cohort for immunogenicity

The ATP Complete Year 3 cohort for immunogenicity included all subjects who belonged to the ATP Year 3 cohort for immunogenicity and the previously defined Year 1 ATP cohorts.

5.10.5. Derived and transformed data

Immunogenicity

- The cut-off value was defined by the laboratory before the analysis and is described in Section 5.6.
- A seronegative subject was a subject whose antibody concentration was below the assay cut-off value.
- A seropositive subject was a subject whose antibody concentration was greater than or equal to the assay cut-off value.
- Seroprotection rate was defined as the percentage of subjects with antibody concentrations greater than or equal to the seroprotection cut-off value defined for that antibody.
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (Vero) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 3 years following vaccination was derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 3 years following vaccination was derived to evaluate the first secondary objective.
- The GMC calculations were performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off

of the assay was given an arbitrary value of half the cut-off for the purpose of GMC calculation.

- Anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN GMCs 3 years after vaccination with *Boostrix* were derived to evaluate the other secondary objectives.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

5.10.6. Analysis of demographics

Demographic characteristics (age in years at Year 3 and gender) for the Year 3 cohort and the ATP Year 3 cohort for immunogenicity were tabulated.

The number of subjects vaccinated in the 106316 study, in the ATP Year 3 cohort and in the ATP Complete Year 3 cohort for immunogenicity was tabulated.

The time from vaccination in the 106316 study to blood sampling at Year 3 follow-up time point (in weeks) was summarized by vaccine group, using descriptive statistics.

5.10.7. Analysis of immunogenicity

The analysis of antibody persistence at Year 3 was performed on the ATP Year 3 cohort for immunogenicity. Since the percentage of subjects eliminated from the ATP Year 3 cohort for immunogenicity was more than 5%, a complementary persistence analysis based on the Year 3 cohort was performed.

5.10.7.1. Within group assessment

For each vaccine group, at Year 3:

- Seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA) and overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by Vero cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) for anti-D with exact 95% confidence interval (CI) were calculated per group.
- Seroprotection rates for anti-T (percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI were calculated per group.
- Seropositivity rates (percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U) with exact 95% CI were calculated per group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated per group.

In addition the distribution of antibody concentrations for each antigen was displayed using reverse cumulative curves (RCCs) per group.

5.10.7.2. Comparability between Groups

Exploratory analyses

- For anti-D and anti-T antibody response:
  - The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 3 years after vaccination was calculated.
  - The two-sided 95% CI for the adjusted GMC ratio (Boostrix group divided by Adacel group) 3 years after vaccination was calculated. The GMC ratio was obtained using an Analysis of Co-variance (ANCOVA) model on the logarithm-transformed concentrations. The ANCOVA model included the group as fixed effect, the age at Year 3 blood sampling in years and baseline (pre vaccine) antibody concentration as regressors.
- The two-sided standardized asymptotic 95% CI for the group differences (Boostrix group - Adacel group) in the overall seroprotection rates for D, 3 years after vaccination was calculated.

If the 95% CI on the group differences in seroprotection rates excluded 0, or if the 95% CI on the between-group GMC ratios excluded 1, then this was taken as an indication of potential differences between groups. The exploratory comparisons are to be interpreted with caution since there was no adjustment for multiplicity of endpoints.

The persistence and exploratory analyses were also stratified by age (19-29 years, 30-49 years and 50-64 years) and gender (male and female) as defined in the 106316 study.

5.10.8. Analysis of safety

No safety analyses were performed in this persistence study since no SAE or pregnancy was reported. If GSK received information from an investigator of an SAE that in his/her medical judgment was reasonably related to the study vaccine administered in the 106316 study or to participation in this persistence study, the pertinent clinical details were to be summarized in the study report.

5.10.9. Interim analysis

No interim analysis was planned for this persistence study.

5.11. Changes in the conduct of the study or planned analyses

5.11.1. Protocol amendments

There were no amendments to the protocol of this study.

5.11.2. Other changes

Analyses were performed as planned in the protocol and RAP amendment.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject visit for Year 3 (Visit 4) was on 18 June 2009 and the last subject visit took place on 22 September 2009.

6.2. Subject eligibility and attrition from the study

6.2.1. Number of subjects

Subjects were enrolled at 39 centers in the US. The number of subjects enrolled at Year 3 and the number of subjects included into the Year 3 cohort and the ATP Year 3 cohort for immunogenicity are presented in Table 5.

Table 5 Number of subjects included in each follow-up time point up to Year 3

Title (Number of subjects)	Boostrix Group	Adacel Group	Total
	n	n	n
Vaccinated in the 106316 study (Tdap 0.3-007)	1522	762	2284
ATP cohort for immunogenicity in 106316 study (Tdap 0.3-007)	1448	728	2176
Year 1 follow-up time point (Year 1 cohort)	1069	523	1592
Year 1 follow-up time point (ATP Year 1 cohort for immunogenicity)	1015	506	1521
Year 3 follow-up time point (Year 3 cohort)	976	465	1441
Year 3 follow-up time point (ATP Year 3 cohort for immunogenicity)	**937**	**449**	**1386**
Year 3 follow-up time point (ATP Complete Year 3 cohort for immunogenicity)	776	367	1143

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
n = number of subjects included in each group or in total for a defined cohort.
Numbers in bold represent the total number and percentage of subjects in a given category

The number of enrolled subjects by center for the Year 3 cohort is presented in Supplement 1.

The time in weeks from the vaccination in the 106316 study to the blood sampling for each group for the Year 3 cohort is presented in Supplement 2.

6.2.2. Study completion and withdrawal from study

A total of 2284 subjects (1522 subjects in the Boostrix group and 762 subjects in the Adacel group) were vaccinated in the 106316 study. Of these, 1441 subjects (976 in the Boostrix group and 465 in the Adacel group) returned for the Year 3 blood sampling visit (Visit 4). These subjects had serological results available for at least 1 antigen at Year 3. A total of 1386 subjects (937 in the Boostrix group and 449 in the Adacel group) were included in the ATP Year 3 cohort for immunogenicity (Table 5).

6.2.3. Protocol deviations

A summary of the subjects enrolled into the study as well as the number eliminated from ATP analyses with reasons for elimination is presented in Table 6. Subjects are listed in the text based on the lowest elimination code, as more than 1 elimination code could have been assigned to the same subject.

Table 6 Number of subjects enrolled into the study as well as the number excluded from ATP Year 3 analyses with reasons for exclusion

Title	Total			Boostrix Group		Adacel Group	
	n	s	%	n	s	n	s
Total cohort	1505						
Total vaccinated cohort	**1505**		**100**	**1019**		**486**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	39	39		28	28	11	11
ATP cohort for safety	**1466**		**97.4**	**991**		**475**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	7	8		6	6	1	2
Administration of any medication forbidden by the protocol (code 2040)	0	8		0	6	0	2
Underlying medical condition forbidden by the protocol (code 2050)	0	4		0	2	0	2
Essential serological data missing (code 2100)	61	64		40	43	21	21
Others (immuno) (code 2500)	12	12		8	8	4	4
ATP Year 3 cohort for immunogenicity	**1386**		**92.1**	**937**		**449**	

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N= total number of subjects
n = number of subjects with the elimination code assigned excluding subjects who had been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the number of subjects returning for blood sampling at Year 3
Numbers in bold represent the total number and percentage of subjects in a given category
Note: Subjects may have more than 1 elimination code assigned

Out of the 1505 vaccinated subjects (subjects vaccinated in the 106316 study), a total of 80 subjects (54 in the Boostrix Group and 26 in the Adacel Group) were eliminated from the ATP Year 3 cohort for immunogenicity due to the following reasons:

- Seven subjects (6 in the Boostrix Group and 1 in Adacel Group) were assigned the elimination code 2010 at Year 3 for having met the protocol-defined elimination criteria since these subjects had an immunosuppressive condition.
- A total of 61 subjects (40 in the Boostrix Group and 21 in the Adacel Group) were assigned the elimination code 2100 since for these subjects the serological results were not available post-vaccination for all antigens. This included the subjects for whom the samples were lost during shipment from one of the participating centers.
- A total of 12 subjects (8 in the Boostrix Group and 4 in the Adacel Group) were assigned the elimination code 2500. The serum samples of these subjects were not frozen properly during storage.

Thus, 1386 subjects (937 in the Boostrix Group and 449 in the Adacel Group) were included in the ATP Year 3 cohort for immunogenicity.

6.3. Demographic characteristics

6.3.1. ATP Year 3 cohort for immunogenicity

The summary of demographic characteristics for the ATP Year 3 cohort for immunogenicity is presented in Table 7.

Table 7 Summary of demographic characteristics (ATP Year 3 cohort for immunogenicity)

		Boostrix Group N = 937		Adacel Group N = 449		Total N = 1386	
Characteristics	**Parameters**	**Value**		**Value**		**Value**	
Age (years)	Mean	44.8		45.3		44.9	
	SD	13.38		13.26		13.34	
	Median	47.0		47.0		47.0	
	Minimum	21		22		21	
	Maximum	67		67		67	
	Categories	**n**	**%**	**n**	**%**	**n**	**%**
Age stratum	19-29(Y)	261	27.9	113	25.2	374	27.0
	30-49(Y)	314	33.5	162	36.1	476	34.3
	50-64(Y)	362	38.6	174	38.7	536	38.7
Gender	Female	615	65.6	303	67.5	918	66.2
	Male	322	34.4	146	32.5	468	33.8

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = total number of subjects
Value = value of the considered parameter
n (%) = number (percentage) of subjects in a given category
SD = standard deviation
Age (years) = age at Year 3 blood sampling, expressed in years
Age stratum: based on the age at vaccination in 106316 study

The groups appeared to be similar to each other with respect to mean age, age distribution and gender. Demographic characteristics of the groups were similar to that seen in the ATP Year 1 cohort.

6.3.2. Year 3 cohort

The summary of demographic characteristics for the Year 3 cohort is presented in Supplement 3.

The demographic profile of the Year 3 cohort was similar to the ATP Year 3 cohort for immunogenicity.

7. IMMUNOGENICITY RESULTS

7.1. Data sets analyzed

The primary analysis of immunogenicity was performed on the ATP Year 3 cohort for immunogenicity. A complementary analysis based on the Year 3 cohort was performed as more than 5% of the vaccinated subjects who returned for blood sampling at Year 3 were eliminated from the ATP Year 3 cohort for immunogenicity. An analysis on the ATP Complete Year 3 cohort for immunogenicity was also performed. See Section 5.10.4 for the definition of the cohorts identified for the analyses and Section 6.2 for eligibility for the analyses.

7.2. According-to-protocol analysis

A total of 1386 subjects (937 in the Boostrix group and 449 in the Adacel group) were included into the ATP Year 3 cohort for immunogenicity.

7.2.1. Persistence of antibodies to diphtheria and tetanus toxoids

The percentages of subjects with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL (by ELISA) and GMCs by vaccine groups for the ATP Year 3 cohort for immunogenicity are presented in Table 8.

Table 8 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU per mL and 1.0 IU per mL (by ELISA) and GMCs at Year 3 by group (ATP Year 3 cohort for immunogenicity)

				≥ 0.1 IU/mL				≥ 1.0 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	PRE	930	789	84.8	82.4	87.1	219	23.5	20.9	26.4	0.4	0.4	0.4
		PI(M1)	926	906	97.8	96.7	98.7	806	87.0	84.7	89.1	4.6	4.2	5.0
		PI(Y1)	802	768	95.8	94.1	97.0	530	66.1	62.7	69.4	1.4	1.3	1.6
		PI(Y3)	934	876	93.8	92.0	95.3	494	52.9	49.6	56.1	0.9	0.8	1.0
	Adacel	PRE	443	397	89.6	86.4	92.3	114	25.7	21.7	30.1	0.5	0.4	0.5
		PI(M1)	444	438	98.6	97.1	99.5	407	91.7	88.7	94.1	4.9	4.4	5.4
		PI(Y1)	375	364	97.1	94.8	98.5	261	69.6	64.7	74.2	1.4	1.3	1.6
		PI(Y3)	449	432	96.2	94.0	97.8	250	55.7	50.9	60.3	1.0	0.9	1.1
Anti-T	Boostrix	PRE	936	897	95.8	94.3	97.0	669	71.5	68.5	74.3	1.5	1.4	1.7
		PI(M1)	927	921	99.4	98.6	99.8	906	97.7	96.6	98.6	8.3	7.9	8.8
		PI(Y1)	806	794	98.5	97.4	99.2	753	93.4	91.5	95.0	3.3	3.1	3.5
		PI(Y3)	937	919	98.1	97.0	98.9	827	88.3	86.0	90.3	2.2	2.1	2.3
	Adacel	PRE	448	435	97.1	95.1	98.4	344	76.8	72.6	80.6	1.7	1.6	1.9
		PI(M1)	445	445	100	99.2	100	440	98.9	97.4	99.6	12.8	11.8	13.8
		PI(Y1)	377	376	99.7	98.5	100	361	95.8	93.2	97.6	4.4	4.0	4.7
		PI(Y3)	449	447	99.6	98.4	99.9	414	92.2	89.3	94.5	2.9	2.7	3.1

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Three years after vaccination, the percentage of subjects with seroprotective anti-D antibody concentrations (≥ 0.1 IU/mL) was slightly decreased from that observed at Month 1 following vaccination, and was comparable to that observed at Year 1. The percentage of subjects with seroprotective anti-T antibody concentrations (≥ 0.1 IU/mL) was comparable to those observed at Month 1 and Year 1 following vaccination. The percentages of subjects with anti-D or anti-T antibody concentrations ≥ 1.0 IU/mL were decreased from that observed at Month 1 and Year 1 after vaccination in both groups. GMCs for anti-D and anti-T antibodies were decreased from Year 1 to Year 3 in both groups, and remained higher than the pre-vaccination levels (Table 8).

The distribution of anti-D and anti-T antibody concentrations for the ATP Year 3 cohort for immunogenicity is presented in Supplement 4.

Subjects with anti-D concentrations < 0.1 IU/mL were retested using a more sensitive Vero cell assay. Seroprotection for D was defined in this assay by an antibody concentration ≥ 0.016 IU/mL. The overall anti-D seroprotection rates in the ATP Year 3 cohort were shown by the percentage of subjects with anti-D antibody concentrations ≥

0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by Vero cell assay with exact 95% CI. This information is presented in Table 9.

Table 9 Overall seroprotection status for anti-D antibody concentration by ELISA and Vero at Year 3 by group (ATP Year 3 cohort for immunogenicity)

			Seronegativity assessed by ELISA		Seronegativity assessed by the Vero test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated percentage of subjects seroprotected (SP) and its 95% CI		
Group	Timing	N	n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Boostrix	PRE	930	141/930	15.2	67/141	47.5	141/930 x 67/141	7.2	92.8	90.9	94.4
	PI(M1)	926	20/926	2.2	8/20	40.0	20/926 x 8/20	0.9	99.1	98.3	99.6
	PI(Y1)	804	36/804	4.5	12/36	33.3	36/804 x 12/36	1.5	98.5	97.4	99.2
	PI(Y3)	934	58/934	6.2	29/58	50.0	58/934 x 29/58	3.1	96.9	95.6	97.9
Adacel	PRE	443	46/443	10.4	16/45	35.6	46/443 x 16/45	3.7	96.3	94.2	97.8
	PI(M1)	444	6/444	1.4	4/6	66.7	6/444 x 4/6	0.9	99.1	97.7	99.8
	PI(Y1)	376	12/376	3.2	8/12	66.7	12/376 x 8/12	2.1	97.9	95.9	99.1
	PI(Y3)	449	17/449	3.8	10/17	58.8	17/449 x 10/17	2.2	97.8	95.9	98.9

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below 0.1 IU/mL/number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below 0.016 IU/mL/number of subjects tested by Vero neutralization test
% = percentage of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for Vero)
n/N x n'/N' = the multiplication of the 2 percentages = overall seronegativity for anti-D
Overall = based on both the ELISA and the Vero testing
95% CI = exact 95% confidence interval
SP= seroprotected, LL = Lower Limit, UL =Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

The overall anti-D seroprotection rates were at least 96.9% in both groups, decreasing slightly compared to Month 1 following vaccination and comparable to Year 1.

The percentage of subjects with anti-D and anti-T antibody concentrations of ≥ 0.1 IU/mL (by ELISA) and GMCs according to group, stratified by age and gender for the ATP Year 3 cohort for immunogenicity are presented in Supplement 5 and Supplement 6, respectively.

The overall seroprotection status for anti-D antibody concentrations for the ATP Year 3 cohort for immunogenicity, stratified by age and gender is presented in Supplement 7 and Supplement 8, respectively.

The RCCs for anti-D and anti-T antibody concentrations in the Boostrix and Adacel groups, 3 years after vaccination for the ATP Year 3 cohort for immunogenicity are presented in Supplement 9 and Supplement 10, respectively.

7.2.2. Persistence of antibodies to acellular pertussis antigens

The seropositivity rates for anti-PT, anti-FHA and anti-PRN (≥ 5 EL.U/mL) and their respective GMCs according to group for the ATP Year 3 cohort for immunogenicity are presented in Table 10.

Table 10 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at Year 3 (ATP Year 3 cohort for immunogenicity)

				≥ 5 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	PRE	927	518	55.9	52.6	59.1	7.1	6.6	7.6
		PI(M1)	922	895	97.1	95.8	98.1	62.7	58.5	67.2
		PI(Y1)	805	733	91.1	88.9	92.9	22.7	21.1	24.5
		PI(Y3)	934	767	82.1	79.5	84.5	14.1	13.1	15.1
	Adacel	PRE	445	284	63.8	59.2	68.3	8.5	7.7	9.5
		PI(M1)	439	410	93.4	90.7	95.5	32.7	29.3	36.6
		PI(Y1)	377	326	86.5	82.6	89.8	15.8	14.2	17.7
		PI(Y3)	449	323	71.9	67.5	76.0	10.0	9.1	11.1
Anti-FHA	Boostrix	PRE	930	897	96.5	95.1	97.5	31.0	28.8	33.3
		PI(M1)	928	928	100	99.6	100	597.6	561.0	636.7
		PI(Y1)	806	804	99.8	99.1	100	183.7	171.0	197.4
		PI(Y3)	936	933	99.7	99.1	99.9	115.0	108.0	122.4
	Adacel	PRE	441	427	96.8	94.7	98.3	35.2	31.6	39.1
		PI(M1)	443	443	100	99.2	100	365.8	335.8	398.5
		PI(Y1)	375	375	100	99.0	100	119.4	107.8	132.1
		PI(Y3)	446	444	99.6	98.4	99.9	81.5	74.6	89.1
Anti-PRN	Boostrix	PRE	934	712	76.2	73.4	78.9	13.6	12.5	14.8
		PI(M1)	926	915	98.8	97.9	99.4	393.7	354.3	437.4
		PI(Y1)	803	771	96.0	94.4	97.3	151.7	135.2	170.3
		PI(Y3)	935	882	94.3	92.7	95.7	83.1	75.1	92.1
	Adacel	PRE	448	337	75.2	71.0	79.2	14.8	13.0	16.9
		PI(M1)	445	442	99.3	98.0	99.9	329.0	285.4	379.4
		PI(Y1)	374	368	98.4	96.5	99.4	130.6	111.4	153.0
		PI(Y3)	449	433	96.4	94.3	97.9	70.2	61.2	80.4

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

The percentages of subjects seropositive for anti-FHA and anti-PRN antibodies at Year 3 in each group did not appear to have decreased from Month 1 and Year 1, while the seropositivity rate for anti-PT antibodies at Year 3appeared to have decreased from the values observed at Month 1 and Year 1. However, the seropositivity rates for the anti-PT, anti-FHA and anti-PRN antibodies remained higher than the pre-vaccination levels. GMCs for anti-pertussis antibodies decreased at Year 3 compared to Month 1 and Year 1 and remained higher than pre-vaccination GMCs.

The distribution of anti-PT, anti-FHA and anti-PRN antibody concentrations for the ATP Year 3 cohort for immunogenicity is presented in Supplement 11.

The seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies stratified by age and gender for the ATP Year 3 cohort for immunogenicity are presented in Supplement 12 and Supplement 13, respectively.

The RCCs for anti-PT, anti-FHA and anti-PRN antibody concentrations in Boostrix and Adacel groups, 3 years after vaccination for the ATP Year 3 cohort for immunogenicity are presented in Supplement 14 to Supplement 16, respectively.

7.3. Year 3 cohort analysis

The results of the Year 3 cohort analyses are presented in Supplement 17 to Supplement 19. The results for all antibodies showed similar results as the ATP Year 3 cohort for immunogenicity for both groups.

7.4. Exploratory analyses

Comparative exploratory analyses were performed to characterize the difference between groups in terms of immunogenicity; these differences are discussed in the subsequent sections. These comparisons are to be interpreted with caution since there was no adjustment for multiplicity of endpoints.

7.4.1. Between-group differences in percentages of subjects seroprotected for D and T

The differences between the Boostrix group and the Adacel group in the anti-D and anti-T seroprotection rates (percentage of subjects with anti-D and anti-T ≥ 0.1 IU/mL by ELISA) for the ATP Year 3 cohort for immunogenicity are presented in Table 11.

Table 11 Difference between groups in anti-D and anti-T seroprotection rates at Year 3 (ATP Year 3 cohort for immunogenicity)

							Difference in seroprotection rate (Boostrix group minus Adacel group)			
									95% CI	
Antibody	Group	N	%	Group	N	%	Difference	%	LL	UL
Anti-D	Adacel	449	96.2	Boostrix	934	93.8	Boostrix - Adacel	-2.42	-4.69	0.14
Anti-T	Adacel	449	99.6	Boostrix	937	98.1	Boostrix - Adacel	-1.48	-2.65	-0.18

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D or anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Exploratory analysis did not indicate a difference between the Boostrix group and the Adacel group with respect to the percentages of subjects with anti-D antibodies ≥ 0.1 IU/mL, since the 95% CI for between-group difference included the value 0.

The exploratory analysis suggested a higher percentage of subjects with anti-T antibodies ≥ 0.1 IU/mL in the Adacel group than in the Boostrix group (95 % CI for the group difference excluded the value 0). This was a change from the previous time points, for which no apparent differences in percentages of subjects with anti-T antibodies ≥ 0.1 IU/mL were noted. Seroprotection rates for anti-T antibodies were very high in both groups (99.6% for Adacel group, 98.1% for Boostrix group). The clinical relevance of this observation is unclear.

The differences in the anti-D and anti-T seroprotection rates at Year 3 between the Boostrix and Adacel groups for the ATP Year 3 cohort for immunogenicity, stratified by age and gender, are presented in Supplement 20 and Supplement 21, respectively.

7.4.2. Between-group differences in overall anti-D seroprotection rate

The difference between the Boostrix group and the Adacel group in the overall anti-D seroprotection rate (percentages of subjects with anti-D ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by Vero) at Year 3 for the ATP Year 3 cohort for immunogenicity is presented in Table 12.

Table 12 Difference between groups in the percentage of subjects with anti-D antibody concentration greater than or equal to 0.1 IU per mL by ELISA or at least 0.016 IU per mL by Vero cell assay (when anti-D concentrations were less than 0.1 IU per mL by ELISA) at Year 3 after vaccination (ATP Year 3 cohort for immunogenicity)

						Difference in seroprotection rate (Boostrix group minus Adacel group)			
								95% CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Adacel	449	97.8	Boostrix	934	96.9	Boostrix - Adacel	-0.88	-2.57	1.15

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL by ELISA or ≥0.016 IU/mL by Vero
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Exploratory analysis did not indicate any difference between the Boostrix group and the Adacel group with respect to overall anti-D seroprotection rate, evidenced by the fact that 95% CI for between-group difference included 0.

The differences in the overall anti-D seroprotection rates between the Boostrix group and the Adacel group for the ATP Year 3 cohort for immunogenicity by age group and gender are presented in Supplement 22 and Supplement 23, respectively.

7.4.3. Between-group differences in anti-D and anti-T GMCs

The adjusted ratios of anti-D and anti-T GMCs at Year 3 for the ATP Year 3 cohort for immunogenicity are presented in Table 13.

Table 13 Adjusted ratios of anti-D and anti-T GMCs at Year 3 (ATP Year 3 cohort for immunogenicity)

					Adjusted GMC ratio (Boostrix group/Adacel group)		
	Boostrix group		Adacel group			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D	930	0.9	443	0.9	0.97	0.89	1.07
Anti-T	936	2.2	448	2.7	0.82	0.76	0.88

Adjusted GMC = geometric mean concentration adjusted at age (Y), for baseline concentration
Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (ANCOVA model: adjustment for age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Three years after vaccination, the exploratory evaluations between groups did not indicate any difference in terms of anti-D GMCs (95% CI for adjusted GMC ratio included 1). The 95% CI for the between-group anti-T GMC ratio excluded 1, indicating a potentially higher anti-T GMC in the Adacel group than in the Boostrix group. This was similar to the results observed at Year 1.

The adjusted ratios of anti-D and anti-T GMCs at Year 3 for the ATP Year 3 cohort for immunogenicity by age and gender are presented in Supplement 24 and Supplement 25, respectively.

7.5. Year 3 cohort analysis

The results for the exploratory analyses for the Year 3 cohort are presented in Supplement 26 to Supplement 28. The results for all antibodies showed similar results as the ATP Year 3 cohort for immunogenicity for both groups.

7.6. ATP Complete Year 3 cohort analysis

The results for the analyses for the ATP Complete Year 3 cohort for immunogenicity are presented in Supplement 29 and Supplement 30.

8. SAFETY RESULTS

There were no pregnancies or SAEs reported in this phase of the study.

9. DISCUSSION

The purpose of this study was to evaluate the antibody persistence at 3 years following vaccination with GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine adsorbed, *Boostrix*, in healthy adults aged 19-64 years.

As expected, a gradual decrease in all antibody concentrations 3 years after vaccination with a single dose of *Boostrix* in the 106316 study was observed from that observed at Year 1 and from the peaks observed at Month 1 after vaccination. However, the values remained higher than the pre-vaccination levels.

The overall seroprotection rates for diphtheria and tetanus remained high in both vaccine groups 3 years after vaccination, with at least 98.1% of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL and 93.8% with anti-D antibody concentrations ≥ 0.1 IU/mL. Seropositivity rates for acellular pertussis antigens antibodies remained high, 3 years after vaccination. GMCs for antibodies to pertussis antigens were higher in the Boostrix group than in the Adacel group 1 year after vaccination. These differences remained apparent 3 years after vaccination, although the magnitude of the differences decreased. Exploratory comparisons indicated that anti-D GMCs and seroprotection rates were similar between groups, while anti-T GMCs and seroprotection rates were greater in the Adacel group than in the Boostrix group. Seroprotection rates in both groups were high and the clinical relevance of this observation is not clear.

The results of this US adult antibody persistence study were found to be consistent with antibody persistence data 5 years following vaccination of the non-US formulation of *Boostrix* in adults [McIntyre, 2009].

10. OVERALL CONCLUSIONS

- Evaluation of anti-D and anti-T antibodies elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus 3 years after vaccination.
- Antibody concentrations to all antigens elicited by a single dose of *Boostrix* were lower compared to the antibody concentrations observed 1 month and 1 year after vaccination and remained higher than the pre-vaccination levels.
- There were no pregnancies or SAEs reported in this study.

11. SUPPLEMENTS

Supplement 1 Number of subjects by center (Year 3 cohort)

Center	Boostrix Group	Adacel Group	Total	
	n	n	n	%
PPD	19	12	31	2.2
	5	2	7	0.5
	10	6	16	1.1
	49	19	68	4.7
	59	28	87	6.0
	47	24	71	4.9
	23	11	34	2.4
	20	10	30	2.1
	13	3	16	1.1
	9	6	15	1.0
	18	8	26	1.8
	6	2	8	0.6
	33	13	46	3.2
	19	9	28	1.9
	7	4	11	0.8
	3	2	5	0.3
	22	11	33	2.3
	30	16	46	3.2
	47	24	71	4.9
	22	12	34	2.4
	16	5	21	1.5
	46	20	66	4.6
	64	32	96	6.7
	28	13	41	2.8
	79	37	116	8.0
	44	25	69	4.8
	8	7	15	1.0
	69	31	100	6.9
	17	5	22	1.5
	18	10	28	1.9
	26	13	39	2.7
	26	10	36	2.5
	14	5	19	1.3
	29	13	42	2.9
	14	10	24	1.7
	17	7	24	1.7
All	976	465	1441	100

n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Supplement 2 Time in weeks from the vaccination in 106316 study to the blood sampling for each group (Year 3 cohort)

Group	N	Mean	SD	Minimum	Median	Maximum
Boostrix	976	154.28	2.54	150.00	154.00	163.00
Adacel	465	154.29	2.49	150.00	154.00	164.00

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = total number of subjects
SD = standard deviation

Supplement 3 Summary of demographic characteristics (Year 3 cohort)

		Boostrix Group N = 976		Adacel Group N = 465		Total N = 1441	
Characteristics	**Parameters**	**Value**		**Value**		**Value**	
Age (years)	Mean	44.7		45.2		44.9	
	SD	13.31		13.33		13.32	
	Median	47.0		47.0		47.0	
	Minimum	21		22		21	
	Maximum	67		67		67	
	Categories	**n**	**%**	**n**	**%**	**n**	**%**
Age stratum	19-29(Y)	271	27.8	118	25.4	389	27.0
	30-49(Y)	335	34.3	166	35.7	501	34.8
	50-64(Y)	370	37.9	181	38.9	551	38.2
Gender	Female	635	65.1	314	67.5	949	65.9
	Male	341	34.9	151	32.5	492	34.1

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = total number of subjects
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Age (years) = age at Year 3 blood sampling, expressed in years
Age stratum = based on the age at vaccination in 106316 study

Supplement 4 Distribution of anti-D and anti-T antibody concentration (ATP Year 3 cohort for immunogenicity)

				< 0.1 IU/mL				≥ 0.1 IU/mL				≥ 1 IU/mL			
						95% CI				95% CI				95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Anti-D	Boostrix	PRE	930	141	15.2	12.9	17.6	789	84.8	82.4	87.1	219	23.5	20.9	26.4
		PI(M1)	926	20	2.2	1.3	3.3	906	97.8	96.7	98.7	806	87.0	84.7	89.1
		PI(Y1)	802	34	4.2	3.0	5.9	768	95.8	94.1	97.0	530	66.1	62.7	69.4
		PI(Y3)	934	58	6.2	4.7	8.0	876	93.8	92.0	95.3	494	52.9	49.6	56.1
	Adacel	PRE	443	46	10.4	7.7	13.6	397	89.6	86.4	92.3	114	25.7	21.7	30.1
		PI(M1)	444	6	1.4	0.5	2.9	438	98.6	97.1	99.5	407	91.7	88.7	94.1
		PI(Y1)	375	11	2.9	1.5	5.2	364	97.1	94.8	98.5	261	69.6	64.7	74.2
		PI(Y3)	449	17	3.8	2.2	6.0	432	96.2	94.0	97.8	250	55.7	50.9	60.3
Anti-T	Boostrix	PRE	936	39	4.2	3.0	5.7	897	95.8	94.3	97.0	669	71.5	68.5	74.3
		PI(M1)	927	6	0.6	0.2	1.4	921	99.4	98.6	99.8	906	97.7	96.6	98.6
		PI(Y1)	806	12	1.5	0.8	2.6	794	98.5	97.4	99.2	753	93.4	91.5	95.0
		PI(Y3)	937	18	1.9	1.1	3.0	919	98.1	97.0	98.9	827	88.3	86.0	90.3
	Adacel	PRE	448	13	2.9	1.6	4.9	435	97.1	95.1	98.4	344	76.8	72.6	80.6
		PI(M1)	445	0	0.0	0.0	0.8	445	100	99.2	100	440	98.9	97.4	99.6
		PI(Y1)	377	1	0.3	0.0	1.5	376	99.7	98.5	100	361	95.8	93.2	97.6
		PI(Y3)	449	2	0.4	0.1	1.6	447	99.6	98.4	99.9	414	92.2	89.3	94.5

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE- blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 5 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU per mL (by ELISA) and GMCs stratified by age (ATP Year 3 cohort for immunogenicity)

					≥ 0.1 IU/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-D	19-29 years	Boostrix	PRE	261	241	92.3	88.4	95.3	0.5	0.4	0.5
			PI(M1)	255	253	99.2	97.2	99.9	8.0	7.1	9.1
			PI(Y1)	225	225	100	98.4	100	2.4	2.1	2.7
			PI(Y3)	261	258	98.9	96.7	99.8	1.4	1.2	1.6
		Adacel	PRE	113	103	91.2	84.3	95.7	0.5	0.4	0.6
			PI(M1)	111	111	100	96.7	100	6.6	5.6	7.8
			PI(Y1)	89	88	98.9	93.9	100	1.9	1.6	2.4
			PI(Y3)	113	109	96.5	91.2	99.0	1.2	1.0	1.5
	30-49 years	Boostrix	PRE	310	277	89.4	85.4	92.6	0.5	0.4	0.5
			PI(M1)	311	307	98.7	96.7	99.6	5.6	4.9	6.4
			PI(Y1)	268	262	97.8	95.2	99.2	1.6	1.4	1.9
			PI(Y3)	313	305	97.4	95.0	98.9	1.1	1.0	1.2
		Adacel	PRE	158	144	91.1	85.6	95.1	0.5	0.4	0.6
			PI(M1)	160	157	98.1	94.6	99.6	5.6	4.7	6.7
			PI(Y1)	138	135	97.8	93.8	99.5	1.7	1.4	2.0
			PI(Y3)	162	159	98.1	94.7	99.6	1.2	1.0	1.4
	50-64 years	Boostrix	PRE	359	271	75.5	70.7	79.9	0.3	0.3	0.4
			PI(M1)	360	346	96.1	93.6	97.9	2.6	2.2	3.1
			PI(Y1)	309	281	90.9	87.2	93.9	0.9	0.7	1.0
			PI(Y3)	360	313	86.9	83.0	90.2	0.6	0.5	0.6
		Adacel	PRE	172	150	87.2	81.3	91.8	0.4	0.3	0.5
			PI(M1)	173	170	98.3	95.0	99.6	3.5	2.9	4.2
			PI(Y1)	148	141	95.3	90.5	98.1	1.0	0.8	1.3
			PI(Y3)	174	164	94.3	89.7	97.2	0.7	0.6	0.9
Anti-T	19-29 years	Boostrix	PRE	261	253	96.9	94.1	98.7	1.6	1.4	1.8
			PI(M1)	256	255	99.6	97.8	100	9.8	8.8	10.8
			PI(Y1)	225	225	100	98.4	100	4.2	3.9	4.6
			PI(Y3)	261	260	99.6	97.9	100	2.5	2.3	2.7
		Adacel	PRE	113	108	95.6	90.0	98.5	1.8	1.4	2.3
			PI(M1)	111	111	100	96.7	100	13.2	11.4	15.4
			PI(Y1)	89	89	100	95.9	100	4.5	3.8	5.4
			PI(Y3)	113	113	100	96.8	100	2.9	2.5	3.4
	30-49 years	Boostrix	PRE	313	308	98.4	96.3	99.5	1.8	1.6	2.0
			PI(M1)	312	312	100	98.8	100	8.9	8.2	9.6
			PI(Y1)	269	269	100	98.6	100	3.6	3.3	3.9
			PI(Y3)	314	314	100	98.8	100	2.5	2.3	2.7
		Adacel	PRE	161	158	98.1	94.7	99.6	1.8	1.5	2.2
			PI(M1)	160	160	100	97.7	100	13.5	11.7	15.5
			PI(Y1)	139	138	99.3	96.1	100	5.0	4.4	5.7
			PI(Y3)	162	161	99.4	96.6	100	3.1	2.8	3.5
	50-64 years	Boostrix	PRE	362	336	92.8	89.7	95.3	1.3	1.1	1.5
			PI(M1)	359	354	98.6	96.8	99.5	7.0	6.3	7.9
			PI(Y1)	312	300	96.2	93.4	98.0	2.6	2.3	3.0
			PI(Y3)	362	345	95.3	92.6	97.2	1.8	1.6	2.0
		Adacel	PRE	174	169	97.1	93.4	99.1	1.6	1.4	1.9
			PI(M1)	174	174	100	97.9	100	11.9	10.6	13.5
			PI(Y1)	149	149	100	97.6	100	3.7	3.3	4.2
			PI(Y3)	174	173	99.4	96.8	100	2.6	2.3	2.9

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE- blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 6 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU per mL (by ELISA) and GMCs at Year 3, stratified by gender (ATP Year 3 cohort for immunogenicity)

					≥ 0.1 IU/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-D	Male	Boostrix	PRE	321	287	89.4	85.5	92.6	0.5	0.4	0.6
			PI(M1)	317	312	98.4	96.4	99.5	5.2	4.5	6.0
			PI(Y1)	270	261	96.7	93.8	98.5	1.5	1.3	1.8
			PI(Y3)	322	308	95.7	92.8	97.6	1.0	0.9	1.2
		Adacel	PRE	145	138	95.2	90.3	98.0	0.5	0.5	0.6
			PI(M1)	142	142	100	97.4	100	5.3	4.5	6.2
			PI(Y1)	111	109	98.2	93.6	99.8	1.5	1.2	1.8
			PI(Y3)	146	140	95.9	91.3	98.5	1.0	0.8	1.2
	Female	Boostrix	PRE	609	502	82.4	79.2	85.4	0.4	0.3	0.4
			PI(M1)	609	594	97.5	96.0	98.6	4.3	3.9	4.8
			PI(Y1)	532	507	95.3	93.1	96.9	1.4	1.2	1.5
			PI(Y3)	612	568	92.8	90.5	94.7	0.8	0.8	0.9
		Adacel	PRE	298	259	86.9	82.5	90.5	0.4	0.4	0.5
			PI(M1)	302	296	98.0	95.7	99.3	4.7	4.1	5.4
			PI(Y1)	264	255	96.6	93.6	98.4	1.4	1.2	1.6
			PI(Y3)	303	292	96.4	93.6	98.2	1.0	0.9	1.1
Anti-T	Male	Boostrix	PRE	323	314	97.2	94.8	98.7	1.9	1.7	2.1
			PI(M1)	317	317	100	98.8	100	7.8	7.2	8.5
			PI(Y1)	272	269	98.9	96.8	99.8	3.3	3.0	3.7
			PI(Y3)	323	319	98.8	96.9	99.7	2.3	2.1	2.5
		Adacel	PRE	146	145	99.3	96.2	100	2.1	1.7	2.5
			PI(M1)	143	143	100	97.5	100	12.2	10.7	13.9
			PI(Y1)	112	112	100	96.8	100	4.7	4.0	5.4
			PI(Y3)	146	146	100	97.5	100	3.1	2.8	3.6
	Female	Boostrix	PRE	613	583	95.1	93.1	96.7	1.4	1.2	1.5
			PI(M1)	610	604	99.0	97.9	99.6	8.6	8.0	9.3
			PI(Y1)	534	525	98.3	96.8	99.2	3.3	3.1	3.6
			PI(Y3)	614	600	97.7	96.2	98.7	2.1	2.0	2.3
		Adacel	PRE	302	290	96.0	93.2	97.9	1.6	1.4	1.8
			PI(M1)	302	302	100	98.8	100	13.1	11.9	14.4
			PI(Y1)	265	264	99.6	97.9	100	4.2	3.8	4.6
			PI(Y3)	303	301	99.3	97.6	99.9	2.7	2.5	3.0

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE- blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 7 Overall seroprotection status for anti-D antibody concentration by ELISA and Vero at Year 3, by group stratified by age (ATP Year 3 cohort for immunogenicity)

				Seronegativity assessed by ELISA		Seronegativity assessed by the Vero test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated percentage of subjects seroprotected (SP) and its 95% CI		
Sub-group	Group	Timing	N	n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
19-29 years	Boostrix	PRE	261	20/261	7.7	8/20	40.0	20/261 x 8/20	3.1	96.9	94.1	98.7
		PI(M1)	255	2/255	0.8	2/2	100	2/255 x 2/2	0.8	99.2	97.2	99.9
		PI(Y1)	225	0/225	0.0	0/0	.	-	.	.	.	.
		PI(Y3)	261	3/261	1.1	2/3	66.7	3/261 x 2/3	0.8	99.2	97.3	99.9
	Adacel	PRE	113	10/113	8.8	3/10	30.0	10/113 x 3/10	2.7	97.3	92.4	99.4
		PI(M1)	111	0/111	0.0	0/0	.	-	.	.	.	.
		PI(Y1)	89	1/89	1.1	1/1	100	1/89 x 1/1	1.1	98.9	93.9	100
		PI(Y3)	113	4/113	3.5	1/4	25.0	4/113 x 1/4	0.9	99.1	95.2	100
30-49 years	Boostrix	PRE	310	33/310	10.6	13/33	39.4	33/310 x 13/33	4.2	95.8	92.9	97.7
		PI(M1)	311	4/311	1.3	0/4	0.0	4/311 x 0/4	0.0	100	98.8	100
		PI(Y1)	269	7/269	2.6	5/7	71.4	7/269 x 5/7	1.9	98.1	95.7	99.4
		PI(Y3)	313	8/313	2.6	3/8	37.5	8/313 x 3/8	1.0	99.0	97.2	99.8
	Adacel	PRE	158	14/158	8.9	4/13	30.8	14/158 x 4/13	2.7	97.3	93.7	99.1
		PI(M1)	160	3/160	1.9	2/3	66.7	3/160 x 2/3	1.3	98.7	95.6	99.8
		PI(Y1)	138	3/138	2.2	2/3	66.7	3/138 x 2/3	1.4	98.6	94.9	99.8
		PI(Y3)	162	3/162	1.9	3/3	100	3/162 x 3/3	1.9	98.1	94.7	99.6
50-64 years	Boostrix	PRE	359	88/359	24.5	46/88	52.3	88/359 x 46/88	12.8	87.2	83.3	90.5
		PI(M1)	360	14/360	3.9	6/14	42.9	14/360 x 6/14	1.7	98.3	96.4	99.4
		PI(Y1)	310	29/310	9.4	7/29	24.1	29/310 x 7/29	2.3	97.7	95.4	99.1
		PI(Y3)	360	47/360	13.1	24/47	51.1	47/360 x 24/47	6.7	93.3	90.2	95.7
	Adacel	PRE	172	22/172	12.8	9/22	40.9	22/172 x 9/22	5.2	94.8	90.3	97.6
		PI(M1)	173	3/173	1.7	2/3	66.7	3/173 x 2/3	1.2	98.8	95.9	99.9
		PI(Y1)	149	8/149	5.4	5/8	62.5	8/149 x 5/8	3.4	96.6	92.3	98.9
		PI(Y3)	174	10/174	5.7	6/10	60.0	10/174 x 6/10	3.4	96.6	92.6	98.7

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below 0.1 IU/mL/number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below 0.016 IU/mL/number of subjects tested by Vero neutralization test
% = percentage of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for Vero)
n/N x n'/N' = the multiplication of the 2 percentages = overall seronegativity for Anti-D
Overall = based on both the ELISA and the Vero testing

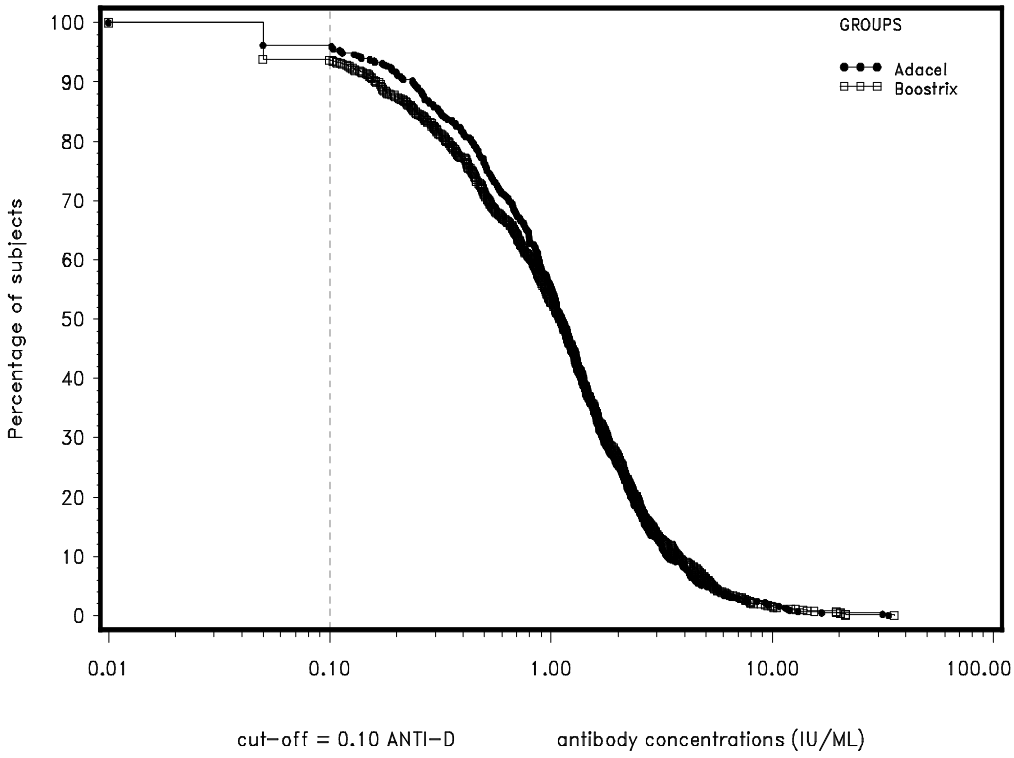
95% CI = exact 95% confidence interval for group(s) 19-29/Boostrix 19-29/Adacel 30-49/Boostrix 50-64/Boostrix 50-64/Adacel 95% confidence interval (normal approximation) for group(s) 30-49/Adacel
SP= seroprotected, LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 8 Overall seroprotection status for anti-D antibody concentration by ELISA and Vero at Year 3 by group stratified by gender (ATP Year 3 cohort for immunogenicity)

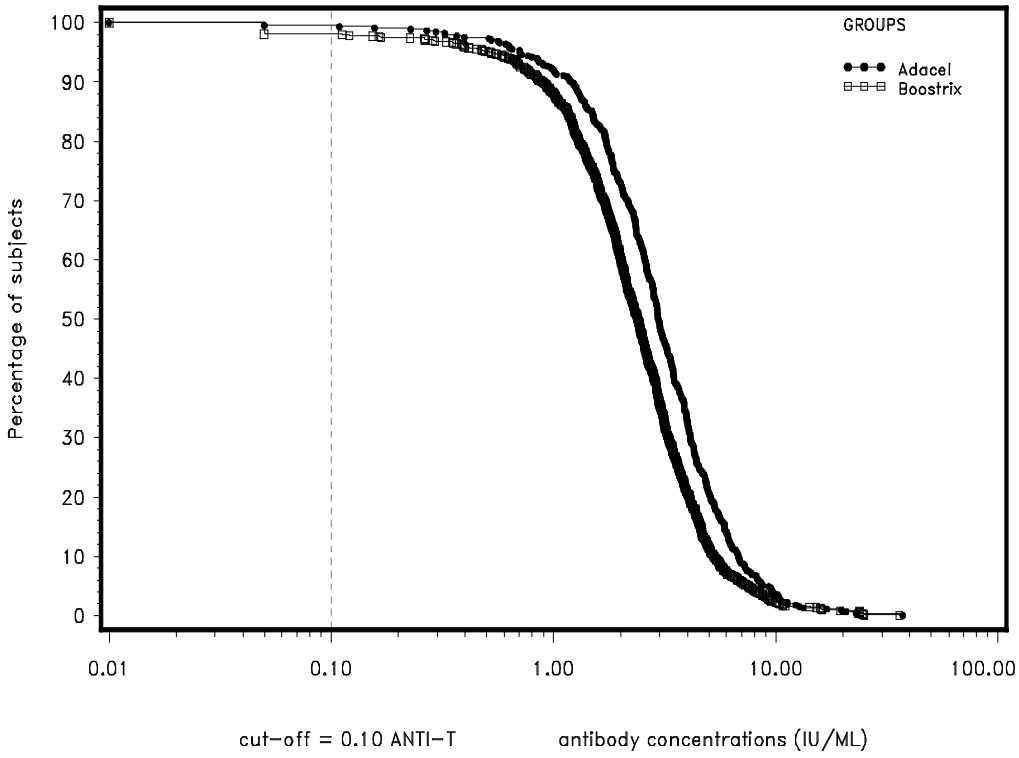
				Seronegativity assessed by ELISA		Seronegativity assessed by the Vero test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated percentage of subjects seroprotected (SP) and its 95% CI		
Sub-group	**Group**	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Male	Boostrix	PRE	321	34/321	10.6	14/34	41.2	34/321 x 14/34	4.4	95.6	92.8	97.6
		PI(M1)	317	5/317	1.6	2/5	40.0	5/317 x 2/5	0.6	99.4	97.7	99.9
		PI(Y1)	271	10/271	3.7	1/10	10.0	10/271 x 1/10	0.4	99.6	98.0	100
		PI(Y3)	322	14/322	4.3	6/14	42.9	14/322 x 6/14	1.9	98.1	96.0	99.3
	Adacel	PRE	145	7/145	4.8	1/7	14.3	7/145 x 1/7	0.7	99.3	96.2	100
		PI(M1)	142	0/142	0.0	0/0	.	-	.	.	.	.
		PI(Y1)	112	3/112	2.7	3/3	100	3/112 x 3/3	2.7	97.3	92.4	99.4
		PI(Y3)	146	6/146	4.1	2/6	33.3	6/146 x 2/6	1.4	98.6	95.1	99.8
Female	Boostrix	PRE	609	107/609	17.6	53/107	49.5	107/609 x 53/107	8.7	91.3	88.8	93.4
		PI(M1)	609	15/609	2.5	6/15	40.0	15/609 x 6/15	1.0	99.0	97.9	99.6
		PI(Y1)	533	26/533	4.9	11/26	42.3	26/533 x 11/26	2.1	97.9	96.3	99.0
		PI(Y3)	612	44/612	7.2	23/44	52.3	44/612 x 23/44	3.8	96.2	94.4	97.6
	Adacel	PRE	298	39/298	13.1	15/38	39.5	39/298 x 15/38	5.2	94.8	91.9	97.0
		PI(M1)	302	6/302	2.0	4/6	66.7	6/302 x 4/6	1.3	98.7	96.6	99.6
		PI(Y1)	264	9/264	3.4	5/9	55.6	9/264 x 5/9	1.9	98.1	95.6	99.4
		PI(Y3)	303	11/303	3.6	8/11	72.7	11/303 x 8/11	2.6	97.4	94.9	98.9

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below 0.1 IU/mL/number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below 0.016 IU/mL/number of subjects tested by Vero neutralization test
% = percentage of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for Vero)
n/N x n'/N' = the multiplication of the 2 percentages = overall seronegativity for anti-D
Overall = based on both the ELISA and the Vero testing
95% CI = exact 95% confidence interval for group(s)
SP= seroprotected, LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 9 Reverse cumulative curves for anti-D concentration at Year 3 (ATP Year 3 cohort for immunogenicity)



Supplement 10 Reverse cumulative curves for anti-T concentration at Year 3 (ATP Year 3 cohort for immunogenicity)



Supplement 11 Distribution of anti-PT, anti-FHA and anti-PRN antibody concentration (ATP Year 3 cohort for immunogenicity)

				< 5 EL.U/mL				≥ 5 EL.U/mL			
						95% CI				95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Anti-PT	Boostrix	PRE	927	409	44.1	40.9	47.4	518	55.9	52.6	59.1
		PI(M1)	922	27	2.9	1.9	4.2	895	97.1	95.8	98.1
		PI(Y1)	805	72	8.9	7.1	11.1	733	91.1	88.9	92.9
		PI(Y3)	934	167	17.9	15.5	20.5	767	82.1	79.5	84.5
	Adacel	PRE	445	161	36.2	31.7	40.8	284	63.8	59.2	68.3
		PI(M1)	439	29	6.6	4.5	9.3	410	93.4	90.7	95.5
		PI(Y1)	377	51	13.5	10.2	17.4	326	86.5	82.6	89.8
		PI(Y3)	449	126	28.1	24.0	32.5	323	71.9	67.5	76.0
Anti-FHA	Boostrix	PRE	930	33	3.5	2.5	4.9	897	96.5	95.1	97.5
		PI(M1)	928	0	0.0	0.0	0.4	928	100	99.6	100
		PI(Y1)	806	2	0.2	0.0	0.9	804	99.8	99.1	100
		PI(Y3)	936	3	0.3	0.1	0.9	933	99.7	99.1	99.9
	Adacel	PRE	441	14	3.2	1.7	5.3	427	96.8	94.7	98.3
		PI(M1)	443	0	0.0	0.0	0.8	443	100	99.2	100
		PI(Y1)	375	0	0.0	0.0	1.0	375	100	99.0	100
		PI(Y3)	446	2	0.4	0.1	1.6	444	99.6	98.4	99.9
Anti -PRN	Boostrix	PRE	934	222	23.8	21.1	26.6	712	76.2	73.4	78.9
		PI(M1)	926	11	1.2	0.6	2.1	915	98.8	97.9	99.4
		PI(Y1)	803	32	4.0	2.7	5.6	771	96.0	94.4	97.3
		PI(Y3)	935	53	5.7	4.3	7.3	882	94.3	92.7	95.7
	Adacel	PRE	448	111	24.8	20.8	29.0	337	75.2	71.0	79.2
		PI(M1)	445	3	0.7	0.1	2.0	442	99.3	98.0	99.9
		PI(Y1)	374	6	1.6	0.6	3.5	368	98.4	96.5	99.4
		PI(Y3)	449	16	3.6	2.1	5.7	433	96.4	94.3	97.9

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group = Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE- blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 12 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies stratified by age (ATP Year 3 cohort for immunogenicity)

					≥ 5 EL.U/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	19-29 years	Boostrix	PRE	258	159	61.6	55.4	67.6	7.8	6.8	8.8
			PI(M1)	254	247	97.2	94.4	98.9	75.4	66.1	86.0
			PI(Y1)	224	210	93.8	89.7	96.5	25.9	22.5	29.8
			PI(Y3)	260	218	83.8	78.8	88.1	15.7	13.6	18.0
		Adacel	PRE	112	78	69.6	60.2	78.0	9.5	7.7	11.7
			PI(M1)	109	104	95.4	89.6	98.5	39.4	32.0	48.5
			PI(Y1)	89	76	85.4	76.3	92.0	16.1	12.8	20.4
			PI(Y3)	113	80	70.8	61.5	79.0	10.6	8.6	13.0
	30-49 years	Boostrix	PRE	310	169	54.5	48.8	60.2	7.2	6.3	8.2
			PI(M1)	310	306	98.7	96.7	99.6	69.1	62.0	77.2
			PI(Y1)	268	251	93.7	90.0	96.3	25.7	22.7	29.1
			PI(Y3)	312	271	86.9	82.6	90.4	16.1	14.3	18.1
		Adacel	PRE	160	102	63.8	55.8	71.2	8.7	7.3	10.4
			PI(M1)	158	151	95.6	91.1	98.2	34.0	28.5	40.6
			PI(Y1)	139	122	87.8	81.1	92.7	16.1	13.5	19.2
			PI(Y3)	162	122	75.3	67.9	81.7	10.3	8.7	12.2
	50-64 years	Boostrix	PRE	359	190	52.9	47.6	58.2	6.7	5.9	7.4
			PI(M1)	358	342	95.5	92.8	97.4	50.6	44.9	56.9
			PI(Y1)	313	272	86.9	82.7	90.4	18.6	16.4	21.1
			PI(Y3)	362	278	76.8	72.1	81.0	11.6	10.4	13.0
		Adacel	PRE	173	104	60.1	52.4	67.5	7.8	6.6	9.2
			PI(M1)	172	155	90.1	84.6	94.1	28.1	23.3	33.9
			PI(Y1)	149	128	85.9	79.3	91.1	15.4	12.9	18.4
			PI(Y3)	174	121	69.5	62.1	76.3	9.5	8.0	11.3
Anti-FHA	19-29 years	Boostrix	PRE	258	249	96.5	93.5	98.4	29.0	25.3	33.2
			PI(M1)	256	256	100	98.6	100	669.6	599.9	747.4
			PI(Y1)	225	224	99.6	97.5	100	202.8	179.1	229.6
			PI(Y3)	261	260	99.6	97.9	100	123.2	110.1	137.9
		Adacel	PRE	112	109	97.3	92.4	99.4	33.7	27.1	41.7
			PI(M1)	111	111	100	96.7	100	400.6	338.1	474.7
			PI(Y1)	88	88	100	95.9	100	136.4	110.0	169.0
			PI(Y3)	113	113	100	96.8	100	83.2	69.5	99.6
	30-49 years	Boostrix	PRE	311	305	98.1	95.8	99.3	32.0	28.6	35.9
			PI(M1)	312	312	100	98.8	100	652.5	588.4	723.7
			PI(Y1)	269	268	99.6	97.9	100	198.4	175.6	224.2
			PI(Y3)	314	313	99.7	98.2	100	127.9	115.4	141.7
		Adacel	PRE	158	152	96.2	91.9	98.6	38.9	32.1	47.2
			PI(M1)	160	160	100	97.7	100	387.4	333.5	450.1
			PI(Y1)	138	138	100	97.4	100	124.4	104.2	148.5
			PI(Y3)	161	160	99.4	96.6	100	88.2	75.4	103.1
	50-64 years	Boostrix	PRE	361	343	95.0	92.2	97.0	31.6	27.9	35.7
			PI(M1)	360	360	100	99.0	100	510.8	457.3	570.5
			PI(Y1)	312	312	100	98.8	100	160.1	141.6	181.0
			PI(Y3)	361	360	99.7	98.5	100	99.7	89.6	111.0
		Adacel	PRE	171	166	97.1	93.3	99.0	32.9	28.1	38.6
			PI(M1)	172	172	100	97.9	100	327.0	286.6	373.1
			PI(Y1)	149	149	100	97.6	100	106.2	91.2	123.6
			PI(Y3)	172	171	99.4	96.8	100	74.7	65.2	85.6

					≥ 5 EL.U/mL				GMC		
							95% CI			95% CI	
Antibody	**Sub-group**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PRN	19-29 years	Boostrix	PRE	261	204	78.2	72.7	83.0	13.2	11.2	15.4
			PI(M1)	256	254	99.2	97.2	99.9	511.5	427.2	612.5
			PI(Y1)	225	221	98.2	95.5	99.5	185.4	152.7	225.1
			PI(Y3)	261	251	96.2	93.1	98.1	100.6	83.6	121.1
		Adacel	PRE	113	92	81.4	73.0	88.1	16.4	12.7	21.2
			PI(M1)	111	110	99.1	95.1	100	402.0	308.8	523.2
			PI(Y1)	88	86	97.7	92.0	99.7	167.2	121.8	229.5
			PI(Y3)	113	109	96.5	91.2	99.0	78.6	60.8	101.7
	30-49 years	Boostrix	PRE	311	247	79.4	74.5	83.8	15.9	13.7	18.4
			PI(M1)	310	306	98.7	96.7	99.6	489.4	408.4	586.3
			PI(Y1)	269	262	97.4	94.7	98.9	206.5	170.4	250.3
			PI(Y3)	314	303	96.5	93.8	98.2	109.3	92.4	129.3
		Adacel	PRE	161	122	75.8	68.4	82.2	16.3	12.9	20.5
			PI(M1)	160	159	99.4	96.6	100	388.1	310.8	484.7
			PI(Y1)	138	137	99.3	96.0	100	154.8	121.2	197.6
			PI(Y3)	162	156	96.3	92.1	98.6	85.0	68.0	106.2
	50-64 years	Boostrix	PRE	362	261	72.1	67.2	76.7	12.1	10.6	13.9
			PI(M1)	360	355	98.6	96.8	99.5	271.0	227.3	323.1
			PI(Y1)	309	288	93.2	89.8	95.7	100.2	82.3	122.1
			PI(Y3)	360	328	91.1	87.7	93.8	57.0	48.1	67.6
		Adacel	PRE	174	123	70.7	63.3	77.3	12.7	10.3	15.6
			PI(M1)	174	173	99.4	96.8	100	248.8	194.1	318.9
			PI(Y1)	148	145	98.0	94.2	99.6	96.2	73.6	125.6
			PI(Y3)	174	168	96.6	92.6	98.7	54.5	43.4	68.4

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

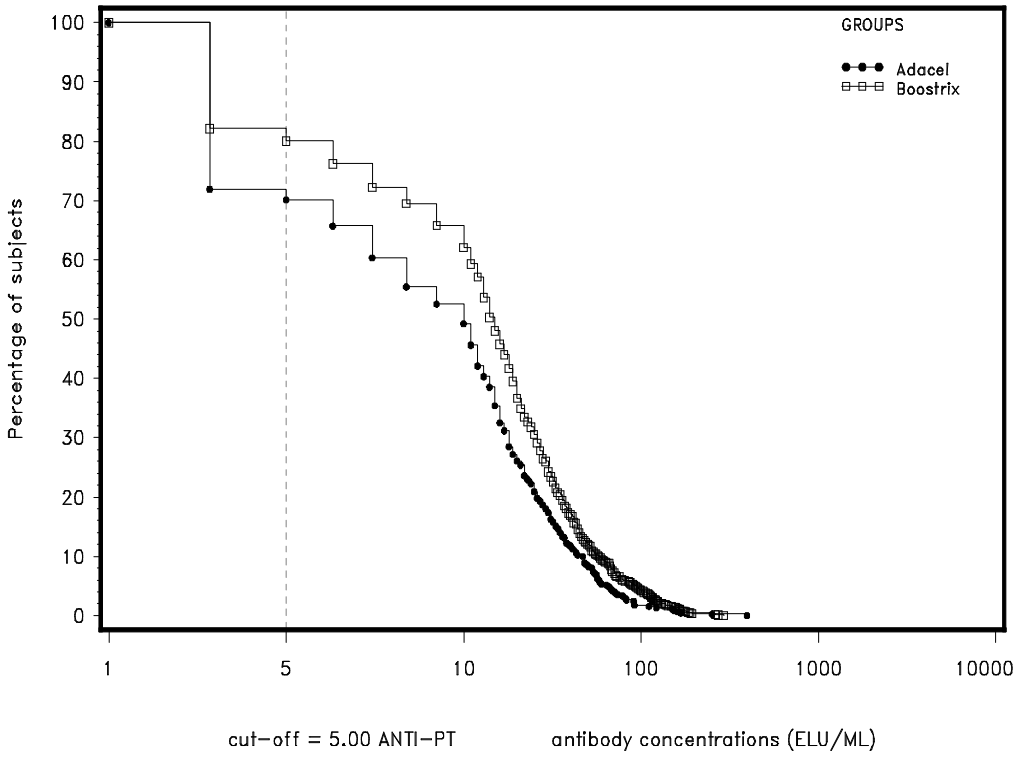
Supplement 13 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies stratified by gender (ATP Year 3 cohort for immunogenicity)

					≥ 5 EL.U/mL				GMC		
							95% CI			95% CI	
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Male	Boostrix	PRE	320	194	60.6	55.0	66.0	7.9	7.0	8.9
			PI(M1)	315	308	97.8	95.5	99.1	70.3	62.2	79.5
			PI(Y1)	272	254	93.4	89.7	96.0	26.8	23.5	30.6
			PI(Y3)	323	278	86.1	81.8	89.7	16.6	14.6	18.7
		Adacel	PRE	144	97	67.4	59.1	74.9	9.2	7.6	11.1
			PI(M1)	140	132	94.3	89.1	97.5	36.6	30.2	44.5
			PI(Y1)	112	96	85.7	77.8	91.6	17.0	13.7	21.1
			PI(Y3)	146	114	78.1	70.5	84.5	11.6	9.6	13.9
	Female	Boostrix	PRE	607	324	53.4	49.3	57.4	6.8	6.2	7.4
			PI(M1)	607	587	96.7	95.0	98.0	59.1	54.3	64.3
			PI(Y1)	533	479	89.9	87.0	92.3	20.9	19.1	22.9
			PI(Y3)	611	489	80.0	76.6	83.1	12.9	11.8	14.1
		Adacel	PRE	301	187	62.1	56.4	67.6	8.2	7.2	9.3
			PI(M1)	299	278	93.0	89.5	95.6	31.1	27.2	35.5
			PI(Y1)	265	230	86.8	82.1	90.6	15.4	13.5	17.5
			PI(Y3)	303	209	69.0	63.4	74.1	9.4	8.3	10.6
Anti-FHA	Male	Boostrix	PRE	320	316	98.8	96.8	99.7	39.5	35.0	44.5
			PI(M1)	318	318	100	98.8	100	648.1	586.5	716.2
			PI(Y1)	272	272	100	98.7	100	211.9	189.4	237.2
			PI(Y3)	323	323	100	98.9	100	136.7	124.1	150.7
		Adacel	PRE	145	143	98.6	95.1	99.8	42.6	35.8	50.7
			PI(M1)	143	143	100	97.5	100	427.2	369.0	494.7
			PI(Y1)	112	112	100	96.8	100	140.4	117.4	167.7
			PI(Y3)	146	146	100	97.5	100	100.5	87.0	116.2
	Female	Boostrix	PRE	610	581	95.2	93.2	96.8	27.3	25.0	29.8
			PI(M1)	610	610	100	99.4	100	572.9	528.3	621.2
			PI(Y1)	534	532	99.6	98.7	100	170.8	155.9	187.2
			PI(Y3)	613	610	99.5	98.6	99.9	105.0	96.9	113.7
		Adacel	PRE	296	284	95.9	93.0	97.9	32.0	28.0	36.6
			PI(M1)	300	300	100	98.8	100	339.7	305.9	377.2
			PI(Y1)	263	263	100	98.6	100	111.4	98.5	126.0
			PI(Y3)	300	298	99.3	97.6	99.9	73.6	65.9	82.3
Anti-PRN	Male	Boostrix	PRE	322	265	82.3	77.7	86.3	16.9	14.6	19.6
			PI(M1)	316	313	99.1	97.3	99.8	502.4	422.3	597.6
			PI(Y1)	272	265	97.4	94.8	99.0	196.4	162.5	237.4
			PI(Y3)	322	311	96.6	94.0	98.3	113.9	96.3	134.8
		Adacel	PRE	146	118	80.8	73.5	86.9	18.0	14.2	22.8
			PI(M1)	143	143	100	97.5	100	396.2	315.3	497.9
			PI(Y1)	110	110	100	96.7	100	156.6	117.1	209.6
			PI(Y3)	146	144	98.6	95.1	99.8	93.6	74.4	117.7
	Female	Boostrix	PRE	612	447	73.0	69.3	76.5	12.1	10.9	13.4
			PI(M1)	610	602	98.7	97.4	99.4	347.0	304.2	395.8
			PI(Y1)	531	506	95.3	93.1	96.9	132.9	115.1	153.5
			PI(Y3)	613	571	93.1	90.9	95.0	70.5	62.1	80.0
		Adacel	PRE	302	219	72.5	67.1	77.5	13.4	11.5	15.8
			PI(M1)	302	299	99.0	97.1	99.8	301.3	251.8	360.7
			PI(Y1)	264	258	97.7	95.1	99.2	121.0	100.2	146.2
			PI(Y3)	303	289	95.4	92.4	97.5	61.1	51.7	72.1

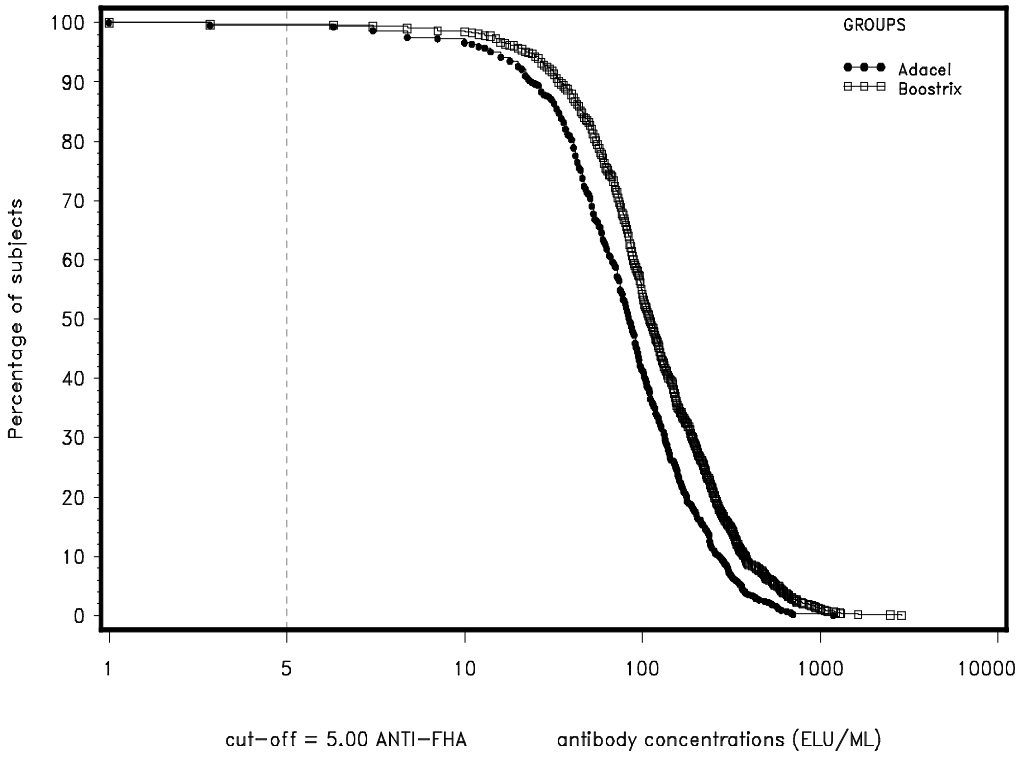
Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.

Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

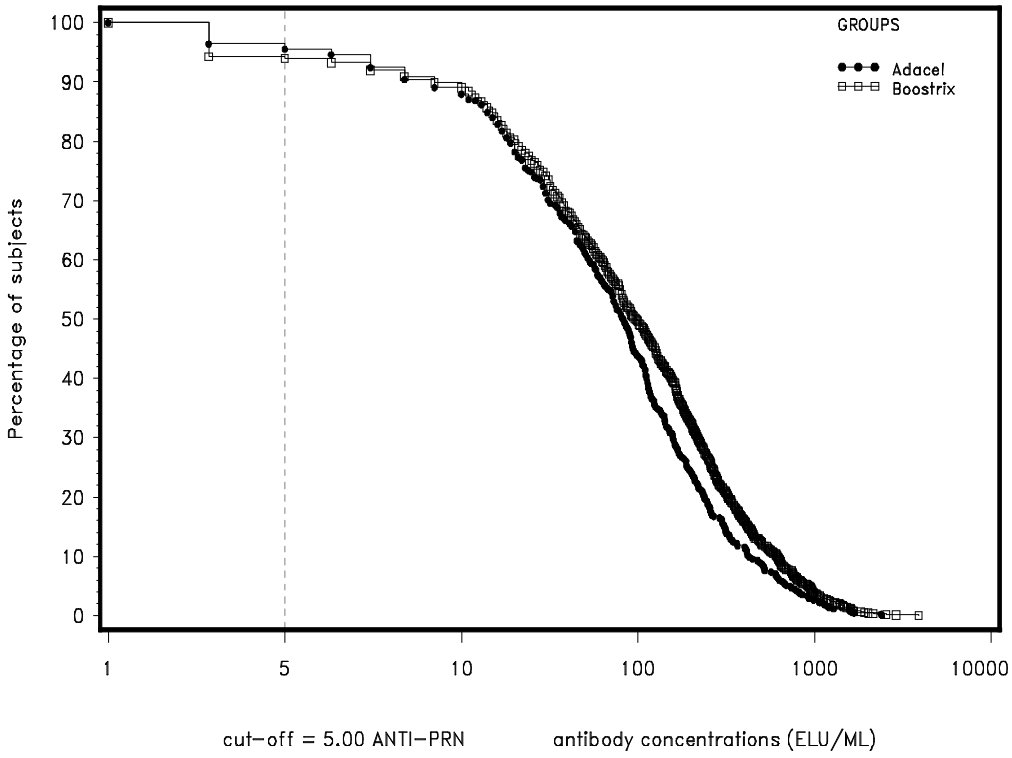
Supplement 14 Reverse cumulative curves for anti-PT concentration at Year 3 (ATP Year 3 cohort for immunogenicity)



Supplement 15 Reverse cumulative curves for anti-FHA concentration at Year 3 (ATP Year 3 cohort for immunogenicity)



Supplement 16 Reverse cumulative curves for anti-PRN concentration at Year 3 (ATP Year 3 cohort for immunogenicity)



Supplement 17 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU per mL (by ELISA) and GMCs by group (Year 3 cohort)

				≥ 0.1 IU/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	PRE	969	824	85.0	82.6	87.2	0.4	0.4	0.4
		PI(M1)	965	944	97.8	96.7	98.6	4.6	4.2	5.0
		PI(Y1)	834	799	95.8	94.2	97.1	1.4	1.3	1.6
		PI(Y3)	973	914	93.9	92.2	95.4	0.9	0.9	1.0
	Adacel	PRE	458	410	89.5	86.3	92.2	0.5	0.4	0.5
		PI(M1)	460	454	98.7	97.2	99.5	4.9	4.4	5.4
		PI(Y1)	390	379	97.2	95.0	98.6	1.4	1.3	1.6
		PI(Y3)	465	448	96.3	94.2	97.9	1.0	0.9	1.1
Anti-T	Boostrix	PRE	975	936	96.0	94.6	97.1	1.5	1.4	1.7
		PI(M1)	966	960	99.4	98.7	99.8	8.4	7.9	8.9
		PI(Y1)	838	826	98.6	97.5	99.3	3.3	3.1	3.5
		PI(Y3)	976	958	98.2	97.1	98.9	2.2	2.1	2.4
	Adacel	PRE	464	451	97.2	95.3	98.5	1.7	1.6	1.9
		PI(M1)	461	461	100	99.2	100	13.0	12.1	14.1
		PI(Y1)	392	391	99.7	98.6	100	4.4	4.1	4.8
		PI(Y3)	465	463	99.6	98.5	99.9	2.9	2.7	3.1

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 18 Overall seroprotection status for anti-D antibody concentration by ELISA and Vero at Year 3 by group (Year 3 cohort)

			Seronegativity assessed by ELISA		Seronegativity assessed by the Vero test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated percentage of subjects seroprotected (SP) and its 95% CI		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Boostrix	PRE	969	145/969	15.0	68/145	46.9	145/969 x 68/145	7.0	93.0	91.2	94.5
	PI(M1)	965	21/965	2.2	8/21	38.1	21/965 x 8/21	0.8	99.2	98.4	99.6
	PI(Y1)	836	37/836	4.4	13/37	35.1	37/836 x 13/37	1.6	98.4	97.4	99.2
	PI(Y3)	973	59/973	6.1	30/59	50.8	59/973 x 30/59	3.1	96.9	95.6	97.9
Adacel	PRE	458	48/458	10.5	16/47	34.0	48/458 x 16/47	3.6	96.4	94.4	97.9
	PI(M1)	460	6/460	1.3	4/6	66.7	6/460 x 4/6	0.9	99.1	97.8	99.8
	PI(Y1)	391	12/391	3.1	8/12	66.7	12/391 x 8/12	2.0	98.0	96.0	99.1
	PI(Y3)	465	17/465	3.7	10/17	58.8	17/465 x 10/17	2.2	97.8	96.1	99.0

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below 0.1 IU/mL/number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below 0.016 IU/mL/number of subjects tested by Vero neutralization test
% = percentage of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for Vero)
n/N x n'/N' = the multiplication of the 2 percentages = overall seronegativity for anti-D
Overall = based on both the ELISA and the Vero testing
95% CI = exact 95% confidence interval for group(s)
SP= seroprotected, LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 19 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (Year 3 cohort)

				≥ 5 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	PRE	966	544	56.3	53.1	59.5	7.2	6.7	7.7
		PI(M1)	959	931	97.1	95.8	98.1	62.9	58.8	67.4
		PI(Y1)	837	764	91.3	89.2	93.1	22.9	21.3	24.7
		PI(Y3)	973	803	82.5	80.0	84.9	14.3	13.3	15.3
	Adacel	PRE	460	290	63.0	58.5	67.5	8.5	7.6	9.4
		PI(M1)	455	424	93.2	90.5	95.3	32.7	29.3	36.5
		PI(Y1)	392	337	86.0	82.1	89.3	15.9	14.2	17.7
		PI(Y3)	465	335	72.0	67.7	76.1	10.2	9.2	11.3
Anti-FHA	Boostrix	PRE	969	936	96.6	95.3	97.6	31.4	29.2	33.6
		PI(M1)	967	967	100	99.6	100	601.4	565.4	639.6
		PI(Y1)	838	836	99.8	99.1	100	185.7	173.1	199.2
		PI(Y3)	974	971	99.7	99.1	99.9	116.3	109.4	123.6
	Adacel	PRE	457	441	96.5	94.4	98.0	34.7	31.2	38.6
		PI(M1)	459	459	100	99.2	100	361.3	331.9	393.3
		PI(Y1)	390	390	100	99.1	100	118.4	107.2	130.8
		PI(Y3)	462	460	99.6	98.4	99.9	81.4	74.6	88.8
Anti-PRN	Boostrix	PRE	973	748	76.9	74.1	79.5	13.7	12.7	14.9
		PI(M1)	965	954	98.9	98.0	99.4	397.4	358.9	440.1
		PI(Y1)	835	803	96.2	94.6	97.4	154.6	138.2	173.0
		PI(Y3)	974	921	94.6	92.9	95.9	84.9	76.9	93.8
	Adacel	PRE	464	350	75.4	71.3	79.3	14.6	12.8	16.6
		PI(M1)	460	457	99.3	98.1	99.9	327.1	284.8	375.8
		PI(Y1)	389	383	98.5	96.7	99.4	132.2	113.3	154.2
		PI(Y3)	465	449	96.6	94.5	98.0	70.8	62.1	80.9

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = blood sample taken before vaccination
PI (M1) = blood sample taken 1 month after vaccination
PI (Y1) = blood sample taken 1 year after vaccination
PI (Y3) = blood sample taken 3 years after vaccination

Supplement 20 Difference between groups in anti-D and anti-T seroprotection rates at Year 3 stratified by age (ATP Year 3 cohort for immunogenicity)

								Difference in seroprotection rate (Boostrix group minus Adacel group)			
										95% CI	
Antibody	Sub-group	Group	N	%	Group	N	%	Difference	%	LL	UL
Anti-D	19-29 years	19-29/Adacel	113	96.5	19-29/Boostrix	261	98.9	19-29/Boostrix - 19-29/Adacel	2.39	-0.58	7.69
	30-49 years	30-49/Adacel	162	98.1	30-49/Boostrix	313	97.4	30-49/Boostrix - 30-49/Adacel	-0.70	-3.46	2.95
	50-64 years	50-64/Adacel	174	94.3	50-64/Boostrix	360	86.9	50-64/Boostrix - 50-64/Adacel	-7.31	-12.09	-1.93
Anti-T	19-29 years	19-29/Adacel	113	100	19-29/Boostrix	261	99.6	19-29/Boostrix - 19-29/Adacel	-0.38	-2.14	2.92
	30-49 years	30-49/Adacel	162	99.4	30-49/Boostrix	314	100	30-49/Boostrix - 30-49/Adacel	0.62	-0.60	3.42
	50-64 years	50-64/Adacel	174	99.4	50-64/Boostrix	362	95.3	50-64/Boostrix - 50-64/Adacel	-4.12	-6.92	-1.22

Boostrix group = Subjects who received a single dose of GSK Biologicals' Boostrix vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's Adacel vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D or anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 21 Difference between groups in anti-D and anti-T seroprotection rates at Year 3 stratified by gender (ATP Year 3 cohort for immunogenicity)

							Difference in seroprotection rate (Boostrix group minus Adacel group)			
									95% CI	
Antibody	Group	N	%	Group	N	%	Difference	%	LL	UL
Anti-D	Male/Adacel	146	95.9	Male/Boostrix	322	95.7	Male/Boostrix - Male/Adacel	-0.24	-3.88	4.64
	Female/Adacel	303	96.4	Female/Boostrix	612	92.8	Female/Boostrix - Female/Adacel	-3.56	-6.44	-0.32
Anti-T	Male/Adacel	146	100	Male/Boostrix	323	98.8	Male/Boostrix - Male/Adacel	-1.24	-3.14	1.34
	Female/Adacel	303	99.3	Female/Boostrix	614	97.7	Female/Boostrix - Female/Adacel	-1.62	-3.25	0.25

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D or anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 22 Difference between groups in the percentage of subjects with anti-D antibody concentration greater than or equal to 0.1 IU per mL by ELISA or at least 0.016 IU per mL by Vero cell assay (when anti-D concentrations less than 0.1 IU per mL by ELISA), at Year 3 after vaccination stratified by age (ATP Year 3 cohort for immunogenicity)

						Difference in seroprotection rate (Boostrix group minus Adacel group)			
								95% CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
19-29/Adacel	113	99.1	19-29 years/Boostrix	261	99.2	19-29/Boostrix - 19-29/Adacel	0.12	-2.02	4.12
30-49/Adacel	162	98.1	30-49 years/Boostrix	313	99.0	30-49/Boostrix - 30-49/Adacel	0.89	-1.27	4.42
50-64/Adacel	174	96.6	50-64 years/Boostrix	360	93.3	50-64/Boostrix - 50-64/Adacel	-3.22	-6.89	1.14

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or ≥ 0.016 IU/mL by Vero
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 23 Difference between groups in the percentage of subjects with anti-D antibody concentration greater than or equal to 0.1 IU per mL by ELISA or at least 0.016 IU per mL by Vero cell assay (when anti-D concentrations less than 0.1 IU per mL by ELISA) at Year 3 after vaccination stratified by gender (ATP Year 3 cohort for immunogenicity)

						Difference in seroprotection rate (Boostrix group minus Adacel group)			
								95% CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Male/Adacel	146	98.6	Male/Boostrix	322	98.1	Male/Boostrix - Male/Adacel	-0.49	-2.91	3.12
Female/Adacel	303	97.4	Female/Boostrix	612	96.2	Female/Boostrix - Female/Adacel	-1.12	-3.39	1.63

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or ≥ 0.016 by Vero
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 24 Adjusted ratios of anti-D, anti-T GMCs at Year 3 stratified by age (ATP Year 3 cohort for immunogenicity)

	Boostrix group			Adacel group			Adjusted GMC ratio (Boostrix group/Adacel group)			
									95% CI	
Antibody	Group description	N	Adjusted GMC	Group description	N	Adjusted GMC	Ratio order	Value	LL	UL
Anti-D	19-29 years /Boostrix	261	1.4	19-29/Adacel	113	1.2	19-29/Boostrix /19-29/Adacel	1.17	0.95	1.44
	30-49 years /Boostrix	310	1.1	30-49/Adacel	158	1.2	30-49/Boostrix /30-49/Adacel	0.95	0.82	1.10
	50-64 years /Boostrix	359	0.6	50-64/Adacel	172	0.7	50-64/Boostrix /50-64/Adacel	0.89	0.78	1.01
Anti-T	19-29 years /Boostrix	261	2.5	19-29/Adacel	113	2.9	19-29/Boostrix /19-29/Adacel	0.87	0.75	1.01
	30-49 years /Boostrix	313	2.5	30-49/Adacel	161	3.1	30-49/Boostrix /30-49/Adacel	0.82	0.74	0.91
	50-64 years /Boostrix	362	1.9	50-64/Adacel	174	2.4	50-64/Boostrix /50-64/Adacel	0.80	0.70	0.90

Adjusted GMC = geometric mean concentration adjusted for age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (ANCOVA model: adjustment for age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Supplement 25 Adjusted ratios of anti-D, anti-T GMCs at Year 3 after vaccination stratified by gender (ATP Year 3 cohort for immunogenicity)

							Adjusted GMC ratio (Boostrix group/Adacel group)			
									95% CI	
Antibody	Group description	N	Adjusted GMC	Group description	N	Adjusted GMC	Ratio order	Value	LL	UL
Anti-D	Male /Boostrix	321	1.0	Male/ Adacel	145	1.0	Male/Boostrix /Male/Adacel	1.04	0.88	1.22
	Female /Boostrix	609	0.9	Female/ Adacel	298	0.9	Female/Boostrix /Female/Adacel	0.95	0.84	1.06
Anti-T	Male /Boostrix	323	2.3	Male/ Adacel	146	3.1	Male/Boostrix /Male/Adacel	0.77	0.68	0.86
	Female /Boostrix	613	2.2	Female/ Adacel	302	2.6	Female/Boostrix /Female/Adacel	0.84	0.77	0.93

Adjusted GMC = geometric mean concentration adjusted for age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (ANCOVA model: adjustment for age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Supplement 26 Difference between groups in anti-D and anti-T seroprotection rates at Year 3 (Year 3 cohort)

							Difference in seroprotection rate (Boostrix group minus Adacel group)			
									95% CI	
Antibody	Group	N	%	Group	N	%	Difference	%	LL	UL
Anti-D	Adacel	465	96.3	Boostrix	973	93.9	Boostrix - Adacel	-2.41	-4.60	0.07
Anti-T	Adacel	465	99.6	Boostrix	976	98.2	Boostrix - Adacel	-1.41	-2.54	-0.17

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D or anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 27 Difference between groups in the percentage of subjects with anti-D antibody concentration greater than or equal to 0.1 IU per mL by ELISA or at least 0.016 IU per mL by Vero cell assay (when anti-D concentrations less than 0.1 IU per mL by ELISA), at Year 3 after vaccination (Year 3 cohort)

						Difference in seroprotection rate (Boostrix group minus Adacel group)			
								95% CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Adacel	465	97.8	Boostrix	973	96.9	Boostrix - Adacel	-0.93	-2.57	1.04

Boostrix group = Subjects who received a single dose of GSK Biologicals' *Boostrix* vaccine in the 106316 study.
Adacel group: Subjects who received a single dose of Sanofi Pasteur's *Adacel* vaccine in the 106316 study.
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL or ≥0.016 by Vero
95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 28 Adjusted ratios of anti-D, anti-T GMCs at Year 3 (Year 3 cohort)

Antibody	Boostrix group		Adacel group		Adjusted GMC ratio (Boostrix group/Adacel group)		
						95% CI	
	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D	969	0.9	458	1.0	0.97	0.88	1.06
Anti-T	975	2.3	464	2.8	0.81	0.75	0.87

Adjusted GMC = geometric mean concentration adjusted for age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (ANCOVA model: adjustment for age (Y), baseline concentration - pooled variance); LL = Lower Limit, UL = Upper Limit

Supplement 29 Percentage of subjects with anti-D and anti-T antibody concentrations greater than or equal to 0.1 IU per mL (by ELISA) and GMCs by group (ATP Complete Year 3 cohort for immunogenicity)

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	PRE	780	656	84.1	81.3	86.6	0.4	0.4	0.4
		PI(M1)	781	764	97.8	96.5	98.7	4.6	4.2	5.1
		PI(Y1)	782	749	95.8	94.1	97.1	1.4	1.3	1.6
		PI(Y3)	784	735	93.8	91.8	95.3	0.9	0.8	1.0
	Adacel	PRE	365	323	88.5	84.8	91.6	0.4	0.4	0.5
		PI(M1)	367	362	98.6	96.8	99.6	4.9	4.3	5.5
		PI(Y1)	368	358	97.3	95.1	98.7	1.4	1.3	1.6
		PI(Y3)	370	357	96.5	94.1	98.1	1.0	0.9	1.1
Anti-T	Boostrix	PRE	786	756	96.2	94.6	97.4	1.5	1.4	1.6
		PI(M1)	782	777	99.4	98.5	99.8	8.5	8.0	9.1
		PI(Y1)	786	774	98.5	97.3	99.2	3.3	3.1	3.5
		PI(Y3)	787	774	98.3	97.2	99.1	2.2	2.1	2.4
	Adacel	PRE	369	360	97.6	95.4	98.9	1.8	1.6	2.0
		PI(M1)	368	368	100	99.0	100	13.0	11.9	14.2
		PI(Y1)	370	369	99.7	98.5	100	4.3	4.0	4.7
		PI(Y3)	370	368	99.5	98.1	99.9	2.8	2.6	3.1

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI (M1) = one month post-vaccination
PI (Y1) = one year post-vaccination
PI (Y3) = three years post-vaccination
PRE = pre vaccination

Supplement 30 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP Complete Year 3 cohort for immunogenicity)

				≥ 5 ELU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	PRE	779	431	55.3	51.8	58.9	7.0	6.5	7.6
		PI(M1)	776	752	96.9	95.4	98.0	62.3	57.7	67.3
		PI(Y1)	785	714	91.0	88.7	92.9	22.7	21.1	24.5
		PI(Y3)	784	645	82.3	79.4	84.9	14.0	12.9	15.1
	Adacel	PRE	367	243	66.2	61.1	71.0	8.6	7.7	9.7
		PI(M1)	363	340	93.7	90.6	95.9	32.8	29.1	36.9
		PI(Y1)	370	320	86.5	82.6	89.8	15.9	14.3	17.8
		PI(Y3)	370	272	73.5	68.7	77.9	10.1	9.0	11.3
Anti-FHA	Boostrix	PRE	780	752	96.4	94.9	97.6	30.6	28.3	33.1
		PI(M1)	782	782	100	99.5	100	601.8	562.1	644.4
		PI(Y1)	786	784	99.7	99.1	100	184.0	171.1	197.8
		PI(Y3)	786	783	99.6	98.9	99.9	113.6	106.2	121.7
	Adacel	PRE	363	351	96.7	94.3	98.3	34.7	30.8	39.0
		PI(M1)	366	366	100	99.0	100	364.1	330.6	401.0
		PI(Y1)	368	368	100	99.0	100	119.9	108.1	132.9
		PI(Y3)	367	365	99.5	98.0	99.9	82.2	74.6	90.6
Anti-PRN	Boostrix	PRE	784	596	76.0	72.9	79.0	13.7	12.5	15.1
		PI(M1)	780	770	98.7	97.7	99.4	393.1	350.0	441.6
		PI(Y1)	783	751	95.9	94.3	97.2	151.3	134.6	170.2
		PI(Y3)	785	742	94.5	92.7	96.0	83.7	75.0	93.5
	Adacel	PRE	369	275	74.5	69.8	78.9	14.8	12.8	17.2
		PI(M1)	368	366	99.5	98.1	99.9	328.0	280.2	383.9
		PI(Y1)	367	361	98.4	96.5	99.4	130.4	111.1	153.0
		PI(Y3)	370	357	96.5	94.1	98.1	70.5	60.6	81.9

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI (M1) = one month post-vaccination
PI (Y1) = one year post-vaccination
PI (Y3) = three years post-vaccination
PRE = pre vaccination

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13. STUDY REPORT AUTHORS/CONTRIBUTING AUTHORS

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MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Sponsor information	-
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs (plus name of committee chair if required by regulatory authority)	16.1.3
Representative written information for patient and sample consent forms.	16.1.3
List of investigators and other important participants in the study	16.1.4
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
Randomization list.	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Sponsor Information

Sponsor Information

eTrack study number(s) and abbreviated title(s)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of document	***19 March 2010***
Version if document	***Version 02***
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

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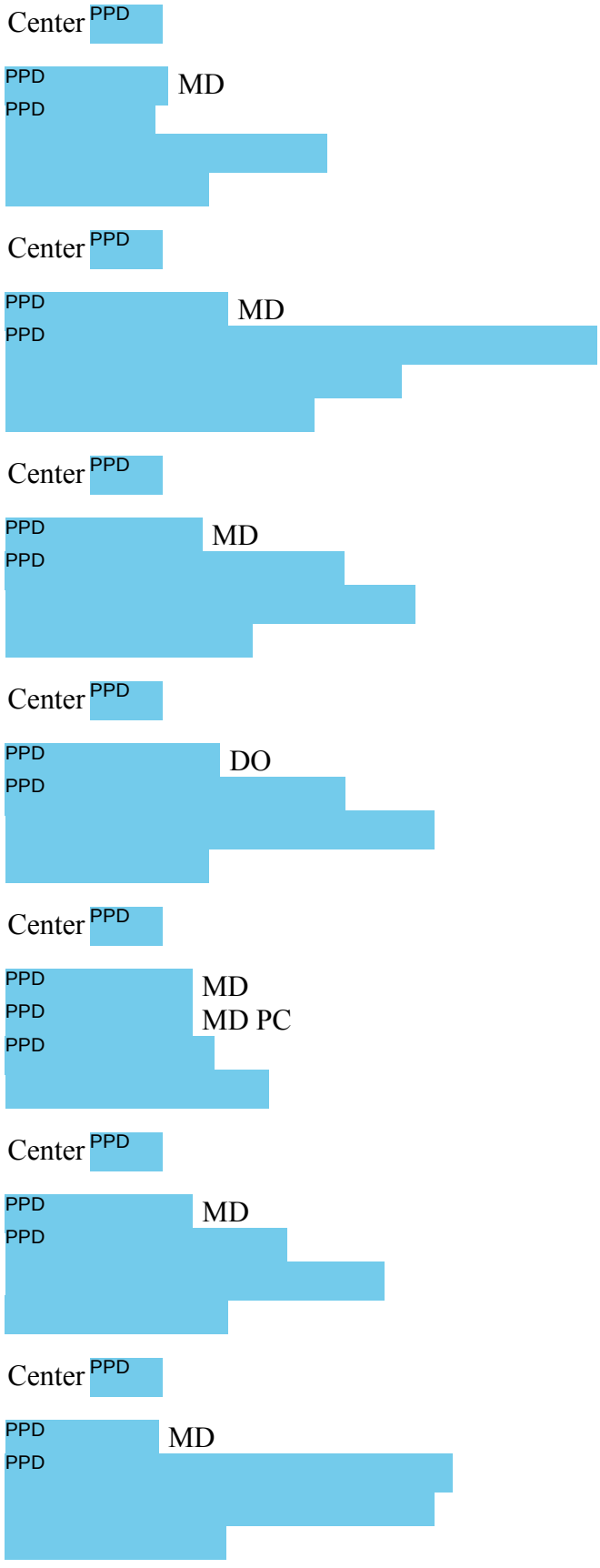
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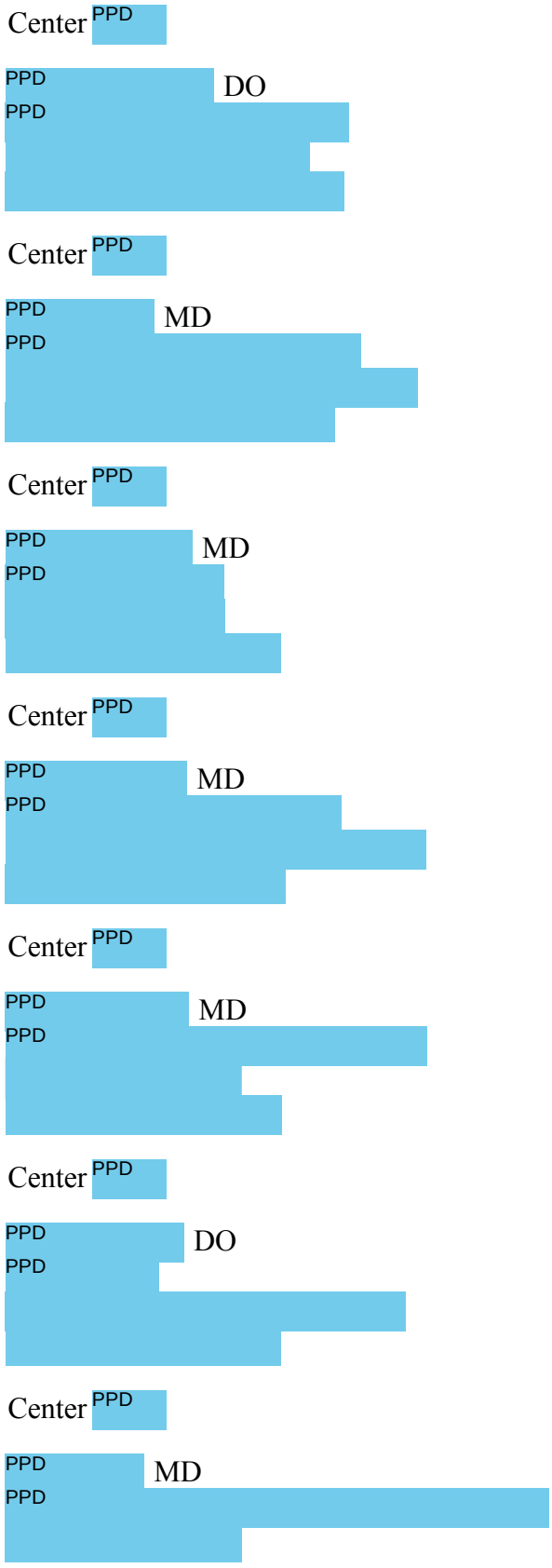
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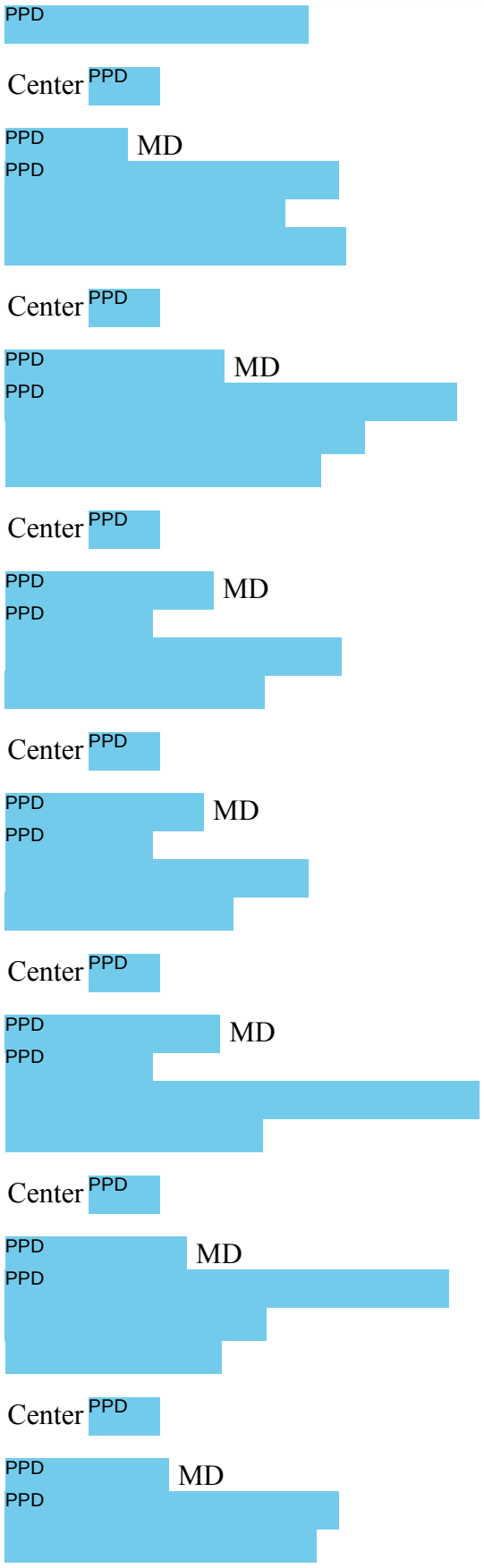
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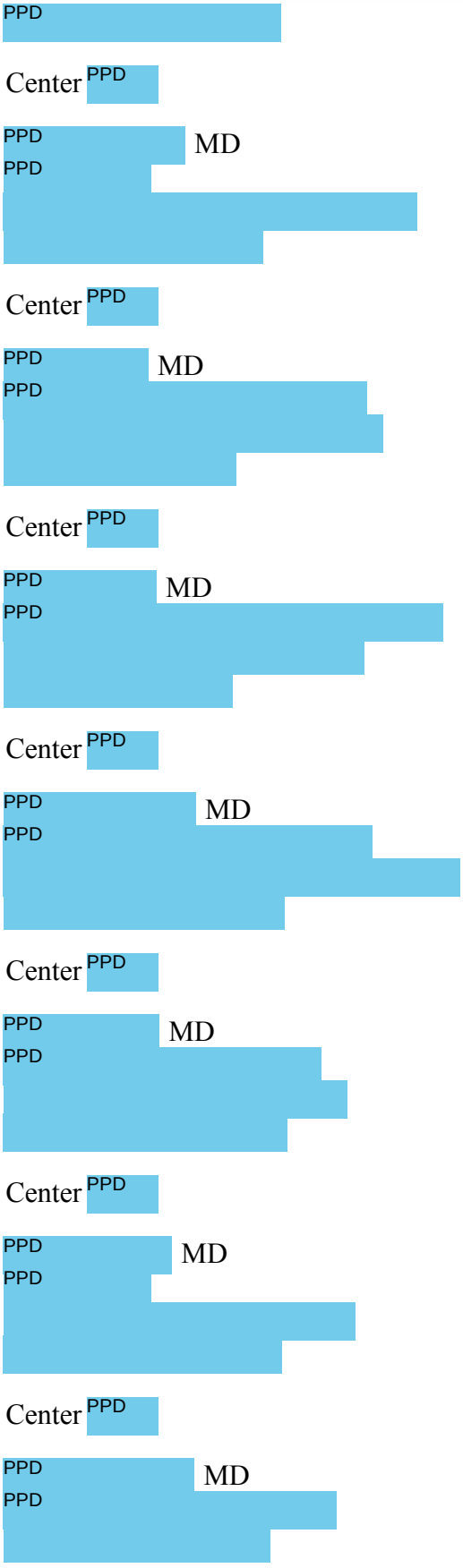
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GSK Biologicals Clinical Safety Physician: PPD MD
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Back-up study contact for reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD ***or*** PPD
24/24 hour and 7/7 day availability

5. Study Contact for Emergency Code Break

Not applicable as there is no vaccine administered in this study.

6. Study Centres

38 Study Centers as listed in item #1

Protocol and Protocol Amendments

CONFIDENTIAL

Tdap-0.3-009 Ext:007
Administrative Change 1

Sponsor
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772

Study vaccine number	776423
Study vaccine	GlaxoSmithKline (GSK) Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, containing 0.3 mg aluminum [776423/Tdap, (Boostrix®)] Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap) vaccine (Adacel™)
eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
Investigational New Drug (IND) number	BB-IND-8461
Date of approval	Final: 17 April 2007 Administrative Change 1: 14 April 2009
Title	Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Co-ordinating author	PPD Scientific writer
Contributing authors	PPD Clinical Development Manager, Vaccine (US) PPD Director, Vaccines (US) PPD Biostatistician (US) PPD Project statistician, Boostrix (US) PPD Study Manager (US) PPD , Director, Clinical R&D, World-Wide Clinical Development, Life-cycle Vaccines PPD Central Study Coordinator

GSK Biologicals' Protocol DS V 12.4

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	Leonard Friedland, MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.

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Tdap-0.3-009 Ext:007
Administrative Change 1

Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: _____

Synopsis

Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Indication/Study population	Healthy adults, 19 years of age and older, who received a single dose study vaccination in study 106316.
Rationale	This study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, up to 10 years following vaccination with GlaxoSmithKline's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).
Objectives	**Primary** To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination. **Secondary** • To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose *of Boostrix*. • To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix.*
Study design	• Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study. • Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be

maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.

- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

Number of subjects

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points. For example, if the subject did not want to participate in the Year 1 evaluation, he can participate at Years 3, 5 and 10.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel*

vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

TABLE OF CONTENTS

PAGE

CONFIDENTIAL

LIST OF TABLES

PAGE

LIST OF APPENDICES

PAGE

CONFIDENTIAL

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
DTPw	Diphtheria, Tetanus Whole Cell Pertussis Vaccine
DTaP	Diphtheria, Tetanus Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FDA	Food And Drug Administration, United States
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter
PRN	Pertactin
PT	Pertussis Toxoid
RDE	Remote Data Entry

CONFIDENTIAL

SAE	Serious Adverse Event
SBIR	GSK Biologicals' Internet Randomization System
SOP	Standard Operating Procedure
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

CONFIDENTIAL

Glossary of Terms

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.3 and 10.4 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain

	further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

1. INTRODUCTION

1.1. Background

Diphtheria, tetanus (toxoids) and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Reported pertussis incidence in the United States increased from 1010 cases in 1976 to 25,827 cases in 2004 [CDC, 2004; CDC, 2002]. On October 26, 2005, ACIP issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.

Recently, GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age. This vaccine is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti , 2002; Greco , 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in Boostrix are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. A total of 6,173,696 doses have been distributed since launch until 02 August 2006.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of *Boostrix*.

1.2. Rationale for the study

Recently a study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by sanofi pasteur's *Adacel* vaccine.

Data on persistence of antibodies and longer-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 years following vaccination with GlaxoSmithKline Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).

2. OBJECTIVES

2.1. Primary objective

To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW

- Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study.
- Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

4. STUDY COHORT

4.1. Number of subjects / centres

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

4.2. Inclusion criteria

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

4.3. Elimination criteria during the study

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

4.4. Contraindications to subsequent vaccination

Not applicable.

4.5. Warnings and Precautions

Not applicable.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 Declaration of Helsinki (Protocol Appendix A), US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.
Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator. A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favorable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favorable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favorable opinion of the IRB/IEC will be transmitted by investigator to CRA prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favorable opinion of an appropriate amendment or administrative change, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].)

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,
- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the October 1996 Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects face to face. The Informed Consent Form may be read to the subjects but, in any event, the investigator or designate shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subjects and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The subjects should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects for participating in the trial.

l. The anticipated expenses, if any, to subjects for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject is authorising such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects will be informed in a timely manner if information becomes available that may be relevant to the subjects' willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be

followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. Subject identification

Subjects will retain their subject numbers as in the 106316 study.

5.3. Outline of study procedures

The summary of study procedures is summarized in Table 1.

Table 1 List of study procedures

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 Year 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. Table 2 presents the intervals between the study visits.

Table 2 Intervals between study visits

Visit	Length of interval
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks

5.4. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Obtain written informed consent from all subjects at all long-term time points.
- Check inclusion criteria at all study visits.
- Check elimination criteria at all study visits.
- Record concomitant medication/vaccination as described in Section 6.3.
- Collect approximately 5 mL of whole venous blood to provide a minimum of 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Study continuation at Years 3, 5 and 10.
- Study conclusion at Year 10 visit (Visit 6).

5.5. Sample handling and analysis

5.5.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

5.5.2. Laboratory assays

Table 3 presents the details of laboratory assays.

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and ten years following study vaccination in 106316 study. After blood centrifugation and serum separation, serum samples will be stored at approximately −20°C until sent to the sponsor. Sera will be sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Belgium for the laboratory assays.

All serological assays will be performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off of both assays is 0.1 IU/mL [Camargo , 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL.

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA or multiplex (Luminex) techniques. The cut-off of the three assays is 5 EL.U/mL [Sato, 1982].

Table 3 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
** VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL

All serological assays will be performed at GSK Biologicals using standardized, validated procedures with adequate controls.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.5.3. Immunological read-outs

Table 4 presents the immunological read-outs.

Table 4 Immunological read-outs for all

Blood sampling time point Timing	Visit no.	Marker
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 10	6	D
		T
		PT
		FHA
		PRN

All: All subjects enrolled at the long-term time point.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

It may be that any findings in the present or in other studies necessitate further investigation by GSK Biologicals into the efficacy or immunogenicity of the *Boostrix* vaccines and its constituents under study or further research in the disease(s) under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.

Any sample testing will be done in line with the consent of the individual subject.

Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to protocol Appendix B, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking above may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.5.4. Activities at study conclusion

All subjects will be offered a booster dose of Td vaccine following the blood draw at the 10 year visit. A booster dose of Tdap may be offered instead if a second dose of Tdap is recommended at that time.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Study vaccines in study 106316 were *Boostrix* and *Adacel*. No additional vaccination will be given as part of this study.

6.1. Treatment allocation and randomisation

Not applicable.

6.2. Method of blinding and breaking the study blind

The study is an open study, since there is no administration of vaccination is this study.

6.3. Concomitant medication/treatment

At each study visit, the investigator should question the subject about any medications taken.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic

name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Section 4.3.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration. Refer to Section 4.3.

7. HEALTH ECONOMICS

Not applicable.

8. SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting SAEs, as detailed in this section of the protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.2. Clinical laboratory parameters and other abnormal assessments qualifying as serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as SAEs if they meet the definition of a SAE, as defined in Section 8.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as SAEs. The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.3. Time period, frequency, and method of detecting serious adverse events

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this

instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2 for details of the back-up reporting system.

8.4. Evaluating serious adverse events

This section is only applicable if an investigator becomes aware of an SAE that warrants notification of the sponsor.

8.4.1. Assessment of intensity

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevents normal, everyday activities. (In adults, such an SAE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

Grade 3 is a category utilised for rating the intensity of an event; and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.

8.4.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying

diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If an event meets the criteria to be determined "serious" (see Section 8.1 for definition of serious adverse event), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.5. Follow-up of serious adverse events and assessment of outcome

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits.

Investigators will follow-up subjects:

- with SAEs, until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.6.1.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2. for details of the back-up reporting system.

Outcome of any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.6. Prompt reporting of serious adverse events to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

8.6.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will fax

the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

8.6.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours as outlined in Section 8.6.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received WITHIN 24 HOURS as outlined in Section 8.6.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.4.2.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 8.6.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.6.1.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.6.1.

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF / sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

Please see Sponsor Information Sheet for contact details.

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: **US Study Contacts for Concerns Relating to an SAE** ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** ***(Administrative Change 1: 14 April 2009)*** GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.

8.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.6. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.8. Post-study adverse events and serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.3. Investigators are not obligated to actively seek SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.

8.9. Pregnancy

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.6. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to GSK Biologicals as described in Section 8.8. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for a study visit as specified in the protocol is considered to have completed the study phase (time point) pertaining to that study visit.

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9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE until resolution of the event (see Section 8.1).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

9.2.2. Subject withdrawal from investigational product

Since subjects will not be administered vaccine in this antibody persistence study, subjects will not be withdrawn from receipt of investigational product, but may be withdrawn from other study procedures.

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

10.2. Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

10.3. Estimated sample size

No sample size is calculated for this study. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study.

With a total of 2284 enrolled subjects in primary study 106316, it is expected approximately 1941 subjects will be present for the 1 year time point, 1402 subjects for the 3 year time point, 1013 subjects for the 5 year time point, and 449 subjects for the 10-year time point, assuming a 15% attrition rate per year.

10.4. Study cohorts to be evaluated

Year X (1, 3, 5, 10) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

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According-To-Protocol (ATP) Year X (1, 3, 5, 10) cohort

The ATP Year X (1, 3, 5, 10) cohort will include all subjects from Year X (1, 3, 5, 10) cohort who is in the ATP cohort for analysis of immunogenicity in 106316 study and who have not met the following elimination criteria.

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

ATP Complete Year X (1, 3, 5, 10) cohort

The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.

10.5. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.5.2.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 10.6.2 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the primary objective.

- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the first secondary objective.

- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

- The geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

10.6. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 10) on cleaned data obtained through Year X. A clinical study report (CSR) will also be written following each analysis.

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year 10) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 10) cohort, in the ATP Year X (1, 3, 5 or 10) cohort and in the ATP complete Year X (1, 3, 5 and 10) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 10) (in years) will be summarized using descriptive statistics.

10.6.2. Analysis of immunogenicity

The primary analysis will be based on the ATP Year X cohort.

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by

group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.

- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 10) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves by group.

Comparability between Groups:

Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), Year X (1, 3, 5, 10) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 10) after vaccination will be calculated.

10.6.3. Analysis of safety

No safety analysis will be performed for this persistence study. If GSK is informed by an investigator of an SAE that in his/her medical judgement could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

10.7. Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5, and Year 10) as available and reported separately.

10.8. Planned interim analysis

No interim analysis is planned for this persistence study.

11. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

12. REFERENCES

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Appendix A World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the

study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments/administrative changes is required prior to implementation.
- Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory

authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is

anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF/ RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability
- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of CRF data

- Reports to the IRB/IEC and the sponsor
    - Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed

Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

Appendix C Overview of the Recruitment Plan

- All subjects who received vaccination in the study 106316 will be invited to participate in this long-term study.
- As part of the visit activities at the study conclusion visit in the 106316 study, subjects were asked to state their interest in participating in an extension study. Subjects who responded positively to this question will be contacted by the site as the sampling time point approaches in order to schedule the study visit.
- Subjects who do not provide samples at earlier long-term time points may still be considered eligible to provide samples at later long-term time points.
- The study will take place at multiple centers in the US.
- The Site Monitor will perform monitoring of actual enrolment against target enrolment on a continuous basis.
- Enrolment will be monitored through RDE.
- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date subject received vaccination in study 106316. A window of ± 5 weeks around the actual time point for each subject will be permitted. Visits for the year 1, 3, 5, and 10 samplings are therefore expected to take place between 8 June – 17 August 2007, 2009, 2011, and 2016.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used to minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimising the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".
- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate label provided by GSK Biologicals (see point 3).

3. Labelling

- The standard labels provided by Quest should be used to label each serum sample.
- If necessary, any hand-written additions to the labels should be made using indelible ink.

4. Sorting and storage

- The tubes of serum should be stored in a vertical position at approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to Quest Diagnostics. Wherever possible, a backup facility for storage of serum samples should be available.
- Detailed instructions concerning the collection, Quest labelling and storage of all serum specimens are provided in the Quest Diagnostics Clinical Trials Investigator Manual for Protocol Number 110080, 110082, 110084 and 110086.

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, Van Nuys, California.

Refer to the separate Quest Diagnostics Clinical Trials Investigator Manual for Protocol Numbers 110080, 110082, 110084 and 110086 for shipping details.

Appendix F Administrative change to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

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GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer

Approved by:

Senior Manager, Global Clinical R&D, Paediatric and Hepatitis Vaccines, GlaxoSmithKline Biologicals.

PPD dd-mm-yyyy

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Tdap-0.3-009 Ext:007
Administrative Change 1

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
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Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Agreed by: Investigator	_____ dd-mm-yyyy

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	Leonard Friedland, MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.
Signature:	PPD
Date:	5/10/07

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Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

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Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Bruce J. Berwald

PPD

Investigator signature

8/14/07

Date

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CONFIDENTIAL

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Mm Blatter

PPD

Investigator signature

6/13/07

Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Alan S. Bock M.D.

PPD

PPD

Investigator signature 12 Jun 2007 **Date**

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: DONALD M. BRANDON M.D.

PPD

Investigator signature

6/11/07

Date

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CONFIDENTIAL

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD

PPD

Investigator signature

6/11/07.
Date

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CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Shane Glade Christensen, MD

PPD

Investigator signature

6/12/07

Date

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CONFIDENTIAL

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- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Dana M. DeSantis, M.D.

PPD

Investigator signature PP

6-12-07

Date

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Final

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Richard S. Dobrusin, D.O., FACOFP

PPD

Investigator signature

6/15/07
Date

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CONFIDENTIAL

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Investigator name: Hugh D. Durrance, MD

PPD

Investigator signature

6/12/07
Date

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CONFIDENTIAL

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Investigator name: Rochelle Elijah, M.D

PPD

Investigator signature PPD

6-21-07

Date

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CONFIDENTIAL

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Investigator name: PPD Thomas Fiel, DO

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Investigator signature 6/3?

Date

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Investigator name: Larry I. Bilderman, Do

PPD

Investigator **Date** 6/12/07

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CONFIDENTIAL

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Final

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Investigator name: CARL P GRIFFIN MD

PPD

Investigator signature 6-22-07 **Date**

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CONFIDENTIAL

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Investigator name: Stephen P. Goetz, M.D

PPD

PPD **Investigator Signature**

Date 6/13/07

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CONFIDENTIAL

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Investigator name: Archie Hearne, MD

PPD

Investigator Signature **Date** 6/14/07

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CONFIDENTIAL

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Investigator name: James A. Hedrick

PPD

Investigator PPD **ture** **Date** 6/29/07

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Investigator name: LAURA L. HELMANN DO

PPD

InvestigPPD**re**

6-15-07
Date

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Investigator name: Dan C. Henry, MD

PPD

Investigator signature PPD

Date 6/11/07

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CONFIDENTIAL

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Investigator name: Kurt W. Lesh, MD

PPD

Investigator signature 6/19/07 **Date**

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Investigator name: Thomas Willard Littlejohn, III, M.D.,

PPD

Investigator signature _____ **Date** 6 2007

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Investigator name: Merritt S. Matthews MD

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Investigator PPD e PP

6/12/07

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Investigator name: Clark D. McKeever, M.D.

PPD

Investigator signature 6/14/2007 **Date**

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Investigator name: DR. Ranelle Middleton

PPD PPD

Investigator signature

6-18-2007

Date

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CONFIDENTIAL

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Investigator name: David J. Morin, MD

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Investigator PPD **e**

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Investigator name: Mark A Nielsen

PPD

Investigator signature

13 Jun 2007

Date

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Investigator name: Fatima Ptuccem

PPD

PPD

Investigator signature **Date** 6/12/07

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Investigator name: Ernie Riffer, MD

PPD PPD

Investigator signatur

6-25-07

Date

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CONFIDENTIAL

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Investigator name: John Rubino, MD

PPD

Investigator signature

06/12/07
Date

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Investigator name: Renee Nilsson Scheidell, MD

PPD

Investigator signature

6-13-07

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Investigator name: Eric A. Sheldon, MD

PPD

Investigator PPD **ature**

10 Jul 2007
Date

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CONFIDENTIAL

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Investigator name: Mark Shepard

PPD

Investigator sig **Date** 6/Apr/7

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CONFIDENTIAL

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Investigator name: Gerald R. Shockey, MD

PPD

Investigator signa _____ **Date** 6-14-07

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Investigator name: Mark A Turner MD

PPD

Investigator signature 6/13/07 **Date**

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Investigator name: Stacey E. Watson, MD

PPD

]Pvestigator signature

6-12-07
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Investigator name: Duane G. Wombolt

PPD

Investigator signature

06/19/07
Date

PPD

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Appendix F Administrative change to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office:~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

CONFIDENTIAL

Tdap-0.3-009 Ext:007
Administrative Change 1

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer

Approved by:

Senior Manager, Global Clinical R&D, Paediatric and Hepatitis Vaccines, GlaxoSmithKline Biologicals

PPD

05-MAY-20

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GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3	110082

Date: 30-MAR-2011

Concerns: DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3 (110082) Protocol Administrative Change 1 Investigator Agreements

Details:

The Investigator Agreements for Protocol Administrative Change 1 were obtained on the Investigator Agreement Page (page 4) not including the 'summary checksum'. However the checksum is included in the document footer of the Investigator Agreement page 4 confirming the signatures were obtained on the final published version.

Made by: PPD

Signature PPD

Function: Lead Study Manager

Signature Date: PPD 31 Mar 2011

(If required) Approved by: _____

Approver's Signature: _____

Function *[Line Manager]*:_____

Signature Date: _____

Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

CONFIDENTIAL

Hence I:

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Investigator name: PPD 15-04 Bruce Bernald MD

Hence I:

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Investigator name: Mark M. Blatter, M.D.

P PPD

Date: 5/27/09

Hence I:

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Investigator name: PPD

PPD M. BRANDON, M.D.

5/19/09

CONFIDENTIAL

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Investigator name: PPD

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Investigator name: PPD 5/26/09.

CONFIDENTIAL

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Investigator name: PPD 5/19/09

CONFIDENTIAL

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PPD

PPD

Investigator name: _____ 7/15/09

2009-05-26 11:30 PPD P 3/3

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD PPD

5/26/09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: John Earl MD 5-19-09

PPD

14 April 2009
ee3fc7b0c180953095209d75934378e9

CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Carl P. Griffin, M.D.

PPD

01 Jun 2009

CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD

6/11/05

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an up[redacted] minutes, Vitae and other FDA required documents.

Investigator name: Archie Hearne, MD 5/27/09

06/02/2009 08:36 FAX PPD KPAR 007

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD June 1/09

JAMES A. HEDRICK DATE

MAY-18-2009 16:30 From:ACCELOVANCE PPD To PPD P.23/23

CONFIDENTIAL

Tdap-0.3-009 Ext:007
Administrative Change 1

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an u PPD Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5-18-09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/22/09

CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: MARTIN L. KABONGO, M[redacted] PPD 5/21/09

9 'd PPD ON May.21. 2009 9:52AM P. 6

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/26/09

May.18. 2009 12:41PM PPD No. PPD P. 2

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD PPD 18 May 2009

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD 5/21/09

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: MURRAY A. KIMMEL, DO

PPD 22MAY2009

MAY-21-2009 THU 11:28 AM Lone Star Bone Joint FAX NO. PPD P. 06/36

CONFIDENTIAL

Tdap-0.3-009 Ext:007
Administrative Change 1

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/20/09

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: JOHN E. ERVIN, M.D. PPD 5-19-09

PPD

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 26 May 2009

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an PPD l Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/29/09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/20/09

CONFIDENTIAL

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents

Investigator name: PPD _____ 14 May 09

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Kerry S Rosinski

Signature: PPD

Date: 23 Apr 2010

CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5-22-09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: John Rubino / PPD 5/27/09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name PPD MD 5-26-09.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an undated Curriculum Vitae and other FDA required documents

Investigator name: PPD

Eric A. Sheldon, MD

PPD

PPD

03 JUN 2009

05/27/09 WED 13:15 FAX PPD ACCELOVANCE ☑016

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK Biologicals with an upda PPD Vitae and other FDA required documents.

Investigator name: PPD

CONFIDENTIAL

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5-12-09

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/22/09

FROM (THU)MAY 21 2009 10:00/ST. 10:00/No. PPD P 2

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5-21-09

CONFIDENTIAL

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Jonathan Paul Wilson, PPD

PPD

21- MAY- 2009

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD

Sample Case Report Form

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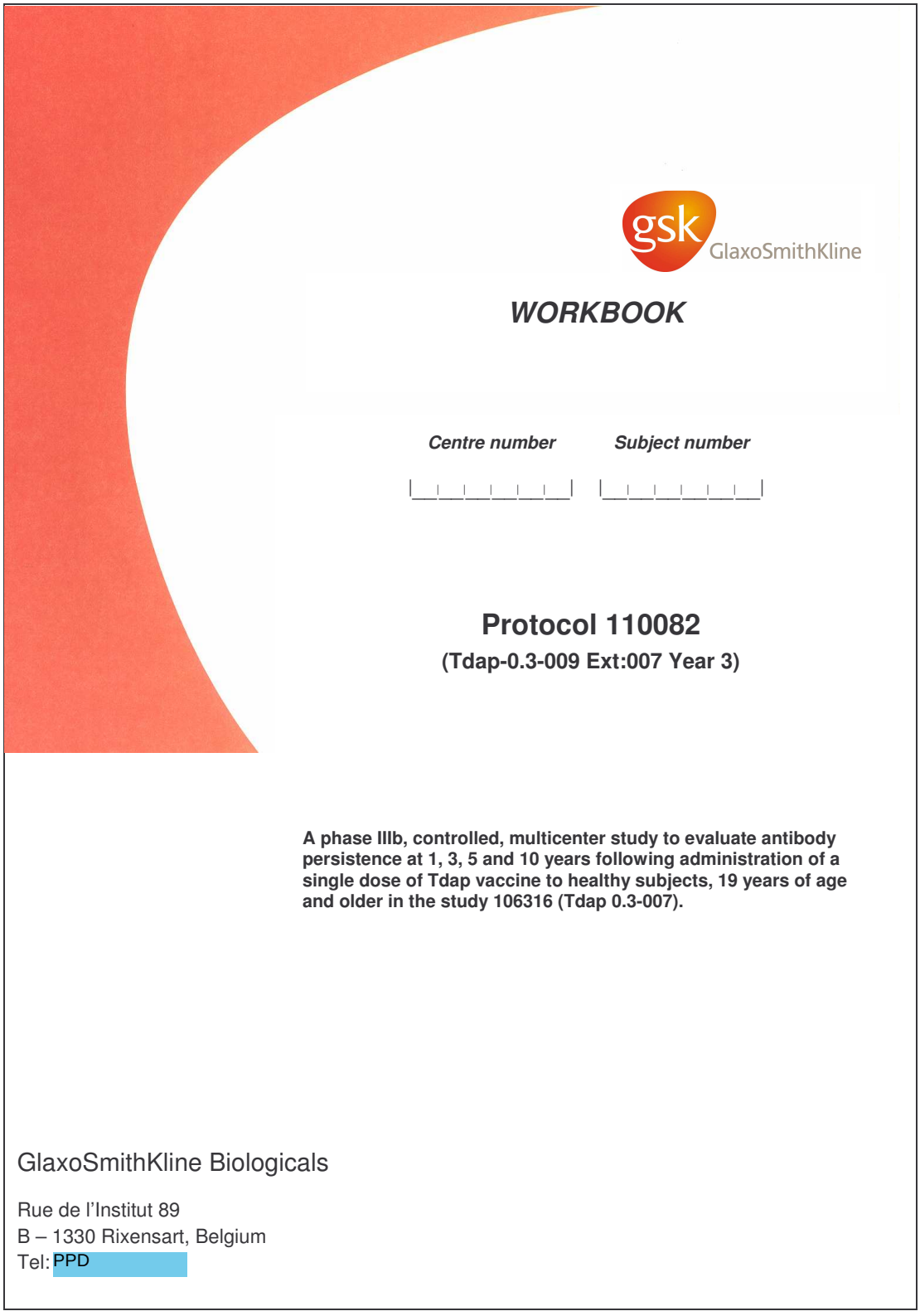

WORKBOOK

Centre number ***Subject number***

|__|__|__|__|__|__|__| |__|__|__|__|__|__|__|

Protocol 110082

(Tdap-0.3-009 Ext:007 Year 3)

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

GlaxoSmithKline Biologicals

Rue de l'Institut 89
B – 1330 Rixensart, Belgium
Tel: PPD

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GENERAL INSTRUCTIONS

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

DATES

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example: | 0 1 | | J A N | | 2 0 0 6 | = 1st January 2006
day month year

The **Medication** and the **Concomitant Vaccination** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at each long-term follow-up study.

For all subjects enrolled, please complete the **Study Continuation** form**.**

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ADVERSE EVENT DEFINITIONS

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.

3: Severe: An adverse event which prevents normal, everyday activities
(In adults/ adolescents, such an adverse event would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO: The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1: Recovered / resolved.

2: Recovering / resolving: If the subject is recovering at the time the subject completes the study or at the time the subject dropped out.

3: Not recovered / not resolved: This means an AE ongoing at the time the subject completes the study or becomes lost to follow-up; if AE/SAE was ongoing at the time of death, but was not the cause of death.

4: Recovered with sequelae / Resolved with sequelae.

5: Fatal: AE is the cause of death (only applicable for SAE reports).

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death.
- is life threatening.
- results in persistent or significant disability / incapacity.
- requires in-patient hospitalization.
- prolongation of existing hospitalization.
- is a congenital anomaly / birth defect in the offspring of a study subject.
- In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

For each serious adverse event related to study participation or related to vaccination in the primary study the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

In case of pregnancy the investigator becomes aware of, please complete and submit a **Pregnancy Notification** form to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

FLOW SHEET

Visit Timing Sampling time point	VISIT 3 YEAR 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 YEAR 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

Intervals between study visits

Visit	Length of interval
VISIT 3 (Tdap vaccination in parent study→VISIT 3)	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks

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VISIT 4
YEAR 3

Informed Consent has to be obtained prior to any study procedure

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. (See section 10.4 for definition of study cohorts to be evaluated.)

[A] Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.

[B] Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.

[C] Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

[D] Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).

[E] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book	Visit	Date of visit	Subject Number
110082		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__| day month year

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study? ☐ Yes ☐ No ☐ NA

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender: [M] ☐ Male
[F] ☐ Female

LONG-TERM FOLLOW-UP

PREVIOUS STUDY

110080
(Tdap-0.3-009 EXT: 007 Year 1)

Subject number will be the same as in the previous study.

1.

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book	Visit		Subject Number
110082		**VISIT 4**		|__|__|__|__|__|__|

ELIGIBILITY CHECK

Did the subject meet all the entry criteria?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed

[1] ☐ All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.

[2] ☐ Written informed consent must be obtained from the subject prior to each study time point.

2.

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book	Visit		Subject Number
110082		**VISIT 4**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample for antibodies determination been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

3.

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CONCOMITANT VACCINATION

At each study visit/contact, the investigator should question the subject about any vaccination(s) administered.

- Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration.

110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book			Subject Number
110082				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any Td or Tdap Vaccine, or any registered or investigational vaccine utilizing a Diphtheria toxoïd or tetanus toxoïd vaccines been administered at any time after the vaccination in the 106316 study?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** **day month year**
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
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For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

Route:

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

4.

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MEDICATION

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GlaxoSmithKline Biologicals

Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
IN	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject about any medication(s) taken.

- Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment

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110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book			Subject Number
110082				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments specifically contraindicated in the protocol been administered?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

5.

CONFIDENTIAL

STUDY CONTINUATION

CONFIDENTIAL

GlaxoSmithKline

110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book			Subject Number
110082				|__|__|__|__|__|__|

FOLLOW-UP STUDIES

If a booster study or a follow-up study is offered in the future, would the subject or parents/guardians be willing to be contacted and learn more about it?

☐ Yes

☐ No, please specify the most appropriate reason:

→ ☐ Adverse Events, or Serious Adverse Events:

please specify: _____

→ ☐ Other:

please specify: _____

OCCURRENCE OF SERIOUS ADVERSE EVENT

Because subjects are not vaccinated as part of the study protocol, investigators are not required to specifically solicit SAE's.

However if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in 106316 study, he/she should do so within 24hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

Did the subject experience any Serious Adverse Event during the study?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

6.

CONFIDENTIAL

GlaxoSmithKline

110082 (Tdap-0.3-009 EXT: 007 Year 3)

Protocol	Book			Subject Number
110082				|__|__|__|__|__|__|

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

7.

110082 (Tdap - 0.3-009 EXT:007 Year 3)

Protocol	**Previous study**	**Tracking Document Reason for non participation**	Center Number
110082	**110080** **(Tdap - 0.3-009 EXT:007 Year 1)**		|__|__|__|__|__|__|__|

Previous Subject Number	**Date of Birth** *(day month year)*	**Reason for non participation**	**Date of Contact** *(day month year)*
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: __________________ [4] ☐ Subject died on : |__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: __________________ [4] ☐ Subject died on : |__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: __________________ [4] ☐ Subject died on : |__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: __________________ [4] ☐ Subject died on : |__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|

Investigator name: (PRINT name)	**Signature**:	**Date:** *(day month year)*
		|__|__||__|__|__||__|__|__|__|

GlaxoSmithKline

110082 (Tdap - 0.3-009 EXT:007 Year 3)

Protocol	Centre	
110082	|__|__|__|__|__|__|	

USE OF HUMAN SAMPLES BY GSK

In addition to the use of samples for the tests described in the protocol, samples might be used for other research by GSK (see protocol). Please tick what is also covered by the subject Informed Consent form of your center.

[2] ☐ **Quality Assurance of tests described in the protocol**

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in the protocol as well as making sure that new tests are comparable to previous methods and work reliably.

[3a] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study (Diphtheria Tetanus Pertussis). These investigations excludes genetics and HIV testing.**

[3b] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study(Diphtheria Tetanus Pertussis). These investigations excludes genetic and HIV testing. Investigator will always ask in advance the permission of the independent Ethics Committee/Institutional Review Board linked to the institution where this research is performed.**

[4] ☐ **Further research by GSK Biologicals that is NOT RELATED to Boostrix (Tdap,776423)or the diseases under study (Diphtheria Tetanus Pertussis) done on an anonymous basis (meaning that any identification linking the subject to the sample is destroyed). This research excludes genetic and HIV testing and does not affect subject participation in the study.**

Please tick below box if a 15 years GSK storage period is covered by the subject's Informed Consent form of your center.

☐ **At least 15 years storage period by GSK Biologicals**

☐ **Other, specify:**_____

ICF Effective date: |__|__| |__|__|__| |__|__|__|__|
day month year

! Complete and submit a new form for each change during the study.

INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

1.

List of Independent Ethics Committees /Institutional Review Boards

Centre Numbers *	Ethics Review Body	Location
PPD	Quorum Review Board	1601 Fifth Avenue Suite 1000 Seattle, WA 98101

* GSK Biologicals assigned centre number

Representative written information for patient and sample consent forms

INFORMED CONSENT FORM

Study Identification: 110080 (Tdap-0.3-009 Ext:007 Year 1)
110082 (Tdap-0.3-009 Ext:007 Year 3)
110084 (Tdap-0.3-009 Ext:007 Year 5)
110086 (Tdap-0.3-009 Ext:007 Year 10)

Study Title: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Version Number: 1 Date: 24 April 2007

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification:

This document should be presented to the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the subject.

What does giving consent for this study mean?

Consent means agreeing to take part in this clinical research study. You have the right to decide if you want to take part in the study or not. Please take time to read the following information carefully and discuss it if you wish with friends, relatives and your personal doctor. Ask us if there is anything that is not clear or if you would like more information.

Why is this study being carried out?

You were vaccinated with a Tdap (tetanus toxoid, diphtheria toxoid and acellular pertussis) vaccine in study 106316. Vaccines work by stimulating antibodies (substances that protect against diseases). This study is being conducted to find out how long information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens remain elevated following a single dose vaccination with GlaxoSmithKline Biologicals's Tdap vaccine (*Boostrix*).

What does this study involve?

In order to be included in this study, the following requirements must be met:

- You have signed this informed consent form.
- You have received a dose of Tdap vaccine (*Boostrix* or *Adacel*) as part of the 106316 study.

If you take part in the study, you will have the following tests and procedures:

- A blood sample of 5 ml will be taken from you.

- You should contact the health care provider immediately should you have any signs or symptoms you think may be serious, or if you are hospitalized during the study period.

How many other subjects are there in the study?

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*.

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, you decline to participate in the study, your refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.

Do you have to stay in the study?

You may decide to stop participating in this study at any time without giving a reason. If you decide to stop participating in the study, you must notify the study doctor immediately. Your leaving the study will not have any effect on future medical care.

Your doctor for this study or GlaxoSmithKline Biologicals may also stop the study at any time before it is completed. If GlaxoSmithKline stops the study, the reason for that decision will be given to you.

If, during the time you are participating in the study, any new information becomes available that might affect whether you are willing to stay in the study, that information will be shared with you in a timely manner.

If you decide the stop participating in the study before it is completed, GlaxoSmithKline will still use the information and data they have collected about you up until that point, as part of the results of their research.

What are the foreseeable risks for taking part in the study?

Blood sampling may cause momentary discomfort, minor bruising or bleeding. The amount to be taken will not be harmful to your health.

Are there any benefits for taking part in the study?

Information from this study may help researchers understand more about protecting adults against tetanus, diphtheria and pertussis diseases in the future.

What payments will be made for the study?

You will receive the following payment for your participation in the study:

$ XXX for each completed scheduled visit, if you do not complete the entire study.

If you have to withdraw from the study for medical reasons related to the study, you will receive full payment.

Will you have to meet any cost/expenses for taking part in the study?

There will be no costs to you to participate in this study.

Who should you contact to answer any questions on the study?

You have the right to ask [**name**] at [**contact details**] any questions concerning this study at any time. This includes questions about your rights, study-related injuries, and the research study itself.

You may ask the study doctor questions about the study. If you have any questions, please contact:

Name of investigator:

Address of investigator:

Telephone number of investigator: _____Fax number _____:

In the event that you are injured in the study what compensation will be available?

If you are injured by any procedure that is done to you as specified by the study, GlaxoSmithKline will pay for reasonable and necessary medical expenses to treat the injury - as long as those expenses are not covered by your medical insurance or an alternative source such as the National Vaccine Injury Compensation Fund. GlaxoSmithKline is not offering to compensate you for any other expenses, but you keep all of your legal rights when you sign this form.

Who will have access to medical and personal information about you that is collected in this study?

If you decide to participate in the study, the study doctor and staff will collect medical and personal information about you as part of doing the study. People who work for or with GSK, and others like the independent ethics committee or the institutional review board (IEC/IRB) for the study or regulatory authorities responsible for approving medicines, will have access to this information at the site in order to check that the study is done properly. GSK staff who see this information at the site will keep it confidential.

The study site will also transfer to GSK some of the information it collects, in a coded form. The information transferred will not include your name, initials, address, or other direct identifiers. It will be assigned a code number that only the site can connect back to your name.

Your permission to the study doctor and staff to use this information or share it with GSK and others as described below for the study doesn't automatically end at a particular time.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

Medical information about you may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your medical care it will be given to the study doctor who will be encouraged to share it with you or your doctor. While you are in the study, however, the study site will not share certain new medical information about you that is created as part of the study (such as whether or not you are getting study drug, or the results of certain tests) unless the study doctor decides it is medically important to do so. This is done to stop the study results from being distorted. Once the study is over, you will be given access to medical information about you that you are entitled to see. You will be told if any of this medical information requires confirmation using a clinical test. This is important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment. At any time, you may ask your study doctor to let you see your personal information, e.g. name and address and to correct it if necessary

What will GlaxoSmithKline do with the information it gets?

- GSK may use the information that the study doctor gives it (i.e. the coded information):
- By storing and analyzing it electronically to find out what this study is telling us.
- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study (this will not include any information that directly identifies you)
- By sharing it as part of research with other companies or universities for the purpose of further understanding or developing this vaccine and with other GlaxoSmithKline offices in this country and in other countries. If the information is sent to another country, GSK will apply the same level of protection to your information, to the extent permitted by local law
- By using it to plan new studies or other types of research or other medical purposes related to the development of the vaccine.

What will happen to blood samples from this study?

- Samples will not be labelled with information that directly identifies you but will be coded with your study identification number.
- Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.
- By agreeing to take part in this study you will be allowing GSK Biologicals to use your samples for the following purposes:
- Testing to measure the immune response (e.g. amount of antibodies) to the vaccine(s) you received during the Study

- Testing to assure that the results from your sample are of good quality, for improvements of those tests or development of new test methods.
- If any findings from related studies require further investigation into the ability of the Boostrix vaccine to protect people or for further research in the diseases under study (diphtheria, tetanus and pertussis), additional testing on your collected samples may be performed by GSK Biologicals. This will, however, exclude testing related to your genes and HIV.

Collected samples will be stored for up to 15 years.

How is GlaxoSmithKline involved?

The study doctor and the institution are paid to conduct this research study by GSK.

The information and the materials that are given to you in relation to the study are confidential information belonging to GlaxoSmithKline and should be kept private. You can discuss this information in confidence with your doctor or friends and family to decide about taking part in this study and talking about your healthcare.

Consent statement

I, (Printed name of Subject)

confirm that I have read the written information (or have had the information read to me) for studies 110080 (Tdap0.3-009 Ext: 007 Year 1, 110082 (Tdap-0.3-009 Ext: 007 Year 3, 110084 (Tdap-0.3-009 Ext-007 Year 5 and 110086 (Tdap-0.3-009 Ext: 007 Year 10), Version 1, dated 24 April 2007, 6 pages and the study procedures have been explained to me by study staff during the consent process for this study.

- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data to authorised persons described in the information sheet
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my primary health care physician will be notified of my participation in this study.

Yes **No**

Tick as appropriate

I agree that my biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study. This will be done on an anonymous basis (meaning that any identification linking me to the sample is destroyed). Testing on my genes or testing for HIV will not be done. I understand that if I select "No", it will not affect my participation in the study.

Yes No

I agree to take part in this study.

Subject's Signature _____ **Date:** _____

Signature of Person conducting Consent _____ **Date:**

Printed Name of Person conducting Consent _____

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
PPD				Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD Phone: PPD Fax: PPD Email: PPD

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
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Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
PPD	PPD			Phone: PPD Fax: PPD Email: PPD
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Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
PPD	PPD			Phone: PPD Ext PPD Fax: PPD Email: PPD
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PPD				Phone: PPD Fax: PPD Email: PPD

* GSK Biologicals' assigned center number

Page(s) removed- Out of Scope of phase 1 of Policy 0070 – Investigator CVs

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Page(s) removed- Out of Scope of phase 1 of Policy 0070 – Investigator CVs

Signature of principal or coordinating investigator or sponsor's responsible

GlaxoSmithKline Biologicals
Global Clinical Research and Development
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110082 (Tdap 0.3-009 Ext: 007 Y3)

Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Karin Hardt
Title of Sponsor Signatory:	Director, Clinical Development, Lead, Combination Vaccines, Global Vaccine Development, GlaxoSmithKline Biologicals.
Signature:	_____
Date:	_____

For internal use only

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GlaxoSmithKline Biologicals
Global Clinical Research and Development
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110082 (Tdap 0.3-009 Ext: 007 Y3)

Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Francesca Ceddia
Title of Sponsor Signatory:	Vice President and Vaccine Development Leader (DTP Portfolio, Neisseria), Global Vaccine Development, GlaxoSmithKline Biologicals.
Signature:	
Date:	

For internal use only

- ----------Checksum----------!Ver.!Created On - -
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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

Randomisation list

Not applicable.

Audit certificates

Not applicable

Documentation of statistical methods

Refer to Section 5.10 of the Study Report.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable.

Publications based on the study

CCI - This section contained journal publication(s), which are protected by third party copyright laws and therefore have been excluded.

Important publications referenced in the report

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Individual Listings

NOTES TO APPENDIX TABLES

The following abbreviations are common throughout the Appendix tables:

Sub. No.		:	Subject number
Eli MA		:	Eligibility (MA: Main Analysis)
	E	:	Eliminated from reactogenicity and immunogenicity analyses
	I	:	Eliminated from immunogenicity analysis
	MC	:	Missing Confirmed
	N	:	No
	Y	:	Yes
	NA	:	Not Applicable

Abbreviations which are unique to a particular appendix are presented below.

Appendix Table IA - Individual subject data: Elimination codes

Elim Codes : Elimination codes

Appendix Table I.B - Individual subject data: Demography

Sex		:	Sex
	F	:	Female
	M	:	Male
Center		:	Study center

Appendix Table ICi - Individual subject data: Dates of Birth - vaccination - sampling - visits

Dates of vaccine administration,
Dates of sampling,
Dates of visits

VIS ND	:	Visit Not Done (the subject did not come)
VAC ND	:	Study vaccine administration not done
ND	:	Not Done

Appendix Table ICii - Individual subject data: Reason for visit not done

Reason		:	Reason for visit not done
	AEX	:	Non serious adverse event
	SAE	:	Serious adverse event
	OTH	:	Other
	SAM	:	Same reason and decision as previous visit

Appendix Table ID - Individual subject data: General medical history - Physical examination

Status

PAST	:	Medical history no more present at the physical examination
CURRENT	:	Medical history present at the physical examination
Both	:	Past and current

Appendix Table IE - Individual subject data: CONCLUSION

Elim Crit		:	Did any elimination criteria become applicable during the study?
	Y	:	Yes
	N	:	No
Link to AE		:	Is the withdrawal of the subject linked to an adverse event ?
	Yes	:	
	No	:	
Date of last contact			Date when last information was collected on subject's condition
Good Condition?			Was the subject in good condition at date of last contact?
SAE?		:	Did the subject experience any Serious Adverse Event during the
		:	study?
	Y	:	Yes
	N		No
Nb of SAE		:	Total number of SAE's recorded in SAE report.
Preg		:	Did the subject become pregnant during the study / since the end of the active phase?

Appendix Table IEii - Individual subject data: Subjects whose the code has been broken

Broken date	:	Unblinding treatment date

Appendix Table IEii - Individual subject data: Extensive safety follow-up

Contact date		:	Date of study conclusion extended safety follow-up contact
Sub Cont		:	Was the subject/subject's parents/guardian contacted after the end of the active phase?
Reason		:	Reason for not being contacted:
	Consent withdrawal / Lost to follow-up		
Non-Serious AE?		:	Did the subject experience any study relevant non-serious adverse event(s) since the end of the active phase?

Serious AE ?		:	Did the subject experience any serious adverse event(s) since the end of the active phase
	YES		
	NO		
	Subjects could not be contacted		
Other vaccine		:	Has the subject received any other investigational and/or non-registered vaccine and/or drug since the end of the active phase?
Other vaccine spec		:	Specification of the vaccine
Pregnant		:	Has the subject become pregnant since the end of the active phase?
	YES	:	Yes
	NO	:	No
	NA	:	Not applicable

Appendix table IF - Individual subject data : Notes RDE (sticky notes)

Tbl. Note			
	3	:	Sticky notes
	2	:	Notes data
	1	:	Force validation
Act		:	Activity
Scr Nb		:	Screen number
Screen		:	Screen name
Seq Nb		:	Sequence number
Note		:	Description of the note

Appendix Table IG - Individual subject data: Vaccination procedure for each subject: list of the administered vaccines and all related information

Trt. No.		:	Treatment number
According to Prot?		:	Is of the study vaccine be administered according to protocol in terms of side/site/route?
Injection?		:	Vaccine administration
Type of vacc.			
	1	:	Study vaccine not administered according to protocol: wrong side/site/route or replacement or wrong vial number
	2	:	Study vaccine planned but not administered for a given visit
	3	:	Administration of a study vaccine not planned in the group
Eff Vial Number		:	Effective vial number administered

Appendix Table IH - Individual subject data : Smoking history

Smoke now?		:	Does the subject smoke on a regular basis?
What?		:	What does the subject smoke?
	CIGARETTES		
	CIGARS		
	PIPE		
	CIGARILLOS		
Daily Average		:	How many cigarettes, cigars,… does the subject smoke on average?
	<= 10 DAILY		
	11-20 DAILY		
	21-40 DAILY		
	> 40 DAILY		
Start Date		:	Specification of the year the subject started smoking
Smoke past?		:	Did the subject smoke on a regular basis in the past?
Stop Date		:	Specification of the year the subject quit smoking

Appendix Table II - Individual subject data: Reason for vaccine not administered

Adm?		:	Study vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
Reason		:	Reason why the study vaccine was not administered:
	SAE	:	Serious adverse event
	AEX	:	Non serious adverse event
	OTH	:	Other

Appendix Table IJ - Individual subject data: Reason for non-Eligibility

Eligib.		:	Did the subject meet all the entry criteria?
	No	:	Some inclusion /exclusion criteria are not met
Study vacc.			
	Yes	:	The subject received at least one dose of study vaccine (study vaccine, Replacement or Wrong vial number)
	No	:	No vaccine received
Criterion number		:	Inclusion OR exclusion criteria number the subject failed
Reason of inclusion and exclusion criteria		:	Description of the criterion number: label from codelist or 'Cfr. description in CRF'

Appendix table IK - Individual subject data : Tracking Document Booster or Long Term Follow-up

Prev_sub		:	Previous PID number
Origin		:	Origin of the information
	Track.Doc	:	From TRACKDOC of the current study
	Demog	:	From DEMOG of the current study
	Err.Track	:	Inconsistensy between demog and trackdoc
	Prev.Study	:	From FU in Previous study
	No Track	:	Subject from primary without information
DOB		:	Date of birth
Crit_nb		:	Criteria number of the reason for non participation into an extension study
	1		
	2		
	3		
	4		
Comment for non eligibility		:	If the criteria for non participation into an extension study is 'Subject not eligible -Please specify criteria that are not fulfilled'?
Crit Description	-Subject not eligible -Please specify criteria that are not fulfilled -Subject lost to follow-up or not reached -Subject eligible but not willing to participate due to -Subject died		Label of the criteria number
Due to AE?		:	If subject is eligible but not willing to participate due to Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No
Due to Other?		:	If subject is eligible but not willing to participate due to Other reason that Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No

Appendix Table IIA - Individual subject data: Solicited local adverse events

L?		:	Has the subject experienced any local symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing
VACC CODE		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Table IIA)

VA		:	Vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
PA		:	Pain (empty or scored from 0 to 3)
RE		:	Redness (greatest diameter)
SW		:	Swelling (greatest diameter)
IN		:	Induration (greatest diameter)
EC		:	Ecchymosis (greatest diameter)
EXP		:	Has the subject experienced some symptoms?
	Y	:	Yes
	N	:	No
MA_TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIB - Individual subject data: Solicited general adverse events

G?		:	Has the subject experienced any general symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing
AC		:	General aches (empty or scored from 0 to 3)
AR		:	Arthralgia (empty or scored from 0 to 3)
DA		:	Diarrhoea (empty or scored from 0 to 3)
DR		:	Drowsiness (empty or scored from 0 to 3)
FA		:	Fatigue (empty or scored from 0 to 3)
FE		:	Fever = Body temperature in °Cs or °Fs
FU		:	Fussiness (empty or scored from 0 to 3)
GI		:	Gastrointestinal symptoms (empty or scored from 0 to 3)
HE		:	Headache (empty or scored from 0 to 3)
IR		:	Irritability/fussiness (empty or scored from 0 to 3)
LO		:	Loss of appetite (empty or scored from 0 to 3)
MA		:	Malaise (empty or scored from 0 to 3)
MY		:	Myalgia (empty or scored from 0 to 3)
NA		:	Nausea (empty or scored from 0 to 3)
SL		:	Sleeping less than usual (empty or scored from 0 to 3)
SH		:	Shivering (empty or scored from 0 to 3)
SW		:	Sweating (empty or scored from 0 to 3)

UC		:	Unusual crying (empty or scored from 0 to 3)
VO		:	Vomiting (empty or scored from 0 to 3)
TE		:	Temperature = Body temperature in °Cs or °Fs
	RTE	:	Route (for body temperature recording)
	O	:	Oral
	A	:	Axillary
	R	:	Rectal
	T	:	Tympanic
	X	:	Tympanic oral
	Y	:	Tympanic rectal
	Rte Pre	:	Route for pre-vaccination temperature recording
	Pre Vac	:	Pre-vaccination temperature
EXP		:	Symptom experienced
Caus		:	Causality
MA TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIC - Individual subject data: Unsolicited Adverse Event

Verbatim	:	Description of experience as recorded in the case report form
Keyword (MedDRA)	:	Specific identification terminology linked to MedDRA classification codes
LLT MedDRA code	:	Lower Level Term Code for MedDRA, Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym. (All PTs have an identical LLT).
Preferred term	:	Medical term assigned to the keyword/verbatim, Represents a single medical concept
SOC code	:	Primary System Organ Class code: Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
Chro	:	Chronic illness
Pr Do	:	Study vaccine dose given prior to the adverse event
M?	:	Medical advice sought for the symptom
Type	:	Type of medical advice
ER	:	Emergency room
HO	:	Hospitalization
MD	:	Medical doctor
Caus	:	Reasonable possibility that the AE have been caused by the investigational product?
Start date	:	Date of onset of adverse event
Imm Pst Vac	:	Adverse event starting during immediate post-vaccination period

Day onset		:	Number of days since last study vaccine dose
End date		:	Date of end of adverse event
Dur (d)		:	Duration (days) of adverse event
Int		:	Maximum intensity
	1	:	Mild
	2	:	Moderate
	3	:	Severe
L/G		:	Local or general symptom
Out		:	Outcome
	1	:	Recovered/Resolved
	2	:	Recovering/Resolving
	3	:	Not recovered/Not resolved
	4	:	Recovered with sequelae/Resolved with sequelae
	5	:	Died
Vacc Code		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Tables IIC)
Ser		:	Serious adverse event

Appendix tables IIDi - Individual subject data: Medication

Prev dose		:	Previous study vaccine dose
Rel. day of onset		:	Day of onset of medication, relative to previous study vaccine dose
Start date		:	Start date of medication
End date		:	End date of medication
Dur (day)		:	Duration (days) of medication
Trade-Generic name		:	Trade and/or generic name of medication
Medical indication		:	Medical indication for which medication was used
GSK Antibiot		:	Antibiotic
	Y	:	Yes
GSK Antipyr		:	Antipyretic
	Y	:	Yes
Proph		:	Prophylactic medication
	Y	:	Yes

Appendix table IIDii - Individual subject data: Concomitant Vaccination

Trade name	:	Trade name of concomitant vaccine administered
Admin. date	:	Date of administration of concomitant vaccine
Previous vaccination date	:	Date of administration of previous study vaccine dose
Prev dose	:	Previous study vaccine dose
Rel. day of onset	:	Day of onset of concomitant vaccination, relative to date of previous study vaccine dose

Appendix Tables IIE - Individual subject data: Extensive swelling limbs

Vac		: Vaccine administered for which the large swelling reaction is reported
Physexam		: Date of physical examination
Exam		: Was the examination performed by a member of study personnel during the large swelling reaction period?
	Y	: Yes
	N	: No
Ext. Swell Start		: Date when the swelling was first considered to be a large swelling reaction
H. advc		: Number of hours between last vaccination and large swelling reaction, if the swelling occured within 24 hours after vaccination
Pr Do		: Previous dose of vaccination
Day onset		: Number of days between the previous vaccination date and the onset date of large swelling reaction
Sw. size		: Measurement of the greatest diameter of swelling (mm)
Swe Typ		: Type of swelling
	LOC	: local swelling around injection site, not involving adjacent joint
	DIF	: diffuse swelling, not involving adjacent joint
	ADJ	: swelling, involving adjacent joint
Circum swo		: Circumference of swollen limb (at the site of max swelling) (mm)
Circum opp		: Circumference of the opposite limb (at the same level) (mm)
Val temp		: Temperature (maximum temperature if temperature has been taken more than once a day)
Rout		: Temperature measurement route
	A	: axilllary
	O	: oral
	R	:: Rectal
	X	tympanic
Red		: Symptom of redness occurring during the large swelling reaction
Red Dia		: Largest diameter of redness (mm)
Ind		: Symptom of induration occurring during the large swelling reaction
Ind Dia		: Largest diameter of induration (mm)
Pain		: Symptom of pain occurring during the large swelling reaction
Pain Int		: Pain intensity (at administration site)
	1	: Minor reaction to touch
	2	: cries/ protests on touch
	3	: cries when limb is moved / spontaneously painful
Func Imp		: Symptom of functional impairment occurring during the large swelling reaction
Imp Int		: Functional impairment intensity
	1	: easily tolerated, causing minimal discomfort and not interfering with everyday activities
	2	: sufficiently discomforting to interfere with normal everyday activities
	3	: prevents normal everyday activities
Ext. Swell. end		: Last date when the swelling was still considered to be large swelling reaction

H. dura		: Duration in hours, if the large swelling reaction lasted for less than 24 hours.
Out		: Outcome of the large swelling reaction
	1	: recovered/resolved
	2	: recovering/resolving
	3	: not recoverd / not resolved
	4	: recovered with sequelae / resolved with sequelae
Alt Expl		: Is there an alternative explanation for the swelling?
	Y	: Yes
	N	: No
Explanat		: Explanation of an alternative for the swelling

Appendix table IIIA - Individual subject data: IMMUNOGENICITY

cut	:	Cut-off of the laboratory assay
GSKBIO	:	GlaxoSmithKline Biologicals
AP	:	Absence of parallelism
BS ND	:	Blood sampling not done
IR	:	Invalid result
QNS	:	Quantity of serum not sufficient
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IIIB - Individual subject data: CMI

QCNF	:	Quality Criteria Not Fulfilled
TP	:	Technical Problem
NM	:	No Material
ND	:	Not Done
NR	:	Not recorded
IR	:	Invalid results
BSNA	:	Blood Sample Not Available

Appendix table IVA - Individual subject data: Haematology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVB - Individual subject data: Biochemistry

cut	:	Cut-off of the laboratory assay
INVESTIG		Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVC - Individual subject data: Urinology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
SBCODE/RES	:	SmithKline Beecham code/Result
VIS ND	:	Visit not done
ND	:	Not done
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Document 1 : IA - ELIM_ID(PR) - Y3.DOC

PC\ RDE\ ENABLE Appendix table IA - Individual subject data : Elimination codes (Eli_type : Y3)

Pages 350 to 490 have been removed - Out of Scope of phase 1 of Policy 0070 - Individual Subject Data Listings

Case report forms (CRFs /eCRFs)

Not applicable.

Sponsor
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772

Study vaccines	• GlaxoSmithKline (GSK) Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, containing 0.3 mg aluminum [776423/Tdap, (Boostrix®)] • Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap) vaccine (Adacel®)
eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
Investigational New Drug (IND) number	BB-IND-8461
Date of approval	Final: 17 April 2007
Date of amendments/ administrative change approval	Administrative Change 1 Final: 14 April 2009 Amendment 1 Final: 09 November 2010 Amendment 2 Final: 18 February 2014 Amendment 3 Final: 10 December 2014 Administrative Change 2 Final: 03 February 2015
Title	Persistence study of GSK Biologicals' Tdap vaccine (776423), 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Co-ordinating authors	PPD Scientific writer
Contributing authors	• PPD Senior Manager, Clinical Development, Combination Vaccines, Global Vaccine Development • PPD Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
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Contributing authors	• PPD Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development • PPD Project Level Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development • PPD Study Delivery Lead • PPD Director, Clinical Development, Lead, DTP Combination Vaccines, Global Vaccine Development Htay Htay Han, Director, Project Level Clinical Research and Development Lead, DTP Combination Vaccines and Rotavirus Vaccines • PPD Biostatistician, *Boostrix* • PPD Project statistician, *Boostrix* • PPD Director, Biometrics • PPD Global Study Manager, Harrison Clinical Research Benelux for GSK Biologicals • PPD Study Manager • PPD Clinical Data Coordinator • PPD Study Data Manager • PPD Study Data Manager • PPD Senior Manager, Biologicals Clinical Safety & Pharmacovigilance • PPD Safety Physician, Vaccines Clinical Safety & Pharmacovigilance

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
Investigational New Drug (IND) number	BB-IND-8461
Title	Persistence study of GSK Biologicals' Tdap vaccine (776423), 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
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Contributing authors	• PPD Safety Physician • PPD Safety Physician • PPD GVCL Project Manager • PPD GVCL Study Manager • PPD Global Patents Representative • PPD Global Clinical Regulatory Affairs Representative • PPD Vaccine Supply Coordinator • PPD Vaccine Supply Coordinator • PPD Director, Global Regulatory Affairs • PPD US Vaccines Medical Affairs Lead • PPD Local Delivery Lead • PPD Specialist, Science Writing

GSK Biologicals' Protocol DS V 12.4

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Protocol Administrative Change 2 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Sponsor signatory	Narcisa Elena Mesaros, Project Level Clinical and Research Development Lead, Combination Vaccines, Global Vaccine Development
Signature	_____
Date	_____

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Protocol Administrative Change 2 Rationale

Amendment number:	Administrative Change 2

Rationale/background for changes:

For the persistence only group, serious adverse events occurring due to study related procedures will be collected. This is noted in section 8.4 “Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies”, but due to a typographical error, it has not been noted in section 5.5 “Outline of study procedures”. This administrative change has been prepared to correct this typographical error in Table 3 “List of study procedures” as seen under section 5.5 “Outline of study procedures”.

Protocol Administrative Change 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut, 89
1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.9.2.

Synopsis

Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Indication/Study population	Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.
Rationale	This study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, up to 9 years following vaccination with GlaxoSmithKline's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (*Boostrix*). In addition, this study will provide the immunogenicity and safety data of *Boostrix* as a second dose of Tdap vaccine ***9*** years following vaccination with either *Boostrix* or *Adacel* in the study 106316. The data from this study is planned to support the indication of *Boostrix* as a second dose of Tdap vaccine. As per advice from Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the control group will receive *Boostrix* as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.
Objectives	**Co-Primary** • To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years. • To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

The criterion for meeting the above objective is defined as:

- One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).
- One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  - One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.
  - One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

The criterion for meeting the above objective is defined as:

- One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

[$]Booster response to D and T antigens is defined as:

- for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and
- for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.

[$]Booster response to PT, FHA and PRN antigens is defined as:

- for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;
- for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
- for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.

Secondary

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA,

and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.

- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

*Refer to co-primary objectives for the definition of booster response.

*Alternative Booster response to D and T antigens is defined as:

- for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
- for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration

≥ 6.0 IU/mL are not evaluable for vaccine response.

*Alternative Booster response to PT, FHA and PRN antigens is defined as:

- for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
- for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
- for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase in antibody concentration from the pre-vaccination concentration, one month after vaccination.

Study design

- Experimental design: A phase III, parallel, open-label, interventional, multicenter study with the same two parallel groups as in the 106316 study and one Control group receiving the first dose of Tdap vaccine (*Boostrix*).
- Study groups:
  - Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (*Boostrix*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (*Adacel*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

Synopsis Table 1 Study groups foreseen in the study

Study Groups	Number of subjects	Age (Min - Max) (age unit)
Boostrix Group	Approximately 733	28 years-73 years
Adacel Group	Approximately 367	28 years-73 years
Control Group	Approximately 367	28 years-73 years

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups		
		Boostrix Group	Adacel Group	Control Group
Boostrix	Tdap	x	x	x

- Blinding: This study will be an open study since this is an extension of study 106316 (Tdap 0.3-007) which was un-blinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: Non-randomized, all the study groups will receive a single dose of *Boostrix*.
- Control: Active control.
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects at Visit 6 i.e. at Year 9 (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The stud y procedures will be similar across all groups at Visit 6 and Visit 7).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 and who participated in all phases of the study including Year 9 time point and approximately one month for the Control group.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.
For example, if the subject did not want to participate in the

Year 1 evaluation, he/she can participate at Years 3, 5 and 9.

In addition, approximately 367 subjects will be newly enrolled at Year ***9*** time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups.

Total enrolment in the 106316 study was 2284 subjects, 1522 of whom were vaccinated with *Boostrix*. There were 1587 subjects (1064 *Boostrix* recipients) who returned for the Year 1 time point, 1441 subjects (976 *Boostrix* recipients) returned for the Year 3 time point and 1257 subjects (856 *Boostrix* recipients) returned for the Year 5 time point. Assuming an attrition rate of 15% from Year 5, it is estimated that 1100 subjects (733 *Boostrix* recipients) might return for the Year 9 time point. Also, approximately 367 subjects are planned to be enrolled in the Control group.

Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination (Refer to the co-primary objectives for the definition of booster response).

Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study

vaccine at Year ***9*** time point.

- Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
- Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to secondary objectives for the definition of booster response).

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
D	Diphtheria
DTaP	Diphtheria, Tetanus, Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EDD	Estimated Date of Delivery
eTDF	Electronic Temperature excursion Decision Form
EGA	Estimated Gestational Age
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FHA	Filamentous Hemagglutinin from Bordetella pertussis
GCP	Good Clinical Practice
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medical Products
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
LMP	Last Menstrual Period
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter

PRN	Pertactin from Bordetella pertussis
PT	Pertussis Toxoid from Bordetella pertussis
RCC	Reverse Cumulative distribution Curve
RDE	Remote Data Entry
SAE	Serious Adverse Event
SBIR	Randomization System on Internet
SPM	Study Procedures Manual
SOP	Standard Operating Procedure
T	Tetanus
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

Glossary of Terms

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,
- The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or

misuse.

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 10.4 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, the larche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively

	solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Boostrix®	Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine
Infanrix®	Combined diphtheria, tetanus and acellular pertussis vaccine

1. INTRODUCTION

1.1. Background

Diphtheria, tetanus (toxoids) and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Since the 1980s, there has been an increase in the number of reported cases of pertussis in the United States (US), especially among 10-19 year olds and infants younger than six months of age. By December 2012, 48,227 cases of pertussis were reported to Centers for Disease Control and Prevention (CDC), more than twice the number reported during the same time period in 2011 [CDC, 2012a]. The incidence of confirmed and probable pertussis among persons aged ≤ 19 years, by age and vaccine received in the US shows that high rates of pertussis is observed among adolescents and older children 7 through 10 years of age suggesting early waning of immunity [CDC, 2012b]. According to the recent General Recommendations on Immunization, adolescents and adults 11-18 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults 19 years of age and older who have not received a dose of Tdap [ACIP, 2012]. All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should receive a Tdap vaccine at 27-36 weeks gestation during each pregnancy [CDC, 2012c; CDC, 2012d].

Boostrix is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti, 2002; Greco, 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in *Boostrix* are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. In 2005, *Boostrix* (0.3 mg) was approved in the US for use in 10-18 year olds. In December 2008, it was approved for use in adults 19-64 years of age and in 2011, it was approved in the US for use in adults 65 years of age and older.

Please refer to the Prescribing Information for information regarding the potential risks and benefits of *Boostrix*.

1.2. Rationale for the study

A study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by Sanofi Pasteur's *Adacel* vaccine. All primary objectives were met with the exception of pertactin booster response which was observed to be below the 80% margin. Despite this failure, *Boostrix* recommendation in adults 19 years of age or older has been obtained.

Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005] and recent data shows that protection starts to wane within three years [Koepke, 2014]. Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first ***five*** years after vaccination [Weston, 2011; GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5)]. The current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to ***9*** years following vaccination with *Boostrix*.

Providing pertussis booster vaccination aims to boost immunity and disrupt the disease cycle. Currently in the US, no data is available on the immunogenicity and safety of *Boostrix* given as a second dose of Tdap vaccine. This study is intended to assess subjects who were vaccinated in the 106316 study and they will be invited to participate in this long-term follow-up and re-vaccination study at Year 9 time point. The purpose of vaccination with *Boostrix* at Year 9 time point instead of the previously intended Year 10 time point is to evaluate the immunogenicity and safety of a second dose of *Boostrix* at a time point earlier than the ten year interval. This study will also evaluate the immune response to the booster dose with *Boostrix* in subjects whose previous Tdap vaccination was a non-GSK vaccine.

As per advice from the Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive *Boostrix* as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.

2. OBJECTIVES

2.1. *Co*-Primary objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

  – One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of Infanrix vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

  – One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

Refer to Section 10.1 for definition of the co-primary endpoints and Section 10.3.1 for the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.

[$]Refer to Section 10.5 for the definition of booster response.

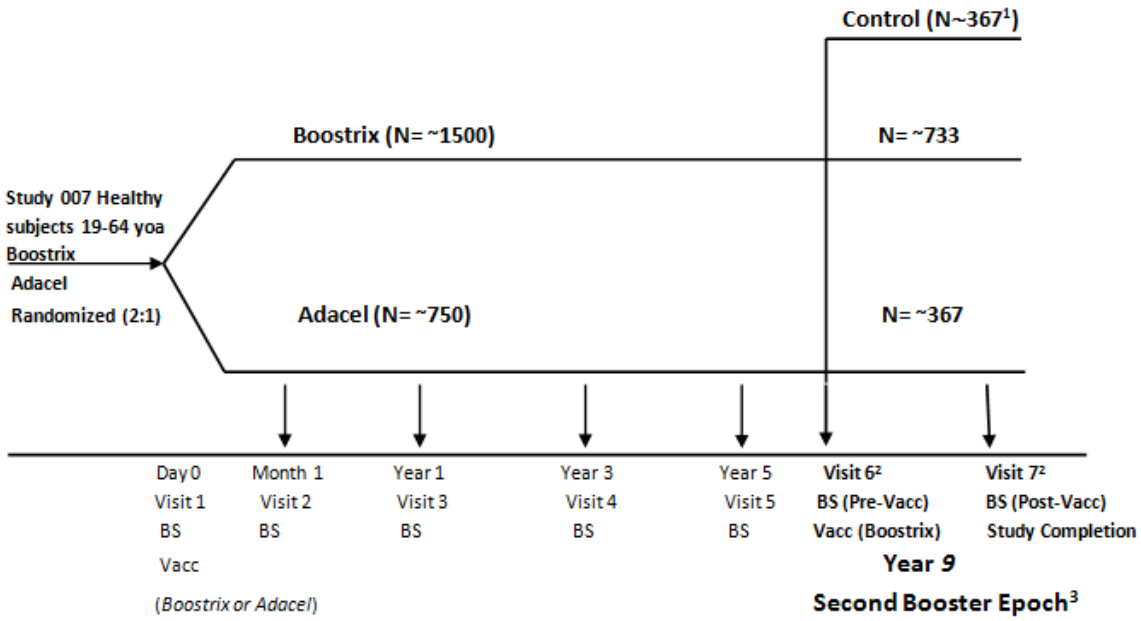
2.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.
- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination**.**
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of alternate booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 10.2 for definitions of secondary endpoints.

*Refer to Section 10.5 for the definitions of booster response and alternate booster response.

3. STUDY DESIGN OVERVIEW



Yoa= Year of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch is a non-randomized study, for practical purposes group ratio of 1:2 :1 is assigned for the Control, Boostrix and Adacel groups respectively for the Year ***9*** time point.
[1]Subjects who were not part of the 106316 study will be recruited as the Control group.
[2]For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch has been added for practical purposes and it has no relation to the number of epochs in this study.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: A phase III, parallel, open-label, interventional, multicenter study with the same two parallel groups as in the 106316 study and one new Control group receiving the first dose of Tdap vaccine (*Boostrix*).
- Study groups:
  - Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (*Boostrix*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (*Adacel*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

– Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

Table 1 Study groups foreseen in the study

Study Groups	Number of subjects	Age (Min - Max) (age unit)
Boostrix Group	Approximately 733	28 years-73 years
Adacel Group	Approximately 367	28 years-73 years
Control Group	Approximately 367	28 years-73 years

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups		
		Boostrix Group	Adacel Group	Control Group
Boostrix	Tdap	x	x	x

- Blinding: This study will be an open study since this is an extension of study 106316 (Tdap 0.3-007) which was unblinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups. Subjects in the Control group will also be analyzed as a separate group.
- Treatment allocation: Non-randomized, all the study groups will receive a single dose of *Boostrix* at Year 9 (Visit 6).
- Control: Active control.
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9 (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 and who participated in all phases of the study including Year 9 time point and approximately one month for the Control group.
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects / centers

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

For example, if the subject did not want to participate in the Year 1 evaluation, he/she can participate at Years 3, 5 and 9.

In addition, approximately 367 subjects will be newly enrolled at Year 9 time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- 28-38 years:~25.4%
- 39-58 years: ~35.5%
- 59-73 years: ~39.1%

Total enrolment in the 106316 study was 2284 subjects, 1522 of whom were vaccinated with *Boostrix*. There were 1587 subjects (1064 *Boostrix* recipients) who returned for the Year 1 time point, 1441 subjects (976 *Boostrix* recipients) returned for the Year 3 time point and 1257 subjects (856 *Boostrix* recipients) returned for the Year 5 time point. Assuming an attrition rate of 15% from Year 5, it is estimated that 1100 subjects (733 *Boostrix* recipients) might return for the Year 9 time point. Also, approximately 367 subjects are planned to be enrolled in the Control group.

4.2. Inclusion criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

Vaccination phase at Year 9 applicable for subjects in the Boostrix and Adacel groups only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix and Adacel groups only:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.

Vaccination phase at Year 9 applicable for subjects in the Control group only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Control group only:

- Subjects within the age range of 28-73 years will be considered eligible to participate in this study in the Control group.

Vaccination phase at Year 9 applicable for ALL subjects (Control, Boostrix and Adacel groups):

The following criteria are applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix, Adacel and Control groups:

All subjects must satisfy the following criteria at study entry at Year 9 time point:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject for vaccination at Year 9 time point.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the Glossary of Terms for the definition of menarche and menopause.

- Female subjects of child bearing potential may be enrolled in the study, if the subject
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception for 1 month after completion of the vaccine dose.

Please refer to the Glossary of Terms for the definition of adequate contraception.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of Year 9 vaccination time point. If any criteria are applicable, the subject must not be vaccinated in the study:

For subjects in the Boostrix and Adacel groups:

- Administration of Tdap vaccine since the last dose received in the study 106316.

For subjects in the Control group:

- Administration of Tdap *(Boostrix or Adacel)* vaccine at any time prior to the administration of *Boostrix* vaccine in this study.

For ALL subjects (Control, Boostrix and Adacel groups):

- Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of *Boostrix* vaccine in this study.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to Visit 6 (pre-vacc). For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with the exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Hypersensitivity to latex.
- History of diphtheria, tetanus or pertussis diseases.
- Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of *Boostrix*.
- History of any neurological disorders or seizures.

- Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 100.4°F by any route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.

4.4. Elimination criteria during the study

The following criteria should be checked at Visit 6 and are applicable to all subjects. If any become applicable during the study, from Visit 6, it will not require withdrawal of the subject from the study but may determine a subject's eligibility in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a vaccine against diphtheria, tetanus or pertussis during the study period (Visit 6 through Visit 7).
- Administration of any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier during the study period (Visit 6 through Visit 7).
- Diphtheria and/or tetanus and/or pertussis disease diagnosed during the study period (Visit 6 through Visit 7).
- Administration of immunoglobulins and/or any blood products within three months of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids are allowed).

- Any confirmed or suspected immunosuppressive or immuno-deficient condition based on medical history and physical examination (no laboratory testing is required) diagnosed during the study period (Visit 6 through Visit 7).

4.5. Contraindications to vaccination

Since this is a single dose booster study, contraindications to vaccination for vaccination at Year 9 time point are included in the exclusion criteria. Refer to Section 4.3.

- The following adverse events (AEs) constitute contraindications to administration of *Boostrix* at that point in time; if any one of these AEs occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).
- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 100.4 °F by any route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the vaccine dose, at the discretion of the investigator.

4.6. Warnings and Precautions

Refer to the approved product label/package insert of *Boostrix*.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 Declaration of Helsinki (Protocol Appendix A), US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator.

A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfill its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favorable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favorable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favorable opinion of the IRB/IEC will be transmitted by investigator to CRA prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favorable opinion of an appropriate amendment or administrative change, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].)

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,

- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the October 1996 Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects face to face. The Informed Consent Form may be read to the subjects but, in any event, the investigator or designate shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subjects and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the

presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The subjects should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects for participating in the trial.

l. The anticipated expenses, if any, to subjects for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject is authorizing such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly

available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects will be informed in a timely manner if information becomes available that may be relevant to the subjects' willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgment, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. Subject identification and randomization of treatment

5.2.1. Subject identification

For the subjects in Boostrix and Adacel groups:

Subjects will retain their subject numbers as in the 106316 study.

For the subjects in the Control group:

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.2.2. Allocation of treatment

5.2.2.1. Numbering of supplies

The numbering of supplies will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

5.2.2.2. Treatment allocation to the subject

5.2.2.2.1. Study group and treatment number allocation

There will be no randomization of subjects into groups in this study. The subjects in this study will be allocated to the same groups as in the vaccination study 106316. Subjects will be allocated a new treatment number, but will retain the same subject number as in the 106316 study (Boostrix and Adacel groups), or subject numbers will be assigned sequentially (for the subjects in the Control group).

The central randomisation system on internet (SBIR) will be used at the investigator site to track enrolment at Year 9 i.e. to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- 28-38 years: ~25.4%
- 39-58 years: ~35.5%
- 59-73 years: ~39.1%

The number of the administered treatment must be recorded in the eCRF on the Vaccine Administration form.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.3. Method of blinding

This study will be conducted in an open manner.

Investigators will be provided with the identification of subjects with low immunogenicity results (see Section 5.7.2).

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site

personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

(Administrative change: 03 February 2015)

The summary of study procedures is summarized in Table 3.

Table 3 List of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 AND 7[1] Year *9* *9* years following *Boostrix/ Adacel* vaccination Administration of *Boostrix* vaccine	
				Visit 6	Visit 7
Informed consent for persistence follow-up	●	●	●	●[3]	
Informed consent for vaccination				●	
Check inclusion criteria	●	●	●	●[3]	
Check exclusion criteria				●	
Check elimination criteria	●	●	●	●[3]	●
Collect demographic data[2]				●	
Medical history				●	
Vaccination history				●[3]	
Pre-vaccination body temperature				●	
Recording of administered treatment number				●	
Urine Pregnancy test[4]				●	
Check contraindications to vaccination				O	
Check warnings and precautions				O	
Blood sampling (~5 mL) for antibody determination	●	●	●	●[3]	●
Vaccination				●	
Distribution of diary card				O	
Daily recording of solicited adverse events during the 4-day Day (0-3) follow-up period post-vaccination, by subjects				●	
Recording of non-serious adverse events during the 31 day Day (0-30) follow-up period post-vaccination, by subjects				●	●
Return of diary cards					O

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following *Boostrix*/ *Adacel* vaccination**	**VISIT 4** **Year 3** **3 years following *Boostrix*/ *Adacel* vaccination**	**VISIT 5** **Year 5** **5 years following *Boostrix*/ *Adacel* vaccination**	**VISITS 6 AND 7[1]** **Year *9*** ***9* years following *Boostrix*/ *Adacel* vaccination** **Administration of *Boostrix* vaccine**	
				Visit 6	**Visit 7**
Diary card transcription by investigator					●
Record concomitant medication/vaccination	●	●	●	●[3]	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●[3]	●
Recording of any large injection site reactions in the eCRF by the investigator[5]				●	
Reporting of SAEs				●[3]	●
Recording of pregnancies				●	●
Record any intercurrent medical conditions					●
Study Continuation	●	●	●	O (NA for Control group)	●
Study conclusion for persistence follow-up				●[3]	
Study Conclusion for vaccinated groups					●
Investigator sign-off on data for persistence follow-up				●[3]	
Investigator sign-off on data					●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
[1]Applicable to Control, Boostrix and Adacel groups.
[2]Year of birth, gender, ethnicity and race for subjects in the Control group.
[3]These are the only study procedures applicable for subjects who refuse vaccination at Year 9 time point.
[4]Applicable to female subjects of childbearing potential only.
[5]Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed.

Table 4 Intervals between study visits

Intervals between study visits for subjects in Boostrix and Adacel groups:

Visit	Optimum length of interval [1]	Maximum interval allowed [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	9 years – 3 months	9 years +6 months
Visit 7 (Visit 6→ Visit 7)	30-48 days (at least 30 days[3])	21-48[3] days

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year ***9*** cohort for analysis if they make the study visit outside this interval.
[3]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Intervals between study visits for subjects in Control group:

Visit	Optimum length of interval [1]	Maximum interval allowed[2]
Visit 6→Visit 7[3]	30-48 days (at least 30 days[4])	21-48 days

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year 9 cohort for analysis if they make the study visit outside this interval.
[3]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[4]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

5.6. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

Procedures at Visits 3, 4, 5 and 6:

Persistence follow-up phase up to Year 9 time point:

The following study procedures are applicable to subjects who refuse vaccination at Year 9 time point:

- Obtain written informed consent from all subjects at all long-term time points.
- Check inclusion criteria at all study visits.
- Check elimination criteria at all study visits.
- Record concomitant medication/vaccination as described in Section 6.9.
- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Study continuation at Years 3 and 5.
- Study conclusion at Year 9 (Visit 6).

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- Obtain written informed consent from all subjects consenting for vaccination.
- Check inclusion and exclusion criteria.
- Check elimination criteria.
- Check medical and vaccination history:
  - Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.
  - Obtain the subject's vaccination history by interview and/or review of the subject's medical records and record any vaccine administration within 30 days prior to the study vaccination in the eCRF.
- Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.
- Treatment number allocation will be performed as described in Section 5.2.2.2. The number of each administered treatment must be recorded in the eCRF.
- Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 4.5 and 4.6 for more details.
- Record pre-vaccination body temperature.

- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D.
- Administration of a single dose of *Boostrix* vaccine to all study participants as described in Section 6.2. The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.
- Management of diary cards:

  After vaccination, diary cards will be provided to the subject. The subjects will be instructed to record the following information in appropriate sections of the diary card:

  – Record body (oral) temperature and any solicited local/general AEs on the day of vaccination and during the next 4 days, i.e. (Day 0-3).

  – Any unsolicited AEs on the day of vaccination and during the 31 day, i.e. Day (0-30) follow-up period post vaccination.

  – Record any large injection site reactions (Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions).

  – Any concomitant medication/vaccination given after the administration of the study vaccine.

  – The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious and also to contact the investigator in case of large injection site reactions.
- Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.
- Refer to Section 8.4 for procedures for the investigator to record AEs, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.

Procedures at Visit 7:

- The completed diary card will be collected and reviewed during discussion with the subject at this visit. Any unreturned diary cards will be sought from the holder through telephone call(s) or any other convenient procedure such as courier, home pick-up etc.
- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D.
- Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.

- Refer to Section 8.4 for procedures for the investigator to record AEs, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.
- Record any pregnancies up to Visit 7 (post-vacc).
- Study conclusion.

5.6.1. Activities at study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness.
- complete the Study Conclusion section in the eCRF.

At/after study completion, no post-trial commercial vaccines will be provided in this study.

5.7. Sample handling and analysis

5.7.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

5.7.2. Laboratory assays

Please refer to Appendix G for the address of the clinical laboratories used for sample analysis.

Table 5 presents the details of laboratory assays.

A sample of approximately 5 mL of whole venous blood, to provide approximately 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and nine years [at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups following study vaccination in 106316 study, and only at (pre-vacc) and Visit 7 (post-vacc) for the Control group. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C (alternatively at approximately -70°/80°C is also acceptable) until sent to the sponsor. Sera will be sent to Quest Diagnostics Laboratories (Valencia, CA) and subsequently to GSK Biologicals, for the laboratory assays.

All serological assays will be performed at GSK Biologicals' central laboratory or in a laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus (anti-T and anti-D) will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off for seroprotection of both assays is 0.1 IU/mL [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL (The Vero cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL and will be used for pre /post vaccination assays at Year 9. The study will consider anti-D concentrations greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection). The ELISA test will define the seroprotection status for the primary endpoint).

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA technique. The cut-off of the three assays is 5 EL.U/mL [Sato, 1982].

Table 5 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off †
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016/0.004*
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA	In-house assay	EL.U./mL	5

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
**VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.
*VERO cut off is ≥ 0.004 IU/mL for Year 5 and Year ***9*** time points
† The cut-off of the diphtheria (ELISA and VERO-cell), tetanus and pertussis assays may be subject to change.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

The investigator is encouraged to share the immunological assay results for low immunological assay results with the study subjects.

Low result is defined as:

- Antibody concentrations < 0.01 IU/mL for diphtheria antigen and,
- Antibody concentrations < 0.1 IU/mL for tetanus antigen.

For the study subjects identified as low-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

5.7.3. Immunological read-outs

Table 6 Immunological read-outs for all subjects

Blood sampling time point		Marker
Timing	**Visit no.**	
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 9	6 and 7†	D*
		T
		PT
		FHA
		PRN

†Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7, respectively to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
*VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.

Samples will not be labeled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.

- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Study vaccines in study 106316 were *Boostrix* and *Adacel*.

6.1. Study vaccine

The study vaccine to be used at the Year 9 time point has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine

Treatment name	Vaccine/product name	Formulation	Presentation	Volume	Number of doses
Boostrix	Tdap	Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf , Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as $Al(OH)_3$:≤ 0.39 mg, Sodium chloride	Pre-filled syringes, Homogeneous turbid white suspension	0.5 mL	1

6.2. Dosage and administration

In order to monitor enrolment and to control age distribution in the Control group, allocation of treatment number will be performed using SBIR. The application will ensure enrolment in the Control group is performed as per target age distribution (see Section 4.1).

The vaccines will be administered as detailed in Table 8.

The vaccine is to be administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. *Boostrix* should in no circumstances be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1 - 1 1/2 inch length, 25 gauge will be used [ACIP, 2011; Zuckerman, 2000].

* Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

Table 8 Dosage and Administration

Visit	Dose	Vaccine	Route	Site	Side
Visit 6[e]	1	Tdap[a]	IM[b]	D[c]	Non-Dominant[d]

a. Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
b. Intramuscular (IM)
c. Deltoid (D)
d. Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.
e. Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

6.3. Storage

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Temperature excursions must be reported in degree Celsius.

Vaccines will be stored at the defined temperature range (i.e. 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature monitoring device will be used as a backup device and it will be opened in case of any temperature deviation (temperature outside the defined range, i.e. 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature monitoring device), if:

- proper functioning was demonstrated during the monitor's site evaluation,
- if the system continues to work in case of a power failure, and
- if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working after the alarm is activated.

It is also required to place a validated freezing point indicator close to the vaccines as a back-up device.

Any temperature excursion outside the range of 0.0 to +8.0°C impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix F.

6.4. Treatment allocation and randomization

Subjects in the treatment groups- Boostrix, Adacel and Control will be analyzed as separate groups and will receive a dose of Tdap vaccine (*Boostrix*) at Year 9 time point.

It is anticipated that approximately 1100 subjects (733 subjects from Boostrix group and 367 from Adacel group in the primary study) would return for the Year 9 vaccination visit. Approximately 367 subjects who were not part of the 106316 study will be enrolled in the Control group to receive the first dose of Tdap vaccine (*Boostrix*). All subjects participating in the vaccination phase will receive a single dose of *Boostrix*.

6.5. Method of blinding and breaking the study blind

The study is an open study, since this is an extension of study 106316 which was un-blinded at the time of primary analysis. At Year 9 time point all the subjects in all the groups will receive a single dose of *Boostrix*.

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix F for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF, in SBIR and on the vaccine accountability form.

6.7. Packaging

Vaccination phase at Year 9 time point, refer to Appendix F.

6.8. Vaccine accountability

Vaccination phase at Year 9 time point, refer to Appendix F.

6.9. Concomitant medication/treatment

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

At each study visit, the investigator should question the subject about any medication /product taken and vaccination received by the subject.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to any study blood sampling) are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration.

Vaccination phase at Year 9 time point:

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of the dose of study vaccine and ending up to next study visit after the dose of study vaccine are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to study vaccination or at any time during the study period are to be recorded with the generic name for the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Sections 4.3 and 4.4

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding the dose of study vaccine and ending 31 days (Day 0-30) after the dose of study vaccine is to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [Temperature by any route < 100.4 °F. The preferred route for recording temperature in this study will be oral] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for

combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

During the period starting with administration of the dose of study vaccine and ending 31 (Day 0-30) days after the dose of study vaccine, concomitant medication administered for the treatment of an AE must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form/ SAE screens in the eCRF, as applicable. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study (i.e. from Visit 6 through Visit 7) must be recorded in the eCRF.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action.
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Aes to be recorded as endpoints (solicited Aes) are described in Section 8.6. All other Aes will be recorded as UNSOLICITED Aes.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Aes may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. Aes to be recorded as endpoints (solicited events) are described in Section 8.5. All other Aes will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

8.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation

and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are Aes. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.3. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE, (Refer to Sections 8.1 and 8.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as Aes or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.4. Time period, frequency, and method of detecting *adverse* events, serious adverse events and pregnancies

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

Because subjects are not being vaccinated as part of the time points Year 1, 3 and 5, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after removal of write access of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.9.2 for details of the back-up reporting system.

Vaccination phase at Year 9 time point:

For subjects who receive vaccination at the Year 9 time point: All AEs occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to riter international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting pregnancies.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 9.

Table 9 Reporting periods for adverse events, serious adverse events and pregnancies

Event	Pre-vacc (consent obtained)	Vaccination	4 days (Day 0-3) post-vacc	31 days (Day 0-30) post-vacc
				Study conclusion
Solicited local and general Aes including large injection site reactions				
Unsolicited Aes				
Aes/SAEs leading to withdrawal from the study				
SAEs				
SAEs related to study participation or concurrent GSK medication/vaccination				
Pregnancies				

Pre-vacc.: pre-vaccination; Post-vacc.: post-vaccination.

The investigator will inquire about the occurrence of Aes/SAEs at every visit during the study and throughout the follow-up phase as appropriate.

All Aes either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. Aes not previously documented in the study will be recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. Refer to Section 6.9.

8.5. Solicited adverse events

The following local (injection-site) Aes will be solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they will be asked to contact study personnel and to visit the investigator's office and/or home visit for evaluation as soon as possible. The investigator will record detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

Table 11 Solicited general adverse events

The following general Aes will be solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

8.6. Evaluating adverse events and serious adverse events

8.6.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting Aes, the subject should be asked a non-leading question such as:

"Have you felt different in any way since receiving the vaccine or since the previous visit?"

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6.2. Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 12.

Table 12 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 100.4 °F by any route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0	:	Absent
1	:	≤ 20 mm
2	:	> 20 mm and < 50 mm
3	:	≥ 50 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0	:	<100.4°F
1	:	≥100.4°F to ≤102.2°F
2	:	>102.2°F to ≤104.0°F
3	:	> 104.0°F

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited Aes (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity of each AE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. (In adults, such an AE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.2.

8.6.3. Assessment of causality

The definitions for "NO" and "YES" have been written in such a way that all events that have been attributed a "NO" can be pooled with events which in the primary vaccination study were determined to be "not related" or "unlikely to be related" to vaccination. Those events that are attributed a "YES" can be pooled with those events that in the past were determined to have a "suspected" or "probable" relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general Aes to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other Aes should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.
YES	:	There is a reasonable possibility that the vaccine contributed to the AE.

Non-serious and serious Aes will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.7. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if they received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.8. Follow-up of adverse events, serious adverse events, pregnancies and assessment of outcome

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until the end of the study.

All Aes documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Investigators will follow-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE; until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.9.1.

In case the electronic SAE reporting system does not work or after removal of write ***access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.9.2. for details of the back-up reporting system.

Outcome of any non-serious AE occurring during the 31 day (Day 0-30) follow-up period post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

Follow-up of pregnancies

Pregnant subjects will be followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.9. Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after removal of write access of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

8.9.1. Time frames for submitting serious adverse event reports and pregnancies to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. Because subjects are not being vaccinated as part of the study protocol at the Year 1, 3 and 5 time points investigators are not required to specifically solicit SAEs in the persistence follow-up phase. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 or in case of vaccination phase at Year ***9***, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information (Refer Table 13).

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after removal of write access of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Table 13 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information.

8.9.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours as outlined in Section 8.9.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received WITHIN 24 HOURS as outlined in Section 8.9.1.

8.9.2.1. Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.9.2.2. Updating of SAE or pregnancy information after removal of write access of the subject's eCRF

When additional SAE or pregnancy information is received after removal of write access of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 13.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.3.

Please see Sponsor Information Sheet for contact details

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD **US Study Contacts for Concerns Relating to an SAE** GSK Biologicals Medical Monitor: PPD Office: PPD Cell: PPD Fax: PPD GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD or PPD

8.9.3. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.10. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.9. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.11. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 9. Investigators are not obligated to actively seek Aes or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.12. Pregnancy

Persistence follow-up phase up to Year 9 time point:

The following criterion is applicable to subjects who refuse vaccination at Year 9 time point:

Because subjects are not being vaccinated as part of the time points at Year 1, 3 and 5, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit during the time points at Year 1, 3 and 5 should not be excluded from the visit on the basis of their pregnancy.

Vaccination phase at Year 9 time point:

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on a electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.9 and 8.9.1:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of fetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.9.2. While the investigator is not obligated

to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.13. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for a study visit as specified in the protocol is considered to have completed the study phase (time point) pertaining to that study visit.

9.2. Subject withdrawal

Subjects who are withdrawn because of Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE/ AE until resolution of the event (see Section 8.1).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5 and 9 year persistence analyses.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter.

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the

decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event*
- Moved from the study area
- Lost to follow-up
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.8).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.

Refer to Section 10.5 for the definition of booster response.

10.2. Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and ***9*** years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at the Year ***9*** time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the definitions of booster response and alternate booster response).

  * Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited Aes during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.

10.3. Estimated sample size

No sample size is calculated for the time points at Year 1, 3 and 5. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study.

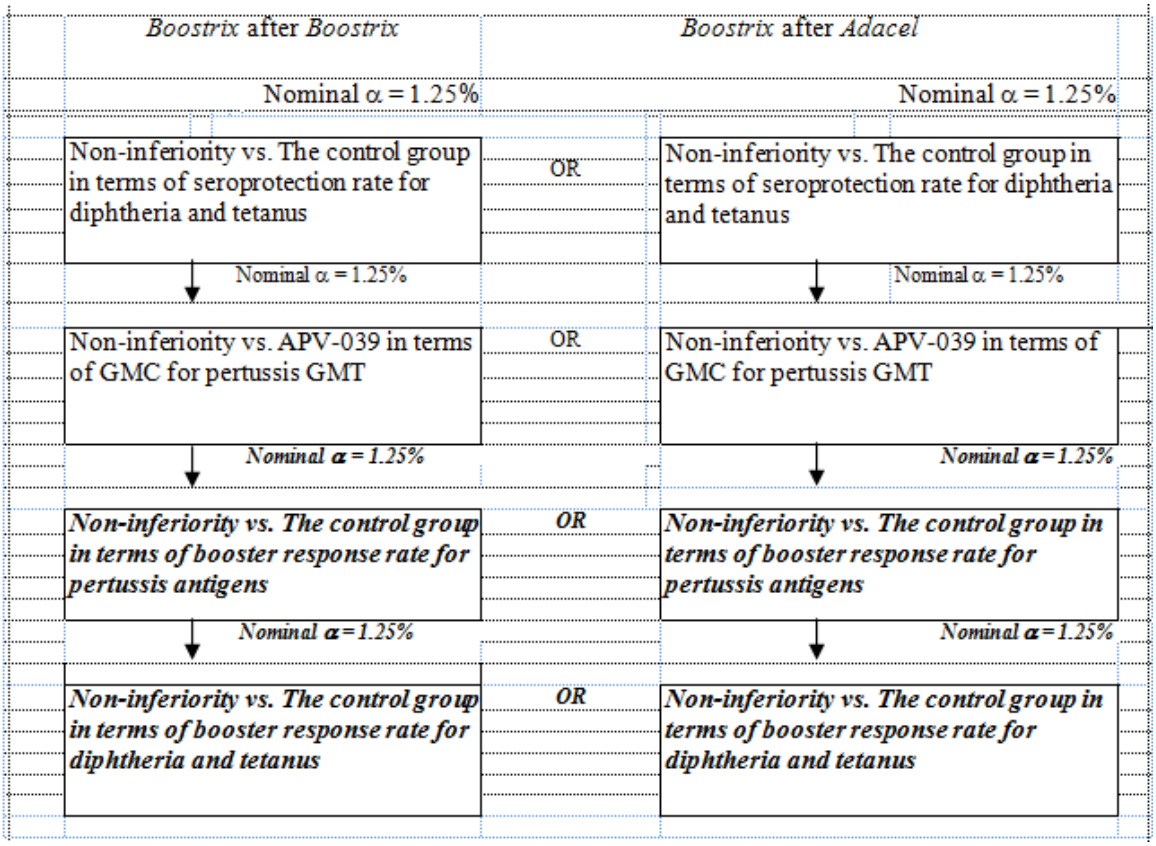
It is estimated that around 1100 subjects (733 subjects from Boostrix group and 367 subjects from Adacel group in the primary study) would return for Year 9 study. Around 367 subjects are to be recruited for the Control group to receive the first dose of Tdap vaccine (*Boostrix*). Assuming 80% of enrolled subjects will be evaluable, this gives 586 evaluable subjects in Boostrix group, 293 evaluable subjects in Adacel group and 293 evaluable subjects in the Control group.

10.3.1. Control on type I error

This study is designed to assess independently non-inferiority of Boostrix group to the Control group, and non-inferiority of Adacel group to the Control group. To control the overall type I error below 2.5%, a Bonferroni adjustment is used, i.e., type I error allowed for each non-inferiority assessment is 1.25% (one-sided). In addition to further control misinterpretation related to multiple primary objectives, a hierarchy procedure will be used as described in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%

An objective will be reached if the associated criteria are met and the previous objectives were reached



10.3.2. Power computation

With 293 evaluable subjects in the Adacel group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Adacel group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Adacel group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 88.91% (See Table 14 and Table 15 respectively).

As shown in Table 16, the power to demonstrate non-inferiority of Adacel group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be very low (4%). In

other words, there is a big chance that non-inferiority would not be demonstrated for one or more of the antibodies.

With 586 evaluable subjects in the Boostrix group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Boostrix group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Boostrix group to *Infanrix* in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 97.87 % (See Table 17 and Table 18 respectively).

As shown in Table 19, the power to demonstrate non-inferiority of Boostrix group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be 48%. It is likely that non-inferiority might not be demonstrated for one or more of the antibodies.

Table 14 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	**DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)**	**Non-inferiority criterion Difference(2nd dose-1st dose)**	**293 (*Boostrix* following *Adacel*) 293 (First *Boostrix*)**
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 15 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 (BOOSTRIX)-007 (*Boostrix*)**	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =293 in Adacel+Boostrix**
Anti-PT	0.480	0.306	2884	99.99%
Anti-FHA	0.422	0.370	685	99.99%
Anti-PRN	0.710	0.413	631	88.93%
Overall power**				88.91%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 16 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
	DTPA 0.3 (BOOSTRIX)-007 (Boostrix Group)	Non-inferiority criterion Difference(2nd dose- 1st dose)	293 (Boostrix following Adacel) 293 (First Boostrix)
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	74.19%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	57.51%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	73.64%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	98.81%
		Overall power**	4.14%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

Table 17 Power to demonstrate non-inferiority of a second dose of *Boostrix* following the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)	Non-inferiority criterion Difference(2nd dose- 1st dose)	586 (*Boostrix* following *Boostrix*) 293 (First *Boostrix*)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 18 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 (BOOSTRIX)-007 (*Boostrix)***	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =586 in Boostrix+Boostrix**
Anti-PT	0.480	0.306	2884	>99.99%
Anti-FHA	0.422	0.370	685	>99.99%
Anti-PRN	0.710	0.413	631	97.87%
Overall power**				97.87%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 19 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to the first dose of *Boostrix* with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	**Reference values**	**Non-inferiority criterion Difference(2nd dose- 1st dose)**	**Power* to reject H0: LL of 97.5%CI of difference <-10%**
	DTPA 0.3 (BOOSTRIX)-007 (Boostrix Group)		**586 (Boostrix following Boostrix) 293 (First Boostrix)**
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	88.89%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	71.39%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	88.45%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	99.96%
Overall power**			48.69%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

10.4. Study cohorts to be evaluated

10.4.1. Year X (1, 3, 5, 9) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

10.4.2. According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5) cohort

The ATP Year X (1, 3, 5) cohort will include all subjects from Year X (1, 3, 5) cohort who were in the ATP cohort for analysis of immunogenicity in 106316 study and who did not meet the following elimination criteria:

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

10.4.3. Additional cohorts defined for Year 9 analysis

10.4.3.1. Total Vaccinated Cohort (TVC) at Year 9

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

10.4.3.2. ATP cohort for analysis of safety at Year 9

The ATP cohort for analysis of safety at Year 9 time point will include all eligible and vaccinated subjects.

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis as listed in Section 6.9.

10.4.3.3. ATP cohort for analysis of immunogenicity at Year 9 (ATP Year 9)

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who comply with the procedures and intervals defined in the protocol (refer to Section 5.5 and Table 4).
- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 4.4) during the study.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after Year 9 vaccination.

10.5. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.2.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 10.6.2 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years, 5 years, and 9 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years, 5 years and 9 years following vaccination will be derived to evaluate the first secondary objective.
- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 9 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

Booster responses to be considered for Year 9 time point:

- Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and
  - for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL, one month after vaccination;
  - for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
  - for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.
- Alternative Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
  - for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
  - for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
  - Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.
- Alternative Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  - for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and

- for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

Handling of missing data:

Immunogenicity:

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Reactogenicity and Safety:

- For a given subject and the analysis of solicited symptom during the 4 day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

10.6. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 9) on cleaned data obtained through each Year X. A clinical study report (CSR) will also be written following each analysis.

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, time since last DT vaccination, gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year 9) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 9) cohort and in the ATP Year X (1, 3, 5 or 9) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 9) (in years) will be summarized using descriptive statistics.

10.6.2. Analysis of persistence

The primary analysis will be based on the ATP cohort for analysis of immunogenicity Year X (1, 3, 5, 9).

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 9) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves (RCC) by group.

Comparability between Groups - Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO), Year X (1, 3, 5, 9) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 9) after vaccination will be calculated.
- For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 5 EL.U/mL by ELISA, Year X (1, 3, 5, 9) after vaccination will also be calculated.

10.6.3. Analysis of immunogenicity at booster dose

The following analyses will be carried out after Year 9 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 9 cohort. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC at Year 9 will be performed to complement the ATP analysis.

Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% Cis.
- GMCs or GMTs at pre-vaccination, one month post-vaccination will be tabulated with 95% Cis.
- Booster response rate one month post-vaccination will be calculated with exact 95% Cis.
- Antibody concentrations/titres distribution at pre-vaccination and one month post-vaccination will be displayed using RCC.

Comparability between Groups – confirmatory analyses:

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm_{10} transformation of the concentrations.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.

Comparability between Groups – exploratory analyses:

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.
- For anti-D, anti-T antibody response, the two-sided 95% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Boostrix group and Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) will be calculated.

Sensitivity analysis

A complementary analysis will be carried out in order to evaluate the robustness of GMT/GMC results with respect to drop-out from the parent study (106316). More specifically multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC/GMT that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

In addition, within group assessment for the ATP analysis of immunogenicity at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***-3***8*** years old, 3***9***-5***8*** years old and 5***9***-7***3*** years old).

10.6.4. Analysis of safety

Persistence follow-up phase up to Year ***9*** time point:

The following is applicable to subjects who refuse vaccination at Year ***9*** time point:

No safety analysis will be performed for this study. If GSK is informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

Vaccination phase at Year 9 time point:

The primary analysis will be based on the TVC at Year 9. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 9 is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the treatment groups by solicited local and general symptom terms, and, for unsolicited Aes, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 0.9°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

The percentage of subjects who reports at least one unsolicited adverse event classified by MedDRA during the 31 day (Day 0-30) follow-up period after vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, Aes resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

In addition, safety analysis for TVC at Year 9 will be performed separately for each level of the age stratum (Subjects age at Year 9 vaccination will be classified into three categories, 28-38 years old, 39-58 years old and 59-73 years old).

10.6.5. Statistical methods

- The exact Cis for a proportion within a group will be computed using SAS, [Clopper, 1934].
- The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].
- The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown

variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

10.7. Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5 and Year 9) as available and reported separately. At Year 9 time point immunogenicity and safety of vaccine administration will be reported.

10.8. Planned interim analysis

No interim analysis is planned for this persistence study.

11. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

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Appendix A World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the

study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments/administrative changes is required prior to implementation.
- Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local

regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favourable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

V. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

VI. Record retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location (except for those required by local regulations to be maintained elsewhere). The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that there is an acceptable quality control procedure in place.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/

institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability

- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of CRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.
- GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

IX. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

X. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before criterion of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

XI. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Appendix C Overview of the Recruitment Plan

- All subjects who received vaccination in the study 106316 will be invited to participate in this long-term study.
- As part of the visit activities at the study conclusion visit in the 106316 study, subjects were asked to state their interest in participating in an extension study. Subjects who responded positively to this question will be contacted by the site as the sampling time point approaches in order to schedule the study visit.
- Subjects who do not provide samples at earlier long-term time points may still be considered eligible to provide samples at later long-term time points.
- The study will take place at multiple centres in the US.
- The Site Monitor will perform monitoring of actual enrolment against target enrolment on a continuous basis.
- Enrolment will be monitored through RDE.
- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date the subject received vaccination in study 106316. A window of ± 8 weeks around the actual time point for each subject will be permitted.

For the Control group:

- Approximately 367 subjects will be recruited to receive the first dose of Tdap vaccine (*Boostrix*) in this study.
- The study will take place at multiple centers in the US.
- The study duration per subject will be approximately one month.
- The recruitment of subjects into the study will be performed using RDE.
- Recruitment will be monitored by the site monitor.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used to minimize the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".
- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- The tube should not be overfilled (max. ¾ of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate label provided by GSK Biologicals (see point 3).

3. Labeling

- The standard labels provided by Quest should be used to label each serum sample.
- If necessary, any hand-written additions to the labels should be made using indelible ink.

4. Sorting and storage

- The tubes of serum should be stored in a vertical position at approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to Quest Diagnostics. Wherever possible, a backup facility for storage of serum samples should be available.
- Detailed instructions concerning the collection, Quest labelling and storage of all serum specimens are provided in the Quest Diagnostics Clinical Trials Investigator Manual for Protocol Number 110080, 110082, 110084, and 110086.

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, Valencia, California.

Refer to the separate Quest Diagnostics Clinical Trials Investigator Manual for Protocol Numbers 110080, 110082, 110084, 110086 for shipping details.

Appendix F Vaccine supplies, packaging and accountability

1. Vaccine and/or other supplies

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- *Boostrix* in pre-filled syringes

At least an additional 10% of the study vaccine will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject).

All pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:

The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each time point. Each label will contain the following information: study number, identification number for the subject (e.g. **Subject number)**, sampling time point (e.g., post ri 3), timing (e.g., study Month 7).

- Other supplies provided by GSK Biologicals:
  In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:
  - tubes with screw caps for serum samples,
  - racks and cardboard boxes for the tubes of serum.

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in criterio boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site from local country medical department to investigational site

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : PPD
E-mail: PPD

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

4. Vaccine accountability

At all times the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP WWD-1102, used and unused vaccine syringes should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine syringes are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP WWD-1102.

If no processes for destruction of unused clinical trial supplies are in place in the local GSK Biologicals site in the US, the unused supplies must be returned to GSK according to the instructions given by the GSK Biologicals responsible staff (in accordance with SOP-NPD-7200).

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Appendix G Clinical laboratories

Table 20 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, North America-Laval	Biospecimen Reception – Clinical Serology 525 Cartier blvd West – Laval – Quebec – Canada – H7V 3S8
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 – B-1300 Wavre – Belgium

Appendix H Amendments and Administrative changes to the protocol

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change 1

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer

Rationale/background for changes: This administrative change is being done to reflect a change of study personnel.

Amended text has been included in *bold italics* in the following section:

US Safety Contact for Faxing/Reporting SAE Information

Fax to:

US Safety Contact, GSK Biologicals
Fax: PPD
Tel: PPD

US Study Contacts for Concerns Relating to an SAE *(Amended 14 April 2009)*

~~GSK Biologicals Medical Monitor: PPD MD~~
~~Office: PPD~~
~~Cell: PPD~~
GSK Biologicals Medical Monitor: PPD ***MD***
Office: PPD
Cell: PPD
Fax: PPD

GSK Biologicals Clinical Safety Physician: PPD MD
Office: PPD
Cell: PPD

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Amendment number:	Amendment 1
Amendment date:	09 November 2010
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

- The list of coordinating and contributing authors for this amendment was updated.
- The maximum window period allowed for the return of subjects for the Year 5 and Year 10 follow-up visits (Visit 5 and Visit 6) has been extended from ± 5 weeks to ± 8 weeks.
- The contact details for reporting of SAEs have been clarified. As of now, two fax numbers will be used as back-up for the safety contact for reporting SAEs.
- Text pertaining to the reporting of spontaneous abortion has been removed from the protocol. Since this follow-up study involves no vaccine exposure, investigators are not obligated to report such an event.
- The number of attempts to contact subjects who do not return for scheduled persistence visits has been clarified.

Amended text has been included in *bold italics* in the following section:

Title page:

Co-ordinating author
(Amended 09 November 2010)

PPD Scientific writer

Contributing authors
(Amended 09 November 2010)

- PPD ***Senior Manager, Clinical Development, Boostrix/Hepatitis Vaccines, Global Vaccine Development***
- PPD ***Director, Lead Clinical Development, DTP Combination Vaccines, Global Vaccine Development***
- PPD ***Biostatistician, Boostrix (US)***
- PPD Project statistician, Boostrix (US)
- PPD ***Global Study Manager***
- PPD ***Clinical Data Coordinator***
- PPD ***Senior Manager, Biologicals Clinical Safety & Pharmacovigilance***
- ~~PPD Director, Vaccines (US)~~
- ~~PPD Biostatistician (US)~~
- PPD Clinical Development Manager, Vaccine (US)
- PPD Study Manager (US)
- ~~PPD , Director, Clinical R&D, World-Wide Clinical Development, Life-cycle Vaccines~~
- ~~PPD Central Study Coordinator~~

Section 5.3 Outline of study procedures

Table 2 Intervals between study visits *(Amended 09 November 2010)*

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	***1 year ± 5 weeks***
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	***3 years ± 5 weeks***
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	***5 years ± 8 weeks***
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	***10 years ± 8 weeks***

1. Whenever possible the investigator should arrange study visits within this interval
2. Subjects will not be eligible for inclusion in the ATP Year X cohort for analysis if they make the study visit outside this interval.

Section 8.6.2 Completion and transmission of serious adverse event reports to GSK Biologicals

US Safety Contact for Faxing/Reporting SAE Information

Fax to:

US Safety Contact, GSK Biologicals
Fax: PPD
Tel: PPD

US Study Contacts for Concerns Relating to an SAE

GSK Biologicals Medical Monitor: PPD MD
Office: PPD
Cell: PPD
Fax: PPD

GSK Biologicals Clinical Safety Physician: PPD MD
Office: PPD
Cell: PPD

After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e.

- Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service.
- The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call.
- The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.

Back-up Study Contact for Reporting SAEs (Amended 09 November 2010)

24/24 hour and 7/7 day availability
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD ***r*** PPD

Section 8.9 Pregnancy *(Amended 09 November 2010)*

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

~~A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.6. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to GSK Biologicals as described in Section 8.8. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.~~

Section 9.2.1 Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, ***7*** and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter. (Amended 09 November 2010)

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

Appendix C Overview of the Recruitment Plan

- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date ***the*** subject received vaccination in study 106316. A window of ~~± 5~~ ***± 8*** weeks around the actual time point for each subject will be permitted. ~~Visits for the year 1, 3, 5, and 10 samplings are therefore expected to take place between 8 June – 17 August 2007, 2009, 2011, and 2016.~~ ***(Amended 09 November 2010)***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 2

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***8***)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***8*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) ***and evaluation of immunogenicity and safety of an additional dose of Boostrix, when administered at Year 8.***
Amendment number:	Amendment 2
Amendment date:	Amendment 2 Final: 18 February 2014
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

The main purpose of this amendment is to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap vaccine when administered 8 years after an initial dose of Tdap. To evaluate *Boostrix* as a second dose of Tdap vaccine at Year 8, administration of *Boostrix* at Year 8 to the returning subjects from initial cohort has been added. This study will also evaluate the persistence of antibodies against diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, 8 years instead of 10 years after an initial dose of Tdap vaccine [*Boostrix* or *Adacel* (Sanofi-Pasteur)] administered in 106316 (Tdap 0.3-007) study. The Year 10 time point for evaluation of persistence has been cancelled because it is no longer feasible to conduct after a second dose of Tdap vaccine has been administered at Year 8.

For evaluation of *Boostrix* as a second dose of Tdap vaccine and as per advice from Centre for Biological Research and Evaluation (CBER):

- An additional treatment group acting as control is also added and the subjects enrolled in the control group will receive *Boostrix* as a first dose of Tdap vaccine.

Alternative booster response definitions are given for diphtheria, tetanus and pertussis antigens since the traditional booster response definitions applied for evaluation of initial dose of *Boostrix* are based on the level of antibodies observed in subjects prior to the first dose of *Boostrix*. The definition of booster responses to D, T and pertussis antigens currently used may not accurately depict a true immunologic booster response of the vaccine in the context where subjects have high pre-vaccination concentrations (≥ 6.0 IU/mL for diphtheria and tetanus and ≥ 60 EL.U/mL for pertussis). Therefore, applying the traditional booster response definitions in such a context would lead to lower booster response rate despite a higher observed geometric mean antibody concentration (GMC) after the second booster dose.

The data from this study are planned to support the indication of *Boostrix* as a second dose of Tdap vaccine.

Amended text has been included in *bold italics* in the following section:

Title page:
The names of the contributing authors have been updated in the title page.

Protocol Amendment 2 Sponsor Signatory Approval page:
The name of the sponsor signatory has also been updated on the protocol amendment 2 sponsor signatory approval page.

eTrack study numbers and abbreviated titles
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, ***Y8***~~Y10~~)

The title and detailed title was updated in all applicable sections of the protocol

Title
Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and ***8***~~10~~ years following the administration as a single dose in ~~the~~ 106316 study ***and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 8.***

Detailed Title
A phase III~~b~~, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5, and ***8***~~10~~ years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) ***and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 8***.

Indication/Study population

Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.
~~Healthy adults, 19 years of age and older, who received a single dose study vaccination in study 106316~~.

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***8*** ~~10~~)
Sponsor Information	
1. Sponsor	
GlaxoSmithKline Biologicals ***Rue de l'Institut, 89*** ***1330 Rixensart, Belgium***	
2. Sponsor Medical Expert for the Study	
Refer to the local study contact information document.	
3. Sponsor Study Monitor	
Refer to the local study contact information document.	
4. Sponsor Study Contact for Reporting of a Serious Adverse Event	
GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.9.2.	
List of Abbreviations:	
~~**DTPw**~~	~~Diphtheria, Tetanus Whole Cell Pertussis Vaccine~~
~~**FDA**~~	~~Food And Drug Administration, United States~~
~~**IB**~~	~~Investigator Brochure~~
D	***Diphtheria***
EDD	***Estimated Date of Delivery***
eTDF	***Electronic Temperature excursion Decision Form***
EGA	***Estimated Gestational Age***
FHA	Filamentous Hemagglutinin **from** ***Bordetella pertussis***
IMP	***Investigational Medical Products***
LMP	***Last Menstrual Period***
PRN	Pertactin **from** ***Bordetella pertussis***
PT	Pertussis Toxoid **from** ***Bordetella pertussis***
RCC	***Reverse Cumulative distribution Curve***
SPM	***Study Procedures Manual***
T	***Tetanus***

Glossary of Terms	
Adequate contraception:	***Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:*** • ***abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,*** • ***oral contraceptives, either combined or progestogen alone,*** • ***injectable progestogen,*** • ***implants of etenogestrel or levonorgestrel,*** • ***estrogenic vaginal ring,*** • ***percutaneous contraceptive patches,*** • ***intrauterine device or intrauterine system,*** • ***male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,*** • ***The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.*** • ***male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),*** • ***male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).*** ***Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.***
Adverse event:	***Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*** ***An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.***

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. ~~In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group.~~ The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. ***In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.***
~~**Central Study Co-ordinator:**~~	~~An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.~~
Epoch:	***An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.***
Primary completion date:	***The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.***

Menarche:	***Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, the larche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).***
Menopause:	***Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.***
Primary completion date:	***The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.***
Randomization:	***Process of random attribution of treatment to subjects in order to reduce bias of selection.***
Solicited adverse event:	***Aes to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.***
Unsolicited adverse event:	***Any AE reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.***

Trademarks
The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	***Generic description***
Boostrix®	***Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine***
Infanrix®	***Combined diphtheria, tetanus and acellular pertussis vaccine***

Section 1.1 Background

~~Reported pertussis incidence in the United States increased from 1010 cases in 1976 to 25,827 cases in 2004 [CDC, 2004; CDC 2002]. On October 26, 2005, ACIP issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.~~ ***Since the 1980s, there has been an increase in the number of reported cases of pertussis in the United States (US), especially among 10-19 year olds and infants younger than six months of age. By December 2012, 48,227 cases of pertussis were reported to Centers for Disease Control and Prevention (CDC), more than twice the number reported during the same time period in 2011 [CDC, 2012a]. The incidence of confirmed and probable pertussis among persons aged ≤ 19 years, by age and vaccine received in the US shows that high rates of pertussis is observed among adolescents and older children 7 through 10 years of age suggesting early waning of immunity [CDC, 2012b]. According to the recent General Recommendations on Immunization, adolescents and adults 11-18 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults 19 years of age and older who have not received a dose of Tdap [ACIP, 2012]. All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should take a Tdap vaccine [CDC, 2012c; CDC, 2012d].***

~~This vaccine~~ ***Boostrix*** is based on GSK Biologicals' DtaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti , 2002; Greco , 1996; Schmitt , 1996a; Schmitt , 1996b].~~Recently, GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age.~~ ***In 2005, Boostrix (0.3 mg) was approved in the US for use in 10-18 year olds. In December 2008, it was approved for use in adults 19-64 years of age and in 2011, it was approved in the US for use in elderly adults 65 years of age and older.***

~~A total of 6,173,696 doses have been distributed since launch until 02 August 2006.~~

~~Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of *Boostrix*.~~ ***Please refer to the Prescribing Information for information regarding the potential risks and benefits of Boostrix.***

Section 1.2 Rationale for the study

~~Recently~~ ***A*** study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. ***All primary objectives were met with the exception of pertactin booster response which was observed to be below the 80% margin. Despite this failure Boostrix recommendation in adults 19 years of age or older has been obtained.***

~~Data on persistence of antibodies and longer-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 **8** years following vaccination with GlaxoSmithKline Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).~~

Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005]. Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first three years after vaccination [Weston, 2011]. The current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 8 years following vaccination with Boostrix.

Providing pertussis booster vaccination aims to boost immunity and disrupt the disease cycle. Currently in the US, no data is available on the immunogenicity and safety of Boostrix given as a second dose of Tdap vaccine. This study is intended to assess subjects who were vaccinated in the 106316 study and they will be invited to participate in this long-term follow-up and re-vaccination study at Year 8 time point. The purpose of vaccination with Boostrix at Year 8 time point instead of the previously intended Year 10 time point is to evaluate the immunogenicity and safety of a second dose of Boostrix at a time point earlier than the ten year interval. This study will also evaluate the immune response to the booster dose with Boostrix in subjects whose previous Tdap vaccination was a non-GSK vaccine. The data from this study is planned to support the indication of Boostrix as a second dose of Tdap vaccine.

As per advice from Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive Boostrix as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.

Section 2.1 *Co*-Primary Objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of ***Tdap vaccine*** (*Boostrix* ***and Adacel)***, ~~with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL), and anti-T antibody concentrations ≥ 0.1 IU/mL,~~ ***at*** 1 year, 3 years, 5 years***,*** and ***8*** years ~~10 following Tdap vaccination~~.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  - ***One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).***
  - ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).***
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of Infanrix vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  - ***One month after vaccination, the lower limit of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.***
  - ***One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.***

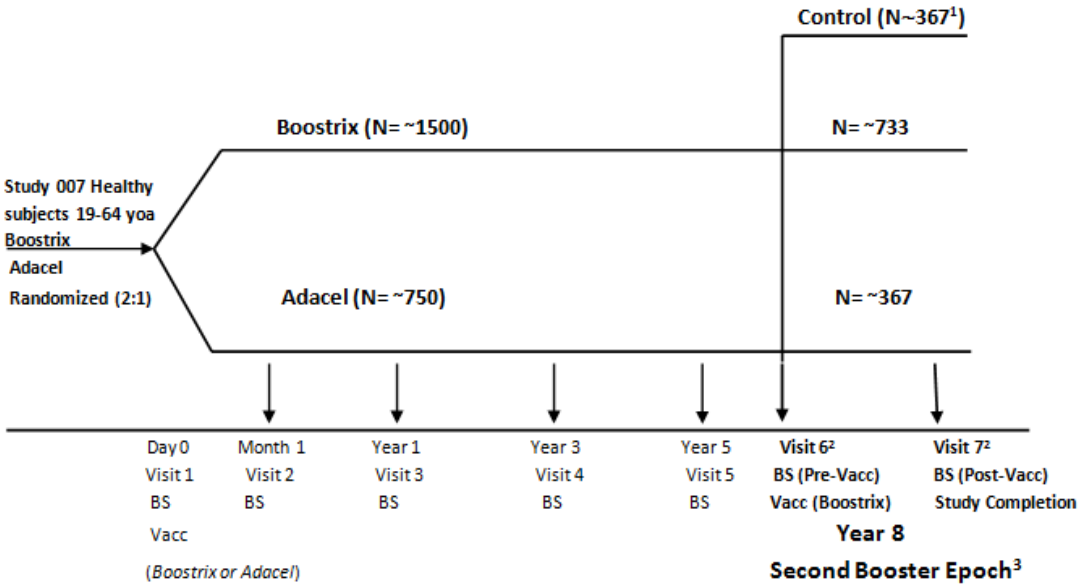
Refer to Section 10.1 for definition of the ***co-***primary endpoint***s and Section 10.3.1 for the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.***

Section 2.2 Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-~~pertussis toxoid (~~PT~~)~~, anti-~~filamentous hemagglutinin (~~FHA~~)~~, and anti-~~pertactin (~~PRN~~)~~ antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years~~,~~ and ***8*** years ~~10~~ following a single dose of *Boostrix* ***and Adacel***.
- To evaluate ~~geometric mean antibody concentrations (~~GMCs~~)~~ of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and ~~10~~ ***8*** years after vaccination with *Boostrix* ***and Adacel***.
- ***To assess the immunogenicity of Boostrix in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.***
- ***To assess the immunogenicity of Boostrix in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination***
- ***To explore the potential difference in terms of booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.***
- ***To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).***
- ***To evaluate and compare the safety of an second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).***

****Refer to Section 10.5 for definition of booster response.***

Section 3 Study design overview



Yoa=Years of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch is a non-randomized study, for practical purposes group ratio of 1:2 :1 is assigned for the Control, Boostrix and Adacel groups respectively for the Year 8 time point.
[1]Subjects who were not part of the 106316 study will be recruited as the Control group
[2]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch has been added for practical purposes and it has no relation to the number of epochs in this study.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: ***A phase III,*** ~~Non-~~ ***parallel, open-label***, interventional**,** ~~observational~~ multicenter ***study*** with the same two parallel groups as in the 106316 study ***and one new Control group receiving the first dose of Tdap vaccine (Boostrix)***.
- ***Study groups:***
  - ***Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (Boostrix) in study 106316 will receive a second dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***

- ***Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (Adacel) in study 106316 will receive a second dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***
- ***Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***

Table 1 Study groups foreseen in the study

Study Groups	*Number of subjects*	*Age (Min – Max) (age unit)*
Boostrix Group	*Approximately 733*	*27 years-72 years*
Adacel Group	*Approximately 367*	*27 years-72 years*
Control Group	*Approximately 367*	*27 years-72 years*

Table 2 Study groups and treatment foreseen in the study

Treatment name	*Vaccine/Product name*	*Study Groups*		
		Boostrix Group	*Adacel Group*	*Control Group*
Boostrix	*Tdap*	*x*	*x*	*x*

- Blinding: This study will be an open study since ***this is an extension of study 106316 (Tdap 0.3-007) which was un-blinded at the time of primary analysis.*** ~~There is no vaccination this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.~~
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups. ***Subjects in the Control group will also be analyzed as a separate group.***
- Treatment allocation: ***Non-randomized, all the study groups will receive a single dose of Boostrix at Year 8 (Visit 6).*** ~~No treatment is planned to be given in this study.Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).~~
- ***Control: Active control.***
- ***Vaccination schedule: A single dose of Boostrix vaccine will be administered to all subjects at Visit 6 i.e.at Year 8 time point (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The stud y procedures will be similar across all groups at Visit 6 and Visit 7).***
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and ~~10 years after the dose of vaccination~~ ***8 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.***

- Duration of the study: Approximately ~~10~~ ***8*** years for subjects who ***were enrolled in study 106316 and who*** ~~participate~~ ***participated*** in all phases ~~of the extension~~ ***of the study including Year 8 time point and approximately one month for the Control group.***
- Data collection: ~~Remote Data Entry (RDE)~~ ***Electronic Case Report Form (eCRF).***

Section 4.1 Number of subjects/centers

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will ***attempt to*** contact ALL subjects who received vaccination in study 106316 ***and indicated approval of further contact for study related activities at their last attended study visit.*** If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented ~~as instructed on the "subject tracking document" provided by GSK Biologicals.~~ ***In the study continuation screen in eCRF***.

For example, if the subject did not want to participate in the Year 1 evaluation, he***/she*** can participate at Years 3, 5 and ***8***.

In addition, approximately 367 subjects will be newly enrolled at Year 8 time point as Control group to receive the first dose of Tdap vaccine (Boostrix). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- ***27-37 years: ~25.4%***
- ***38-57 years: ~35.5%***
- ***58-72 years: ~39.1%***

Total enrolment in the 106316 study was 2284 subjects, ~~approximately~~ 1522 of whom were vaccinated with *Boostrix*. ***There were 1587 subjects (1064 Boostrix recipients) who returned for the Year 1 time point, 1441 subjects (976 Boostrix recipients) returned for the Year 3 time point and 1257 subjects (856 Boostrix recipients) returned for the Year 5 time point. Assuming an attrition of 15% from Year 5, it is estimated that 1100 subjects (733 Boostrix recipients) might return for the Year 8 time point. Also, approximately 367 sujects are planned to be enrolled in the Control group.*** ~~Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, *and 1100 subjects (733 Boostrix recipients) for the 7 year time point.* And 449 subjects (300 *Boostrix* recipients) for the 10-year time point.~~

Section 4.2 Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

Vaccination phase at Year 8 applicable for subjects in Boostrix and Adacel groups only:

- ***All subjects who received study vaccination (Boostrix or Adacel) in study 106316 will be considered eligible to participate in this study.***

Vaccination phase at Year 8 applicable for subjects in the Control group only:

- ***Subjects within the age range of 27-72 years will be considered eligible to participate in this study in the Control group.***

Vaccination phase at Year 8 applicable for ALL subjects (Control, Boostrix and Adacel groups):

All subjects must satisfy the following criteria at study entry at Year 8 time point:

- ***Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).***
- ***Written informed consent obtained from the subject for vaccination at Year 8 time point.***
- ***Healthy subjects as established by medical history and clinical examination before entering into the study.***
- ***Female subjects of non-childbearing potential may be enrolled in the study.***
  - ***Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.***

Please refer to the Glossary of Terms for the definition of menarche and menopause.

- ***Female subjects of child bearing potential may be enrolled in the study, if the subject***
  - ***has practiced adequate contraception for 30 days prior to vaccination, and***
  - ***has a negative pregnancy test on the day of vaccination, and***
  - ***has agreed to continue adequate contraception for 1 month after completion of the vaccine dose.***

Please refer to the Glossary of Terms for the definition of adequate contraception.

Section 4.3 Exclusion Criteria for enrolment

Section 8.4 ***Exclusion criteria for enrolment***

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of Year 8 vaccination time point. If any criteria is applicable, the subject must not be vaccinated in the study:

For subjects in Boostrix and Adacel groups:

- ***Previous booster vaccination against diphtheria, tetanus or pertussis since the last dose received in the study 106316.***

For subjects in the Control group:

- ***Administration of Tdap vaccine at any time prior to study entry.***

For ALL subjects (Control, Boostrix and Adacel groups):

- ***Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).***
- ***Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to Visit 6 (pre-vacc). For corticosteroids, this will mean prednisone ≥ 20 mg/day , or equivalent. Inhaled and topical steroids are allowed.***
- ***Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with the exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).***
- ***Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).***

- ***Hypersensitivity to latex.***
- ***History of diphtheria, tetanus or pertussis diseases.***
- ***Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.***
- ***History of any neurological disorders or seizures.***
- ***Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.***
- ***Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).***
- ***Acute disease and/or fever at the time of enrolment.***
  - ***Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***
  - ***Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.***
- ***Administration of immunoglobulins and/or any blood products within three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).***
- ***Pregnant or lactating female.***
- ***Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.***

Section 4.4 Elimination Criteria during the study

The following criteria should be checked at ***Visit 6*** ~~each long-term visit~~ ***and are applicable to all subjects***. If any become applicable during the study, ***from Visit 6,*** it will not require withdrawal of the subject from the study but may determine a subject's ~~evaluability~~ ***eligibility*** in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier ~~after the vaccination in 106316 study.~~***during the study period.***
- Diphtheria and/or tetanus and/or pertussis disease diagnosed ~~after the vaccination in 106316 study.~~***during the study period.***

- Administration of immunoglobulins and/or any blood products within ***three months*** ~~90 days~~ of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ ***20*** ~~0.5~~ mg/~~kg/~~day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required) ***diagnosed during the study period***.

Section 4.5 Contraindications to vaccination

Section 8.4 Contraindications to ~~subsequent~~ vaccination

~~Not applicable~~ ***Since this is a single dose booster study, contraindications to vaccination for vaccination at Year 8 time point are included in the exclusion criteria. Refer to Section 4.3.***

- ***The following adverse events (Aes) constitute contraindications to administration of Boostrix at that point in time; if any one of these Aes occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).***
- ***Acute disease and/or fever at the time of vaccination.***
  - ***Fever is defined as temperature ≥ 99.5 F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***
  - ***Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the vaccine dose, at the discretion of the investigator.***

Section 4.6 Warnings and Precautions

~~Not Applicable~~***. Refer to the approved product label/package insert of Boostrix.***

Section 5.1 Ethics and regulatory considerations

The study will be conducted in accordance with all applicable regulatory requirements.

Section 5.2 Subject identification and randomization of treatment

5.2 Subject identification ***and randomization of treatment***

5.2.1 Subject identification

For the subjects in Boostrix and Adacel groups:

Subjects will retain their subject numbers as in the 106316 study.

For the subjects in the Control group:

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

Section 5.2.2 Allocationof treatment

Numberingof supplies

The numbering of supplies within blocks will be performed at GSK Biologicals, using MATerial Excellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

5.2.2.2 Trearment allocation to the subject

5.2.2.2.1 Study group and treatment number allocation

There will be no randomization of subjects into groups in this study. The subjects in this study will be allocated to the same groups as in the vaccination study 106316. Subjects will be allocated a new treatment number, but will retain the same subject number as in the 106316 study (Boostrix and Adacel groups),or subject numbers will be assigned sequentially (for the subjects in the Control group).

The central randomisation system on internet (SBIR) will be used at the investigator site to track enrolment at Year 8 i.e. to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- ***27-37 years: ~25.4%***
- ***38-57 years: ~35.5%***
- ***58-72 years: ~39.1%***

The number of the administered treatment must be recorded in the eCRF on the Vaccine Administration form.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

Section 5.3 Method of blinding

This study will be conducted in an open manner.

Investigators will be provided with the identification of subjects with low immunogenicity results (see Section 5.7.2).

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Section 5.4 General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

Section 5.5 Outline of study procedures

Table 3 List of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 *AND 7*[1] ~~Year 10~~ *Year 8* ~~10 years~~ *8 years* following *Boostrix/ Adacel* vaccination *Administration of Boostrix vaccine*	
				Visit 6	*Visit 7*
Informed consent ***for persistence follow-up***	●	●	●	●[3]	
Informed consent for vaccination				●	
Check inclusion criteria	●	●	●	●[3]	
Check exclusion criteria				●	
Check elimination criteria	●	●	●	●[3]	●
Collect demographic data[2]				●	
Medical history				●	
Vaccination history				●[3]	
Pre-vaccination body temperature				●	
Recording of administered treatment number				●	
Urine Pregnancy test[4]				●	
Check contraindications to vaccination				O	
Check warnings and precautions				O	
Blood sampling (~5 mL) for antibody determination	●	●	●	●[3]	●
Vaccination				●	
Distribution of diary card				O	
Daily recording of solicited adverse events during the 4-day Day (0-3) follow-up period post-vaccination, by subjects				●	
Recording of non-serious adverse events during the 31 day Day (0-30) follow-up period post-vaccination, by subjects				●	●
Return of diary cards					O
Diary card transcription by investigator					●
Record concomitant medication/vaccination	●	●	●	●[3]	●

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following *Boostrix/ Adacel* vaccination**	**VISIT 4** **Year 3** **3 years following *Boostrix/ Adacel* vaccination**	**VISIT 5** **Year 5** **5 years following *Boostrix/ Adacel* vaccination**	**VISITS 6 *AND 7*[1]** **~~Year 10~~ *Year 8*** **~~10 years~~ *8 years* following *Boostrix/ Adacel* vaccination** ***Administration of Boostrix vaccine***	
				Visit 6	***Visit 7***
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●	●
Recording of any large injection site reactions in the eCRF by the investigator[5]				●	
Reporting of SAEs				●	●
Recording of pregnancies				●	●
Record any intercurrent medical conditions					●
Study Continuation	●	●	●	● (NA for Control group)	
Study conclusion for persistence follow-up				●[3]	
Study Conclusion					●
Investigator sign-off on data for persistence follow-up				●[3]	
Investigator sign-off on data					●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ ***is used to indicate a study procedure that does not require documentation in the individual eCRF.***
[1]***Applicable to Control, Boostrix and Adacel groups.***
[2] ***DOB, gender, ethnicity and race for subjects in the Control group.***
[3]***These are the only study procedures applicable for subjects who refuse vaccination at Year 8 time point.***
[4]***Applicable to female subjects of childbearing potential only.***
[5] ***Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions.***

Section 5.3

Table 4 Intervals between study visits

Intervals between study visits for subjects in Boostrix and Adacel groups:

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 6 (Tdap vaccination in parent study →Visit 6)	*8 years ± 3 months*	*8 years – 3 months to 8 years +6 months*
Visit 7 (Visit 6→ Visit 7)	*30-48 days (at least 30 days[3])*	*21-48[3] days*

[2] Subjects will not be eligible for inclusion in the ATP Year ~~X~~ ***8*** cohort for analysis if they make the study visit outside this interval.

[3]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Intervals between study visits for subjects in Control group:

Visit	*Optimum* length of interval [1]	*Maximum interval allowed*[2]
Visit 6→Visit 7[3]	*30-48 days (at least 30 days[4])*	*21-48 days*

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year 8 cohort for analysis if they make the study visit outside this interval.
[3]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[4] If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Section 5.6 Detailed description of study stages/visits

Procedures at Visits 3,4,5 and 6:

Persistence follow-up phase up to Year 8 time point:

The following study procedures are applicable to subjects who refuse vaccination at Year 8 time point :

- Study continuation at Years 3, 5~~,~~ and ***8*** ~~10~~.
- Study conclusion at Year ***8*** ~~10~~ ~~visit~~ (Visit 6-).

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- ***Obtain written informed consent from all subjects consenting for vaccination.***
- ***Check inclusion and exclusion criteria.***
- ***Check elimination criteria.***

- ***Check medical and vaccination history:***
  - ***Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.***
  - ***Obtain the subject's vaccination history by interview and/or review of the subject's medical records and record any vaccine administration within 30 days prior to the study vaccination in the eCRF.***
- ***Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.***
- ***Treatment number allocation will be performed as described in Section 5.2.2.2. The number of each administered treatment must be recorded in the eCRF.***
- ***Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 4.5 and 4.6 for more details.***
- ***Record pre-vaccination body temperature.***
- ***Collect approximately 5 mL of whole venous blood to provide at least 1.5 mL of serum for antibody testing, according to instructions in Appendix D.***
- ***Administration of a single dose of Boostrix vaccine for all study participants as described in Section 6.2. The criterio will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.***

Management of diary cards:

After vaccination, diary cards will be provided to the subject. The subjects will be instructed to record the following information in appropriate sections of the diary card:

- ***Record body (oral) temperature and any solicited local/general Aes on the day of vaccination and during the next 4 days, i.e. Day (0-3).***
- ***Any unsolicited Aes on the day of vaccination and during the 31 day, i.e. Day (0-30) follow-up period post vaccination.***
- ***Record any large injection site reactions (Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions).***
- ***Any concomitant medication/vaccination given after the administration of the study vaccine.***
- ***The subject will be instructed to return the completed diary card to the investigator at the next study visit.***

- ***The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious and also to contact the investigator in case of large injection site reactions.***
- ***Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9***.
- ***Refer to Section 8.4 for procedures for the investigator to record Aes, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.***

Procedures at Visit 7:

- ***The completed diary card will be collected and reviewed during discussion with the subject at this visit. Any unreturned diary cards will be sought from the holder through telephone call(s) or any other convenient procedure such as courier, home pick-up etc.***

- ***Collect approximately 5 mL of whole venous blood to provide at least 1.5 mL of serum for antibody testing, according to instructions in Appendix D.***
- ***Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.***
- ***Refer to Section 8.4 for procedures for the investigator to record Aes, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.***
- ***Record any pregnancies up to Visit 7 (post-vacc).***
- ***Study conclusion.***

Section 5.6.1 Activities at study conclusion

~~All subjects will be offered a booster dose of Td vaccine following the blood draw at the 10 year visit. A booster dose of Tdap may be offered instead if a second dose of Tdap is recommended at that time.~~

The investigator will:

- ***review data collected to ensure accuracy and completeness.***
- ***complete the Study Conclusion section in the eCRF.***

At/after study completion, no post-trial commercial vaccines will be provided in this study.

Section 5.7.2 Laboratory assays

Please refer to APPENDIX G for the address of the clinical laboratories used for sample analysis.

A sample of approximately 5 mL of whole venous blood, to provide ~~a minimum of~~ ***at least*** 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years~~,~~ and ***eight*** ~~ten~~ years [***at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups*** following study vaccination in 106316 study, ***and only at Visit 6 (pre-vacc) and Visit 7 (post-vacc) for the Control Group***. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C ***(alternatively at approximately -70°/80°C is also acceptable)*** until sent to the sponsor. Sera will be sent to Quest ***Diagnostics*** ~~Laboratories~~ (***Valencia*** ~~Van Nuys~~, CA) and subsequently to GSK Biologicals, Belgium for the laboratory assays.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus ***(anti-T and anti-D)*** will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off ***for seroprotection*** of both assays is 0.1 IU/mL [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL mL ***(The Vero cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL and will be used for pre /post vaccination assays at Year 8. The study will consider anti-D concentrations greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection). The ELISA test will define the seroprotection status for the primary endpoint.***

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA ~~or multiplex (Luminex)~~ techniques~~.~~

Table 5 Laboratory assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016/***0.004****
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5

VERO cut off is ≥ 0.004 IU/mL for Year 5 and Year 8 time points

The investigator is encouraged to share the immunological assay results for low immunological assay results with the study subjects.

Low-result is defined as:

- ***Antibody concentrations < 0.01 IU/mL for diphtheria antigen and,***
- ***Antibody concentrations < 0.1 IU/mL for tetanus antigen.***

For the study subjects identified as low-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

Section 5.5.3 Immunological read-outs

Table 6 Immunological read-outs for all subjects

Blood sampling time point		**Marker**
Timing	**Visit no.**	
Year 8	***6 and 7†***	***D****
		T
		PT
		FHA
		PRN
~~Year 10~~	~~6~~	~~D~~
		~~T~~
		~~PT~~
		~~FHA~~

~~All: All subjects enrolled at the long-term time point~~

†Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7, respectively to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.

****VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.***

Samples will not be criterio with information that directly identifies the subjects but will be coded with the identification number for the subject ***(subject number).***

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- ***Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.***
- ***Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.***

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored ***for*** ~~up to~~ ~~15~~ ***a maximum of 20*** years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent.

Section 6 Investigational Product and Administration

Study vaccines in study 106316 were *Boostrix* and *Adacel*. ~~No additional vaccination will be given as part of this study.~~

Section 6.1 Study Vaccine

The study vaccine to be used at the Year 8 time point has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine

Treatment name	*Vaccine/product name*	*Formulation*	*Presentation*	*Volume*	*Number of doses*
Boostrix	*Tdap*	*Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf , Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as $Al(OH)_3$:≤ 0.39 mg, Sodium chloride*	*Pre-filled syringes, Homogeneous turbid white suspension*	*0.5 mL*	*1*

Section 6.2 Dosage and Administration

In order to monitor enrolment and to control age distribution in the Control group, allocation of treatment number will be performed using SBIR. The application will ensure enrolment in the Control group is performed as per target age distribution (see section 4.1).

The vaccines will be administered as detailed in Table 8.

The vaccine is to be administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. Boostrix should in no circumstances be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1 – 1 ½ inch length, 25 gauge will be used [ACIP, 2011b; Zuckerman, 2000].

** Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.*

Table 8 Dosage and administration

Visit	*Dose*	*Vaccine*	*Route*	*Site*	*Side*
Visit 6[e]	*1*	*Tdap[a]*	*IM[b]*	*D[c]*	*Non-Dominant[d]*

a. Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
b. Intramuscular (IM)
c. Deltoid (D)
d. Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.
e. Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups.

The criterio will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Section 6.3 Storage

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Temperature excursions must be reported in degree Celsius.

Vaccines will be stored at the defined temperature range (i.e. 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature monitoring device will be used as a backup device and it will be opened in case of any temperature deviation (temperature outside the defined range, i.e. 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature monitoring device), if:

- ***proper functioning was demonstrated during the monitor's site evaluation,***
- ***if the system continues to work in case of a power failure, and***
- ***if the system is maintained regularly (e.g. once/year) as documented in the site files.***

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working after the alarm is activated.

It is also required to place a validated freezing point indicator close to the vaccines as a back-up device.

Any temperature excursion outside the range of 0.0 to +8.0°C impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix F.

Section 6.4 Treatment allocation and randomization

~~Not applicable~~ ***Subjects in the treatment groups- Boostrix, Adacel and Control will be analyzed as separate groups and will receive a dose of Tdap vaccine (Boostrix) at Year 8 time point.***

It is anticipated that approximately 1100 subjects (733 subjects from Boostrix group and 367 from Adacel group in the primary study) would return for the Year 8 vaccination visit. Approximately 367 subjects who were not part of the 106316 study will be enrolled in the Control group to receive the first dose of Tdap vaccine (Boostrix). All subjects will receive a single dose of Boostrix.

Section 6.5 Method of blinding and breaking the study blind

The study is an open study, since ***this is an extension of study 106316 which was un-blinded at the time of primary analysis. At Year 8 time point all the subjects in all the groups will receive a single dose of Boostrix.*** ~~There is no administration of vaccination in this study.~~

Section 6.6 Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix F for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF, in SBIR and on the vaccine accountability form.

Section 6.7 Packaging

Vaccination phase at Year 8 time point, refer to Appendix F.

Section 6.8 Vaccine accountability

Vaccination phase at Year 8 time point, refer to Appendix F

Section 6.9 Concomitant medication/treatment

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point :

At each study visit, the investigator should question the subject about any medication~~s taken.~~ ***/product taken and vaccination received by the subject***.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within ***three months*** prior to any study blood sampling) are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment. ~~Refer to Section 4.4.~~

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration. ~~Refer to Section 4.4.~~

Vaccination phase at Year 8 time point:

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of the dose of study vaccine and ending up to next study visit after the dose of study vaccine are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to study vaccination or at any time during the study period are to be recorded with the generic name for the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Sections 4.3 and 4.4.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine and ending 31 days (Day 0-30) after the dose of study vaccine is to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [Oral temperature < 99.5°F] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

During the period starting with administration of each dose of study vaccine and ending 31 days (Day 0-30) after each dose of study vaccine, concomitant medication administered for the treatment of an AE must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form/ SAE screens in the eCRF, as applicable. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study (i.e. from Visit 6 through Visit 7) must be recorded in the eCRF.

Section 8 Adverse events and Serious adverse events

Section 8 Adverse events and Serious adverse events

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

~~The investigator is responsible for the detection and documentation of events meeting the criteria and definition of serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting SAEs, as detailed in this section of the protocol.~~

Section 8.1 Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- ***Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.***
- ***New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.***
- ***Signs, symptoms, or the clinical sequelae of a suspected interaction.***
- ***Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).***
- ***Significant failure of expected pharmacological or biological action.***
- ***Signs, symptoms temporally associated with vaccine administration.***
- ***Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).***

Aes to be recorded as endpoints (solicited Aes) are described in Section 8.6. All other Aes will be recorded as UNSOLICITED Aes.

Examples of an AE DO NOT include:

- ***Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.***
- ***Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).***
- ***Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.***

Aes may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. Aes to be recorded as endpoints (solicited events) are described in Section 8.5. All other Aes will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- ***Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).***

Section 8.2 Definition of a serious adverse event

A ~~serious adverse event (~~SAE~~)~~ is any untoward medical occurrence that

Hospitalization for elective treatment of a pre-existing condition ***(known or diagnosed prior to informed consent signature)*** *that did not worsen from baseline is not considered an AE.*

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza ***like illness****, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

Section 8.3 Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Section 8.3 Clinical laboratory parameters and other abnormal assessments qualifying as *adverse events or* serious adverse events

In absence of diagnosis, ~~*A*~~***a***bnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as ***AE or*** SAE~~s~~ if they meet the definition of ***an AE or*** SAE, ~~as defined in~~ ***(Refer*** to Section***s 8.1 and*** 8.2***)***. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as ***Aes or*** SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Section 8.4 Time period, frequency and method of detecting adverse events, serious adverse events and pregnancies

Section 8.4 Time period, frequency and method of detecting *adverse events*, serious adverse events *and pregnancies*

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point :

Because subjects are not being vaccinated as part of the ***time points Year 1, 3 and 5*** ~~study protocol~~, investigators are not required to specifically solicit SAEs.

In case this electronic system for reporting SAEs does not work or after ***removal of write access*** ~~freezing~~ of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Vaccination phase at Year 8 time point:

All Aes occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to riter international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting pregnancies.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 9.

Table 9 Reporting periods for adverse events, serious adverse events and pregnancies

Event	*Pre-vacc (consent obtained)*	*Vaccination*	*4 days (Day 0-3) post-vacc*	*31 days (Day 0-30) post-vacc*
				Study conclusion
Solicited local and general Aes including large injection site reactions				
Unsolicited Aes				
Aes/SAEs leading to withdrawal from the study				
SAEs				
SAEs related to study participation or concurrent GSK medication/vaccination				
Pregnancies				

Pre-vacc.: pre-vaccination; Post-vacc.: post-vaccination.

The investigator will inquire about the occurrence of Aes/SAEs at every visit during the study and throughout the follow-up phase as appropriate.

All Aes either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. Aes not previously documented in the study will be recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. Refer to Section 6.9.

Section 8.5 Solicited adverse events

The following local (injection-site) Aes will be solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they will be asked to contact study personnel and to visit the investigator's office and/or home visit for evaluation as soon as possible. The investigator will record detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

Table 11 Solicited general adverse events

The following general Aes will be solicited:

Fatigue
Fever
Gastrointestinal symptoms†
Headache

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

Section 8.6 Evaluating adverse events and serious adverse events

Section 8.6 Evaluating *adverse events and* serious adverse events

~~This section is only applicable if an investigator becomes aware of an SAE that warrants notification of the sponsor.~~

Section 8.6.1 ***Active questioning to detect adverse events and serious adverse events***

As a consistent method of soliciting Aes, the subject should be asked a non-leading question such as:

"Have you felt different in any way since receiving the vaccine or since the previous visit?"

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Section 8.6.2 Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 12.

Table 12 Intensity scales for solicited symptoms in adults

Adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	~~Absent~~ ***None***
	1	~~Painful on touch~~ ***Mild: Any pain neither interfering with nor preventing normal every day activities.***
	2	~~Painful when limb is moved~~ ***Moderate: Painful when limb is moved and interferes with every day activities.***
	3	~~Pain that prevents normal activity~~ ***Severe: Significant pain at rest. Prevents normal every day activities.***
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in ~~°C /~~ °F
Headache	0	Normal
	1	***Mild:*** Headache that is easily tolerated
	2	***Moderate:*** Headache that interferes with normal activity
	3	***Severe:*** Headache that prevents normal activity
Fatigue	0	Normal
	1	***Mild:*** Fatigue that is easily tolerated
	2	***Moderate:*** Fatigue that interferes with normal activity
	3	***Severe:*** Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	***Mild:*** Gastrointestinal symptoms that are easily tolerated
	2	***Moderate:*** Gastrointestinal symptoms that interfere with normal activity
	3	***Severe:*** Gastrointestinal symptoms that prevent normal activity

~~*Fever is defined as: rectal temperature ≥38°C (100.4°F) / axillary temperature ≥37.5°C (99.5°F) / oral temperature ≥37.5°C (99.5°F) / tympanic temperature on oral setting ≥37.5°C (99.5°F) / tympanic temperature on rectal setting ≥38°C (100.4°F).~~ ****Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0	***:***	***Absent***
1	***:***	***≤ 20 mm***
2	***:***	***> 20 mm and < 50 mm***
3	***:***	***≥ 50 mm***

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		Oral
0	***:***	***< 99.5°F***
1	***:***	***≥ 99.5°F and ≤ 100.4°F***
2	***:***	***> 100.4°F and ≤ 102.2°F***
3	***:***	***> 102.2°F***

~~The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study.~~ ***The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited Aes (including SAEs) recorded during the study.***

The intensity of each ***AE*** recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An ***AE*** ~~SAE~~ which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An ***AE*** ~~SAE~~ which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An ~~S~~AE which prevents normal, everyday activities. (In adults, such an ***AE*** ~~SAE~~ would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as Grade 3. ~~Grade 3 is a category utilized for rating the intensity of an event; *Aes* and SAEs can be assessed as Grade 3~~

Section 8.6.3 Assessment of causality

The definitions for "NO" and "YES" have been written in such a way that all events that have been attributed a "NO" can be pooled with events which in the primary vaccination study were determined to be "not related" or "unlikely to be related" to vaccination. Those events that are attributed a "YES" can be pooled with those events that in the past were determined to have a "suspected" or "probable" relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each ***AE/***SAE.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general Aes to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other Aes should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product ?

NO	***:***	***There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.***
YES	***:***	***There is a reasonable possibility that the vaccine contributed to the AE.***

Non-serious and serious Aes will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 for definition of serious adverse event), ***additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.*** ~~it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.~~

~~Other possible contributors include:~~ ***Possible contributing factors include***:

Section 8.7 Medically attended visits

Section 8.7 Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if they received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

Section 8.8 Follow-up of adverse events, serious adverse events, pregnancies and assessment of outcome

Section 8.8 Follow-up of *adverse events,* serious adverse events, *pregnancies* and assessment of outcome

After the initial ***AE/***SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

In case the electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until the end of the study.

All Aes documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until 30 days after the last vaccination.

~~All SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits.~~

Investigators will follow-up subjects:

- with SAEs ***or subjects withdrawn from the study as a result of an AE*****;** until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the ***AE or*** SAE.

Outcome of any ***non-serious AE occurring during the 31 days (Day 0-30) follow-up period post-vaccination (i.e. unsolicited AE)*** **or any** SAE reported during the entire study will be assessed as:

Follow-up of pregnancies

Pregnant subjects will be followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

Section 8.9 Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

Section 8.9 Prompt reporting of serious adverse events *and pregnancies* to GSK Biologicals

In case the electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Section 8.9.1 Time frames for submitting serious adverse event reports *and pregnancies* to GSK Biologicals

Because subjects are not being vaccinated as part of the study protocol ***at the Year 1, 3 and 5 time points***, investigators are not required to specifically solicit SAEs ***in the persistence follow-up phase***. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 ***or in case of vaccination phase at Year 8***, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information ***(Refer Table 13).***

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Table 13 Timeframes for submitting serious adverse event, pregnancy and other event reports to GSK Biologicals

Type of Event	*Initial Reports*		*Follow-up of Relevant Information on a Previous Report*	
	Timeframe	*Documents*	*Timeframe*	*Documents*
SAEs	*24 hours**	*electronic SAE report*	*24 hours**	*electronic SAE report*
Pregnancies	*2 weeks**	*electronic pregnancy report*	*2 weeks**	*electronic pregnancy report*

** Timeframe allowed after receipt or awareness of the information.*

Section 8.9.2 Completion and transmission of serious adverse event reports to GSK Biologicals

~~When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 8.9.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.~~

~~When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.9.1.~~

~~In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.9.1.~~

~~In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.~~

Section 8.9.2.1 Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

Section 8.9.2.2 Updating of SAE or pregnancy information after removal of write access of the subject's eCRF

When additional SAE or pregnancy information is received after removal of write access of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 13.

GSK Biologicals Medical Monitor: PPD ~~MD~~ PPD
Office: PPD
Cell: PPD
Fax: PPD

~~GSK Biologicals Clinical Safety Physician:~~ PPD ~~MD~~
~~Office:~~ PPD
~~Cell:~~ PPD

GSK Biologicals Clinical Safety Physician:
PPD ***MD***
Office: PPD
Cell: PPD

Section 8.9.3 Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

Section 8.10 Regulatory reporting requirements for serious adverse events

~~The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.~~

~~An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.~~

Section 8.11 Post-study adverse events and serious adverse events

~~A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.4. Investigators are not obligated to actively seek SAEs in former study participants.~~

~~However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.~~

~~After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.~~

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 9. Investigators are not obligated to actively seek Aes or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

Section 8.12 Pregnancy

Persistence follow-up phase up to Year 8 time point:

The following criteria is applicable to subjects who refuse vaccination at Year 8 time point :

Because subjects are not being vaccinated as part of ~~this study protocol~~ ***the time points at Year 1, 3 and 5***, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit ***during the time points at Year 1, 3 and 5*** should not be excluded from the visit on the basis of their pregnancy.

Vaccination phase at Year 8 time point:

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on a electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.9 and 8.9.1:

- ***Spontaneous pregnancy loss, including:***
  - ***spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)***
  - ***ectopic and molar pregnancy***
  - ***stillbirth (intrauterine death of fetus after 22 weeks of gestation).***

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- ***Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).***
- ***Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.***

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.9.2. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Section 8.13 Treatment of adverse events

Section 8.13 Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

Section 9.2 Subject withdrawal

Subjects who are withdrawn because of ~~S~~SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE***/ AE*** until resolution of the event (see Section 8.1).

Section 9.2.1 Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5~~,~~ and ***8***~~10~~ year persistence analyses.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

- Consent withdrawal, not due to an adverse event*****

****In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.***

Subjects who are withdrawn from the study because of SAEs/Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.8).

Section 10.1 Primary endpoint

Section 10.1 *Co*-Primary endpoint*s*

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ~~≥ 0.016 IU/mL~~ ***≥ 0.01 IU/mL (VERO)*** and anti-T antibody concentrations ≥ 0.1 IU/mL ***(ELISA)*** in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and ***8***~~10~~ years following ***first Tdap*** vaccination.
- ***Immunogenicity with respect to components of the study vaccine at Year 8 time point.***
  - ***Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.***
  - ***Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.***
  - ***Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.***

Section 10.2 Secondary endpoints

- Subjects with anti-~~pertussis toxoid (~~PT~~)~~, anti-~~filamentous hemagglutinin (~~FHA~~)~~, and anti-~~pertactin (~~PRN~~)~~ antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years~~,~~ and ***8***~~10~~ years following ***first Tdap*** vaccination.
- ~~Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~
- ~~Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~
- ~~Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~
- ~~Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~
- ~~Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~
- ***Immunogenicity with respect to components of the study vaccine at the Year 8 time point.***
  - ***Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.***
  - ***Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the definition of booster response).***

  **** Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.***
- ***Solicited local and general symptoms.***
  - ***Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.***
  - ***Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.***

- ***Unsolicited adverse events.***
  - ***Occurrence of unsolicited Aes during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.***
- ***Serious adverse events.***
  - ***Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.***

Section 10.3 Estimated sample size

No sample size is calculated for ***the time points Year 1, 3 and 5*** ~~this study~~. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study

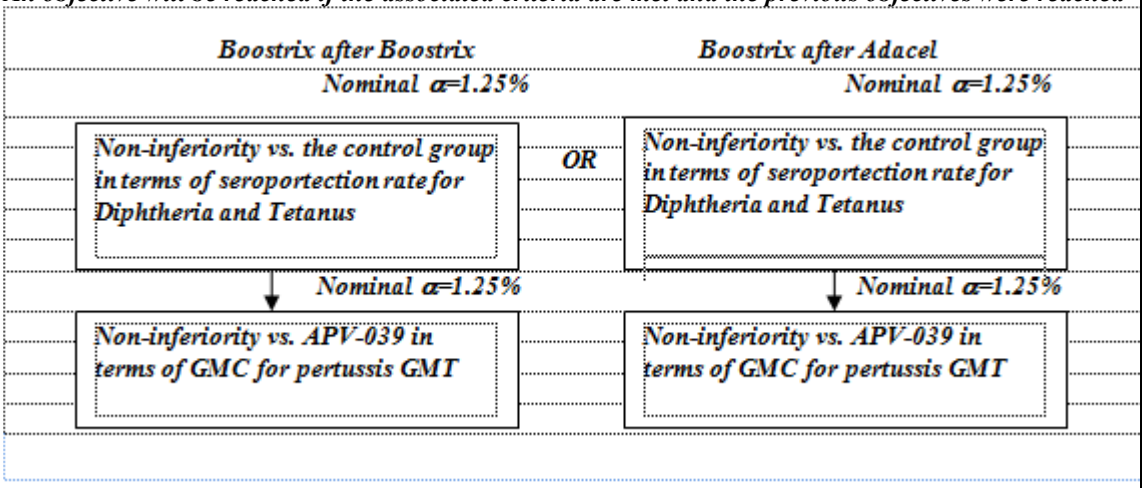
~~With a total of 2284 enrolled subjects in primary study 106316, it is expected approximately 1941 subjects will be present for the 1 year time point, 1402 subjects for the 3 year time point, 1013 subjects for the 5 year time point, and 449 subjects for the 10 year time point, assuming a 15% attrition rate per year.~~

It is estimated that around 1100 subjects (733 subjects from Boostrix group and 367 subjects from Adacel group in the primary study) would return for Year 8 study. Around 367 subjects are to be recruited for the Control group to receive the first dose of Tdap vaccine (Boostrix). Assuming 80% of enrolled subjects will be evaluable, this gives 586 evaluable subjects in Boostrix group, 293 evaluable subjects in Adacel group, and 293 evaluable subjects in Control group.

Section 10.3.1 Control on type 1 error

This study is designed to assess independently non-inferiority of Boostrix group to the Control group, and non-inferiority of Adacel group to the Control group. To control the overall type I error below 2.5%, a Bonferroni adjustment is used, i.e., type I error allowed for each non-inferiority assessment is 1.25% (one-sided). In addition to further control misinterpretation related to multiple primary objectives, a hierarchy procedure will be used as described in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%



Section 10.3.2 Power computation

With 293 evaluable subjects in the Adacel group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Adacel group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Adacel group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 88.91%. (See Table 14 and Table 15 respectively).

With 586 evaluable subjects in the Boostrix group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Boostrix group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Boostrix group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 97.87 %. (See Table 16 and Table 17 respectively).

Table 14 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <- 10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)	Non-inferiority criterion Difference(2nd dose- first dose)	293 (Boostrix following Adacel) 293 (First Boostrix)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 15 Power to demonstrate non-inferiority of Boostrix following Adacel to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (Boostrix/Infanrix) < 0.67	
Endpoint (GMCs)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix)	APV-039 Infanrix	N in APV-039 (TVC)	N =293 in Adacel+Boostrix
Anti-PT	0.480	0.306	2884	99.99%
Anti-FHA	0.422	0.370	685	99.99%
Anti-PRN	0.710	0.413	631	88.93%
Overall power**				88.91%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 16 Power to demonstrate non-inferiority of a second dose of Boostrix following the first dose of Boostrix with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <- 10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)	Non-inferiority criterion Difference(2nd dose- first dose)	586 (Boostrix following Boostrix) 293 (First Boostrix)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 17 Power to demonstrate non-inferiority of Boostrix following Boostrix to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (Boostrix/Infanrix) < 0.67	
Endpoint (GMCs)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix)	APV-039 Infanrix	N in APV-039 (TVC)	N =586 in Boostrix+Boostrix
Anti-PT	0.480	0.306	2884	>99.99%
Anti-FHA	0.422	0.370	685	>99.99%
Anti-PRN	0.710	0.413	631	97.87%
Overall power**				97.87%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}(0.67)$, variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Section 10.4 Study cohorts to be evaluated

Section 10.4.1 **Year X (1, 3, 5, *8,* ~~10~~) cohort**

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

Section 10.4.2 **According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5,~~10~~) cohort**

The ATP Year X (1, 3, 5,~~10~~) cohort will include all subjects from Year X (1, 3, 5,~~10~~) cohort who ***were*** is in the ATP cohort for analysis of immunogenicity in 106316 study and who ***did*** ~~have~~ not ***meet*** the following elimination criteria.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ ~~0.5~~ ***20*** mg/~~kg/~~day. Inhaled and topical steroids are allowed).

~~**ATP Complete Year X (1, 3, 5, 10) cohort**~~

~~The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.~~

Section 10.4.3 Additional cohorts defined for Year 8 analysis

Section 10.4.3.1 Total Vaccinated Cohort (TVC) at Year 8

The TVC will include all subjects with a study vaccine administration dose documented:

- ***A safety analysis based on the TVC will include all vaccinated subjects.***
- ***An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.***

Section 10.4.3.2 ATP cohort for analysis of safety at Year 8

The ATP cohort for analysis of safety at Year 8 time point will include all eligible and vaccinated subjects.

- ***Who have received the dose of study vaccine.***
- ***For whom administration site of study vaccine is known.***
- ***Who did not receive a vaccine leading to elimination from an ATP analysis as listed in Section 6.9.***

Section 10.4.3.3 ATP cohort for analysis of immunogenicity at Year 8 (ATP Year 8)

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- ***Who comply with the procedures and intervals defined in the protocol (refer to Section 5.5 and Table 4).***
- ***Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 4.4) during the study.***
- ***For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after Year 8 vaccination.***

Section 10.5 Derived and transformed data

- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) ~~or ≥ 0.016 IU/mL~~ and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and ***8 years*** ~~10~~ following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and ***8***~~10~~ years following vaccination will be derived to evaluate the first secondary objective.
- The ~~geometric mean antibody concentrations (~~GMCs~~)~~ of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and ***8*** years ~~10~~ after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

Booster responses to be considered for Year 8 time point:

- ***Traditional Booster response to D and T antigens is defined as:***
  - ***for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and***
  - ***for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***
- ***Traditional Booster response to PT, FHA and PRN antigens is defined as:***
  - ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL, one month after vaccination;***
  - ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
  - ***for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.***
- ***Alternative Booster response to D and T antigens is defined as:***
  - ***for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and***
  - ***for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***
  - ***for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.***
  - ***Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.***

- ***Alternative Booster response to PT, FHA and PRN antigens defined as:***
  - ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;***
  - ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
  - ***for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.***
  - ***for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase in antibody concentration from the pre-vaccination concentration, one month after vaccination.***

Handling of missing data:

Immunogenicity:

- ***For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.***

Reactogenicity and Safety:

- ***For a given subject and the analysis of solicited symptom during the 4 day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).***
- ***For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.***
- ***For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.***

Section 10.6 Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5~~,~~and Year ***8*** ~~10~~) on cleaned data obtained through ***each*** Year X. A clinical study report (CSR) will also be written following each analysis.

Section 10.6.1 Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, ***time since last DT vaccination,*** gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year ***8*** ~~10~~) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5~~,~~ or ***8***~~10~~) cohort ***and*** in the ATP Year X (1, 3, 5~~,~~ or ***8***~~10~~) cohort ~~and in the ATP complete Year X (1, 3, 5, and 10) cohort~~ will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, ***8***~~10~~) (in years) will be summarized using descriptive statistics.

Section 10.6.2 Analysis of *persistence* ~~immunogenicity~~

The primary analysis will be based on the ATP ***cohort for analysis of immunogenicity*** Year X ~~cohort~~ ***(1, 3, 5, 8)***.

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.01~~6~~ IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.

In addition, at Year X (1, 3, 5, ***8,*** ~~10~~) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves ***(RCC)*** by group.

Comparability between Groups:

Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group – *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA ~~or ≥ 0.016 IU/mL by VERO cell assay when~~ ***or*** anti-D concentrations ***≥0.01 IU/mL by VERO*** ~~< 0.1 IU/mL by ELISA~~), Year X (1, 3, 5, ***8,*** ~~10~~) after vaccination will be calculated.

- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group – *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, ***8,*** ~~10~~) after vaccination will be calculated.
- ***For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 5 EL.U/mL by ELISA, Year X (1, 3, 5, 8) after vaccination will also be calculated.***

Section 10.6.3 Analysis of immunogenicity at booster dose

The following analyses will be carried out after Year 8 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 8. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC at Year 8 will be performed to complement the ATP analysis

Within groups assessment

For each group and each antigen:

- ***Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% Cis.***
- ***GMCs or GMTs at pre-vaccination, one month post-vaccination will be tabulated with 95% Cis.***
- ***Booster response rate one month post-vaccination will be calculated with exact 95% Cis.***
- ***Antibody concentrations/titres distribution at pre-vaccination and one month post-vaccination will be displayed using RCC.***

Between groups assessment

- ***For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.***
- ***For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm$_{10}$ transformation of the concentrations.***

Exploratory between group assessment

- ***For anti-D, anti-T antibody response, the two-sided 95% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm$_{10}$ transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.***
- ***For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Boostrix group and Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm$_{10}$ transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.***
- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) will be calculated.***

Sensitivity analysis

A complementary analysis will be carried out in order to evaluate the robustness of GMT/GMC results with respect to drop-out from the parent study (106316). More specifically multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC/GMT that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

In addition, within group assessment for the ATP analysis of immunogenicity at Year 8 will be performed separately for each level of the age stratum (Subjects age at Year 8 vaccination will be classified into three categories, 27-37 years old, 38-57 years old and 58-72 years old).

Section 10.6.4 Analysis of Safety

Persistence follow-up phase up to Year 8 time point:

No safety analysis will be performed for this study. If GSK is informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

Vaccination phase at Year 8 time point:

The primary analysis will be based on the TVC at Year 8. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 8 is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the treatment groups by solicited local and general symptom terms, and, for unsolicited Aes, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 32.9°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

The percentage of subjects who reports at least one report of an unsolicited adverse event classified by MedDRA during the 31 day (Day 0-30) follow-up period after vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, Aes resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

In addition, safety analysis for TVC at Year 8 will be performed separately for each level of the age stratum (Subjects age at Year 8 vaccination will be classified into three categories, 27-37 years old, 38-57 years old and 58-72 years old).

Section 10.6.5 Statistical methods

- ***The exact Cis for a proportion within a group will be computed using SAS, [Clopper, 1934].***
- ***The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].***
- ***The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.***

Section 10.7 Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5~~,~~ and Year 8 ~~10~~) as available and reported separately. ***At Year 8 time point immunogenicity and safety of vaccine administration will be reported.***

Section 12 References

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Appendix B Administrative matters

IV Remote Data Entry Instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

~~Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.~~

~~Specific instructions for use of RDE will be included in the training material provided to the investigational site.~~

V *Study* Monitoring by GSK Biologicals

~~To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.~~

~~These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF/ RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.~~

GSK will monitor the study to verify that, amongst others, the:

- ***Data are authentic, accurate, and complete.***
- ***Safety and rights of subjects are being protected.***
- ***Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.***

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

VI ~~Archiving of Data~~ ***Record retention***

Following closure of the study, the investigator must maintain all site study records in a safe and secure location ***(except for those required by local regulations to be maintained elsewhere)***. ~~The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff.~~ ***The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff***. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must ~~assure~~ ***ensure*** that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that ~~an acceptable quality control process exists for making these reproductions~~ ***there is an acceptable quality control procedure in place***.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to ~~that~~ ***a particular*** site for the study, as dictated by ICH GCP ~~E6 Section 4.9~~, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

IX Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

X Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

XI Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Appendix C Overview of recruitment plan

For the Control group:

- ***Approximately 367 subjects will be recruited to receive the first dose of Tdap vaccine (Boostrix) in this study.***
- ***The study will take place at multiple centers in the US.***
- ***The study duration per subject will be approximately one month.***
- ***The recruitment of subjects into the study will be performed using RDE.***
- ***Recruitment will be monitored by the site monitor.***

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, ~~Van Nuys~~ ***Valencia***, California.

Appendix F Vaccine supplies, packaging and accountability

1. Vaccine and/or other supplies

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- ***Boostrix in pre-filled syringes***

At least an additional 10% of the study vaccine will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject).

All pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:
The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each time point. Each label will contain the following information: study number, identification number for the subject (e.g. Subject number), sampling time point (e.g., post ri 3), timing (e.g., study Month 7).

Other supplies provided by GSK Biologicals:
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:

- ***tubes with screw caps for serum samples,***
- ***racks and cardboard boxes for the tubes of serum.***

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site from local country medical department to investigational site

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : PPD
E-mail: PPD

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

4. Vaccine accountability

At all times the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP WWD-1102, used and unused vaccine syringes should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine syringes are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP WWD-1102.

If no processes for destruction of unused clinical trial supplies are in place in the local GSK Biologicals site in the US, the unused supplies must be returned to GSK according to the instructions given by the GSK Biologicals responsible staff (in accordance with SOP-NPD-7200).

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Appendix G Clinical laboratories

Table 18 GSK Biologicals laboratories

Laboratory	***Address***
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	***Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium***
GSK Biologicals Global Vaccine Clinical Laboratory, North America-Laval	***Biospecimen Reception – Clinical Serology 525 Cartier blvd West – Laval – Quebec – Canada – H7V 3S8***
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	***Avenue Fleming, 20 – B-1300 Wavre – Belgium***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 3

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and evaluation of immunogenicity and safety of an additional dose of *Boostrix*, when administered at Year ***9***.
Amendment number:	Amendment 3
Amendment date:	Amendment 3 Final: 10 December 2014
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

- Following feedback from the Centre for Biological Research and Evaluation (CBER), the following changes have been made to this protocol:
  - A co-primary objective has been added to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.
  - The interval between study visits for Year 8 time-point has been updated to include the maximum number of subjects from the previous time-points.
  - The statistical section has been updated to include the power computation for the new objective.
  - Exclusion criteria for subjects in the Boostrix and Adacel groups as well as Control group has been updated.
  - The text regarding documentation of non-participation of subjects who decline to participate in this long-term study has been removed.
  - Measurement of temperature for fever has been amended.
- The list of contributing authors for this amendment was updated.
- Typographical errors have been corrected. These changes have not been reflected as amended text.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Throughout the protocol, the year 8 time point has been amended to year 9 time point to reflect the change in study start. This change can be seen in bold italics within the protocol.

Synopsis

Co-primary objectives

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, ***Boostrix*** (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  - ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).***

[$] Booster response to D and T antigens is defined as:

- ***for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and***
- ***for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***

$Booster response to PT, FHA and PRN antigens is defined as:

- ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;***
- ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
- ***for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination***.

Secondary objectives

- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.

****Refer to co-primary objective for the definition of booster response*** ~~Booster response to D and T antigens is defined as:~~

- ~~for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and~~
- ~~for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.~~

~~*Booster response to PT, FHA and PRN antigens is defined as:~~

- ~~for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;~~
- ~~for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and~~
- ~~for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.~~

Synopsis Table 1: Study groups foreseen in the study

Study Groups	***Number of subjects***	***Age (Min – Max) (age unit)***
Boostrix Group	Approximately 733	2~~*8*7~~ years-7*3*~~2~~ years
Adacel Group	Approximately 367	2~~*8*7~~ years-7*3*~~2~~ years
Control Group	Approximately 367	2~~*8*7~~ years-7*3*~~2~~ years

Number of subjects ***All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.*** Co-primary endpoints – ***Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination (Refer to the co-primary objectives for the definition of booster response).***
Section 1 Introduction All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should ~~take~~ ***receive*** a Tdap vaccine ***at 27-36 weeks gestation during each pregnancy*** [CDC, 2012c; CDC, 2012d]. **Section 1.2 Rationale for the study** ~~The data from this study is planned to support the indication of *Boostrix* as a second dose of Tdap vaccine.~~ Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005] ***and recent data shows that protection starts to wane within three years*** [***Koepke, 2014].*** Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first ~~three~~ ***five*** years after vaccination [Weston, 2011; ***GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5)***]. As per advice from ***the*** Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive Boostrix as a first dose of Tdap vaccine.

Section 2.1: Co-Primary Objectives

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, ***Boostrix*** (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  – ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).***

[$]Refer to Section 10.5 for the definition of booster response.

Section 2.2: Secondary Objectives

- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.

****Refer to Section 10.5 for the definitions of booster response and alternate booster response.***

Section 3 Study design overview

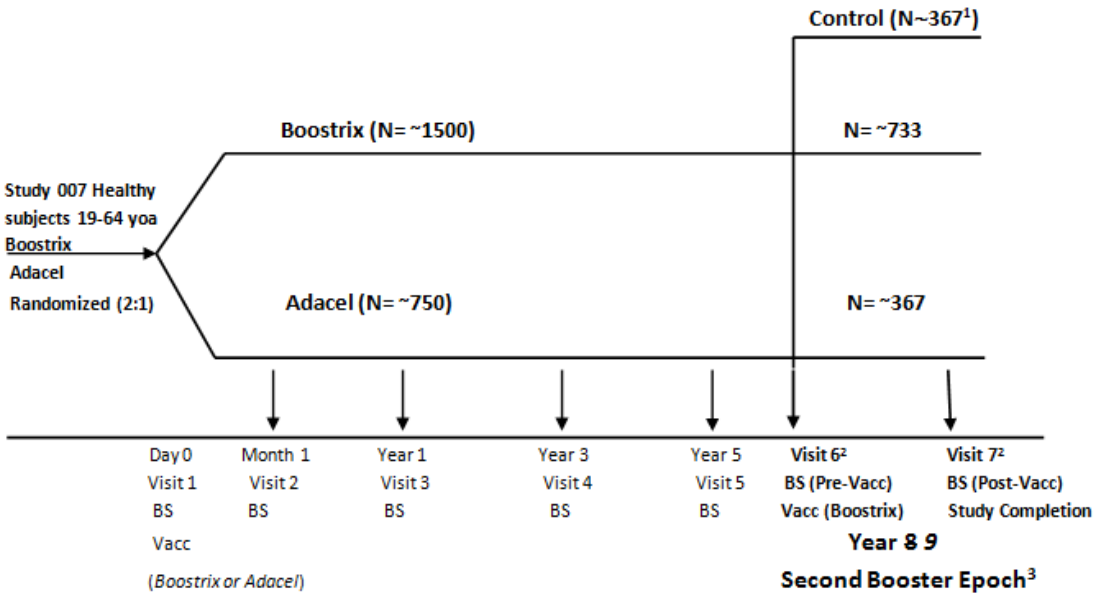


Table 1 Study groups foreseen in the study

Study Groups	*Number of subjects*	*Age (Min – Max) (age unit)*
Boostrix Group	Approximately 733	2~~8~~7 years-7~~3~~2 years
Adacel Group	Approximately 367	2~~8~~7 years-7~~3~~2 years
Control Group	Approximately 367	2~~8~~7 years-7~~3~~2 years

- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects ***participating in the vaccination phase*** at Visit 6 i.e. at Year ***9*** (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7).

Section 4: Study cohort

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. ~~At the time of initiation of the study, the investigator will ***attempt to*** contact ALL subjects who received vaccination in study 106316 ***and indicated approval of further contact for study related activities at their last attended study visit.*** If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented ***in the study continuation screen in eCRF.*** The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.~~Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

In addition, approximately 367 subjects will be newly enrolled at Year ***9*** time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- 2***8***~~7~~-3***8***~~7~~ years: ~25.4%
- 3***9***~~8~~-5***8***~~7~~ years: ~35.5%
- 5***9***~~8~~-7***3***~~2~~ years: ~39.1%

Section 4.2 Inclusion criteria

Vaccination phase at Year ***9*** applicable for subjects in the Boostrix and Adacel groups only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix and Adacel groups:

Vaccination phase at Year ***9*** applicable for subjects in the Control group only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Control group only:

Vaccination phase at Year ***9*** applicable for ALL subjects (Control, Boostrix and Adacel groups):

The following criteria are applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix, Adacel and Control groups:

- Subjects within the age range of 2***8***~~7~~-7***3***~~2~~ years will be considered eligible to participate in this study in the Control group.

Section 4.3: Exclusion criteria for enrolment

The following criteria should be checked at the time of Year 8 vaccination time point. If any ***criteria are*** applicable, the subject must not be vaccinated in the study:

For subjects in the Boostrix and Adacel groups:

- ***Administration of Tdap vaccine since the last dose received in the study 106316.***
- ~~***Previous booster vaccination against diphtheria, tetanus or pertussis since the last dose received in the study 106316.***~~

For subjects in the Control group:

- Administration of Tdap ***(Boostrix or Adacel)*** vaccine at any time prior to ***the administration of Boostrix vaccine in this*** study ~~entry~~.

For ALL subjects (Control, Boostrix and Adacel groups):

- ***Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of Boostrix vaccine in this study.***
- ***Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.***
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

Section 4.4: Elimination criteria during the study

- Administration of a ~~Td or Tdap~~ vaccine ~~or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier~~ ~~***during the study period***~~ ***against diphtheria, tetanus or pertussis during the study period (Visit 6 through Visit 7).***
- ***Administration of*** any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier ***during the study period (Visit 6 through Visit 7).***
- Diphtheria and/or tetanus and/or pertussis disease diagnosed during the study period ***(Visit 6 through Visit 7)***.
- Any confirmed or suspected immunosuppressive or immuno-deficient condition based on medical history and physical examination (no laboratory testing is required) diagnosed during the study period ***(Visit 6 through Visit 7)***.

Section 4.5 Contraindications to vaccination

- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

Section 5.2.2.2.1 Study group and treatment number allocation

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- 2***8***~~7~~-3***8***~~7~~ years: ~25.4%
- 3***9***~~8~~-5***8***~~7~~ years: ~35.5%
- 5***9***~~8~~-7***3***~~2~~ years: ~39.1%

Section 5.5 Outline of study procedures

Table 3 List of study procedures

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following Boostrix/ Adacel vaccination**	**VISIT 4** **Year 3** **3 years following Boostrix/ Adacel vaccination**	**VISIT 5** **Year 5** **5 years following Boostrix/ Adacel vaccination**	**VISITS 6 AND 7[1]** **Year *9*** ***9* years following Boostrix/ Adacel vaccination** **Administration of Boostrix vaccine**	
				Visit 6	**Visit 7**
Study Continuation	●	●	●	***O*** ~~●~~ (NA for Control group)	●
Study Conclusion ***for vaccinated groups***					●

[2] ~~DOB~~ ***Year of birth***, gender, ethnicity and race for subjects in the Control group.

Table 4 Intervals between study visits

Visit	***Optimum* length of interval** [1]	***Maximum interval allowed*** [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	~~8 years ± 3 months~~ ***9 years – 3 months***	~~8 years – 3 months to 8 years +6 months~~ ***9 years +6 months***
Visit 7 (Visit 6→ Visit 7)	30-48 days (at least 30 days[3])	21-48[3] days

Section 5.6 Detailed description of study stages/visits

Procedures at Visits 3, 4, 5 and 6:

Persistence follow-up phase up to Year ***9*** time point:

- Study continuation at Years 3~~,~~ ***and*** 5~~, and ***9***~~.
- Collect approximately 5 mL of whole venous blood to provide ~~a minimum~~ ***approximately*** ~~of~~ 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- Collect approximately 5 mL of whole venous blood to provide ~~at least~~ ***approximately*** 1.5 mL of serum for antibody testing, according to instructions in Appendix D.

Procedures at Visit 7:

- Collect approximately 5 mL of whole venous blood to provide ~~at least~~ ***approximately*** 1.5 mL of serum for antibody testing, according to instructions in Appendix D.

Section 5.7.2 Laboratory assays

A sample of approximately 5 mL of whole venous blood, to provide ~~at least~~ ***approximately*** 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and ~~eight~~ ***nine*** years [at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups following study vaccination in 106316 study, and only at (pre-vacc) and Visit 7 (post-vacc) for the Control group.

Section 6.4 Treatment allocation and randomization

All subjects ***participating in the vaccination phase*** will receive a single dose of *Boostrix*.

Section 6.9 Concomitant medication/treatment

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [~~Oral~~ Temperature ***by any route*** < ***100.4*** ~~99.5~~ °F. ***The preferred route for recording temperature in this study will be oral***] and any other symptom, to prevent fever from occurring).

Section 8.4 Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies

For subjects who receive vaccination at the Year 9 time point: All AEs occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Section 8.6.2 Assessment of intensity

Table 12 Intensity scales for solicited symptoms in adults

*Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		~~Oral~~
0	:	~~< 99.5°F~~ ***<100.4°F***
1	:	~~≥ 99.5°F and ≤ 100.4°F~~ ***≥100.4°F to ≤102.2°F***
2	:	~~> 100.4°F and ≤ 102.2°F~~ ***>102.2°F to ≤104.0°F***
3	:	~~> 102.2°F~~ ***> 104.0°F***

Section 10.1: Co-primary endpoints

- ***Immunogenicity with respect to components of the study vaccine at Year 9 time point.***
  - ***Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.***

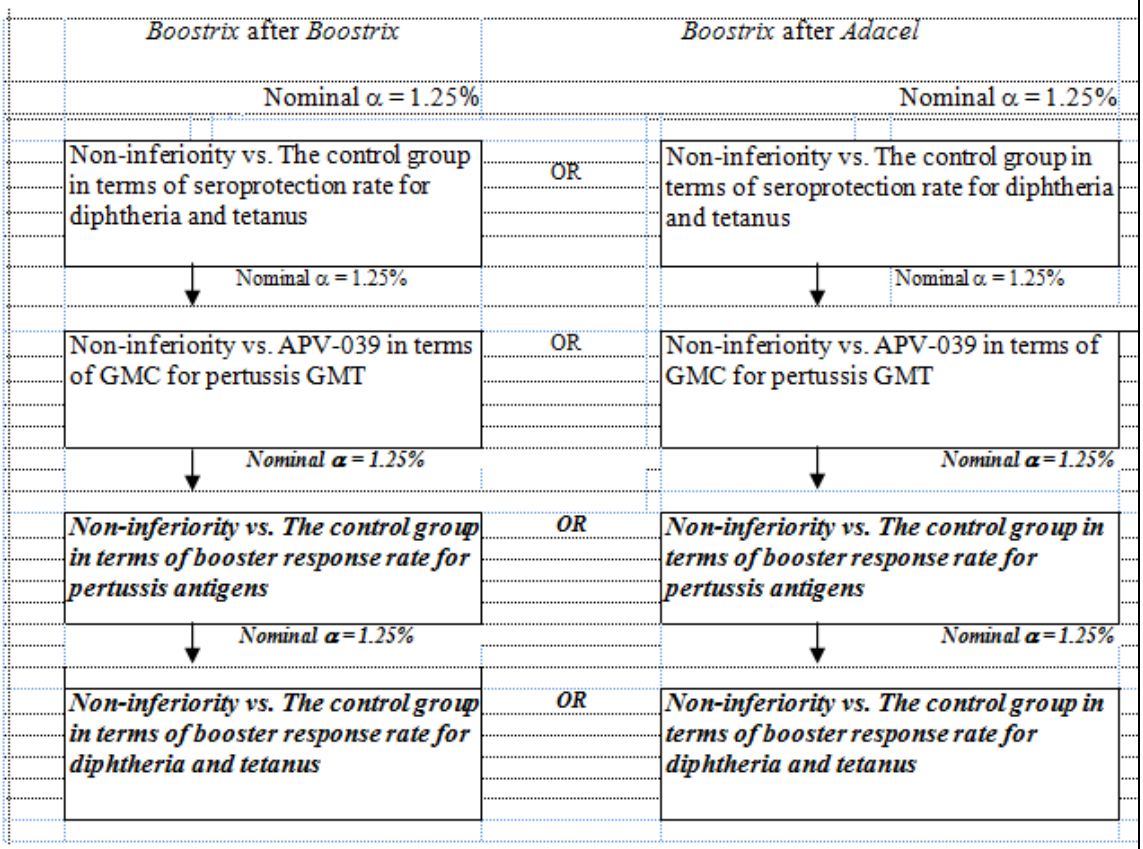
Refer to Section 10.5 for the definition of booster response.

Section 10.2: Secondary endpoints

- Immunogenicity with respect to components of the study vaccine at the Year 8 time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - ***Alternate*** ~~***B***~~***b***ooster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the ***definitions of booster response and alternate booster response***).

Section 10.3.1 Control on type I error

The figure 1 showing Sequence for evaluating the study objectives in order to control the overall type I error below 2.5% was updated to include the new co-primary objective.



Section 10.3: Power computation

As shown in Table 16, the power to demonstrate non-inferiority of Adacel group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be very low (4%). In other words, there is a big chance that non-inferiority would not be demonstrated for one or more of the antibodies.

Table 16 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

	Reference values		*Power* to reject H0: LL of 97.5%CI of difference <- 10%*
Endpoint (booster response rate)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)*	*Non-inferiority criterion Difference(2nd dose- 1st dose)*	*293 (Boostrix following Adacel) 293 (First Boostrix)*
Anti-D	*77.6%*	*LL of 97.5% CI ≥ -10%*	*74.19%*
Anti-T	*48.8%*	*LL of 97.5% CI ≥ -10%*	*57.51%*
Anti-PT	*77.2%*	*LL of 97.5% CI ≥ -10%*	*73.64%*
Anti-FHA	*96.9%*	*LL of 97.5% CI ≥ -10%*	*99.99%*
Anti-PRN	*93.2%*	*LL of 97.5% CI ≥ -10%*	*98.81%*
*Overall power***			*4.14%*

***Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.**

****Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.**

As shown in Table 19, the power to demonstrate non-inferiority of Boostrix group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be 48%. It is likely that non-inferiority might not be demonstrated for one or more of the antibodies.

Table 19 Power to demonstrate non-inferiority of Boostrix following Boostrix to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

	Reference values		*Power* to reject H0: LL of 97.5%CI of difference <- 10%*
Endpoint (booster response rate)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)*	*Non-inferiority criterion Difference(2nd dose- 1st dose)*	*586 (Boostrix following Boostrix) 293 (First Boostrix)*
Anti-D	*77.6%*	*LL of 97.5% CI ≥ -10%*	*88.89%*
Anti-T	*48.8%*	*LL of 97.5% CI ≥ -10%*	*71.39%*
Anti-PT	*77.2%*	*LL of 97.5% CI ≥ -10%*	*88.45%*
Anti-FHA	*96.9%*	*LL of 97.5% CI ≥ -10%*	*>99.99%*
Anti-PRN	*93.2%*	*LL of 97.5% CI ≥ -10%*	*99.96%*
*Overall power***			*48.69%*

** Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.*
***Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.*

Section 10.5 Derived and transformed data

- ~~Traditional~~ Booster response to D and T antigens is defined as:
- ~~Traditional~~ Booster response to PT, FHA and PRN antigens is defined as:

Section 10.6.3: Analysis of immunogenicity at booster dose

~~Between groups assessment~~ ***Comparability between Groups - confirmatory analyses:***

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm_{10} transformation of the concentrations.
- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.***

~~Exploratory between group assessment~~ ***Comparability between Groups - exploratory analyses:***

- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.***

In addition, within group assessment for the ATP analysis of immunogenicity at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***~~7~~-3***8***~~7~~ years old, 3***9***~~8~~-5***8***~~7~~ years old and 5***9***~~8~~-7***3***~~2~~ years old).

Section 10.6.4 Analysis of safety

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per ~~32~~***0.9***°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

In addition, safety analysis for TVC at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***~~7~~-3***8***~~7~~ years old, 3***9***~~8~~-5***8***~~7~~ years old and 5***9***~~8~~-7***3***~~2~~ years old).

Section 12 References

GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5). A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Koepke R, et al, Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis 2014; 210:942–53].

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change 2

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and evaluation of immunogenicity and safety of an additional dose of *Boostrix*, when administered at Year 9.
Administrative change number:	Administrative change 2
Administrative change date:	Administrative change 2 Final: 03 February 2015
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:
For the persistence only group, serious adverse events occurring due to study related procedures will be collected. This is noted in section 8.4 "Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies", but due to a typographical error, it has not been noted in section 5.5 "Outline of study procedures". This administrative change has been prepared to correct this typographical error in Table 3 "List of study procedures" as seen under section 5.5 "Outline of study procedures".

Amended text has been indicated in *bold italics* in the following sections:
Section 5.5 Outline of study procedures
Table 3 List of study procedures

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following *Boostrix/ Adacel* vaccination**	**VISIT 4** **Year 3** **3 years following *Boostrix/ Adacel* vaccination**	**VISIT 5** **Year 5** **5 years following *Boostrix/ Adacel* vaccination**	**VISITS 6 AND 7[1]** **Year *9*** **9 years following *Boostrix/ Adacel* vaccination** **Administration of *Boostrix* vaccine**	
				Visit 6	**Visit 7**
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●[3]	●
Reporting of SAEs				●[3]	●

Signature of principal or coordinating investigator or sponsor's responsible

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Global Clinical Research and Development

Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110082 (Tdap 0.3-009 Ext: 007 Y3)

Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Karin Hardt
Title of Sponsor Signatory:	Director, Clinical Development, Lead, Combination Vaccines, Global Vaccine Development, GlaxoSmithKline PPD
Signature:	PPD
Date:	6 APR 2011

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GlaxoSmithKline Biologicals
Global Clinical Research and Development
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Study: 110082 (Tdap 0.3-009 Ext: 007 Y3)

Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Francesca Ceddia
Title of Sponsor Signatory:	Vice President and Vaccine Development Leader (DTP Portfolio, Neisseria), Global Vaccine Development, GlaxoSmithKline BioPPDicals
Signature:	PPD
Date:	6 April 2011

PPD

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In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

GlaxoSmithKline Biologicals

Study title

Persistence study of GSK Biologicals' Tdap vaccine 776423, 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.

Study detailed title

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Note: The results of the Year 5 persistence is presented in this report.

Clinical Study Report for Study 110084 (Tdap-0.3-009 Ext: 007 Year 5)

Development Phase IIIb

IND Number: BB-IND-8461

Indication Studied: Healthy adults, 19 years of age and older, who received a single dose of the Tdap vaccine (*Boostrix* or *Adacel*) in the primary study 106316.

Study initiation date:	06 June 2011
Study completion date:	26 September 2011
Data lock point (Date of database freeze):	02 July 2012
Date of report:	Final 20 May 2013
Earlier Study Reports:	
Clinical study report 106316 (Tdap 0.3-007):	13 December 2007
Clinical study report 110080 (Tdap 0.3-009 EXT: 007 Year 1):	09 July 2008
Clinical study report 110082 (Tdap 0.3-009 EXT: 007 Year 3):	13 December 2010

Sponsor Signatory: Htay Htay Han, Director
Lead, Clinical Development, Combination Vaccines-
Infanrix, Boostrix, Hepatitis and Rotavirus Vaccines
GlaxoSmithKline Biologicals

This study was performed in compliance with Good Clinical Practice including the archiving of essential documents.

GSK Biologicals' Study Report INS-BIO-CLIN-1010 v03

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SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Study No.: 110084 (Tdap-0.3-009 EXT:007 Year 5)

Title of the study: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Principal investigators and study centers: This was a multicenter study conducted across 37 centers in the United States (US) by multiple investigators.

Publications (references):

- Blatter M, Friedland LR, Weston WM, et al. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine* 2009; 27(5): 765-72.
- Weston W, Messier M, Friedland LR, et al. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoid vaccine. *Vaccine* 2011; 29(47): 8483-86.

Study period: **Study initiation date:** 06 June 2011 **Study completion date:** 26 September 2011 **Data lock point (Date of database freeze):** 02 July 2012	**Phase:** IIIb

Indication: Healthy adults, 19 years of age and older, who received a single dose of the Tdap vaccine (*Boostrix* or *Adacel*) in the primary study 106316.

Treatment:

No treatment was given as a part of this study. Subjects in the 106316 study were randomized into treatment groups, Boostrix or Adacel (2:1 ratio, with stratified age group of 19-29 years, 30-49 years, and 50-64 years old). The study groups were as follows:

- **Boostrix group**: Subjects who received a single dose of GSK Biologicals' *Boostrix* in the 106316 study.
- **Adacel group**: Subjects who received a single dose of Sanofi Pasteur's *Adacel* in the 106316 study.

Objectives:

Primary:

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL [Enzyme-linked immunosorbent assay (ELISA)] or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Secondary:

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Note: This report presents the results of the analyses performed at Year 5.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** Boostrix® **Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Study design:

- Open-label, controlled, non-interventional, long-term follow-up study with 2 parallel groups.
- Blood samples were collected at Year 5 for evaluation of antibody persistence.

Study vaccine, dose, mode of administration, lot no.:
Refer to the 106316 study report for details of the composition and administration of vaccines.

Reference vaccine /Comparator, dose and mode of administration, lot no.:
Refer to the 106316 study report for details of the composition and administration of comparator vaccines.

Study Population:
All subjects who had received the study vaccination (*Boostrix* or *Adacel*) in the study 106316 were considered eligible to participate in this study. Written informed consent was obtained from the subject prior to the enrollment at Year 5.

Duration of treatment:
No protocol specific treatment was planned at the Year 5 time point. The duration of the study from vaccination in the 106316 study up to Year 5 was approximately 5 years per subject.

Primary Outcome/Efficacy Variable:
Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

Secondary Outcomes/Efficacy Variable:

- Subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-T concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PT concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-FHA concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PRN concentration for each subject at the time of analysis in the Boostrix and Adacel groups.

Statistical methods: Analyses were performed as planned in the protocol with the following exception: The VERO cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL which was previously used for Year 1 and Year 3 analysis. The study considered anti-D concentrations greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection.

Three cohorts were described for the purpose of analysis:

- The Year 5 cohort was a subset of the Total Vaccinated Cohort (TVC) in the 106316 study. This cohort included subjects for whom serological results for at least one antigen were available after a blood sample taken 5 years after vaccination.
- The according to protocol (ATP) Year 5 cohort for immunogenicity included all subjects from Year 5 cohort who were in the ATP cohort for immunogenicity in 106316 study and who had not met the protocol specified elimination criteria. This cohort was the primary cohort for the immunogenicity persistence analysis.
- The ATP Complete Year 5 cohort included all subjects who belonged to the ATP Year 5 cohort for immunogenicity and the previously defined Year 1 and Year 3 ATP cohorts.

Persistence data were analyzed at Year 5 on the ATP Year 5 cohort for immunogenicity. Some of the analyses were repeated on the ATP Complete Year 5 cohort.

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Analysis of Demography/Baseline characteristics:

- Demographic characteristics (age in years at Year 5 and gender) for Year 5 cohort and ATP Year 5 cohort for immunogenicity were tabulated.
- The number of subjects included in the TVC in the 106316 study and in each follow-up cohort up to Year 5, ATP Year 5 cohort and ATP complete Year 5 cohort was tabulated.
- Time from the vaccination in the 106316 study to the blood sampling at Year 5 (in weeks) by vaccine group were summarized using descriptive statistics.

Analysis of Immunogenicity: The analysis of antibody persistence at Year 5 was performed on the ATP Year 5 cohort for immunogenicity. Since the percentage of subjects eliminated from the ATP Year 5 cohort for immunogenicity was more than 5%, a complementary persistence analysis based on the Year 5 cohort was performed.

Within group assessment:
For each vaccine group, at Year 5:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% confidence interval (CI) were calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.01 IU/mL for Year 5 results by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, was calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) were calculated by group.
- Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN GMCs (with 95% CI) were tabulated by group.
- In addition, the distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves (RCC) by group.

Comparability between groups (exploratory analysis):

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group-Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), 5 years after vaccination were calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group-Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 5 years after vaccination were calculated.
- For anti-D and anti-T antibody response, the two-sided 95% CIs of the GMC ratio between subjects in the Boostrix group and (divided by) the Adacel group were computed using an Analysis of Covariance (ANCOVA) model adjusted for age and pre-vaccination titers on the logarithm_{10} transformation of the concentrations 5 years after vaccination.

The above analyses were repeated for subgroup of age strata (19-29 years, 30-49 years and 50-64 years) and gender (male and female) defined in the primary study. To investigate a potential bias due to the drop out of ATP cohort, the primary objectives defined in the primary study were re-evaluated using Year 5 cohort.
If the 95% CI on the group differences in seroprotection rates excluded 0, or if the 95% CI on the between group GMC ratio excluded 1, then this was taken as an indication of potential differences between groups. The exploratory comparisons are to be interpreted with caution since there was no adjustment for multiplicity of endpoints.

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Analysis of safety: No safety analyses were to be performed in this persistence study. If GSK was informed by an investigator of an SAE that in his/her medical judgment could be reasonably related tothe study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details were to be summarized in the study report.

Study population-Year 5 time point

Number of subjects	**Boostrix**	**Adacel**
Planned, N	856	401
Randomized, N (Total Cohort)	856	401
Completed, n (%)	856 (100)	401 (100)
Demographics	**Boostrix**	**Adacel**
N (Total Cohort)	856	401
Females: Males	545:311	279:122
Mean Age, years (SD)	47.1 (13.30)	47.9 (13.17)
White - Caucasian / European heritage, n (%)	763 (89.1)	357 (89.0)

Summary:

Immunogenicity: Analyses of immunogenicity were performed on the ATP Year 5 cohort for immunogenicity (primary analyses) and on the Year 5 cohort (secondary analyses).

- The proportion of subjects estimated to be seroprotected for anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) was 96.5% for Boostrix group and 97.8% for Adacel group at Year 5 after vaccination.
- The percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL was 98.0% for Boostrix group and 99.5% for Adacel group at Year 5 after vaccination.
- At Year 5, seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies were 84.8%, 99.9% and 96.6% respectively for Boostrix group and 76.6%, 99.2% and 97.6% respectively for Adacel group.
- GMCs for anti-D and anti-T antibodies were 0.8 IU/mL and 2.0 IU/mL, respectively for Boostrix group and 0.9 IU/mL and 2.5 IU/mL, respectively for Adacel group.
- GMCs for anti-PT, anti-FHA and anti-PRN were 14.6 EL U/mL, 110 EL U/mL and 85.2 EL U/mL respectively for Boostrix group and 11.6 EL U/mL, 80.8 EL U/mL and 77.4 EL U/mL respectively for Adacel group.
- Majority of the subjects continued to have seroprotective antibody concentrations to anti-D, anti-T and remained seropositive to anti-FHA and anti-PRN and anti-PT in both the groups.

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Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and GMC by vaccine groups (ATP Year 5 cohort)

Antibody	Group	Timing		≥ 0.1 IU/mL				GMC		
						95% CI			95% CI	
			N	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	Pre	785	667	85.0	82.3	87.4	0.4	0.4	0.4
		1 month post	789	772	97.8	96.6	98.7	4.6	4.2	5.1
		1 year post	682	651	95.5	93.6	96.9	1.4	1.3	1.5
		3 year post	724	679	93.8	91.8	95.4	0.9	0.8	1.0
		5 year post	790	736	93.2	91.2	94.8	0.8	0.7	0.9
	Adacel	Pre	366	326	89.1	85.4	92.1	0.5	0.4	0.5
		1 month post	371	364	98.1	96.2	99.2	5.0	4.4	5.6
		1 year post	317	308	97.2	94.7	98.7	1.5	1.3	1.7
		3 year post	342	330	96.5	94.0	98.2	1.0	0.9	1.2
		5 year post	372	359	96.5	94.1	98.1	0.9	0.8	1.0
Anti-T	Boostrix	Pre	790	757	95.8	94.2	97.1	1.5	1.4	1.7
		1 month post	788	783	99.4	98.5	99.8	8.3	7.8	8.8
		1 year post	685	674	98.4	97.1	99.2	3.3	3.0	3.5
		3 year post	726	710	97.8	96.4	98.7	2.2	2.0	2.3
		5 year post	789	773	98.0	96.7	98.8	2.0	1.9	2.1
	Adacel	Pre	371	362	97.6	95.4	98.9	1.7	1.6	2.0
		1 month post	372	372	100	99.0	100	12.5	11.5	13.6
		1 year post	319	318	99.7	98.3	100	4.4	4.1	4.8
		3 year post	342	340	99.4	97.9	99.9	2.9	2.7	3.2
		5 year post	372	370	99.5	98.1	99.9	2.5	2.3	2.7

GMC = geometric mean concentration calculated on all subjects
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

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Seronegativity status for anti-D antibody concentration by ELISA and VERO (ATP Year 5 cohort)

Group	Timing	N	Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
			n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Boostrix	Pre	785	118/785	15.0	57/118	48.3	118/785 x 57/118	7.3	92.7	90.7	94.5
	1 month post	789	17/789	2.2	7/17	41.2	17/789 x 7/17	0.9	99.1	98.2	99.6
	1 year post	684	33/684	4.8	11/33	33.3	33/684 x 11/33	1.6	98.4	97.1	99.2
	3 year post	724	45/724	6.2	23/45	51.1	45/724 x 23/45	3.2	96.8	95.3	98.0
	5 year post*	790	54/790	6.8	28/54	51.9	54/790 x 28/54	3.5	96.5	94.9	97.6
Adacel	Pre	366	40/366	10.9	15/40	37.5	40/366 x 15/40	4.1	95.9	93.3	97.7
	1 month post	371	7/371	1.9	4/7	57.1	7/371 x 4/7	1.1	98.9	97.3	99.7
	1 year post	318	10/318	3.1	7/10	70.0	10/318 x 7/10	2.2	97.8	95.5	99.1
	3 year post	342	12/342	3.5	9/12	75.0	12/342 x 9/12	2.6	97.4	95.1	98.8
	5 year post*	372	13/372	3.5	8/13	61.5	13/372 x 8/13	2.2	97.8	95.8	99.1

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ML / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ML / number of subjects tested by VERO test for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for VERO) for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
*n'/N' = number of subjects with concentrations below the 0.01IU/ML / number of subjects tested by VERO test for 5 year post-vaccination.
*% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.01IU/ML for VERO) for 5 years post-vaccination.
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for groups; LL = lower limit, UL = upper limit

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Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP Year 5 cohort)

Antibody	Group	Timing	N	≥ 5 ELU/ML				GMC		
						95% CI			95% CI	
				n	%	LL	UL	value	LL	UL
ANTI-PT	Boostrix	Pre	783	437	55.8	52.3	59.3	7.1	6.5	7.6
		1 month post	786	764	97.2	95.8	98.2	62.0	57.6	66.8
		1 year post	686	625	91.1	88.7	93.1	22.6	20.8	24.5
		3 year post	725	603	83.2	80.2	85.8	14.1	13.0	15.3
		5 year post	791	671	84.8	82.1	87.3	14.6	13.6	15.8
	Adacel	Pre	368	231	62.8	57.6	67.7	8.1	7.2	9.1
		1 month post	368	344	93.5	90.5	95.8	32.5	28.8	36.6
		1 year post	319	278	87.1	83.0	90.6	16.1	14.3	18.1
		3 year post	342	251	73.4	68.4	78.0	10.2	9.1	11.5
		5 year post	372	285	76.6	72.0	80.8	11.6	10.3	13.0
ANTI-FHA	Boostrix	Pre	784	759	96.8	95.3	97.9	30.2	27.9	32.6
		1 month post	789	789	100	99.5	100	619.4	580.0	661.5
		1 year post	685	684	99.9	99.2	100	192.0	177.8	207.3
		3 year post	725	724	99.9	99.2	100	118.2	110.4	126.7
		5 year post	790	789	99.9	99.3	100	110.0	103.1	117.4
	Adacel	Pre	364	351	96.4	94.0	98.1	35.0	31.1	39.4
		1 month post	370	370	100	99.0	100	358.4	327.2	392.5
		1 year post	316	316	100	98.8	100	116.4	104.2	130.0
		3 year post	339	337	99.4	97.9	99.9	83.0	74.8	92.0
		5 year post	371	368	99.2	97.7	99.8	80.8	73.1	89.4
ANTI-PRN	Boostrix	Pre	788	603	76.5	73.4	79.4	13.7	12.5	15.0
		1 month post	787	778	98.9	97.8	99.5	398.5	355.7	446.5
		1 year post	682	658	96.5	94.8	97.7	153.3	135.5	173.6
		3 year post	724	689	95.2	93.3	96.6	86.2	76.8	96.6
		5 year post	783	756	96.6	95.0	97.7	85.2	76.6	94.8
	Adacel	Pre	371	279	75.2	70.5	79.5	14.9	12.9	17.2
		1 month post	372	371	99.7	98.5	100	341.3	293.5	397.0
		1 year post	316	311	98.4	96.3	99.5	139.5	117.8	165.2
		3 year post	342	333	97.4	95.1	98.8	76.0	65.3	88.3
		5 year post	371	362	97.6	95.4	98.9	77.4	66.9	89.6

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Safety /reactogenicity: There were no pregnancies or SAEs reported at Year 5.

Conclusion:

The Study Analysis Outcomes are based on the ATP Year 5 cohort:

- Evaluation of anti-D and anti-T antibodies elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus 5 years after vaccination.
- At Year 5 time point, observed GMCs to all antigens remained higher than the pre-vaccination levels for both the study vaccines.
- There were no pregnancies or SAEs reported at Year 5 time point.

Date of report: Final: 20 May 2013

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ACIP	Advisory Committee on Immunization Practices
ANCOVA	Analysis of Covariance
ATP	According-To-Protocol
CDC	Centers for Disease Control
CI	Confidence Interval
eCRF	electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
EL.U	ELISA Units
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
IU	International Units
IND	Investigational New Drug
IRB	Institutional Review Board
PI	Principal Investigator
PRN	Pertactin
PT	Pertussis Toxoid
RAP	Reporting and Analysis Plan
RCC	Reverse Cumulative distribution Curve
RDE	Remote Data Entry
SAE	Serious Adverse Event

SAS	Statistical Analysis System
SOP	Standard Operating Procedure
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Td	reduced-antigen-content diphtheria–Tetanus vaccine
TVC	Total Vaccinated Cohort

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) was therefore any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Completed:	Subjects who completed the last study visit.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion /exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: ‘A written description of a change(s) to or formal clarification of a protocol.’ GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Subject(s):	Term used throughout the clinical study report to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control.
Seronegative subject:	A subject whose antibody concentration was below the cut-off value.
Seropositive subject:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Seroprotected subject:	A seroprotected subject was a subject with antibody concentrations greater than or equal to the seroprotection cut-off value defined for that antibody.

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in *italics*.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Infanrix®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed (DTaP) vaccine
Boostrix®	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap).

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Adacel® (Sanofi Pasteur)	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, amendment, the informed consent, and other information that required pre-approval were reviewed and approved by a central IRB (Quorum Review IRB).

1.2. Ethical conduct of the study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki.

1.3. Subject information and consent

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures, in accordance with 21 CFR 50.25. Data collection was done by Remote Data Entry (RDE) using individual electronic case report forms (eCRFs).

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted by 35 investigators across multiple centers in the United States (US). GSK Biologicals, King of Prussia, PA, US was responsible for administration of the study including clinical trial supply management and laboratory facilities. There was a reduction in the number of participating centers at Year 5 (37 centers) when compared to the Year 3 (39 centers) and the 106316 study (45 centers) [GlaxoSmithKline Biologicals Study Report 106316 (Tdap-0.03-007)] since several investigators declined to participate in this phase of the study. The non-participating centers will be invited to participate in the Year 10 phase of the study.

3. INTRODUCTION

Pertussis (whooping cough) is a highly contagious respiratory tract infection caused by the etiologic bacterial agent, *Bordetella pertussis*. Since the 1980s, there has been an increase in the number of reported cases of pertussis in the US, especially among 10-19 year olds and infants younger than 6 months of age. In 2010, about 27,550 cases of pertussis were reported in the US [CDC, 2011].

According to the recent General Recommendations on Immunization, adolescents and adults ≥ 11 years of age are recommended to receive a single tetanus toxoid, reduced

diphtheria toxoid and acellular pertussis vaccine (Tdap) dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults who have or anticipate having close contact with an infant aged < 12 months, pregnant women and postpartum mothers who have not received Tdap previously [ACIP, 2011; CDC, 2012].

GSK Biologicals' *Boostrix* has been evaluated as a booster dose in adults, adolescents and children with a variety of previous vaccination and/or natural infection histories. Results obtained after immunization with Tdap vaccine demonstrated that regardless of vaccination or natural infection history and age, local and general reactions were all within clinically acceptable ranges. In addition, the vaccine was shown to be immunogenic, since most subjects developed protective antibody concentrations against diphtheria and tetanus as well as a vaccine response against pertussis after vaccination, [Zepp, 2007; Blatter, 2009] and are comparable to other booster vaccines such as reduced-antigen-content diphtheria–tetanus vaccine (Td) vaccine [Frampton, 2006; Pichichero, 2006].

The 106316 study was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age [Blatter, 2009]. The immunogenicity and reactogenicity of *Boostrix* was compared to that elicited by Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, *Adacel* vaccine, which is licensed in the US for individuals 11-64 years of age. In December 2008, *Boostrix* (0.3 mg) was approved in the US for use in adults 19-64 years of age. In 2011, it was approved in the US for use in elderly adults 65 years of age and older.

Currently in the US, no data is available for long-term persistence of Tdap vaccine, though a three year antibody persistence following Tdap vaccination supports the immunogenicity of this vaccine in US adolescents and adults and demonstrates the persistence of antibodies against vaccine antigens through the first three years after vaccination [Weston, 2011]. Immunogenicity results from Year 1 and Year 3 showed that concentrations of antibodies to *Boostrix* antigens were lower than those observed 1 month post-vaccination but remained elevated relative to pre-vaccination levels. This report presents results of immunogenicity analyses for subjects in the 106316 study, 5 years following vaccination in that study.

4. STUDY OBJECTIVES

4.1. Primary objective

To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

4.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

This report presents the results of the analyses performed up to Year 5.

See Section 5.9 for details of the study endpoints.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall study design – Description

- Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study [GlaxoSmithKline Biologicals Study Report 106316 (Tdap-0.03-007)]:
  - **Boostrix group:** Subjects who received a single dose of GSK Biologicals' *Boostrix* in the 106316 study.
  - **Adacel group**: Subjects who received a single dose of Sanofi Pasteur's *Adacel* in the 106316 study.
- Blinding: This study was an open study since there was no vaccine administration.
- Treatment allocation: No treatment was given in this study. Subjects in the 106316 study were randomized into treatment groups, Boostrix or Adacel (2:1 ratio, with stratified age group of 19-29 years, 30-49 years, and 50-64 years old).
- Blood samples were collected at Year 5 for antibody persistence.
- Duration of the study: The duration of the study from vaccination in the 106316 study up to Year 5 (Visit 5) was approximately 5 years per subject.
- Data collection: RDE.

5.2. Study procedures

5.2.1. Outline of study procedures

The list of study procedures are outlined in Table 1.

Table 1 Outline of study procedures

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISIT 6 Year 10 10 years following *Boostrix/ Adacel* vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that required documentation in the individual eCRF.
The gray shaded area represents the time point for which the analyses are presented in this report.

5.2.2. Intervals between study visits

It was the investigator's responsibility to ensure that the intervals between visits were strictly followed. The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	10 years ± 8 weeks

[1]. Whenever possible the investigator should have arranged study visits within this interval.
[2]. Subjects were not eligible for inclusion in the ATP Year 5 cohort for analysis if they made the study visit outside this interval.
The gray shaded area represents the time point for which the analyses are presented in this report.

5.3. Selection of study population

A total of 37 centers in the US participated in the blood sample collection at Year 5. The total number of subjects enrolled in the 106316 study was 2284, randomized into Boostrix or Adacel groups in the ratio 2:1. The number of vaccinated subjects in the primary study was 1522 for Boostrix group and 762 for Adacel group. The number of subjects included in the according-to-protocol (ATP) Year 5 cohort was 791 for Boostrix

group and 372 for Adacel group. About half of the vaccinated subjects did not come back or were eliminated from the ATP Year 5 analysis.

5.3.1. Inclusion criteria for enrolment

All subjects had to satisfy the following criteria at study entry:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 were considered eligible to participate in this study.
- Written informed consent was obtained from the subject prior to Year 5 follow-up study.

5.3.2. Exclusion criteria

Not applicable for this time point of the study.

5.3.3. Elimination criteria

The following criteria were checked at Year 5 (Visit 5). If any became applicable during the study, it did not require withdrawal of the subject from the study but were considered in determining a subject's evaluability in the ATP analysis. See Section 5.9.4 for definition of study cohorts that were evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in the 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in the 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators deferred the blood draw for these subjects until the time the criterion no longer applied.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to Visit 5. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

5.3.4. Subject completion and withdrawal

5.3.4.1. Subject completion

A subject who returned for Visit 5 as specified in the protocol was considered to have completed the Year 5 follow-up time point.

5.3.4.2. Subject withdrawal

5.3.4.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study was any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects could participate in each persistence time point independent of other persistence time points. For example, a subject who did not participate in the Year 5 antibody persistence analysis could be approached for participation in the Year 10 persistence analyses.

A subject qualified as a 'withdrawal' from the study when no study procedure had occurred, no follow-up had been performed, and no further information had been collected for the subject since the last contact.

Investigators were to make at least four attempts to contact subjects who did not return for scheduled persistence visit at Year 5. The first three attempts were by phone contact. The fourth attempt was done through a certified letter. Subjects lost to follow-up were confirmed by a returned certified letter.

Information relative to the withdrawal of a subject was documented on the study continuation/conclusion screens of the eCRF. The investigator documented whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event (SAE)
- Non-serious adverse event (AE)
- Protocol violation (included receipt of prohibited vaccine or medication; was to be specified)
- Consent withdrawal, not due to an AE
- Moved from the study area
- Lost to follow-up
- Other (was to be specified).

5.3.4.2.2. Subject withdrawal from investigational vaccine

Not applicable for this phase of the study.

5.4. Composition and administration of vaccines

Refer to the 106316 study report for details of the composition of vaccines administered in the 106316 study [GlaxoSmithKline Biologicals Study Report 106316 (Tdap-0.03-007)].

5.4.1. Treatment allocation and randomization

Not applicable for this phase of the study. No treatment was given in this persistence study at Year 5 time point. Subjects in the 106316 study were randomized into treatment groups, Boostrix or Adacel (2:1 ratio, with stratified age group of 19-29 years, 30-49 years, and 50-64 years old).

5.4.2. Blinding

The Year 5 time point was an open study, since there was no administration of vaccination in this study.

5.5. Prior and concomitant medication /vaccinations

At Visit 5, the investigator questioned the subject about any medications taken:

Any treatments and/or medications specifically contraindicated (e.g. any immunoglobulins, other blood products and any immune modifying drugs) administered within 90 days prior to any study blood sampling, were to be recorded in the eCRF with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, was to be recorded in the eCRF with the trade name, route of administration, and date of administration.

5.6. Laboratory assays and time points

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus were measured by ELISA. The cut-off of both assays was 0.1 IU/mL. All samples with anti-D antibody concentrations < 0.1 IU/mL were re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and had a cut-off of 0.004 IU/mL.

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN were measured by ELISA or multiplex (Luminex) techniques. The cut-off of the three assays was 5 EL.U/mL.

The details of laboratory assays that were performed are presented in Table 3.

Table 3 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory †
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-D	Neutralization test on VERO cell*	In-house assay	IU/mL	0.016**	Rixensart
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1	Laval
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5	Laval
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5	Laval
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5	Laval

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
*VERO cell testing were performed in subjects with an ELISA result of < 0.1 IU/mL
**The cut-off of VERO cell assay was re-validated to evaluate the precision around the cut-off. The cut-off for the test was calculated at 0.004 IU/mL. For Year 5 we have used 0.01 IU/mL as the minimum level providing some level of seroprotection instead of 0.016 IU/mL which was previously used for Year 1 and Year 3 analysis.
†All serological assays were performed using standardized, validated procedures with adequate controls in laboratories in Laval, Quebec Canada and Rixensart, Belgium.

5.7. Assessment of immunogenicity variables

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum was obtained at Year 5 following study vaccination in the 106316 study. After blood centrifugation and serum separation, serum samples were stored at approximately -20°C until they were sent to the sponsor. Sera were sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Laval for storage prior to analysis.

The priority listing for antibody testing was as shown in Table 4.

Table 4 Immunological read-outs for all subjects

Blood sampling time point		Marker
Timing	Visit no.	
Year 5	5	D (ELISA and VERO)
		T
		PT
		FHA
		PRN

ELISA = enzyme-linked immunosorbent assay
VERO cell testing were performed in subjects with an ELISA result of < 0.1 IU/mL

5.7.1. Immunological correlates of protection

- The assay cut-offs for antibodies against diphtheria and tetanus toxoids was set at 0.1 IU/mL (ELISA), which provided a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].

- The cut-off of the VERO cell assay (performed for serum samples with ELISA anti-D antibody concentrations < 0.1 IU/mL) was 0.004 IU/mL. Antibody concentrations greater than or equal to 0.01 IU/mL was considered as protective [Camargo, 1984].
- No correlate of protection has been defined for the immune response to pertussis antigens. Antibodies against the pertussis components PT, FHA and PRN were measured by an ELISA technique developed in-house. The cut-off for all three pertussis antibodies was 5 ELISA Units per mL (EL.U/mL). Subjects with antibody concentration below this cut-off were considered seronegative [Granström, 1987; Karpinsky, 1987].

5.8. Assessment of safety variables

5.8.1. Serious adverse events

Since subjects were not vaccinated as part of the study protocol, investigators were not required to specifically solicit SAEs in this phase of the study. However, if an investigator became aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in the 106316 study, he/she was to report to GSK Biologicals within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations, SAEs that were considered to be related to study participation (e.g. blood draws) were to be collected and recorded from the time the subject consented to participate in the study until she/he was discharged.

An SAE was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occurred during hospitalization were AEs. If a complication prolonged hospitalization or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE was to be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

e. was a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgment was to be exercised in deciding whether reporting was appropriate in other situations, such as important medical events that might not have been immediately life-threatening or resulted in death or hospitalization but might have jeopardized the subject or might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization.

Assessment of intensity:

The investigator was to make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment was to be based on the investigator's clinical judgment.

The intensity of each SAE recorded in the eCRF, as applicable, was to be assigned to one of the following categories:

1 (mild)	=	An SAE which was easily tolerated by the subject, caused minimal discomfort and did not interfere with everyday activities.
2 (moderate)	=	An SAE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevented normal, everyday activities. (In adults, such an SAE, for example, prevented attendance at work/ school and necessitated the administration of corrective therapy.)

Grade 3 is a category utilized for rating the intensity of an event; and SAEs can be assessed as Grade 3. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in Section 5.8.1.

Assessment of causality:

The investigator was obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator was to use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product was considered and investigated. The investigator also consulted the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

In situations when an SAE occurred and the investigator had minimal information to include in the initial report to GSK Biologicals, it was very important that the investigator always made an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. If the investigator changed his/her opinion of causality in light of follow-up information, he was to amend the SAE information accordingly. The causality

assessment was to be one of the criteria used when determining regulatory reporting requirements.

If an event met the criteria determined as "serious" (see Section 5.8.1 for definition of SAE), it was to be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE.

Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccines, if applicable
- Erroneous administration
- Other cause (was to be specified).

5.8.2. Pregnancy

Since subjects were not vaccinated as part of the study protocol, investigators were not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who were pregnant at the time of Year 5 (Visit 5) were not to be excluded from the visit on the basis of their pregnancy.

5.8.3. Clinical laboratory evaluations

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. vital signs) that were judged by the investigator to be clinically significant were to be recorded as SAEs if they met the definition of a SAE, as defined in Section 5.8.1. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study was to be reported as SAEs. The investigator was to exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

5.9. Statistical methods

This report summarizes the planned statistical analyses based on the report analysis plan (RAP) Amendment 1 dated 04 February 2010. It covers the immunogenicity analyses pertaining to the follow-up period up to Year 5 post-vaccination of the study 106316. Refer to Section 5.10.2 for changes from the planned analysis of the protocol.

The statistical analyses were performed using the Statistical Analysis Systems (SAS) Drug Development 3.5 and StatXact-8.1 procedure on SAS.

5.9.1. Primary outcome/Efficacy Variable

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years 5 years and 10 years following vaccination.

5.9.2. Secondary Outcome/Efficacy Variables

- Subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-T concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PT concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-FHA concentration for each subject at the time of analysis in the Boostrix and Adacel groups.
- Anti-PRN concentration for each subject at the time of analysis in the Boostrix and Adacel groups.

5.9.3. Determination of sample size

All subjects who had received vaccination in the 106316 study were eligible for enrollment in this study. Refer to the 106316 study report for sample size estimation [GlaxoSmithKline Biologicals Study Report 106316 (Tdap-0.03-007)].

5.9.4. Study cohorts/data sets analyzed

Year 5 cohort

The Year 5 cohort was a subset of the Total Vaccinated Cohort (TVC) in 106316 study. This cohort included subjects for whom serological results for at least one antigen were available after a blood sample taken 5 years after vaccination.

ATP Year 5 cohort

The ATP Year 5 cohort included all subjects from Year 5 cohort who were in the ATP cohort for immunogenicity in the 106316 study [GlaxoSmithKline Biologicals Study Report 106316 (Tdap-0.03-007)] and who did not meet the elimination criteria as described in Section 5.3.3. This cohort was the primary cohort for the immunogenicity persistence analysis.

ATP Complete Year 5 cohort

The ATP Complete Year 5 cohort included all subjects who belonged to the ATP Year 5 and the previously defined Year 1 and Year 3 ATP cohorts.

5.9.4.1. Derived and transformed data

- The cut-off value was defined by the laboratory before the analysis and is described in Section 5.6. Also refer to Section 5.10.2 for changes in cut-off value for VERO cell assay.
- A seronegative subject was a subject whose antibody concentration was below the assay cut-off value except VERO cell assay.
- A seropositive subject was a subject whose antibody concentration was greater than or equal to the assay cut-off value.
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL for Year 5 results (VERO) and anti-T antibody concentrations ≥ 0.1IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years and 5 years following vaccination were derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years and 5 years following vaccination were derived to evaluate the first secondary objective.
- The GMC calculations were computed by taking the anti-$\log_{10}$ of the mean of the log antibody concentration transformations. Antibody concentrations below the cut-off of the assay were given a value of half of the cut-off for the purpose of GMC calculation.
- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years and 5 years after vaccination with *Boostrix* were derived to evaluate the other secondary objectives.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

5.9.5. Analysis of demographics

Demographic characteristics (age in years at Year 5 and gender) for Year 5 cohort and ATP Year 5 cohort were tabulated.

The number of subjects included in the TVC in the 106316 study and in each follow-up cohort up to Year 5 cohort in the ATP Year 5 cohort and in the ATP complete Year 5 cohort was tabulated.

Time from the vaccination in the 106316 study to the blood sampling at Year 5 (in weeks) by vaccine group were summarized using descriptive statistics.

5.9.6. Analysis of immunogenicity

Persistence (immunogenicity) data were analyzed at Year 5.

Persistence was analyzed on ATP Year 5 cohort including data from all previous years. Since more than 5% of subjects were excluded from the ATP Year 5 cohort, a complementary persistence analysis was performed on the Year 5 cohort.

5.9.6.1. Within group assessment:

For each vaccine group and each blood sample time point:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% confidence interval (CI) were calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL (≥ 0.01 IU/mL for Year 5 results) by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, was calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) were calculated by group.
- Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN GMCs (with 95% CI) were tabulated by group.
- In addition, the distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves (RCC) by group.

5.9.6.2. Comparability between Groups (exploratory analyses):

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group-Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), 5 years after vaccination were calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group-Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, 5 years after vaccination were calculated.
- For anti-D and anti-T antibody response, the two-sided 95% CIs of the GMC ratio between subjects in the Boostrix vaccine group and (divided by) the Adacel group were computed using an ANCOVA model adjusted for age and pre-vaccination titers on the logarithm_{10} transformation of the concentrations at 5 years after vaccination.

The above analyses were repeated for subgroup of age strata (19-29 years, 30-49 years and 50-64 years) and gender (male and female) defined in the primary study.

To investigate a potential bias due to the drop out of ATP cohort, the primary objectives defined in the primary study were re-evaluated using Year 5 cohort.

Estimation of GMCs by Modeling Method

An exploratory analysis was performed to examine the immunogenicity persistence over time. A mean antibody concentration over time was summarized. An analysis of persistence was carried out by using a two-piece repeated generalized linear model. The first piece of linear model used results from Year 1 and Year 3. The second piece of linear model used Year 3 and Year 5 results. Analysis was based on all available results in the ATP cohorts corresponding to each time point. Serology results below cut-off were considered as left censored at the assay cut-off [Thiébaut, 2004]. The model included treatment group and time since vaccination as fixed effects, intercept as a random effect to account for variation between subjects and measurements, age and pre-vaccination antibody concentration as covariates.

The results of the exploratory group comparisons should be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that the clinical relevance of any differences was not accounted for in the planning of the exploratory analyses.

5.9.7. Analysis of safety

No safety analyses were performed in this persistence study since no SAE or pregnancy was to be reported. If GSK received information from an investigator of an SAE that in his/her medical judgment was reasonably related to the study vaccine administered in the 106316 study or to participation in this persistence study, the pertinent clinical details were to be summarized in the study report.

5.9.8. Sequence of analyses

An analysis was performed on cleaned data obtained through Year 5. Persistence data analyzed at each time point (Year 1, Year 3 and Year 5) was reported separately.

5.9.9. Interim analysis

No interim analysis was planned for this persistence study.

5.9.10. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, (eCRF) and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

Independent Audit statement:

- No study specific audits were performed for Year 5 time point.

5.10. Changes in the conduct of the study or planned analyses

5.10.1. Protocol amendments

The study protocol (dated 17 April 2007) was modified twice. The first was an administrative change dated 14 April 2009 which was done to clarify the contact details for reporting of SAEs. The second was an amendment dated 09 November 2010 which was done to extend the window period allowed for the return of subjects, to clarify reporting of SAEs, to clarify reporting of spontaneous abortion and the number of attempts required to contact a subject.

5.10.2. Other changes

All analyses were done according to the protocol dated 09 November 2010 and SAP dated 04 February 2010 with the following exception:

The VERO cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL which was previously used for Year 1 and Year 3 analysis. The study considered anti-D titers greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject visit for Year 5 (Visit 5) was on 06 June 2011 and the last subject visit took place on 26 September 2011.

6.2. Subject eligibility and attrition from the study

6.2.1. Number of subjects

The number of subjects enrolled at Year 5 and the number of subjects included into the Year 5 cohort and the ATP Year 5 cohort for immunogenicity are presented in Table 5.

The number of enrolled subjects by center for the Year 5 cohort is presented in Table 6.

The time (in weeks) from the vaccination in the 106316 study to the blood sampling for each group for the Year 5 cohort is presented in Table 7.

Table 5 Number of subjects included in each follow-up period up to 5 Years (Total cohort)

Table 6 Number of subjects by center (Year 5 cohort)

Table 7 Duration (in weeks) from the vaccination in primary study to Year 5 blood sampling for each group (Year 5 cohort)

6.2.2. Study completion and withdrawal from study

There were no withdrawals at the Year 5 time point.

6.2.3. Protocol deviations

A summary of the subjects enrolled into the study as well as the number eliminated from ATP analyses with reasons for elimination is presented in Table 8. Subjects are listed in the text based on the lowest elimination code, as more than one elimination code could have been assigned to the same subject.

Table 8 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

6.3. Demographic characteristics

6.3.1. ATP Year 5 cohort for immunogenicity

The demographic characteristics for ATP Year 5 cohort are presented in the following table:

Table 9 Summary of demographic characteristics (ATP Year 5 cohort)

6.3.2. Year 5 cohort

The demographic characteristics for Year 5 cohort are presented in the following table:

Table 10 Summary of demographic characteristics (Year 5 cohort)

7. IMMUNOGENICITY RESULTS

7.1. Data sets analyzed

The primary analysis of immunogenicity was performed on the ATP Year 5 cohort for immunogenicity. A complementary analysis based on the Year 5 cohort was performed as more than 5% of the vaccinated subjects who returned for blood sampling at Year 5 were eliminated from the ATP Year 5 cohort for immunogenicity. An analysis on the ATP Complete Year 5 cohort for immunogenicity was also performed. See Section 5.9.4 for the definition of the cohorts identified for the analyses and Section 6.2 for eligibility for the analysis.

7.2. According-to-protocol analysis

7.2.1. Persistence of antibodies to diphtheria and tetanus toxoids

The percentages of subjects with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL (by ELISA) and GMCs by vaccine groups for the ATP Year 5 cohort for immunogenicity are presented in Table 11:

Table 11 Percentage of subjects with anti-D and anti-T concentrations equal to or above the cut-off values of 0.1 IU/mL and 1.0 IU/mL and GMCs (ATP Year 5 cohort)

Five years after vaccination:

- Seroprotective anti-D antibody concentrations (≥ 0.1 IU/mL) were observed in 93.2% of subjects in the Boostrix group and 96.5% of subjects in the Adacel group.
- Seroprotective anti-T antibody concentrations (≥ 0.1 IU/mL) were observed in 98% of subjects in the Boostrix group and 99.5% of subjects in the Adacel group.
- Anti-D antibody concentrations (≥ 1.0 IU/mL) were observed in 47.8% of subjects in the Boostrix group and 51.1% of subjects in the Adacel group and anti-T antibody concentrations (≥ 1.0 IU/mL) were observed in 84.4% of subjects in the Boostrix group and 90.6% of subjects in the Adacel group.
- GMCs for anti-D and anti-T antibodies were 0.8 IU/mL and 2.0 IU/mL, respectively for Boostrix group and 0.9 IU/mL and 2.5 IU/mL, respectively for Adacel group (Table 11).

The estimated proportion of subjects seroprotected in the ATP Year 5 cohort were shown by the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay with exact 95% CI. This information is presented in Table 12:

Table 12 Seronegativity status for anti-D antibody concentration by ELISA and VERO (ATP Year 5 cohort)

- The percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) was 96.5% for the Boostrix group and 97.8% for the Adacel group at Year 5 after vaccination.

The percentage of subjects with anti-D and anti-T antibody concentrations of ≥ 0.1 IU/mL (by ELISA) and GMCs according to group, stratified by age and gender for the ATP Year 5 cohort for immunogenicity are presented in Table 13 and Table 14, respectively:

Table 13 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups by age (ATP Year 5 cohort)

Table 14 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups by gender (ATP Year 5 cohort)

The estimated proportion of subjects seroprotected for anti-D antibody concentrations for the ATP Year 5 cohort for immunogenicity, stratified by age and gender is presented in Table 15 and Table 16, respectively:

Table 15 Seronegativity status for anti-D antibody concentration by ELISA and VERO by age (ATP Year 5 cohort)

Table 16 Seronegativity status for anti-D antibody concentration by ELISA and VERO by gender (ATP Year 5 cohort)

The RCCs for anti-D and anti-T antibody concentrations in the Boostrix and Adacel groups, 5 years after vaccination for the ATP Year 5 cohort for immunogenicity are presented in Figure 1 and Figure 2, respectively:

Figure 1 Reverse cumulative curves for anti-D concentration at Year 5 (ATP Year 5 cohort)

Figure 2 Reverse cumulative curves for anti-T concentration at Year 5 (ATP Year 5 cohort)

7.2.2. Persistence of antibodies to acellular pertussis antigens

The seropositivity rates for anti-PT, anti-FHA and anti-PRN (≥ 5 EL.U/mL) and their respective GMCs according to group for the ATP Year 5 cohort for immunogenicity are presented in Table 17.

Table 17 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP Year 5 cohort)

Five years after vaccination:

- Seropositivity rates for anti-PT, anti-FHA and anti-PRN were 84.8%, 99.9% and 96.6% respectively for the Boostrix group, and 76.6%, 99.2% and 97.6% respectively for the Adacel group.
- GMCs for anti-PT, anti-FHA and anti-PRN were 14.6 EL U/mL, 110 EL U/mL and 85.2 EL U/mL respectively for Boostrix group and 11.6 EL U/mL, 80.8 EL U/mL and 77.4 EL U/mL respectively for Adacel group.

The seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies stratified by age and gender for the ATP Year 5 cohort for immunogenicity are presented in Table 18 and Table 19, respectively.

The RCCs for anti-PT, anti-FHA and anti-PRN antibody concentrations in the Boostrix and Adacel groups, 5 years after vaccination for the ATP Year 5 cohort for immunogenicity are presented in Figure 3, Figure 4, and Figure 5, respectively.

7.3. Year 5 cohort analysis

The results of the Year 5 cohort analyses are presented in Table 20, Table 21 and Table 22.

7.4. Exploratory Analyses

Comparative exploratory analyses were performed to characterize the difference between groups in terms of immunogenicity; these differences are presented in tables in the subsequent sections. The standardized asymptotic 95% CI on the group differences excluding 0, or the 95% CI on the group ratios excluding one were used to detect the possible differences between groups.

These differences should, however, be interpreted with caution considering that group comparisons were not adjusted for multiplicity of endpoints, and that a statistically significant difference may not necessarily have clinical significance.

7.4.1. Between group differences in percentages of subjects seroprotected for D and T

The differences between the Boostrix group and the Adacel group in the anti-D and anti-T seroprotection rates (percentage of subjects with anti-D and anti-T ≥ 0.1 IU/mL by ELISA) for the ATP Year 5 cohort for immunogenicity are presented in Table 23.

Table 23 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination (ATP Year 5 cohort)

- Exploratory analysis indicated a difference between the Boostrix group and the Adacel group with respect to the percentage of subjects with anti-D antibodies ≥ 0.1IU/mL, since the 95% CI for between-group difference did not include the value 0. Seroprotection rates for anti-D antibodies were 93.2 % for the Boostrix group and 96.5% for the Adacel group by this criterion.
- Exploratory analysis did not indicate a difference between the Boostrix group and the Adacel group with respect to the percentage of subjects with anti-T antibodies ≥ 0.1IU/mL, since the 95% CI for between-group difference included the value 0. Seroprotection rates for anti-T antibodies were 98% for Boostrix group and 99.5% for Adacel group by this criterion.

The difference between the Boostrix group and the Adacel group in the overall anti-D seroprotection rate (percentages of subjects with anti-D ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO) at Year 5 for the ATP Year 5 cohort for immunogenicity is presented in Table 24.

Table 24 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA between the Boostrix and Adacel, at Year 5 after vaccination (ATP Year 5 cohort)

- Exploratory analysis did not indicate a difference between the Boostrix group and the Adacel group with respect to the percentage of subjects with anti-D antibodies ≥ 0.01IU/mL (minimum level considered as seroprotective by VERO cell assay), since the 95% CI for between-group difference included the value 0.

The differences in the anti-D and anti-T seroprotection rates at Year 5 between the Boostrix and Adacel groups for the ATP Year 5 cohort for immunogenicity, stratified by age and gender, are presented in Table 24 and Table 26, respectively.

Table 25 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination by age (ATP Year 5 cohort)

Table 26 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination by gender (ATP Year 5 cohort)

The differences in the overall anti-D seroprotection rates between the Boostrix group and the Adacel group for the ATP Year 5 cohort for immunogenicity by age group and gender are presented in Table 27 and Table 28, respectively.

Table 27 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year 5 after vaccination by age (ATP Year 5 cohort)

Table 28 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year 5 after vaccination by gender (ATP Year 5 cohort)

7.4.2. Between group ratios in anti-D and anti-T GMCs

The adjusted ratios of anti-D and anti-T GMCs at Year 5 for the ATP Year 5 cohort for immunogenicity are presented in Table 29.

Table 29 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination (ATP Year 5 cohort)

- Five years after vaccination, the exploratory evaluations between groups did not indicate any difference in terms of anti-D GMCs (95% CI for adjusted GMC ratio included 1). The 95% CI for the between-group anti-T GMC ratio excluded 1, indicating a difference between the groups.

The adjusted ratios of anti-D and anti-T GMCs at Year 5 for the ATP Year 5 cohort for immunogenicity by age and gender are presented in Table 30 and Table 31, respectively.

Table 30 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination by age (ATP Year 5 cohort)

Table 31 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination by gender (ATP Year 5 cohort)

7.5. Year 5 cohort analysis (Exploratory analysis)

The results for the exploratory analyses for the Year 5 cohort are presented in Table 32 Table 33 and Table 34.

Table 32 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination (Year 5 Cohort)

Table 33 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA between the Boostrix and Adacel, at Year 5 after vaccination (Year 5 Cohort)

Table 34 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination (Year 5 Cohort)

7.6. Estimation of GMC by modeling method

The estimated GMCs and seropositivity at Year 5 and Year 10 by modeling method for all the antibody concentrations are given in Table 35, Table 36 and Table 37. The modeling method was applied for Adapted ATP cohort. Adapted ATP cohort includes subjects from ATP Year 1 cohort for the Year 1 time point, subjects from ATP Year 3 cohort for the Year 3 time point, and from ATP Year 5 cohort for the Year 5 time point.

Table 35 Percentage of subjects with anti-D and anti-T concentrations above 0.1 IU/mL and 1 IU/mL and GMC predicted by modeling (Adapted ATP cohort)

Table 36 Percentage of subjects with anti-PT, anti-FHA, anti-PRN concentrations above 5 EL U/mL and GMCs predicted by modeling (Adapted ATP cohort)

Table 37 Group GMC ratio predicted by modeling (Adapted ATP cohort)

The RCCs observed and predicted for anti-D, anti-T, anti-PT, anti-FHA and anti-PRN GMCs in the Boostrix and Adacel groups, 5 years after vaccination for the ATP Year 5 cohort for persistence are presented in Figure 6, Figure 7, Figure 8, Figure 9 and Figure 10 respectively.

Figure 6 Observed and predicted anti-D GMCs (Adapted ATP Year 5 cohort for persistence)

Figure 7 Observed and predicted anti-T GMCs (Adapted ATP Year 5 cohort for persistence)

Figure 8 Observed and predicted anti-PT GMCs (Adapted ATP Year 5 cohort for persistence)

7.7. ATP Complete Year 5 cohort analysis

The results for the analyses for the ATP Complete Year 5 cohort for immunogenicity are presented in Table 38 and Table 39. The results for all antibodies showed similar results as the ATP cohort for immunogenicity in 106316 study.

7.8. Immunogenicity summary

- The proportion of subjects estimated to be seroprotected for anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) was 96.5% for Boostrix group and 97.8% for Adacel group at Year 5 after vaccination.
- The percentage of subjects with anti-T antibody concentrations ≥ 0.1 IU/mL was 98.0% for Boostrix group and 99.5% for Adacel group at Year 5 after vaccination.
- At Year 5, seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies were 84.8%, 99.9% and 96.6% respectively for Boostrix group and 76.6%, 99.2% and 97.6% respectively for Adacel group.
- GMCs for anti-D and anti-T antibodies were 0.8 IU/mL and 2.0 IU/mL, respectively for Boostrix group and 0.9 IU/mL and 2.5 IU/mL, respectively for Adacel group.
- GMCs for anti-PT, anti-FHA and anti-PRN were 14.6 EL U/mL, 110 EL U/mL and 85.2 EL U/mL respectively for Boostrix group and 11.6 EL U/mL, 80.8 EL U/mL and 77.4 EL U/mL respectively for Adacel group.
- Majority of the subjects continued to have seroprotective antibody concentrations to anti-D, anti-T and remained seropositive to anti-FHA and anti-PRN and anti-PT in both the groups.

8. SAFETY RESULTS

No pregnancies or SAEs were reported at Year 5 time point.

9. OVERALL CONCLUSIONS

The Study Analysis Outcomes are based on the ATP Year 5 cohort:

- Evaluation of anti-D and anti-T antibodies elicited by a single dose of *Boostrix* in adult subjects demonstrated high levels of seroprotection against diphtheria and tetanus 5 years after vaccination.
- At Year 5 time point, observed GMCs to all antigens remained higher than the pre-vaccination levels for both the study vaccines.
- There were no pregnancies or SAEs reported at Year 5 time point.

10. TABLES AND FIGURES

10.1. Subject eligibility and attrition from the study

10.1.1. Number of subjects

Table 5 Number of subjects included in each follow-up period up to 5 Years (Total cohort)

Categories	Boostrix N = 1522	Adacel N = 762	Total N = 2284
	n	n	n
Number of subjects vaccinates in Primary study	1522	762	2284
Year 1 follow-up Year 1 cohort	1064	523	1587
Year 1 follow-up ATP Year 1 cohort	1015	506	1521
Year 3 follow-up Year 3 cohort	976	465	1441
Year 3 follow-up ATP Year 3 cohort	918	442	1360
Year 3 follow-up ATP Year 3 complete cohort	776	367	1143
Year 5 follow-up Year 5 cohort	856	401	1257
Year 5 follow-up ATP Year 5 cohort	791	372	1163
Year 5 follow-up ATP Year 5 complete cohort	625	289	914

N = number of subjects
n = number of subjects included in each group or in total for a defined cohort

Table 6 Number of subjects by center (Year 5 cohort)

	Tdap	Adacel	Total	
Center	n	n	n	%
PPD	9	6	15	1.2
	41	16	57	4.5
	58	30	88	7.0
	46	20	66	5.3
	15	12	27	2.1
	17	6	23	1.8
	12	2	14	1.1
	6	2	8	0.6
	15	6	21	1.7
	7	2	9	0.7
	13	8	21	1.7
	5	4	9	0.7
	2	1	3	0.2
	21	10	31	2.5
	25	15	40	3.2
	52	26	78	6.2
	24	7	31	2.5
	27	9	36	2.9
	13	3	16	1.3
	48	27	75	6.0
	28	11	39	3.1
	73	34	107	8.5
	10	6	16	1.3
	8	1	9	0.7
	9	6	15	1.2
	45	24	69	5.5
	10	6	16	1.3
	68	29	97	7.7
	12	3	15	1.2
	10	8	18	1.4
	22	13	35	2.8
	16	9	25	2.0
	26	9	35	2.8
	40	17	57	4.5
	12	9	21	1.7
	11	4	15	1.2
All	856	401	1257	100

n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Table 7 Duration (in weeks) from the vaccination in primary study to Year 5 blood sampling for each group (Year 5 cohort)

Vaccine Group	N	Mean	SD	Median	Minimum	Maximum
Boostrix	856	257.30	3.09	257.00	252.00	268.00
Adacel	401	257.42	2.98	257.00	252.00	267.00

10.1.2. Protocol deviations

Table 8 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

Title	Total			Boostrix		Adacel	
	n	s	%	n	s	n	s
Total cohort	1257			856		401	
Total vaccinated cohort	1257		100	856		401	
Administration of vaccine(s) forbidden in the protocol (code 1040)	61	61		38	38	23	23
ATP cohort for safety	1196		95.1	818		378	
Administration of any medication forbidden by the protocol (code 2040)	9	10		7	7	2	3
Underlying medical condition forbidden by the protocol (code 2050)	2	6		2	4	0	2
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	1	1		1	1	0	0
Subjects who were eliminated from the ATP primary cohort	21	44		17	36	4	8
ATP cohort for immunogenicity	1163		92.5	791		372	

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated Cohort

10.2. Demographic characteristics

10.2.1. ATP Year 5 cohort for immunogenicity

Table 9 Summary of demographic characteristics (ATP Year 5 cohort)

Characteristics	Parameters or Categories	Boostrix N = 791		Adacel N = 372		Total N = 1163	
		Value or n	%	Value or n	%	Value or n	%
Age (years) at blood sampling: PI(Y5)	Mean	47.3	-	48.3	-	47.6	-
	SD	13.23	-	12.96	-	13.15	-
	Median	50.0	-	50.0	-	50.0	-
	Minimum	23	-	24	-	23	-
	Maximum	69	-	69	-	69	-
Age stratum	19-29 (Y)	205	25.9	79	21.2	284	24.4
	30-49 (Y)	275	34.8	140	37.6	415	35.7
	50-64 (Y)	311	39.3	153	41.1	464	39.9
Gender	Female	507	64.1	258	69.4	765	65.8
	Male	284	35.9	114	30.6	398	34.2

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = standard deviation
Age(Y) = age at Year 5 blood sampling, expressed in years
Age stratum: based on the age at vaccination in primary study

10.2.2. Year 5 cohort

Table 10 Summary of demographic characteristics (Year 5 cohort)

Characteristics	Parameters or Categories	Boostrix N = 856		Adacel N = 401		Total N = 1257	
		Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	47.1	-	47.9	-	47.4	-
	SD	13.30	-	13.17	-	13.26	-
	Median	50.0	-	50.0	-	50.0	-
	Minimum	23	-	24	-	23	-
	Maximum	69	-	69	-	69	-
Age stratum	19-29 (Y)	226	26.4	93	23.2	319	25.4
	30-49 (Y)	300	35.0	146	36.4	446	35.5
	50-64 (Y)	330	38.6	162	40.4	492	39.1
Gender	Female	545	63.7	279	69.6	824	65.6
	Male	311	36.3	122	30.4	433	34.4

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n/Number of subjects with available results x 100
SD = standard deviation
Age(Y) = age at Year 5 blood sampling, expressed in years
Age stratum: based on the age at vaccination in primary study

10.3. Immunogenicity results

10.3.1. According-to-protocol analysis

10.3.1.1. Persistence of antibodies to diphtheria and tetanus toxoids

Table 11 Percentage of subjects with anti-D and anti-T concentrations equal to or above the cut-off values of 0.1 IU/mL and 1.0 IU/mL and GMCs (ATP Year 5 cohort)

Antibody	Group	Timing	N	≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
				n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	Pre	785	667	85.0	82.3	87.4	177	22.5	19.7	25.6	0.4	0.4	0.4
		1 month post	789	772	97.8	96.6	98.7	684	86.7	84.1	89.0	4.6	4.2	5.1
		1 year post	682	651	95.5	93.6	96.9	444	65.1	61.4	68.7	1.4	1.3	1.5
		3 year post	724	679	93.8	91.8	95.4	377	52.1	48.4	55.8	0.9	0.8	1.0
		5 year post	790	736	93.2	91.2	94.8	378	47.8	44.3	51.4	0.8	0.7	0.9
	Adacel	Pre	366	326	89.1	85.4	92.1	94	25.7	21.3	30.5	0.5	0.4	0.5
		1 month post	371	364	98.1	96.2	99.2	341	91.9	88.7	94.5	5.0	4.4	5.6
		1 year post	317	308	97.2	94.7	98.7	226	71.3	66.0	76.2	1.5	1.3	1.7
		3 year post	342	330	96.5	94.0	98.2	204	59.6	54.2	64.9	1.0	0.9	1.2
		5 year post	372	359	96.5	94.1	98.1	190	51.1	45.9	56.3	0.9	0.8	1.0
Anti-T	Boostrix	Pre	790	757	95.8	94.2	97.1	568	71.9	68.6	75.0	1.5	1.4	1.7
		1 month post	788	783	99.4	98.5	99.8	772	98.0	96.7	98.8	8.3	7.8	8.8
		1 year post	685	674	98.4	97.1	99.2	639	93.3	91.1	95.0	3.3	3.0	3.5
		3 year post	726	710	97.8	96.4	98.7	640	88.2	85.6	90.4	2.2	2.0	2.3
		5 year post	789	773	98.0	96.7	98.8	666	84.4	81.7	86.9	2.0	1.9	2.1
	Adacel	Pre	371	362	97.6	95.4	98.9	288	77.6	73.0	81.8	1.7	1.6	2.0
		1 month post	372	372	100	99.0	100	368	98.9	97.3	99.7	12.5	11.5	13.6
		1 year post	319	318	99.7	98.3	100	309	96.9	94.3	98.5	4.4	4.1	4.8
		3 year post	342	340	99.4	97.9	99.9	317	92.7	89.4	95.2	2.9	2.7	3.2
		5 year post	372	370	99.5	98.1	99.9	337	90.6	87.2	93.4	2.5	2.3	2.7

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination

Table 12 Seronegativity status for anti-D antibody concentration by ELISA and VERO (ATP Year 5 cohort)

Group	Timing	N	Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
			n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Boostrix	Pre	785	118/785	15.0	57/118	48.3	118/785 x 57/118	7.3	92.7	90.7	94.5
	1 month post	789	17/789	2.2	7/17	41.2	17/789 x 7/17	0.9	99.1	98.2	99.6
	1 year post	684	33/684	4.8	11/33	33.3	33/684 x 11/33	1.6	98.4	97.1	99.2
	3 year post	724	45/724	6.2	23/45	51.1	45/724 x 23/45	3.2	96.8	95.3	98.0
	5 year post*	790	54/790	6.8	28/54	51.9	54/790 x 28/54	3.5	96.5	94.9	97.6
Adacel	Pre	366	40/366	10.9	15/40	37.5	40/366 x 15/40	4.1	95.9	93.3	97.7
	1 month post	371	7/371	1.9	4/7	57.1	7/371 x 4/7	1.1	98.9	97.3	99.7
	1 year post	318	10/318	3.1	7/10	70.0	10/318 x 7/10	2.2	97.8	95.5	99.1
	3 year post	342	12/342	3.5	9/12	75.0	12/342 x 9/12	2.6	97.4	95.1	98.8
	5 year post*	372	13/372	3.5	8/13	61.5	13/372 x 8/13	2.2	97.8	95.8	99.1

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO test for Pre, 1 month post, 1 year post, and 3 year post-vaccination
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for VERO) - for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
*n'/N' = number of subjects with concentrations below the 0.01 IU/mL / number of subjects tested by VERO test for 5 years post-vaccination.
*% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.01 IU/ML for VERO) for 5 years post-vaccination.
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for groups; LL = lower limit, UL = upper limit

Table 13 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups by age (ATP Year 5 cohort)

Antibody	Sub-group	Group	Timing	N	≥ 0.1 IU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
Anti-D	19-29	Boostrix	Pre	204	187	91.7	87.0	95.1	0.5	0.4	0.5
			1 month post	205	204	99.5	97.3	100	8.3	7.2	9.5
			1 year post	175	175	100	97.9	100	2.4	2.0	2.7
			3 year post	180	178	98.9	96.0	99.9	1.6	1.4	1.8
			5 year post	205	201	98.0	95.1	99.5	1.2	1.0	1.3
		Adacel	Pre	79	72	91.1	82.6	96.4	0.5	0.4	0.7
			1 month post	79	78	98.7	93.1	100	6.7	5.4	8.3
			1 year post	65	64	98.5	91.7	100	2.0	1.6	2.6
			3 year post	71	69	97.2	90.2	99.7	1.4	1.1	1.8
			5 year post	79	77	97.5	91.2	99.7	1.2	0.9	1.5
	30-49	Boostrix	Pre	272	249	91.5	87.6	94.6	0.5	0.4	0.6
			1 month post	274	271	98.9	96.8	99.8	5.8	5.1	6.7
			1 year post	243	238	97.9	95.3	99.3	1.7	1.5	2.0
			3 year post	256	251	98.0	95.5	99.4	1.1	1.0	1.3
			5 year post	275	267	97.1	94.3	98.7	1.0	0.8	1.1
		Adacel	Pre	136	124	91.2	85.1	95.4	0.5	0.4	0.6
			1 month post	140	137	97.9	93.9	99.6	5.8	4.8	7.0
			1 year post	120	117	97.5	92.9	99.5	1.7	1.4	2.0
			3 year post	130	127	97.7	93.4	99.5	1.3	1.1	1.5
			5 year post	140	137	97.9	93.9	99.6	1.0	0.9	1.2
	50-64	Boostrix	Pre	309	231	74.8	69.5	79.5	0.3	0.3	0.4
			1 month post	310	297	95.8	92.9	97.7	2.5	2.1	3.0
			1 year post	264	238	90.2	85.9	93.5	0.8	0.7	1.0
			3 year post	288	250	86.8	82.3	90.5	0.6	0.5	0.6
			5 year post	310	268	86.5	82.1	90.1	0.5	0.5	0.6
		Adacel	Pre	151	130	86.1	79.5	91.2	0.4	0.3	0.5
			1 month post	152	149	98.0	94.3	99.6	3.8	3.1	4.6
			1 year post	132	127	96.2	91.4	98.8	1.1	0.9	1.4
			3 year post	141	134	95.0	90.0	98.0	0.8	0.6	0.9
			5 year post	153	145	94.8	90.0	97.7	0.7	0.6	0.8
Anti-T	19-29	Boostrix	Pre	205	199	97.1	93.7	98.9	1.6	1.4	1.9
			1 month post	205	205	100	98.2	100	9.7	8.8	10.6
			1 year post	175	175	100	97.9	100	4.1	3.7	4.5
			3 year post	180	179	99.4	96.9	100	2.5	2.3	2.8
			5 year post	205	204	99.5	97.3	100	2.2	1.9	2.4
		Adacel	Pre	79	76	96.2	89.3	99.2	1.8	1.4	2.5
			1 month post	79	79	100	95.4	100	13.7	11.4	16.4
			1 year post	65	65	100	94.5	100	5.4	4.4	6.5
			3 year post	71	71	100	94.9	100	3.1	2.6	3.8
			5 year post	79	79	100	95.4	100	2.8	2.3	3.3
	30-49	Boostrix	Pre	274	270	98.5	96.3	99.6	1.7	1.6	2.0
			1 month post	275	275	100	98.7	100	9.0	8.3	9.8
			1 year post	244	244	100	98.5	100	3.6	3.3	3.9
			3 year post	257	257	100	98.6	100	2.5	2.3	2.7
			5 year post	275	275	100	98.7	100	2.2	2.0	2.4
		Adacel	Pre	139	137	98.6	94.9	99.8	1.8	1.5	2.1
			1 month post	140	140	100	97.4	100	12.9	11.2	15.0
			1 year post	121	120	99.2	95.5	100	4.9	4.3	5.6
			3 year post	130	129	99.2	95.8	100	3.2	2.8	3.6

Antibody	Sub-group	Group	Timing	N	≥ 0.1 IU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
			5 year post	140	139	99.3	96.1	100	2.7	2.4	3.1
	50-64	Boostrix	Pre	311	288	92.6	89.1	95.3	1.3	1.1	1.5
			1 month post	308	303	98.4	96.3	99.5	6.9	6.1	7.8
			1 year post	266	255	95.9	92.7	97.9	2.6	2.2	3.0
			3 year post	289	274	94.8	91.6	97.1	1.8	1.5	2.0
			5 year post	309	294	95.1	92.1	97.3	1.7	1.5	2.0
		Adacel	Pre	153	149	97.4	93.4	99.3	1.7	1.4	2.0
			1 month post	153	153	100	97.6	100	11.6	10.3	13.1
			1 year post	133	133	100	97.3	100	3.7	3.3	4.2
			3 year post	141	140	99.3	96.1	100	2.6	2.2	3.0
			5 year post	153	152	99.3	96.4	100	2.3	2.0	2.6

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 14 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups by gender (ATP Year 5 cohort)

Antibody	Sub-group	Group	Timing		≥ 0.1 IU/mL				GMC		
							95% CI			95% CI	
				N	n	%	LL	UL	value	LL	UL
Anti-D	Male	Boostrix	Pre	283	247	87.3	82.8	90.9	0.5	0.4	0.5
			1 month post	284	278	97.9	95.5	99.2	4.9	4.2	5.8
			1 year post	237	228	96.2	92.9	98.2	1.5	1.2	1.7
			3 year post	258	246	95.3	92.0	97.6	1.0	0.9	1.2
			5 year post	284	270	95.1	91.9	97.3	0.9	0.8	1.0
		Adacel	Pre	113	106	93.8	87.7	97.5	0.5	0.4	0.7
			1 month post	113	113	100	96.8	100	5.4	4.6	6.5
			1 year post	93	93	100	96.1	100	1.6	1.3	2.0
			3 year post	107	103	96.3	90.7	99.0	1.1	0.9	1.4
			5 year post	114	111	97.4	92.5	99.5	1.0	0.8	1.3
	Female	Boostrix	Pre	502	420	83.7	80.1	86.8	0.4	0.3	0.4
			1 month post	505	494	97.8	96.1	98.9	4.4	3.9	5.0
			1 year post	445	423	95.1	92.6	96.9	1.4	1.2	1.6
			3 year post	466	433	92.9	90.2	95.1	0.9	0.8	1.0
			5 year post	506	466	92.1	89.4	94.3	0.7	0.7	0.8
		Adacel	Pre	253	220	87.0	82.2	90.8	0.4	0.4	0.5
			1 month post	258	251	97.3	94.5	98.9	4.8	4.1	5.6
			1 year post	224	215	96.0	92.5	98.1	1.4	1.2	1.6
			3 year post	235	227	96.6	93.4	98.5	1.0	0.9	1.2
			5 year post	258	248	96.1	93.0	98.1	0.8	0.7	1.0
Anti-T	Male	Boostrix	Pre	284	277	97.5	95.0	99.0	1.9	1.7	2.2
			1 month post	283	283	100	98.7	100	8.0	7.3	8.7
			1 year post	238	236	99.2	97.0	99.9	3.4	3.0	3.8
			3 year post	258	255	98.8	96.6	99.8	2.3	2.1	2.6
			5 year post	284	281	98.9	96.9	99.8	2.2	2.0	2.5
		Adacel	Pre	114	113	99.1	95.2	100	2.0	1.6	2.4
			1 month post	114	114	100	96.8	100	12.3	10.6	14.3
			1 year post	94	94	100	96.2	100	4.9	4.2	5.7
			3 year post	107	107	100	96.6	100	3.2	2.7	3.7
			5 year post	114	114	100	96.8	100	2.8	2.5	3.3
	Female	Boostrix	Pre	506	480	94.9	92.6	96.6	1.4	1.2	1.5
			1 month post	505	500	99.0	97.7	99.7	8.4	7.7	9.2
			1 year post	447	438	98.0	96.2	99.1	3.2	2.9	3.5
			3 year post	468	455	97.2	95.3	98.5	2.1	1.9	2.3
			5 year post	505	492	97.4	95.6	98.6	1.9	1.7	2.1
		Adacel	Pre	257	249	96.9	94.0	98.6	1.7	1.4	1.9
			1 month post	258	258	100	98.6	100	12.6	11.4	14.0
			1 year post	225	224	99.6	97.5	100	4.3	3.9	4.7
			3 year post	235	233	99.1	97.0	99.9	2.8	2.5	3.1
			5 year post	258	256	99.2	97.2	99.9	2.4	2.2	2.7

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%)= number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 15 Seronegativity status for anti-D antibody concentration by ELISA and VERO by age (ATP Year 5 cohort)

Sub-group	Group	Timing	N	Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
				n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
19-29	Boostrix	Pre	204	17/204	8.3	7/17	41.2	17/204 x 7/17	3.4	96.6	93.1	98.6
		1 month post	205	1/205	0.5	1/1	100	1/205 x 1/1	0.5	99.5	97.3	100
		1 year post	175	0/175	0.0	0/0						
		3 year post	180	2/180	1.1	2/2	100	2/180 x 2/2	1.1	98.9	96.0	99.9
		5 year post*	205	4/205	2.0	3/4	75.0	4/205 x 3/4	1.5	98.5	95.8	99.7
	Adacel	Pre	79	7/79	8.9	2/7	28.6	7/79 x 2/7	2.5	97.5	91.2	99.7
		1 month post	79	1/79	1.3	0/1	0.0	1/79 x 0/1	0.0	100	95.4	100
		1 year post	65	1/65	1.5	1/1	100	1/65 x 1/1	1.5	98.5	91.7	100
		3 year post	71	2/71	2.8	1/2	50.0	2/71 x 1/2	1.4	98.6	92.4	100
		5 year post*	79	2/79	2.5	1/2	50.0	2/79 x 1/2	1.3	98.7	93.1	100
30-49	Boostrix	Pre	272	23/272	8.5	11/23	47.8	23/272 x 11/23	4.0	96.0	92.9	98.0
		1 month post	274	3/274	1.1	0/3	0.0	3/274 x 0/3	0.0	100	98.7	100
		1 year post	244	6/244	2.5	4/6	66.7	6/244 x 4/6	1.6	98.4	95.9	99.6
		3 year post	256	5/256	2.0	1/5	20.0	5/256 x 1/5	0.4	99.6	97.8	100
		5 year post*	275	8/275	2.9	4/8	50.0	8/275 x 4/8	1.5	98.5	96.3	99.6
	Adacel	Pre	136	12/136	8.8	3/12	25.0	12/136 x 3/12	2.2	97.8	93.7	99.5
		1 month post	140	3/140	2.1	2/3	66.7	3/140 x 2/3	1.4	98.6	94.9	99.8
		1 year post	120	3/120	2.5	2/3	66.7	3/120 x 2/3	1.7	98.3	94.1	99.8
		3 year post	130	3/130	2.3	3/3	100	3/130 x 3/3	2.3	97.7	93.4	99.5
		5 year post*	140	3/140	2.1	3/3	100	3/140 x 3/3	2.1	97.9	93.9	99.6
50-64	Boostrix	Pre	309	78/309	25.2	39/78	50.0	78/309 x 39/78	12.6	87.4	83.2	90.9
		1 month post	310	13/310	4.2	6/13	46.2	13/310 x 6/13	1.9	98.1	95.8	99.3
		1 year post	265	27/265	10.2	7/27	25.9	27/265 x 7/27	2.6	97.4	94.6	98.9
		3 year post	288	38/288	13.2	20/38	52.6	38/288 x 20/38	6.9	93.1	89.5	95.7
		5 year post*	310	42/310	13.5	21/42	50.0	42/310 x 21/42	6.8	93.2	89.8	95.8
	Adacel	Pre	151	21/151	13.9	10/21	47.6	21/151 x 10/21	6.6	93.4	88.2	96.8
		1 month post	152	3/152	2.0	2/3	66.7	3/152 x 2/3	1.3	98.7	95.3	99.8
		1 year post	133	6/133	4.5	4/6	66.7	6/133 x 4/6	3.0	97.0	92.5	99.2
		3 year post	141	7/141	5.0	5/7	71.4	7/141 x 5/7	3.5	96.5	91.9	98.8
		5 year post*	153	8/153	5.2	4/8	50.0	8/153 x 4/8	2.6	97.4	93.4	99.3

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ML / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ML / number of subjects tested by VERO test for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for VERO) for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
*n'/N' = number of subjects with concentrations below the 0.01 IU/ML / number of subjects tested by VERO test for 5 years post-vaccination.
*% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.01 IU/ML for VERO) for 5 years post vaccination.
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for groups; LL = lower limit, UL = upper limit

Table 16 Seronegativity status for anti-D antibody concentration by ELISA and VERO by gender (ATP Year 5 cohort)

Sub-group	Group	Timing	N	Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
				n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Male	Boostrix	Pre	283	36/283	12.7	15/36	41.7	36/283 x 15/36	5.3	94.7	91.4	97.0
		1 month post	284	6/284	2.1	2/6	33.3	6/284 x 2/6	0.7	99.3	97.5	99.9
		1 year post	238	10/238	4.2	1/10	10.0	10/238 x 1/10	0.4	99.6	97.7	100
		3 year post	258	12/258	4.7	6/12	50.0	12/258 x 6/12	2.3	97.7	95.0	99.1
		5 year post*	284	14/284	4.9	5/14	35.7	14/284 x 5/14	1.8	98.2	95.9	99.4
	Adacel	Pre	113	7/113	6.2	1/7	14.3	7/113 x 1/7	0.9	99.1	95.2	100
		1 month post	113	0/113	0.0	0/0						
		1 year post	94	1/94	1.1	1/1	100	1/94 x 1/1	1.1	98.9	94.2	100
		3 year post	107	4/107	3.7	1/4	25.0	4/107 x 1/4	0.9	99.1	94.9	100
		5 year post*	114	3/114	2.6	1/3	33.3	3/114 x 1/3	0.9	99.1	95.2	100
Female	Boostrix	Pre	502	82/502	16.3	42/82	51.2	82/502 x 42/82	8.4	91.6	88.9	93.9
		1 month post	505	11/505	2.2	5/11	45.5	11/505 x 5/11	1.0	99.0	97.7	99.7
		1 year post	446	23/446	5.2	10/23	43.5	23/446 x 10/23	2.2	97.8	95.9	98.9
		3 year post	466	33/466	7.1	17/33	51.5	33/466 x 17/33	3.6	96.4	94.2	97.9
		5 year post*	506	40/506	7.9	23/40	57.5	40/506 x 23/40	4.5	95.5	93.3	97.1
	Adacel	Pre	253	33/253	13.0	14/33	42.4	33/253 x 14/33	5.5	94.5	90.9	96.9
		1 month post	258	7/258	2.7	4/7	57.1	7/258 x 4/7	1.6	98.4	96.1	99.6
		1 year post	224	9/224	4.0	6/9	66.7	9/224 x 6/9	2.7	97.3	94.3	99.0
		3 year post	235	8/235	3.4	8/8	100	8/235 x 8/8	3.4	96.6	93.4	98.5
		5 year post*	258	10/258	3.9	7/10	70.0	10/258 x 7/10	2.7	97.3	94.5	98.9

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ML / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ML / number of subjects tested by VERO test - for Pre, 1 month post, 1 year post, and 3 years post- vaccination.
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for VERO) for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
*n'/N' = number of subjects with concentrations below the 0.01 IU/ML / number of subjects tested by VERO test for 5 years post vaccination.
*% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.01 IU/ML for VERO) for 5 years post-vaccination.
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for groups; LL = lower limit, UL = upper limit

Figure 1 Reverse cumulative curves for anti-D concentration at Year 5 (ATP Year 5 cohort)

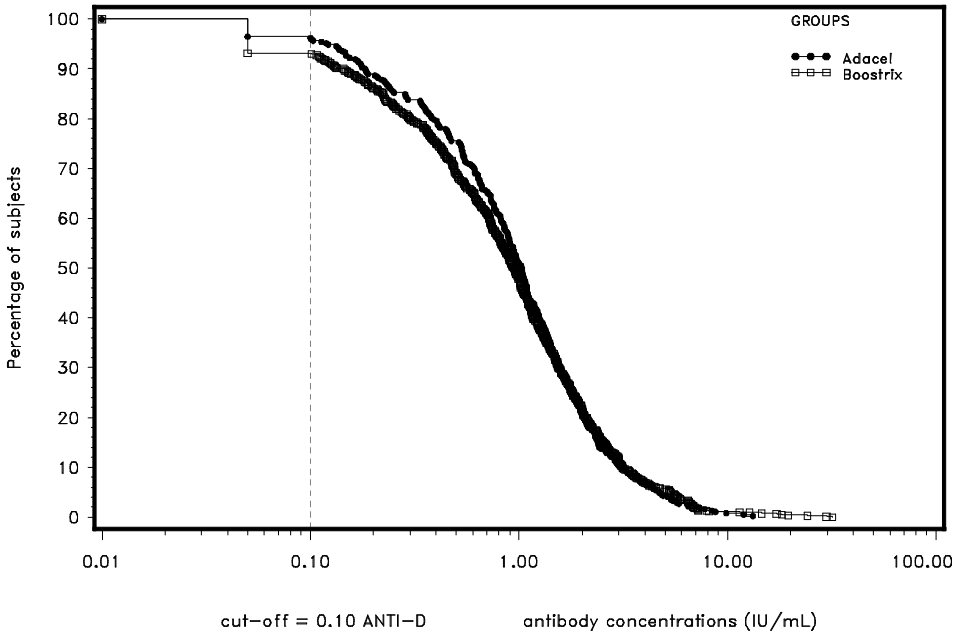
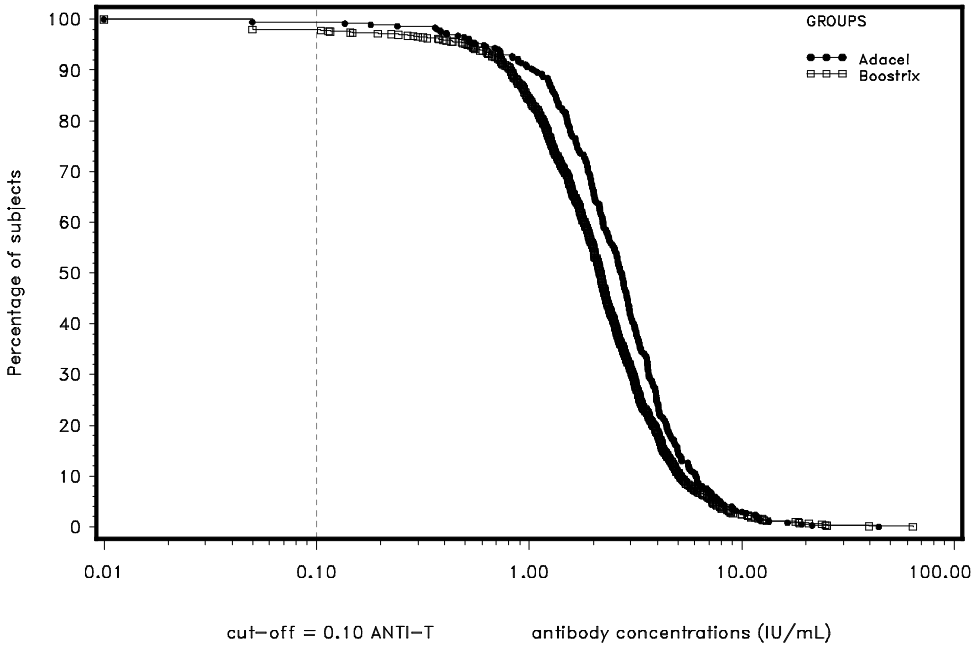


Figure 2 Reverse cumulative curves for anti-T concentration at Year 5 (ATP Year 5 cohort)



10.3.1.2. Persistence of antibodies to acellular pertussis antigens

Table 17 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP Year 5 cohort)

Antibody	Group	Timing	N	≥ 5 ELU/mL				GMC		
						95% CI			95% CI	
				n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	Pre	783	437	55.8	52.3	59.3	7.1	6.5	7.6
		1 month post	786	764	97.2	95.8	98.2	62.0	57.6	66.8
		1 year post	686	625	91.1	88.7	93.1	22.6	20.8	24.5
		3 year post	725	603	83.2	80.2	85.8	14.1	13.0	15.3
		5 year post	791	671	84.8	82.1	87.3	14.6	13.6	15.8
	Adacel	Pre	368	231	62.8	57.6	67.7	8.1	7.2	9.1
		1 month post	368	344	93.5	90.5	95.8	32.5	28.8	36.6
		1 year post	319	278	87.1	83.0	90.6	16.1	14.3	18.1
		3 year post	342	251	73.4	68.4	78.0	10.2	9.1	11.5
		5 year post	372	285	76.6	72.0	80.8	11.6	10.3	13.0
Anti-FHA	Boostrix	Pre	784	759	96.8	95.3	97.9	30.2	27.9	32.6
		1 month post	789	789	100	99.5	100	619.4	580.0	661.5
		1 year post	685	684	99.9	99.2	100	192.0	177.8	207.3
		3 year post	725	724	99.9	99.2	100	118.2	110.4	126.7
		5 year post	790	789	99.9	99.3	100	110.0	103.1	117.4
	Adacel	Pre	364	351	96.4	94.0	98.1	35.0	31.1	39.4
		1 month post	370	370	100	99.0	100	358.4	327.2	392.5
		1 year post	316	316	100	98.8	100	116.4	104.2	130.0
		3 year post	339	337	99.4	97.9	99.9	83.0	74.8	92.0
		5 year post	371	368	99.2	97.7	99.8	80.8	73.1	89.4
Anti-PRN	Boostrix	Pre	788	603	76.5	73.4	79.4	13.7	12.5	15.0
		1 month post	787	778	98.9	97.8	99.5	398.5	355.7	446.5
		1 year post	682	658	96.5	94.8	97.7	153.3	135.5	173.6
		3 year post	724	689	95.2	93.3	96.6	86.2	76.8	96.6
		5 year post	783	756	96.6	95.0	97.7	85.2	76.6	94.8
	Adacel	Pre	371	279	75.2	70.5	79.5	14.9	12.9	17.2
		1 month post	372	371	99.7	98.5	100	341.3	293.5	397.0
		1 year post	316	311	98.4	96.3	99.5	139.5	117.8	165.2
		3 year post	342	333	97.4	95.1	98.8	76.0	65.3	88.3
		5 year post	371	362	97.6	95.4	98.9	77.4	66.9	89.6

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 18 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies by age (ATP Year 5 cohort)

Antibody	Sub-group	Group	Timing	N	≥ 5 ELU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
Anti-PT	19-29	Boostrix	Pre	203	124	61.1	54.0	67.8	7.5	6.5	8.7
			1 month post	205	199	97.1	93.7	98.9	73.2	63.2	84.8
			1 year post	175	167	95.4	91.2	98.0	26.0	22.3	30.3
			3 year post	180	155	86.1	80.2	90.8	16.1	13.7	19.0
			5 year post	205	178	86.8	81.4	91.1	16.1	13.8	18.8
		Adacel	Pre	78	53	67.9	56.4	78.1	9.3	7.2	11.9
			1 month post	78	74	94.9	87.4	98.6	39.5	30.9	50.4
			1 year post	65	58	89.2	79.1	95.6	17.1	13.2	22.1
			3 year post	71	49	69.0	56.9	79.5	10.3	7.8	13.4
			5 year post	79	60	75.9	65.0	84.9	12.4	9.5	16.3
	30-49	Boostrix	Pre	272	149	54.8	48.7	60.8	7.0	6.1	8.0
			1 month post	273	269	98.5	96.3	99.6	65.6	58.4	73.7
			1 year post	244	229	93.9	90.1	96.5	24.9	21.9	28.3
			3 year post	256	223	87.1	82.4	91.0	15.3	13.4	17.4
			5 year post	275	241	87.6	83.2	91.3	15.5	13.7	17.6
		Adacel	Pre	138	84	60.9	52.2	69.1	7.9	6.5	9.6
			1 month post	139	131	94.2	89.0	97.5	31.2	25.9	37.5
			1 year post	121	104	86.0	78.5	91.6	14.9	12.3	18.0
			3 year post	130	99	76.2	67.9	83.2	10.2	8.5	12.2
			5 year post	140	108	77.1	69.3	83.8	11.0	9.2	13.2
	50-64	Boostrix	Pre	308	164	53.2	47.5	58.9	6.8	6.1	7.8
			1 month post	308	296	96.1	93.3	98.0	52.8	46.6	59.8
			1 year post	267	229	85.8	81.0	89.7	18.8	16.3	21.6
			3 year post	289	225	77.9	72.6	82.5	12.1	10.7	13.8
			5 year post	311	252	81.0	76.2	85.2	13.0	11.5	14.7
		Adacel	Pre	152	94	61.8	53.6	69.6	7.7	6.5	9.2
			1 month post	151	139	92.1	86.5	95.8	30.5	25.0	37.2
			1 year post	133	116	87.2	80.3	92.4	16.7	13.8	20.2
			3 year post	141	103	73.0	64.9	80.2	10.3	8.5	12.4
			5 year post	153	117	76.5	68.9	82.9	11.7	9.7	14.1
Anti-FHA	19-29	Boostrix	Pre	203	199	98.0	95.0	99.5	28.2	24.3	32.6
			1 month post	205	205	100	98.2	100	675.1	607.5	750.2
			1 year post	175	175	100	97.9	100	213.2	186.8	243.4
			3 year post	180	180	100	98.0	100	131.5	117.0	147.6
			5 year post	205	205	100	98.2	100	114.0	101.7	127.7
		Adacel	Pre	78	76	97.4	91.0	99.7	33.8	26.1	43.7
			1 month post	79	79	100	95.4	100	374.1	315.1	444.0
			1 year post	64	64	100	94.4	100	128.1	101.2	162.3
			3 year post	71	71	100	94.9	100	86.9	69.8	108.3
			5 year post	79	79	100	95.4	100	88.8	71.8	109.9
	30-49	Boostrix	Pre	273	267	97.8	95.3	99.2	30.0	26.5	33.8
			1 month post	275	275	100	98.7	100	664.2	595.2	741.2
			1 year post	244	243	99.6	97.7	100	204.6	179.4	233.4
			3 year post	256	255	99.6	97.8	100	127.4	113.7	142.8
			5 year post	275	274	99.6	98.0	100	118.5	105.8	132.6
		Adacel	Pre	136	129	94.9	89.7	97.9	36.2	29.2	44.8
			1 month post	140	140	100	97.4	100	360.5	308.1	421.8
			1 year post	120	120	100	97.0	100	114.1	93.8	138.9
			3 year post	129	128	99.2	95.8	100	88.0	73.4	105.3
			5 year post	140	138	98.6	94.9	99.8	77.8	65.1	92.9

Antibody	Sub-group	Group	Timing	N	≥ 5 ELU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
	50-64	Boostrix	Pre	308	293	95.1	92.1	97.2	31.8	27.8	36.4
			1 month post	309	309	100	98.8	100	549.7	489.0	617.9
			1 year post	266	266	100	98.6	100	169.0	148.5	192.4
			3 year post	289	289	100	98.7	100	103.6	91.9	116.8
			5 year post	310	310	100	98.8	100	100.7	90.2	112.4
		Adacel	Pre	150	146	97.3	93.3	99.3	34.6	29.2	41.0
			1 month post	151	151	100	97.6	100	348.5	301.2	403.2
			1 year post	132	132	100	97.2	100	113.0	96.0	133.0
			3 year post	139	138	99.3	96.1	100	76.8	65.8	89.7
			5 year post	152	151	99.3	96.4	100	79.7	68.6	92.7
Anti-PRN	19-29	Boostrix	Pre	205	162	79.0	72.8	84.4	13.3	11.1	15.9
			1 month post	205	205	100	98.2	100	500.2	415.0	603.0
			1 year post	175	175	100	97.9	100	189.6	153.9	233.5
			3 year post	180	178	98.9	96.0	99.9	110.2	89.3	136.0
			5 year post	205	203	99.0	96.5	99.9	102.8	84.9	124.3
		Adacel	Pre	79	64	81.0	70.6	89.0	17.7	12.9	24.3
			1 month post	79	79	100	95.4	100	448.0	351.3	571.4
			1 year post	64	64	100	94.4	100	198.7	145.3	271.6
			3 year post	71	71	100	94.9	100	93.2	70.4	123.3
			5 year post	79	79	100	95.4	100	99.4	75.3	131.4
	30-49	Boostrix	Pre	272	213	78.3	72.9	83.1	15.8	13.4	18.6
			1 month post	273	269	98.5	96.3	99.6	506.9	418.4	614.1
			1 year post	244	237	97.1	94.2	98.8	211.6	172.9	258.9
			3 year post	257	249	96.9	94.0	98.6	116.5	96.8	140.0
			5 year post	272	267	98.2	95.8	99.4	111.7	94.1	132.6
		Adacel	Pre	139	105	75.5	67.5	82.4	15.7	12.4	20.0
			1 month post	140	140	100	97.4	100	382.7	300.5	487.4
			1 year post	120	118	98.3	94.1	99.8	157.0	119.2	206.9
			3 year post	130	126	96.9	92.3	99.2	90.8	71.2	115.8
			5 year post	140	136	97.1	92.8	99.2	86.7	68.5	109.6
	50-64	Boostrix	Pre	311	228	73.3	68.0	78.1	12.3	10.7	14.3
			1 month post	309	304	98.4	96.3	99.5	277.1	228.3	336.4
			1 year post	263	246	93.5	89.9	96.2	98.8	79.9	122.1
			3 year post	287	262	91.3	87.4	94.3	56.4	46.7	68.0
			5 year post	306	286	93.5	90.1	96.0	59.1	49.4	70.7
		Adacel	Pre	153	110	71.9	64.1	78.9	13.0	10.4	16.2
			1 month post	153	152	99.3	96.4	100	267.1	205.3	347.6
			1 year post	132	129	97.7	93.5	99.5	105.5	79.9	139.3
			3 year post	141	136	96.5	91.9	98.8	58.2	45.3	74.7
			5 year post	152	147	96.7	92.5	98.9	61.3	48.1	78.2

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 19 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies by gender (ATP Year 5 cohort)

Antibody	Sub-group	Group	Timing	N	≥ 5 ELU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
Anti-PT	Male	Boostrix	Pre	281	170	60.5	54.5	66.3	7.9	6.9	9.0
			1 month post	283	277	97.9	95.4	99.2	70.8	62.5	80.4
			1 year post	238	223	93.7	89.8	96.4	26.9	23.4	31.0
			3 year post	258	226	87.6	82.9	91.4	16.9	14.8	19.4
			5 year post	284	251	88.4	84.1	91.9	17.3	15.2	19.6
		Adacel	Pre	112	75	67.0	57.4	75.6	8.6	7.0	10.6
			1 month post	111	105	94.6	88.6	98.0	35.6	28.9	43.8
			1 year post	94	82	87.2	78.8	93.2	17.6	14.0	22.2
			3 year post	107	87	81.3	72.6	88.2	11.5	9.4	14.2
			5 year post	114	93	81.6	73.2	88.2	13.5	10.9	16.7
	Female	Boostrix	Pre	502	267	53.2	48.7	57.6	6.6	6.1	7.3
			1 month post	503	487	96.8	94.9	98.2	57.5	52.5	63.1
			1 year post	448	402	89.7	86.5	92.4	20.5	18.6	22.7
			3 year post	467	377	80.7	76.9	84.2	12.8	11.6	14.1
			5 year post	507	420	82.8	79.3	86.0	13.3	12.1	14.7
		Adacel	Pre	256	156	60.9	54.7	67.0	7.9	6.9	9.1
			1 month post	257	239	93.0	89.2	95.8	31.2	27.0	36.1
			1 year post	225	196	87.1	82.0	91.2	15.5	13.5	17.7
			3 year post	235	164	69.8	63.5	75.6	9.7	8.4	11.2
			5 year post	258	192	74.4	68.6	79.6	10.9	9.5	12.5
Anti-FHA	Male	Boostrix	Pre	280	278	99.3	97.4	99.9	38.9	34.2	44.3
			1 month post	284	284	100	98.7	100	672.1	607.7	743.3
			1 year post	238	238	100	98.5	100	224.6	199.6	252.7
			3 year post	257	257	100	98.6	100	139.4	126.1	154.2
			5 year post	283	283	100	98.7	100	131.8	119.2	145.6
		Adacel	Pre	112	111	99.1	95.1	100	44.3	36.5	53.7
			1 month post	113	113	100	96.8	100	437.7	374.7	511.4
			1 year post	93	93	100	96.1	100	149.1	123.8	179.4
			3 year post	107	107	100	96.6	100	105.0	88.8	124.2
			5 year post	113	113	100	96.8	100	100.8	86.1	118.0
	Female	Boostrix	Pre	504	481	95.4	93.2	97.1	26.2	23.8	28.8
			1 month post	505	505	100	99.3	100	591.5	543.0	644.5
			1 year post	447	446	99.8	98.8	100	176.6	160.0	194.9
			3 year post	468	467	99.8	98.8	100	108.0	98.7	118.2
			5 year post	507	506	99.8	98.9	100	99.5	91.5	108.2
		Adacel	Pre	252	240	95.2	91.8	97.5	31.6	27.3	36.6
			1 month post	257	257	100	98.6	100	328.2	293.8	366.6
			1 year post	223	223	100	98.4	100	104.9	91.7	120.1
			3 year post	232	230	99.1	96.9	99.9	74.5	65.5	84.7
			5 year post	258	255	98.8	96.6	99.8	73.4	64.7	83.3
Anti-PRN	Male	Boostrix	Pre	283	237	83.7	78.9	87.8	17.3	14.8	20.1
			1 month post	282	280	99.3	97.5	99.9	537.6	447.5	645.8
			1 year post	238	233	97.9	95.2	99.3	213.0	173.9	260.7
			3 year post	257	249	96.9	94.0	98.6	120.3	99.6	145.3
			5 year post	278	272	97.8	95.4	99.2	120.1	100.9	142.9
		Adacel	Pre	114	95	83.3	75.2	89.7	21.3	16.3	27.9
			1 month post	114	114	100	96.8	100	443.0	348.2	563.6
			1 year post	92	92	100	96.1	100	196.3	146.1	263.8
			3 year post	107	106	99.1	94.9	100	105.5	82.4	135.2
			5 year post	114	113	99.1	95.2	100	111.9	87.7	142.8

Antibody	Sub-group	Group	Timing	N	≥ 5 ELU/mL				GMC		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
	Female	Boostrix	Pre	505	366	72.5	68.4	76.3	12.0	10.7	13.5
			1 month post	505	498	98.6	97.2	99.4	337.2	292.4	388.9
			1 year post	444	425	95.7	93.4	97.4	128.6	110.2	150.0
			3 year post	467	440	94.2	91.7	96.2	71.7	62.3	82.6
			5 year post	505	484	95.8	93.7	97.4	70.6	61.9	80.5
		Adacel	Pre	257	184	71.6	65.7	77.0	12.7	10.7	15.0
			1 month post	258	257	99.6	97.9	100	304.2	251.8	367.5
			1 year post	224	219	97.8	94.9	99.3	121.2	98.8	148.7
			3 year post	235	227	96.6	93.4	98.5	65.4	54.3	78.8
			5 year post	257	249	96.9	94.0	98.6	65.8	55.0	78.6

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Figure 3 Reverse cumulative curves for anti-PT concentration at Year 5 (ATP Year 5 cohort)

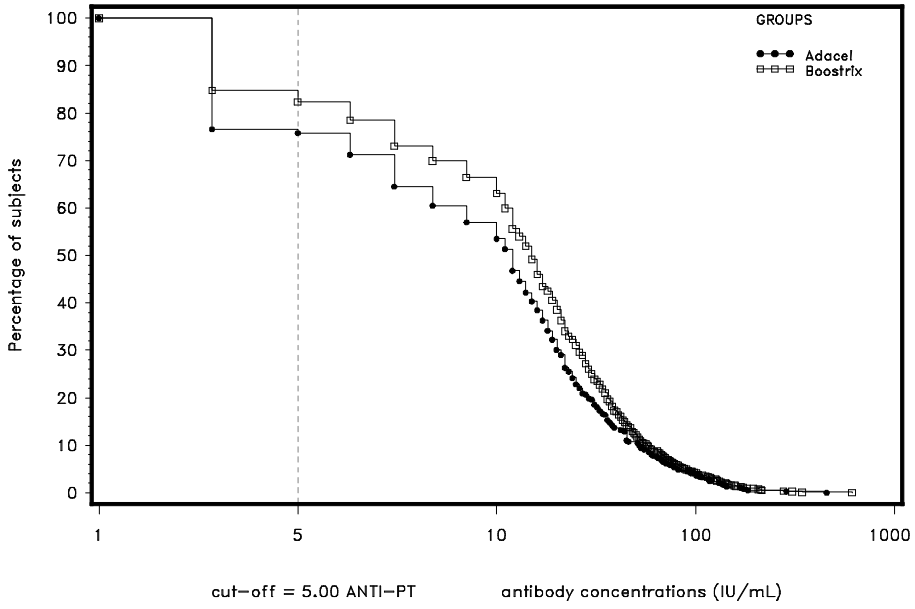


Figure 4 Reverse cumulative curves for anti-FHA concentration at Year 5 (ATP Year 5 cohort)

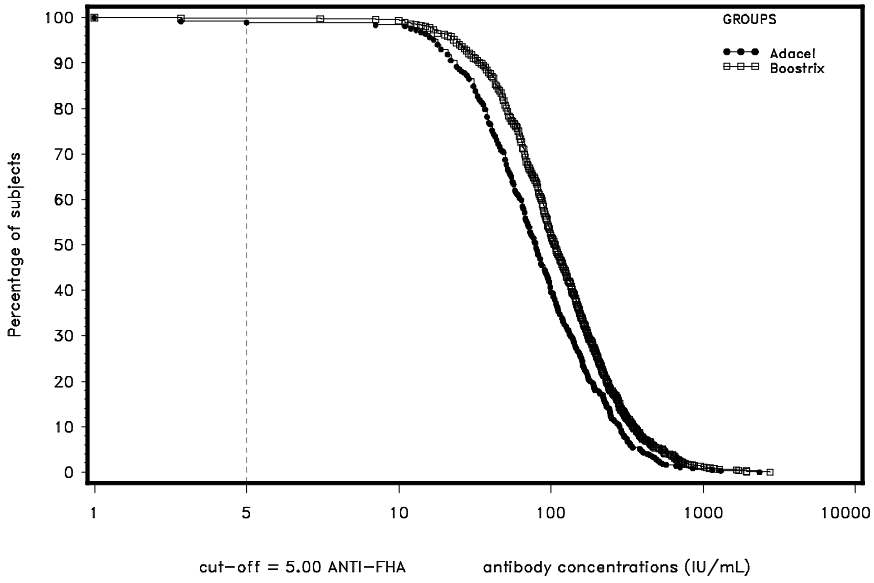
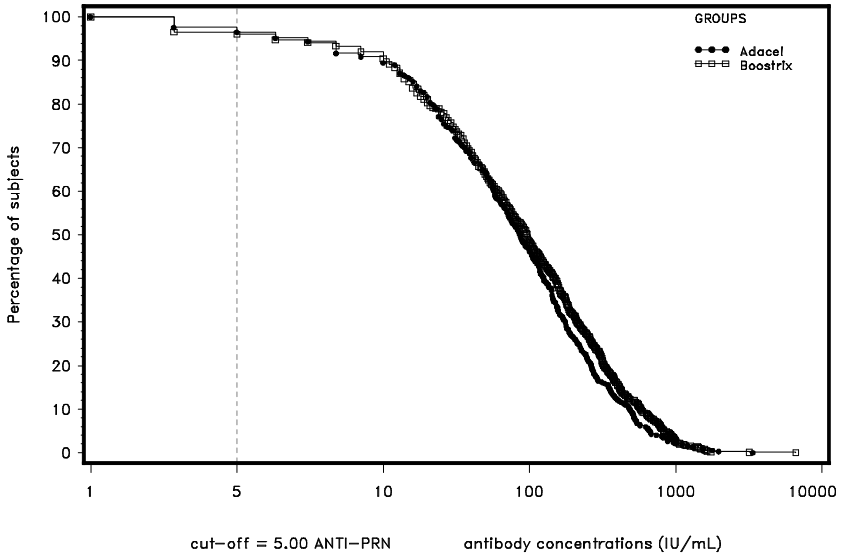


Figure 5 Reverse cumulative curves for anti-PRN concentration at Year 5 (ATP Year 5 cohort)



10.3.2. Year 5 cohort analysis

Table 20 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentrations (GMC) by vaccine groups (Year 5 Cohort)

Antibody	Group	Timing		≥ 0.1 IU/mL				GMC		
						95% CI			95% CI	
			N	n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	Pre	850	726	85.4	82.9	87.7	0.4	0.4	0.4
		1 month post	845	826	97.8	96.5	98.6	4.6	4.2	5.1
		1 year post	731	697	95.3	93.6	96.8	1.4	1.3	1.6
		3 year post	784	736	93.9	92.0	95.5	1.0	0.9	1.0
		5 year post	855	798	93.3	91.4	94.9	0.8	0.8	0.9
	Adacel	Pre	395	353	89.4	85.9	92.2	0.5	0.4	0.5
		1 month post	398	391	98.2	96.4	99.3	5.0	4.5	5.6
		1 year post	340	330	97.1	94.7	98.6	1.5	1.3	1.7
		3 year post	369	355	96.2	93.7	97.9	1.1	1.0	1.2
		5 year post	401	387	96.5	94.2	98.1	0.9	0.8	1.0
Anti-T	Boostrix	Pre	855	820	95.9	94.4	97.1	1.6	1.4	1.7
		1 month post	844	839	99.4	98.6	99.8	8.2	7.7	8.7
		1 year post	734	722	98.4	97.2	99.2	3.2	3.0	3.5
		3 year post	786	769	97.8	96.6	98.7	2.2	2.1	2.4
		5 year post	854	837	98.0	96.8	98.8	2.0	1.9	2.2
	Adacel	Pre	400	390	97.5	95.5	98.8	1.8	1.6	2.0
		1 month post	399	399	100	99.1	100	12.8	11.8	13.9
		1 year post	342	341	99.7	98.4	100	4.5	4.2	4.9
		3 year post	369	367	99.5	98.1	99.9	3.0	2.8	3.3
		5 year post	401	399	99.5	98.2	99.9	2.6	2.4	2.9

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 21 Seronegativity status for anti-D antibody concentration by ELISA and VERO (Year 5 Cohort)

Group	Timing	N	Seronegativity assessed by ELISA		Seronegativity assessed by the VERO test for subjects seronegative by ELISA		Overall seronegativity for anti-D antibodies		Estimated proportion of subjects seroprotected (SP) and its 95% CI		
			n/N	%	n'/N'	%	n/N x n'/N'	%	SP	LL	UL
Boostrix	Pre	850	124/850	14.6	60/124	48.4	124/850 x 60/124	7.1	92.9	91.0	94.6
	1 month post	845	19/845	2.2	7/19	36.8	19/845 x 7/19	0.8	99.2	98.3	99.7
	1 year post	733	36/733	4.9	12/36	33.3	36/733 x 12/36	1.6	98.4	97.2	99.2
	3 year post	784	48/784	6.1	26/48	54.2	48/784 x 26/48	3.3	96.7	95.2	97.8
	5 year post*	855	57/855	6.7	30/57	52.6	57/855 x 30/57	3.5	96.5	95.0	97.6
Adacel	Pre	395	42/395	10.6	15/42	35.7	42/395 x 15/42	3.8	96.2	93.8	97.9
	1 month post	398	7/398	1.8	4/7	57.1	7/398 x 4/7	1.0	99.0	97.4	99.7
	1 year post	341	11/341	3.2	8/11	72.7	11/341 x 8/11	2.3	97.7	95.4	99.0
	3 year post	369	14/369	3.8	10/14	71.4	14/369 x 10/14	2.7	97.3	95.1	98.7
	5 year post*	401	14/401	3.5	9/14	64.3	14/401 x 9/14	2.2	97.8	95.8	99.0

N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ML / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ML / number of subjects tested by VERO test for Pre, 1 month post, 1 year post, and 3 years post-vaccination.
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.016 IU/ML for VERO) for Pre, 1 month post, 1 year post, and 3 years post vaccination
*n'/N' = number of subjects with concentrations below the 0.01 IU/ML / number of subjects tested by VERO test for 5 years post-vaccination
*% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ML for ELISA and 0.01 IU/ML for VERO) for 5 years post-vaccination
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-D
Overall = based on both the ELISA and the VERO testing
95% CI = exact 95% confidence interval for groups; LL = lower limit, UL = upper limit

Table 22 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (Year 5 Cohort)

Antibody	Group	Timing	N	≥ 5 ELU/mL				GMC		
						95% CI			95% CI	
				n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	Pre	848	478	56.4	53.0	59.7	7.1	6.6	7.6
		1 month post	839	815	97.1	95.8	98.2	61.4	57.1	66.0
		1 year post	735	672	91.4	89.2	93.4	22.7	21.0	24.5
		3 year post	785	655	83.4	80.7	86.0	14.3	13.3	15.5
		5 year post	856	730	85.3	82.7	87.6	14.9	13.9	16.1
	Adacel	Pre	396	248	62.6	57.7	67.4	8.1	7.3	9.0
		1 month post	395	369	93.4	90.5	95.7	31.8	28.3	35.8
		1 year post	342	297	86.8	82.8	90.2	16.0	14.3	18.0
		3 year post	369	269	72.9	68.1	77.4	10.3	9.2	11.6
		5 year post	401	307	76.6	72.1	80.6	11.7	10.5	13.1
Anti-FHA	Boostrix	Pre	848	822	96.9	95.5	98.0	30.9	28.7	33.3
		1 month post	845	845	100	99.6	100	615.3	577.5	655.6
		1 year post	734	733	99.9	99.2	100	191.9	178.3	206.7
		3 year post	785	783	99.7	99.1	100	119.5	111.7	127.8
		5 year post	855	854	99.9	99.4	100	112.0	105.1	119.4
	Adacel	Pre	393	378	96.2	93.8	97.8	34.9	31.1	39.1
		1 month post	397	397	100	99.1	100	352.6	323.0	384.8
		1 year post	339	339	100	98.9	100	116.7	105.0	129.8
		3 year post	366	364	99.5	98.0	99.9	83.2	75.4	91.9
		5 year post	400	397	99.3	97.8	99.8	81.3	73.9	89.5
Anti-PRN	Boostrix	Pre	853	662	77.6	74.7	80.4	14.1	12.9	15.4
		1 month post	843	834	98.9	98.0	99.5	401.5	360.5	447.2
		1 year post	731	707	96.7	95.2	97.9	157.8	140.3	177.5
		3 year post	784	748	95.4	93.7	96.8	88.7	79.5	98.9
		5 year post	848	821	96.8	95.4	97.9	87.7	79.2	97.0
	Adacel	Pre	400	304	76.0	71.5	80.1	14.8	12.9	17.0
		1 month post	398	397	99.7	98.6	100	339.7	293.9	392.6
		1 year post	339	334	98.5	96.6	99.5	141.3	120.2	166.2
		3 year post	369	359	97.3	95.1	98.7	77.1	66.7	89.0
		5 year post	400	391	97.8	95.8	99.0	78.6	68.4	90.2

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

10.4. Exploratory Analyses

10.4.1. Between group differences in percentages of subjects seroprotected for D and T

Table 23 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination (ATP Year 5 cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seroprotection rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/mL)	Adacel	372	96.5	Boostrix	790	93.2	Boostrix - Adacel	-3.34	-5.84	-0.52
Anti-T (IU/mL)	Adacel	372	99.5	Boostrix	789	98.0	Boostrix - Adacel	-1.49	-2.83	0.05

N = number of subjects with available results
% = percentage of subjects with anti-D and anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 24 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA between the Boostrix and Adacel, at Year 5 after vaccination (ATP Year 5 cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seropositivity rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/mL)	Adacel	372	97.8	Boostrix	790	96.5	Boostrix - Adacel	-1.39	-3.29	0.88

Boostrix = Subjects who received *Boostrix* vaccine in the 106316 study
Adacel = Subjects who received *Adacel* vaccine in the 106316 study
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/ML by ELISA or ≥ 0.01 IU/mL by VERO
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 25 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination by age (ATP Year 5 cohort)

Antibody	Sub-group	Group 1	N	%	Group 2	N	%	Difference in seropositivity rate (Group 2 minus Group 1)			
										95 % CI	
								Difference	%	LL	UL
Anti-D (IU/mL)	19-29	19-29/Adacel	79	97.5	19-29/Boostrix	205	98.0	19-29/Boostrix - 19-29/Adacel	0.58	-2.94	6.95
	30-49	30-49/Adacel	140	97.9	30-49/Boostrix	275	97.1	30-49/Boostrix - 30-49/Adacel	-0.77	-3.90	3.43
	50-64	50-64/Adacel	153	94.8	50-64/Boostrix	310	86.5	50-64/Boostrix - 50-64/Adacel	-8.32	-13.43	-2.61
Anti-T (IU/mL)	19-29	19-29/Adacel	79	100	19-29/Boostrix	205	99.5	19-29/Boostrix - 19-29/Adacel	-0.49	-2.72	4.17
	30-49	30-49/Adacel	140	99.3	30-49/Boostrix	275	100	30-49/Boostrix - 30-49/Adacel	0.71	-0.67	3.94
	50-64	50-64/Adacel	153	99.3	50-64/Boostrix	309	95.1	50-64/Boostrix - 50-64/Adacel	-4.20	-7.32	-0.93

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
N = number of subjects with available results
% = percentage of subjects with anti-D and anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 26 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination by gender (ATP Year 5 cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seroprotection rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/mL)	Male/Adacel	114	97.4	Male/Boostrix	284	95.1	Male/Boostrix - Male/Adacel	-2.30	-6.03	2.85
	Female/Adacel	258	96.1	Female/Boostrix	506	92.1	Female/Boostrix - Female/Adacel	-4.03	-7.31	-0.36
Anti-T (IU/mL)	Male/Adacel	114	100	Male/Boostrix	284	98.9	Male/Boostrix - Male/Adacel	-1.06	-3.06	2.22
	Female/Adacel	258	99.2	Female/Boostrix	505	97.4	Female/Boostrix - Female/Adacel	-1.80	-3.72	0.39

N = number of subjects with available results
% = percentage of subjects with anti-D and anti-T concentration ≥ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 27 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year 5 after vaccination by age (ATP Year 5 cohort)

Group 1	N	%	Group 2	N	%	Difference in seroprotection rate (Group 2 minus Group 1)			
								95 % CI	
						Difference	%	LL	UL
19-29/Adacel	79	98.7	19-29/Boostrix	205	98.5	19-29/Boostrix - 19-29/Adacel	-0.20	-3.20	5.45
30-49/Adacel	140	97.9	30-49/Boostrix	275	98.5	30-49/Boostrix - 30-49/Adacel	0.69	-1.95	4.77
50-64/Adacel	153	97.4	50-64/Boostrix	310	93.2	50-64/Boostrix - 50-64/Adacel	-4.16	-7.99	0.27

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU /mL by VERO
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 28 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA) between the Boostrix and Adacel, at Year 5 after vaccination by gender (ATP Year 5 cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seropositivity rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/mL)	Male/Adacel	114	99.1	Male/Boostrix	284	98.2	Male/Boostrix - Male/Adacel	-0.88	-3.36	3.14
	Female/Adacel	258	97.3	Female/Boostrix	506	95.5	Female/Boostrix - Female/Adacel	-1.83	-4.48	1.29

N = number of subjects with available results
% = percentage of subjects with anti-D concentration ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/ML by VERO
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

10.4.2. Between group ratios in anti-D and anti-T GMCs

Table 29 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination (ATP Year 5 cohort)

Antibody	Boostrix		Adacel		Adjusted GMC ratio (Boostrix / Adacel)		
						95% CI	
	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D (IU/mL)	785	0.8	366	0.9	0.95	0.86	1.04
Anti-T (IU/mL)	788	2.0	371	2.4	0.84	0.78	0.91

Adjusted GMC = geometric mean concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = lower limit, UL = upper limit

Table 30 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination by age (ATP Year 5 cohort)

Antibody	Sub-group	Boostrix		Adacel		Adjusted GMC ratio (Boostrix /Adacel)		
							95% CI	
		N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D (IU/mL)	19-29	204	1.2	79	1.1	1.02	0.83	1.26
	30-49	272	1.0	136	1.0	0.96	0.82	1.12
	50-64	309	0.6	151	0.6	0.89	0.77	1.03
Anti-T (IU/mL)	19-29	205	2.2	79	2.7	0.80	0.68	0.95
	30-49	274	2.2	139	2.7	0.83	0.74	0.93
	50-64	309	1.8	153	2.1	0.89	0.78	1.02

19-29 = 19-29 Years
30-49 = 30-49 Years
50-64 = 50-64 Years
Adjusted GMC = geometric mean concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = lower limit, UL = upper limit

Table 31 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination by gender (ATP Year 5 cohort)

Antibody	Sub-group	Boostrix		Adacel		Adjusted GMC ratio (Boostrix /Adacel)		
							95% CI	
		N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D (IU/mL)	Male	283	0.9	113	1.0	0.92	0.78	1.09
	Female	502	0.8	253	0.8	0.96	0.85	1.08
Anti-T (IU/mL)	Male	284	2.2	114	2.8	0.80	0.70	0.90
	Female	504	2.0	257	2.3	0.87	0.78	0.96

Adjusted GMC = geometric mean concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = lower limit, UL = upper limit

10.5. Year 5 cohort analysis (Exploratory analysis)

Table 32 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL to D and T between the Boostrix and Adacel at Year 5 after vaccination (Year 5 Cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seropositivity rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/mL)	Adacel	401	96.5	Boostrix	855	93.3	Boostrix - Adacel	-3.18	-5.56	-0.49
Anti-T (IU/mL)	Adacel	401	99.5	Boostrix	854	98.0	Boostrix - Adacel	-1.49	-2.76	-0.06

N = number of subjects with available results
% = percentage of subjects with anti-D and anti-T concentration $\geq$ 0.1 IU/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 33 Difference in the percentage of subjects with antibody concentration equal to or above 0.1 IU/mL by ELISA to D or at least 0.01 IU/mL by VERO cell assay (when anti-D concentrations < 0.1 IU/mL by ELISA between the Boostrix and Adacel, at Year 5 after vaccination (Year 5 Cohort)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seropositivity rate (Group 2 minus Group 1)			
									95 % CI	
							Difference	%	LL	UL
Anti-D (IU/ML)	Adacel	401	97.8	Boostrix	855	96.5	Boostrix - Adacel	-1.26	-3.10	0.94

N = number of subjects with available results
% = percentage of subjects with anti-D concentration $\geq$ 0.1 IU/mL by ELISA or $\geq$ 0.01 IU/ML by VERO
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 34 Adjusted ratios of anti-D, anti-T GMCs at Year 5 after vaccination (Year 5 Cohort)

Antibody	Boostrix		Adacel		Adjusted GMC ratio (Boostrix / Adacel)		
						95% CI	
	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
Anti-D (IU/mL)	850	0.8	395	0.9	0.94	0.86	1.03
Anti-T (IU/mL)	853	2.1	400	2.5	0.83	0.76	0.89

Adjusted GMC = geometric mean concentration adjusted for Age (Y), baseline concentration
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Age (Y), baseline concentration - pooled variance); LL = lower limit, UL = upper limit

10.6. Estimation of GMC by modeling method

Table 35 Percentage of subjects with anti-D and anti-T concentrations above 0.1 IU/mL and 1 IU/mL and GMC predicted by modeling (Adapted ATP cohort)

Antibody	Group	Timing			GMC		
			≥ 0.1 IU/mL	≥ 1 IU/mL		95% CI	
			%	%	value	LL	UL
Anti-D	Boostrix	PY5	95.8	42.0	0.8	0.7	0.8
		PY10	92.2	30.2	0.5	0.5	0.6
	Adacel	PY5	96.5	45.2	0.9	0.8	1.0
		PY10	93.3	33.1	0.6	0.5	0.7
Anti-T	Boostrix	PY5	100.0	79.2	2.0	1.9	2.1
		PY10	99.9	68.7	1.5	1.4	1.7
	Adacel	PY5	100.0	86.3	2.5	2.4	2.7
		PY10	100.0	78.0	1.9	1.7	2.1

GMC = predicted geometric mean concentration
% = predicted percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Prediction and CI from a linear regression on log-transformed concentration with random intercept and slope, where seronegative results are left censored
PY5 = Predicted at Year 5 (ie: 1804 days after the primary vaccination dose)
PY10 = Predicted at Year 10 (ie: 3650 days after the primary vaccination dose)

Table 36 Percentage of subjects with anti-PT, anti-FHA, anti-PRN concentrations above 5 EL U/mL and GMCs predicted by modeling (Adapted ATP cohort)

Antibody	Group	Timing	≥ 5 ELU/mL	GMC		
					95% CI	
			%	value	LL	UL
Anti-PT	Boostrix	PY5	83.5	15.0	13.9	16.1
		PY10	87.1	17.9	16.1	19.9
	Adacel	PY5	75.6	10.9	9.8	12.1
		PY10	80.3	13.1	11.5	14.9
Anti-FHA	Boostrix	PY5	99.9	108.0	101.6	114.7
		PY10	99.9	91.9	83.4	101.3
	Adacel	PY5	99.8	78.3	71.8	85.3
		PY10	99.6	66.6	59.4	74.7
Anti-PRN	Boostrix	PY5	96.7	83.3	75.6	91.7
		PY10	96.8	84.5	74.9	95.3
	Adacel	PY5	95.9	72.0	62.8	82.7
		PY10	96.0	73.1	62.5	85.4

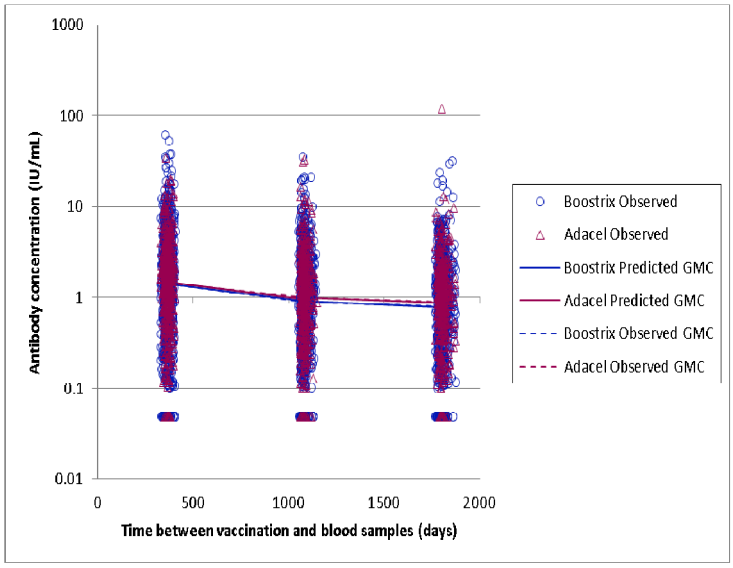
GMC = predicted geometric mean concentration
% = predicted percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Prediction and CI from a linear regression on log-transformed concentration with random intercept, where seronegative results are left censored
PY5 = Predicted at Year 5 (ie: 1804 days after the primary vaccination dose)
PY10 = Predicted at Year 10 (ie: 3650 days after the primary vaccination dose)

Table 37 Group GMC ratio predicted by modeling (Adapted ATP cohort)

Antibody	Timing	Boostrix	Adacel	GMC Ratio (Boostrix/Adacel)		
					95% CI	
		GMC	GMC	value	LL	UL
Anti-D	PY5	0.8	0.9	0.91	0.79	1.03
	PY10	0.5	0.6	0.91	0.79	1.03
Anti-T	PY5	2.0	2.5	0.79	0.71	0.86
	PY10	1.5	1.9	0.79	0.71	0.86
Anti-PT	PY5	15.0	10.9	1.37	1.20	1.54
	PY10	17.9	13.1	1.37	1.20	1.54
Anti-FHA	PY5	108.0	78.3	1.38	1.24	1.52
	PY10	91.9	66.6	1.38	1.24	1.52
Anti-PRN	PY5	83.3	72.0	1.16	0.96	1.35
	PY10	84.5	73.1	1.16	0.96	1.35

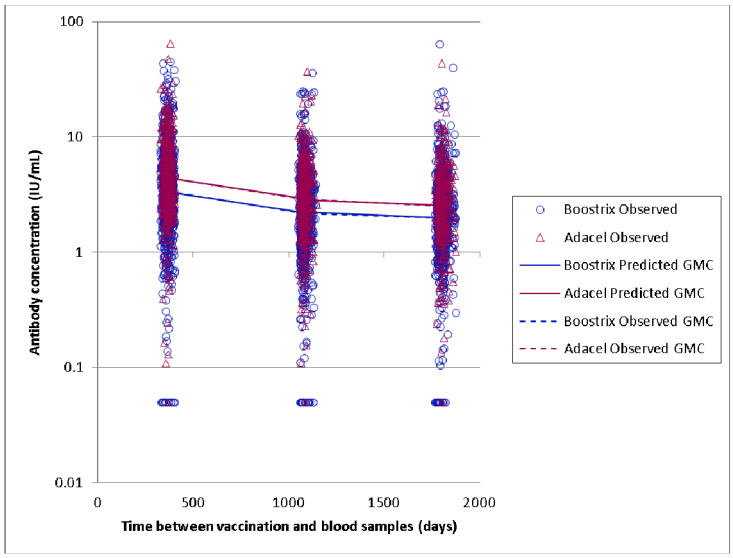
GMC = predicted geometric mean concentration
% = predicted percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Prediction and CI from a linear regression on log-transformed concentration with random intercept and slope, where seronegative results are left censored
PY5 = Predicted at Year 5 (ie: 1804 days after the primary vaccination dose)
PY10 = Predicted at Year 10 (ie: 3650 days after the primary vaccination dose)

Figure 6 Observed and predicted anti-D GMCs (Adapted ATP Year 5 cohort for persistence)



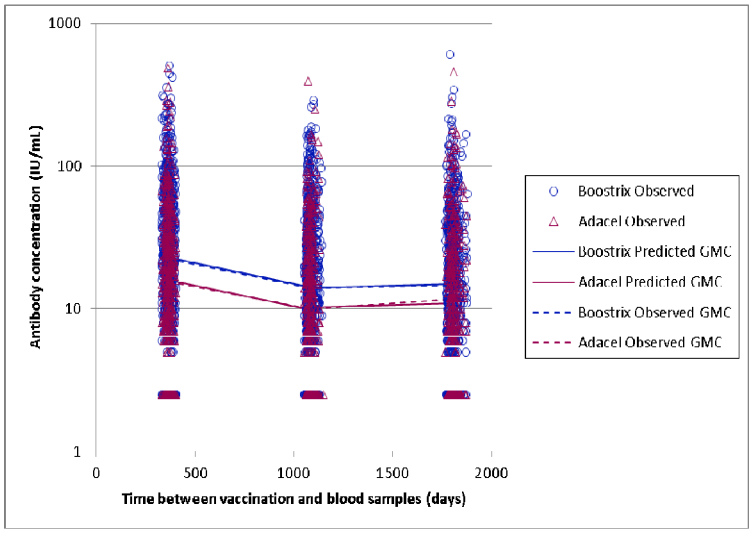
Prediction for Year 1 and Year 3 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored
Prediction for Year 3 and Year 5 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored

Figure 7 Observed and predicted anti-T GMCs (Adapted ATP Year 5 cohort for persistence)



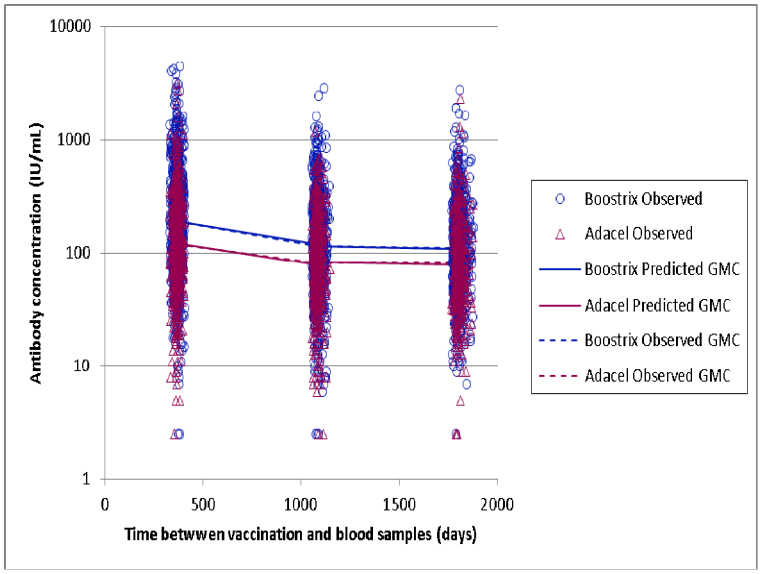
Prediction for Year 1 and Year 3 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored
Prediction for Year 3 and Year 5 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored

Figure 8 Observed and predicted anti-PT GMCs (Adapted ATP Year 5 cohort for persistence)



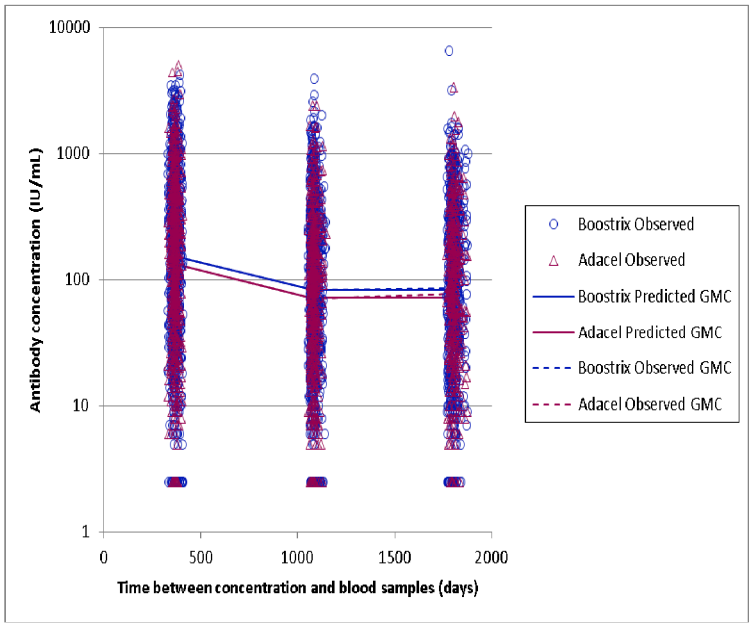
Prediction for Year 1 and Year 3 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored
Prediction for Year 3 and Year 5 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored

Figure 9 Observed and predicted anti-FHA GMCs (Adapted ATP Year 5 cohort for persistence)



Prediction for Year 1 and Year 3 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored
Prediction for Year 3 and Year 5 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored

Figure 10 Observed and predicted anti-PRN GMCs (Adapted ATP Year 5 cohort for persistence)



Prediction for Year 1 and Year 3 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored
Prediction for Year 3 and Year 5 from a linear regression on log-transformed concentration with random intercept, where seronegative results are left-censored

10.7. ATP Complete Year 5 cohort analysis

Table 38 Percentage of subjects with anti-D and anti-T antibody concentrations of at least 0.1 IU/mL (by ELISA) and geometric mean concentration (GMC) by vaccine groups (ATP Year 5 Complete cohort)

Antibody	Group	Timing	N	≥ 0.1 IU/mL				GMC		
						95% CI			95% CI	
				n	%	LL	UL	value	LL	UL
Anti-D	Boostrix	Pre	620	521	84.0	80.9	86.8	0.4	0.4	0.4
		1 month post	623	610	97.9	96.5	98.9	4.6	4.1	5.1
		1 year post	621	594	95.7	93.7	97.1	1.4	1.3	1.6
		3 year post	623	585	93.9	91.7	95.6	0.9	0.8	1.0
		5 year post	624	580	92.9	90.6	94.8	0.8	0.7	0.9
	Adacel	Pre	284	252	88.7	84.5	92.2	0.5	0.4	0.5
		1 month post	288	283	98.3	96.0	99.4	5.0	4.3	5.7
		1 year post	287	280	97.6	95.0	99.0	1.5	1.3	1.7
		3 year post	289	279	96.5	93.7	98.3	1.0	0.9	1.2
		5 year post	289	279	96.5	93.7	98.3	0.9	0.8	1.0
Anti-T	Boostrix	Pre	624	598	95.8	94.0	97.3	1.5	1.4	1.6
		1 month post	623	619	99.4	98.4	99.8	8.4	7.8	9.0
		1 year post	624	613	98.2	96.9	99.1	3.2	3.0	3.5
		3 year post	625	614	98.2	96.9	99.1	2.2	2.1	2.4
		5 year post	624	613	98.2	96.9	99.1	2.0	1.9	2.2
	Adacel	Pre	288	282	97.9	95.5	99.2	1.8	1.6	2.1
		1 month post	289	289	100	98.7	100	12.7	11.5	14.0
		1 year post	289	288	99.7	98.1	100	4.5	4.1	4.9
		3 year post	289	287	99.3	97.5	99.9	3.0	2.7	3.2
		5 year post	289	287	99.3	97.5	99.9	2.5	2.3	2.8

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 39 Seropositivity and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP Year 5 Complete cohort)

Antibody	Group	Timing	N	≥ 5 ELU/mL				GMC		
						95% CI			95% CI	
				n	%	LL	UL	value	LL	UL
Anti-PT	Boostrix	Pre	619	335	54.1	50.1	58.1	6.9	6.3	7.5
		1 month post	621	601	96.8	95.1	98.0	61.5	56.4	67.0
		1 year post	625	569	91.0	88.5	93.2	22.8	20.9	24.8
		3 year post	624	518	83.0	79.8	85.9	14.0	12.8	15.2
		5 year post	625	527	84.3	81.2	87.1	14.6	13.4	15.9
	Adacel	Pre	286	189	66.1	60.3	71.6	8.4	7.4	9.5
		1 month post	285	267	93.7	90.2	96.2	33.0	29.0	37.6
		1 year post	289	254	87.9	83.6	91.4	16.5	14.5	18.6
		3 year post	289	218	75.4	70.1	80.3	10.4	9.2	11.8
		5 year post	289	231	79.9	74.8	84.4	11.9	10.5	13.5
Anti-FHA	Boostrix	Pre	620	599	96.6	94.9	97.9	29.5	27.1	32.2
		1 month post	623	623	100	99.4	100	611.6	568.2	658.3
		1 year post	624	623	99.8	99.1	100	186.2	171.8	201.7
		3 year post	625	624	99.8	99.1	100	116.6	108.3	125.6
		5 year post	624	623	99.8	99.1	100	107.6	100.0	115.7
	Adacel	Pre	282	272	96.5	93.6	98.3	34.0	29.7	38.9
		1 month post	288	288	100	98.7	100	350.2	315.2	389.1
		1 year post	287	287	100	98.7	100	117.3	104.1	132.1
		3 year post	286	284	99.3	97.5	99.9	82.1	73.3	92.0
		5 year post	289	286	99.0	97.0	99.8	79.2	70.4	89.1
Anti-PRN	Boostrix	Pre	622	473	76.0	72.5	79.3	13.7	12.3	15.2
		1 month post	621	614	98.9	97.7	99.5	391.2	343.4	445.6
		1 year post	621	598	96.3	94.5	97.6	151.9	133.2	173.3
		3 year post	623	593	95.2	93.2	96.7	85.7	75.8	96.9
		5 year post	621	599	96.5	94.7	97.8	84.6	75.0	95.4
	Adacel	Pre	288	215	74.7	69.2	79.6	15.1	12.8	17.8
		1 month post	289	288	99.7	98.1	100	337.5	283.3	402.1
		1 year post	286	282	98.6	96.5	99.6	140.2	117.1	167.7
		3 year post	289	280	96.9	94.2	98.6	75.8	64.1	89.6
		5 year post	288	280	97.2	94.6	98.8	77.6	65.5	92.0

GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
Pre = Pre-vaccination
1 month post = One month post-vaccination
1 year post = One year post-vaccination
3 year post = Three years post-vaccination
5 year post = Five years post-vaccination
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

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12. STUDY REPORT AUTHORS/CONTRIBUTING AUTHORS

Scientific Writer: PPD

Project Statistician: PPD

Director, Biometrics: PPD

Global Study Manager: PPD Harrison Clinical Research Benelux for GSK Biologicals

Central Safety Contact: PPD

Clinical Development Manager: PPD

Regulatory Affairs representative: PPD

N + 1 of CDM: PPD

13. SERIOUS ADVERSE EVENTS /PREGNANCY

There were no SAEs and pregnancies reported in the study.

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Sponsor information	-
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs (plus name of committee chair if required by regulatory authority)	16.1.3
Representative written information for patient and sample consent forms.	16.1.3
List of investigators and other important participants in the study	16.1.4
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
Randomization list (patient identification and treatment assigned).	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Sponsor Information

Sponsor Information

eTrack study number(s) and abbreviated title(s)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) **110084 (Tdap-0.3-009 Ext:007 Year 5)** 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of document	***10-September-2012***
Version if document	***Version 04***
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

1. (Principal) Investigator

Centre #	Primary Investigator Name	PI Title	Institution Name	Street Address	Town/City	State	Postal Code
PPD		MD	PPD				
		MD					
		MD					
		MD					
		DO					

Centre #	Primary Investigator Name	PI Title	Institution Name	Street Address	Town/City	State	Postal Code
PPD		MD. CPI	PPD				
		MD					
		MD					
		MD					
		DO					
		MD					
		MD					
		MD					
		MD					
		DO					
		MD					
		MD, PhD					
		DO					
		MD					
		MD					
		MD					
		MD					

Centre #	Primary Investigator Name	PI Title	Institution Name	Street Address	Town/City	State	Postal Code
PPD		MD	PPD				
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		MD					
		DO					
		MD					
		MD					

2. Medical Monitor

PPD MD
GlaxoSmithKline
GSK Vaccines - US
2301 Renaissance Boulevard
King of Prussia, PA 19406
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Cell: PPD
Fax: PPD
Email: PPD

3. Study Monitor(s)

A. Acting US Clinical Medical Affairs (CMA) Representative:

PPD MD
GlaxoSmithKline
US Vaccines
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Office: PPD
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Email: PPD

B. Local US Study Manager:

PPD
Senior Study Manager
GlaxoSmithKline Clinical Operations
GSK Vaccines - US
2301 Renaissance Boulevard
King of Prussia, PA 19406

Mail Code - RN:0220
Office : PPD
Fax : PPD
e-mail address: PPD

4. Study Contact for Reporting of a Serious Adverse Event

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GlaxoSmithKline
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772
Telephone: PPD
Fax: PPD

5. Back-up Study Contact for Reporting of a Serious Adverse Event

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD or PPD
24/24 hour and 7/7 day availability

6. Study Centres

37 Study Centers as listed in item #1

Protocol and Protocol Amendments

Sponsor
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772

Study vaccine	GlaxoSmithKline (GSK) Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, containing 0.3 mg aluminum [776423/Tdap, (Boostrix®)] Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap) vaccine (Adacel™)
eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
Investigational New Drug (IND) number	BB-IND-8461
Date of approval	Final: 17 April 2007
Date of amendment/ administrative change approval	Administrative Change 1 Final: 14 April 2009 Amendment 1 Final: 09 November 2010
Title	Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and 10 years following the administration as a single dose in the 106316 study.
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Co-ordinating author *(Amended 09 November 2010)*	PPD Scientific writer
Contributing authors *(Amended 09 November 2010)*	• PPD ***Senior Manager, Clinical Development, Combination Vaccines, Global Vaccine Development*** • PPD ***Director, Clinical Development, Lead, DTP Combination Vaccines, Global Vaccine Development*** • PPD ***Biostatistician, Boostrix (US)*** • PPD Project statistician, Boostrix (US) • PPD ***Global Study Manager*** • PPD ***Clinical Data Coordinator*** • PPD ***Senior Manager, Biologicals Clinical Safety & Pharmacovigilance*** • PPD Clinical Development Manager, Vaccine (US) • PPD Study Manager (US)

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatories	
	Karin Hardt, Director, Clinical Development, Lead, DTP Combination Vaccines, Global Vaccine Development, GSK Biologicals
Signature	_____
Date	_____
	Francesca Ceddia, Vice President and Vaccine Development Leader (DTP Portfolio, Neisseria), Global Vaccine Development, GSK Biologicals
Signature	_____
Date	_____

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Protocol Amendment 1 Rationale

Amendment number:	Amendment 1

Rationale/background for changes:

- The list of coordinating and contributing authors for this amendment was updated.
- The maximum window period allowed for the return of subjects for the Year 5 and Year 10 follow-up visits (Visit 5 and Visit 6) has been extended from ± 5 weeks to ± 8 weeks.
- The contact details for reporting of SAEs have been clarified. As of now, two fax numbers will be used as back-up for the safety contact for reporting SAEs.
- Text pertaining to the reporting of spontaneous abortion has been removed from the protocol. Since this follow-up study involves no vaccine exposure, investigators are not obligated to report such an event.
- The number of attempts to contact subjects who do not return for scheduled persistence visits has been clarified.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	_____
Signature	_____
Date	_____

For internal use only

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Synopsis

Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Indication/Study population	Healthy adults, 19 years of age and older, who received a single dose study vaccination in study 106316.
Rationale	This study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, up to 10 years following vaccination with GlaxoSmithKline's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).
Objectives	**Primary** To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination. **Secondary** • To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose *of Boostrix*. • To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.
Study design	• Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study. • Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be

maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.

- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

Number of subjects

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points. For example, if the subject did not want to participate in the Year 1 evaluation, he can participate at Years 3, 5 and 10.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF APPENDICES

PAGE

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
DTPw	Diphtheria, Tetanus Whole Cell Pertussis Vaccine
DTaP	Diphtheria, Tetanus Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FDA	Food And Drug Administration, United States
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter
PRN	Pertactin
PT	Pertussis Toxoid
RDE	Remote Data Entry

SAE	Serious Adverse Event
SBIR	GSK Biologicals' Internet Randomization System
SOP	Standard Operating Procedure
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

Glossary of Terms

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.3 and 10.4 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain

	further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

1. INTRODUCTION

1.1. Background

Diphtheria, tetanus (toxoids) and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Reported pertussis incidence in the United States increased from 1010 cases in 1976 to 25,827 cases in 2004 [CDC, 2004; CDC, 2002]. On October 26, 2005, ACIP issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.

Recently, GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age. This vaccine is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti , 2002; Greco , 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in Boostrix are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. A total of 6,173,696 doses have been distributed since launch until 02 August 2006.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of *Boostrix*.

1.2. Rationale for the study

Recently a study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by sanofi pasteur's *Adacel* vaccine.

Data on persistence of antibodies and longer-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 years following vaccination with GlaxoSmithKline Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).

2. OBJECTIVES

2.1. Primary objective

To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of *Boostrix* in adult subjects, with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL) and anti-T antibody concentrations ≥ 0.1 IU/mL, 1 year, 3 years, 5 years and 10 years following Tdap vaccination.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years and 10 years following a single dose of *Boostrix*.
- To evaluate geometric mean concentrations of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix*.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW

- Experimental design: Non-interventional, observational multicenter with the same two parallel groups as in the 106316 study.
- Blinding: This study will be an open study since there is no vaccination in this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: No treatment is planned to be given in this study. Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 10 years after the dose of vaccination.
- Duration of the study: Approximately 10 years for subjects who participate in all phases of the extension.
- Data collection: Remote Data Entry (RDE).

4. STUDY COHORT

4.1. Number of subjects / centres

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation. At each persistence time point, all subjects who expressed willingness to participate in the long-term study will be contacted. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*. Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, and 449 subjects (300 *Boostrix* recipients) for the 10-year time point.

4.2. Inclusion criteria

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

4.3. Elimination criteria during the study

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

4.4. Contraindications to subsequent vaccination

Not applicable.

4.5. Warnings and Precautions

Not applicable.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 Declaration of Helsinki (Protocol Appendix A), US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator.

A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favorable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favorable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favorable opinion of the IRB/IEC will be transmitted by investigator to CRA prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favorable opinion of an appropriate amendment or administrative change, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].)

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,
- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the October 1996 Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects face to face. The Informed Consent Form may be read to the subjects but, in any event, the investigator or designate shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subjects and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The subjects should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects for participating in the trial.

l. The anticipated expenses, if any, to subjects for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject is authorising such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects will be informed in a timely manner if information becomes available that may be relevant to the subjects' willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be

followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. Subject identification

Subjects will retain their subject numbers as in the 106316 study.

5.3. Outline of study procedures

The summary of study procedures is summarized in Table 1.

Table 1 List of study procedures

Visit Timing Sampling time point	VISIT 3 Year 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 Year 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. Table 2 presents the intervals between the study visits.

Table 2 Intervals between study visits *(Amended 09 November 2010)*

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	***1 year ± 5 weeks***
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	***3 years ± 5 weeks***
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	***5 years ± 8 weeks***
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	***10 years ± 8 weeks***

1. Whenever possible the investigator should arrange study visits within this interval
2. Subjects will not be eligible for inclusion in the ATP Year X cohort for analysis if they make the study visit outside this interval.

5.4. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Obtain written informed consent from all subjects at all long-term time points.
- Check inclusion criteria at all study visits.
- Check elimination criteria at all study visits.
- Record concomitant medication/vaccination as described in Section 6.3.
- Collect approximately 5 mL of whole venous blood to provide a minimum of 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Study continuation at Years 3, 5 and 10.
- Study conclusion at Year 10 visit (Visit 6).

5.5. Sample handling and analysis

5.5.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

5.5.2. Laboratory assays

Table 3 presents the details of laboratory assays.

A sample of approximately 5 mL of whole venous blood, to provide a minimum of 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and ten years following study vaccination in 106316 study. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C until sent to the sponsor. Sera will be sent to Quest Laboratories (Van Nuys, CA) and subsequently to GSK Biologicals, Belgium for the laboratory assays.

All serological assays will be performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off of both assays is 0.1 IU/mL [Camargo , 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL.

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA or multiplex (Luminex) techniques. The cut-off of the three assays is 5 EL.U/mL [Sato, 1982].

Table 3 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
** VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL

All serological assays will be performed at GSK Biologicals using standardized, validated procedures with adequate controls.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.5.3. Immunological read-outs

Table 4 presents the immunological read-outs.

Table 4 Immunological read-outs for all subjects

Blood sampling time point Timing	Visit no.	Marker
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 10	6	D
		T
		PT
		FHA
		PRN

All: All subjects enrolled at the long-term time point.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

It may be that any findings in the present or in other studies necessitate further investigation by GSK Biologicals into the efficacy or immunogenicity of the *Boostrix* vaccines and its constituents under study or further research in the disease(s) under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.

Any sample testing will be done in line with the consent of the individual subject.

Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to protocol Appendix B, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking above may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.5.4. Activities at study conclusion

All subjects will be offered a booster dose of Td vaccine following the blood draw at the 10 year visit. A booster dose of Tdap may be offered instead if a second dose of Tdap is recommended at that time.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Study vaccines in study 106316 were *Boostrix* and *Adacel*. No additional vaccination will be given as part of this study.

6.1. Treatment allocation and randomisation

Not applicable.

6.2. Method of blinding and breaking the study blind

The study is an open study, since there is no administration of vaccination is this study.

6.3. Concomitant medication/treatment

At each study visit, the investigator should question the subject about any medications taken.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Section 4.3.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration. Refer to Section 4.3.

7. HEALTH ECONOMICS

Not applicable.

8. SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of a serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting SAEs, as detailed in this section of the protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.2. Clinical laboratory parameters and other abnormal assessments qualifying as serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as SAEs if they meet the definition of a SAE, as defined in Section 8.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as SAEs. The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.3. Time period, frequency, and method of detecting serious adverse events

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2 for details of the back-up reporting system.

8.4. Evaluating serious adverse events

This section is only applicable if an investigator becomes aware of an SAE that warrants notification of the sponsor.

8.4.1. Assessment of intensity

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An SAE which prevents normal, everyday activities. (In adults, such an SAE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

Grade 3 is a category utilised for rating the intensity of an event; and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.

8.4.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If an event meets the criteria to be determined "serious" (see Section 8.1 for definition of serious adverse event), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.5. Follow-up of serious adverse events and assessment of outcome

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits.

Investigators will follow-up subjects:

- with SAEs, until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.6.1.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.6.2. for details of the back-up reporting system.

Outcome of any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.6. Prompt reporting of serious adverse events to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

8.6.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

8.6.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within

24 hours as outlined in Section 8.6.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received WITHIN 24 HOURS as outlined in Section 8.6.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.4.2.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 8.6.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.6.1.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.6.1.

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF / sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

Please see Sponsor Information Sheet for contact details.

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD **US Study Contacts for Concerns Relating to an SAE** GSK Biologicals Medical Monitor: PPD MD Office: PPD Cell: PPD Fax: PPD GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.
Back-up Study Contact for Reporting SAEs (Amended 09 November 2010)
24/24 hour and 7/7 day availability ***GSK Biologicals Clinical Safety & Pharmacovigilance***
Fax: PPD ***or*** PPD

8.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.6. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.8. Post-study adverse events and serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.3. Investigators are not obligated to actively seek SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.

8.9. Pregnancy *(Amended 09 November 2010)*

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for a study visit as specified in the protocol is considered to have completed the study phase (time point) pertaining to that study visit.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE until resolution of the event (see Section 8.1).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence

time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter. (Amended 09 November 2010)

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

9.2.2. Subject withdrawal from investigational product

Since subjects will not be administered vaccine in this antibody persistence study, subjects will not be withdrawn from receipt of investigational product, but may be withdrawn from other study procedures.

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination.

10.2. Secondary endpoints

- Subjects with anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination.
- Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.
- Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.

10.3. Estimated sample size

No sample size is calculated for this study. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study.

With a total of 2284 enrolled subjects in primary study 106316, it is expected approximately 1941 subjects will be present for the 1 year time point, 1402 subjects for the 3 year time point, 1013 subjects for the 5 year time point, and 449 subjects for the 10-year time point, assuming a 15% attrition rate per year.

10.4. Study cohorts to be evaluated

Year X (1, 3, 5, 10) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

According-To-Protocol (ATP) Year X (1, 3, 5, 10) cohort

The ATP Year X (1, 3, 5, 10) cohort will include all subjects from Year X (1, 3, 5, 10) cohort who is in the ATP cohort for analysis of immunogenicity in 106316 study and who have not met the following elimination criteria.

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.

- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

ATP Complete Year X (1, 3, 5, 10) cohort

The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.

10.5. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.5.2.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 10.6.2 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 10 years following vaccination will be derived to evaluate the first secondary objective.
- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

- The geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 10 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

10.6. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 10) on cleaned data obtained through Year X. A clinical study report (CSR) will also be written following each analysis.

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year 10) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 10) cohort, in the ATP Year X (1, 3, 5 or 10) cohort and in the ATP complete Year X (1, 3, 5 and 10) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 10) (in years) will be summarized using descriptive statistics.

10.6.2. Analysis of immunogenicity

The primary analysis will be based on the ATP Year X cohort.

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 10) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves by group.

Comparability between Groups:

Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA), Year X (1, 3, 5, 10) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group - *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 10) after vaccination will be calculated.

10.6.3. Analysis of safety

No safety analysis will be performed for this persistence study. If GSK is informed by an investigator of an SAE that in his/her medical judgement could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

10.7. Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5, and Year 10) as available and reported separately.

10.8. Planned interim analysis

No interim analysis is planned for this persistence study.

11. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

12. REFERENCES

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Appendix A World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the

study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments/administrative changes is required prior to implementation.
- Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory

authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is

anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF/ RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability
- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of CRF data
- Reports to the IRB/IEC and the sponsor

- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

Appendix C Overview of the Recruitment Plan

- All subjects who received vaccination in the study 106316 will be invited to participate in this long-term study.
- As part of the visit activities at the study conclusion visit in the 106316 study, subjects were asked to state their interest in participating in an extension study. Subjects who responded positively to this question will be contacted by the site as the sampling time point approaches in order to schedule the study visit.
- Subjects who do not provide samples at earlier long-term time points may still be considered eligible to provide samples at later long-term time points.
- The study will take place at multiple centers in the US.
- The Site Monitor will perform monitoring of actual enrolment against target enrolment on a continuous basis.
- Enrolment will be monitored through RDE.
- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date ***the*** subject received vaccination in study 106316. A window of ***± 8*** weeks around the actual time point for each subject will be permitted. ***(Amended 09 November 2010)***

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used to minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimising the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".
- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate label provided by GSK Biologicals (see point 3).

3. Labelling

- The standard labels provided by Quest should be used to label each serum sample.
- If necessary, any hand-written additions to the labels should be made using indelible ink.

4. Sorting and storage

- The tubes of serum should be stored in a vertical position at approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to Quest Diagnostics. Wherever possible, a backup facility for storage of serum samples should be available.
- Detailed instructions concerning the collection, Quest labelling and storage of all serum specimens are provided in the Quest Diagnostics Clinical Trials Investigator Manual for Protocol Number 110080, 110082, 110084 and 110086.

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, Van Nuys, California.

Refer to the separate Quest Diagnostics Clinical Trials Investigator Manual for Protocol Numbers 110080, 110082, 110084 and 110086 for shipping details.

Appendix F Amendments and Administrative changes to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to:	
US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE *(Amended 14 April 2009)*	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office:~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Amendment number:	Amendment 1
Amendment date:	09 November 2010
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

- The list of coordinating and contributing authors for this amendment was updated.
- The maximum window period allowed for the return of subjects for the Year 5 and Year 10 follow-up visits (Visit 5 and Visit 6) has been extended from ± 5 weeks to ± 8 weeks.
- The contact details for reporting of SAEs have been clarified. As of now, two fax numbers will be used as back-up for the safety contact for reporting SAEs.
- Text pertaining to the reporting of spontaneous abortion has been removed from the protocol. Since this follow-up study involves no vaccine exposure, investigators are not obligated to report such an event.
- The number of attempts to contact subjects who do not return for scheduled persistence visits has been clarified.

Amended text has been included in *bold italics* in the following section:

Title page:

Co-ordinating author *(Amended 09 November 2010)*	PPD Scientific writer
Contributing authors *(Amended 09 November 2010)*	• PPD ***Senior Manager, Clinical Development, Boostrix/Hepatitis Vaccines, Global Vaccine Development*** • PPD ***Director, Lead Clinical Development, DTP Combination Vaccines, Global Vaccine Development*** • PPD ***Biostatistician, Boostrix (US)*** • PPD Project statistician, Boostrix (US) • PPD ***Global Study Manager*** • PPD ***Clinical Data Coordinator*** • PPD ***Senior Manager, Biologicals Clinical Safety & Pharmacovigilance*** • ~~PPD Director, Vaccines (US)~~ • ~~PPD Biostatistician (US)~~ • PPD Clinical Development Manager, Vaccine (US) • PPD Study Manager (US) • ~~PPD , Director, Clinical R&D, World-Wide Clinical Development, Life-cycle Vaccines~~ • PPD ~~Central Study Coordinator~~

Section 5.3 Outline of study procedures

Table 2 Intervals between study visits *(Amended 09 November 2010)*

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	***1 year ± 5 weeks***
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	***3 years ± 5 weeks***
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	***5 years ± 8 weeks***
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	***10 years ± 8 weeks***

1. Whenever possible the investigator should arrange study visits within this interval
2. Subjects will not be eligible for inclusion in the ATP Year X cohort for analysis if they make the study visit outside this interval.

Section 8.6.2 Completion and transmission of serious adverse event reports to GSK Biologicals

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD
US Study Contacts for Concerns Relating to an SAE
GSK Biologicals Medical Monitor: PPD MD Office: PPD Cell: PPD Fax: PPD GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.
Back-up Study Contact for Reporting SAEs (Amended 09 November 2010)
24/24 hour and 7/7 day availability ***GSK Biologicals Clinical Safety & Pharmacovigilance***
Fax: PPD ***or*** PPD

Section 8.9 Pregnancy ***(Amended 09 November 2010)***

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

~~A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.6. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to GSK Biologicals as described in Section 8.8. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.~~

Section 9.2.1 Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter. (Amended 09 November 2010)

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

Appendix C Overview of the Recruitment Plan

- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date ***the*** subject received vaccination in study 106316. A window of ~~± 5~~ ***± 8*** weeks around the actual time point for each subject will be permitted. ~~Visits for the year 1, 3, 5, and 10 samplings are therefore expected to take place between 8 June – 17 August 2007, 2009, 2011, and 2016.~~ ***(Amended 09 November 2010)***

CONFIDENTIAL

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	Leonard Friedland, MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.
Signature:	PPD
Date:	5/16/07

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Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Bruce J. Berwald

PPD

Investigator signature

8/14/07

Date

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Investigator name: Mm Blatter

PPD

Investigator signature

6/13/07

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Investigator name: Alan S. Bock M.D.

PPD

Investigator signature

12 Jun 2007

Date

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Investigator name: DONALD M. BRANDON M.D.

PPD

Investigator signature

6/11/07

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Investigator name: PPD

PPD

Investigator signature

6/11/07.
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Investigator name: Shane Glade Christensen, MD

PPD

Investigator signature

6/12/07

Date

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Investigator name: Dana M. DeSantis, M.D.

PPD

Investigator signature P

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Date

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Investigator name: Richard S. Dobrusin, D.O., FACOFP

PPD

Investigator signature

6/15/07
Date

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Investigator name: Hugh D. Durrance, MD

PPD

Investigator signature 6/12/07 **Date**

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Investigator name: Rochelle Elijah, M.D

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Investigator signat

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Investigator name: PPD Thomas Fiel, DO

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Investigator name: Larry I. Bilderman, Do

PPD

Investigator 6/12/07 **Date**

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Investigator name: CARL P GRIFFIN M.D

PPD

Investiga **Date** 6-22-07

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Investigator name: Stephen P. Gorbs, M.D

PPD

Date 6/11/07

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Investigator name: Archie Hearne, MD

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Investigator signature 6/14/07 **Date**

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Investigator name: James A. Hedrick

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Investigator name: LAURA L. HELMANN DO

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Investigator name: Dan C. Henry, MD

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Investigator name: Kurt W. Lesh, MD

PPD

Invest

(KURT W. LESH MD)

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Investigator name: Thomas Willard Littlejohn, III, M.D.,

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Investigator signature **Date**

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Investigator name: Merritt S. Matthews MD

PPD

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Investigator name: Clark D. McKeever, M.D.

PPD

Investigator signature 6/14/2007 **Date**

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Investigator name: DR. Ranelle Middeton

PPD

Investigator signature

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Investigator name: David J. Morin, MD

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Investigator name: Mark A Nielsen

PPD

Investigator signature

13 Jun 2007
Date

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Investigator name: Fatima Ptuccem

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Investiga

6/12/07
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Investigator name: Ernie Riffer, MD

PPD

Investigator si

6-25-07

Date

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Investigator name: John Rubino, MD

PPD

Investigator signature

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Date

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Investigator name: Renee Nilsson Scheidell, MD

PPD

Investigator signature

6-13-07

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Investigator name: Eric A. Sheldon, MD

PPD

10 Jul 2007
Date

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Investigator name: Mark Shepard

PPD

Investigator sig **Date** 6/6/07

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Investigator name: Gerald R. Shockey, MD

PPD

Investigator sign _____ **Date** 6-14-07

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Investigator name: Mark A Turner MD

PPD

Investigator signature 6/13/07 **Date**

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Investigator name: Stacey E. Watson, MD

PPD

Investigator signature

6-12-07
Date

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Investigator name: Duane G. Wombolt

PPD

Investigator signature

06/19/07
Date

Duane Wombolt

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Appendix F Administrative change to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to:	
US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office:~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

CONFIDENTIAL

Tdap-0.3-009 Ext:007
Administrative Change 1

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
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Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer

Approved by:

Senior Manager, Global Clinical R&D, Paediatric and Hepatitis Vaccines, GlaxoSmithKline Biologicals PPD

05-MAY-20

dd-mm-yyyy

For internal use only
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ee3fc7b0c180953095209d75934378a9 2.3 28/04/2009

GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3	110082

Date: 30-MAR-2011

Concerns: DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3 (110082) Protocol Administrative Change 1 Investigator Agreements

Details:

The Investigator Agreements for Protocol Administrative Change 1 were obtained on the Investigator Agreement Page (page 4) not including the 'summary checksum'. However the checksum is included in the document footer of the Investigator Agreement page 4 confirming the signatures were obtained on the final published version.

Made by: PPD

Signature PPD

Function: Lead Study Manager

Signature Date: 31 Mar 2011

(If required) Approved by: _____

Approver's Signature: _____

Function *[Line Manager]*:_____

Signature Date: _____

Investigator Agreement

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

CONFIDENTIAL

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD ~ 15-Oct Bruce Bernald MD

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Mark M. Blatter, M.D.
PPD

Date: 5/27/09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD

Do[redacted] M. BRANDON, M.D.

5/19/09

Hence I:

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Investigator name: PPD

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Investigator name: PPD 5/26/09

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Investigator name: PPD 5/19/09

CONFIDENTIAL

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- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financ[redacted].
- Agree to provide GSK Biolog[redacted]n Vitae and other FDA required documents.

Investigator name: [redacted] 7/15/09

2009-05-26 11:30 PPD P 3/3

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
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Investigator name: PPD PPD

5/26/09

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5-19-09

14 April 2009
ee3fc7b0c180953095209d75934378e9

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: Carl P. Griffin, M.D.

PPD

01 Jun 2009

Hence I:

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Investigator name: PPD

6/11/05

Hence I:

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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an up[PPD]other FDA required documents.

Investigator name: Archie Hearne, MD 5/21/09

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biol[PPD] rriculum Vitae and other FDA required documents.

Investigator name: [PPD] June 1/09

JAMES A. HEDRICK DATE

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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- Agree to provide GSK PPD ılum Vitae and other FDA required documents.

Investigator name: PPD 5-18-09

Hence I:

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Investigator name: PPD 5/22/09

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: MURRAY A. KIMMEL, DO

PPD 22MAY2009

Hence I:

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other FDA required documents.

Investigator name: PPD 5/26/09

May.18. 2009 12:41PM PPD No.0040 P. 2

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD 18 May 2009

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Investigator name: PPD 5/21/09

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Investigator name: MARTIN L. KABONGO, M PPD 5/21/09

No.5874 P. 6
May.21. 2009 9:52AM

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD 26 May 2009

Hence I:

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Investigator name: JOHN E. ERVIN, M.D. PPD 5-19-09

THE CENTER FOR PHARMACEUTICAL RESEARCH
1010 Carondelet Drive
Suite 426
Kansas City, MO 64114

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
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Investigator name: PPD 5/20/09

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Investigator name: _____ 5/29/09

Hence I:

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Investigator name: PPD 5/20/09

CONFIDENTIAL

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Investigator name: PPD 14 May 09

Hence I:

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Investigator name: Kerry S Rosinski

Signature: PPD

Date: 23 Apr 2010

Hence I:

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Investigator name: PPD 5-22-09

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Investigator name: John Rubino / PPD 5/22/09

Hence I:

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Investigator name PPD 5-26-09.

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Investigator name: PPD

Eric A. Sheldon, MD PPD

03 Jun 2009

Hence I:

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- Agree to provide GSK Biologicals v PPD Vitae and other FDA required documents.

Investigator name: _____ 5/27/09

Hence I:

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Investigator name: PPD 5-22-09

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Investigator name: PPD 5/22/09

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Investigator name: PPD 5-21-09

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Investigator name: Jonathan Paul Wilson, PPD

PPD

21- MAY- 2009

Hence I:

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Investigator name: PPD

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatories	
	Karin Hardt, Director, Clinical Development, Lead, DTP Combination Vaccines, GPPD K Biologicals
Signature	
Date	22/11/2010
	Francesca Ceddia, Vice President and Vaccine Development Leader (DTP Portfolio, Neisseria), GPPD als
Signature	
Date	22/11/2010

For internal use only

----------Checksum----------!Ver.!Created On - -
884607eb7719a3f47d57b3f46507cf9b4173c47a 2.0 11/18/2010 4:27:24 PM - -

GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	Contained in the Year 5 Regulatory Binders the Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Consequence(s) of Issue/incident	Signature Pages missing CARS checksum for 8 US centers was indexed into CARS causing a query on the missing and discrepancy log and the need for a note to file to be indexed.
Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD – Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	DONALD M. BRANDON, M.D.
Signature	PPD
Date	5/5/11

For internal use only

----------Checksum----------!Ver.!Created On - -
884607eb7719a3f47d57b3f46507cf9b4173c47a 2.0 11/18/2010 4:27:24 PM - -
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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Daniel H Brunemo.
Signature	PPD
Date	5-9-11

For internal use only

- ----------Checksum----------!Ver.!Created On - -
884607eb7719a3f47d57b3f46507cf9b4173c47a 2.0 11/18/2010 4:27:24 PM - -
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GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
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Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	Contained in the Year 5 Regulatory Binders the Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Consequence(s) of Issue/incident	Signature Pages missing CARS checksum for 8 US centers was indexed into CARS causing a query on the missing and discrepancy log and the need for a note to file to be indexed.
Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD – Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	SHANE GLADE CHRISTENSEN, M.D.
Signature	PPD
Date	1-12-2011

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Donna M. DeSantis, MD
Signature	PPD
Date	5-2-11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Richard S. Dobrusin, DO, FACOPPD
Signature	PPD
Date	5/5/11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Hyla R. Rennace
Signature	PPD
Date	5/05/11

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	John Keith Earl, MD
Signature	PPD
Date	4-29-11

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NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

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Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD - Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Rochelle Elijah, M.D.
Signature	PPD
Date	5/24/11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	JOHN E. ERVIN, M.D.
Signature	PPD
Date	4-12-11

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Thomas Charles Fiel, DO
Signature	PPD
Date	02-May-2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Carl P. Griffin
Signature	PPD
Date	17 MAY 2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Stephen D. Grubb, MD
Signature	PPD
Date	5/4/11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Archie Hoarne, MD PPD
Signature	PPD
Date	5/5/2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	James A Hedrick MD
Signature	PPD
Date	5/17/11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Laura L. Helman, DO.
Signature	PPD
Date	5-13-11

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GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
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Cause of Incident/Issue	Contained in the Year 5 Regulatory Binders the Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Consequence(s) of Issue/incident	Signature Pages missing CARS checksum for 8 US centers was indexed into CARS causing a query on the missing and discrepancy log and the need for a note to file to be indexed.
Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD - Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Dan C. Henry, MD
Signature	PPD
Date	1/13/2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	MARTIN L. KABONGO
Signature	PPD
Date	25 APR 2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	WILLIAM A. KIMMEL, DO
Signature	PPD
Date	27 MAY 2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Kurt W. Leah, MD
Signature	PPD
Date	5/26/11

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Randle T. middleton, MD
Signature	PPD
Date	5-18-11

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Mark A. Nielsen
Signature	PPD
Date	09 May 2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Stephanie J. Powell, MD
Signature	PPD
Date	05 May 2011

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GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

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Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD – Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Keith S. Reisinger, MD, MPH
Signature	PPD
Date	12 JAN 2011

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Ernie Riffer, MD
Signature	PPD
Date	5-2-2011

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	John Rubino
Signature	PPD
Date	10/May/2011

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NOTE TO FILE

Alias / Abbreviated Study Title (if applicable)	Tdap 0.3-009 Ext:007 Y5
E-Track Study Number (if applicable)	110084

	Details
Initial Incident/Issue	Discrepancy in the activities carried out by the Principal Investigator (PI) for the study site PPD The Protocol Amendment 1 Investigator Agreement was signed by Dr PPD whereas the study activities were concluded by Dr. PPD at the Year 5 time point.
Cause of Incident/Issue	NA
Consequence(s) of Issue/incident	Protocol Amendment 1 Investigator Agreement was signed by Dr PPD on 20th January 2011 who was the PI of the study at that point in time. The centre was initiated on 31st May 2011. Dr. PPD was replaced by Dr. PPD on 22nd December 2011, who concluded the study activities for the Year 5 time point.
Corrective Action(s) with justification and timeline(s) for completion	NTF for documentation of the reason for the discrepancy in the investigator that signed-off on the Protocol Amendment 1 Investigator agreement and the investigator that concluded the study activities for the centre number PPD
Outcome of Corrective Action(s)	NA
Reference document(s)	NA
Additional Information appended to this Note To File	NA

	Full Name and job function	**Signature**	**Date**
Author	PPD GSM	PPD	27 JUN 13
Reviewed by (if applicable)			
Approved by (if applicable)			

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NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	Contained in the Year 5 Regulatory Binders the Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Consequence(s) of Issue/incident	Signature Pages missing CARS checksum for 8 US centers was indexed into CARS causing a query on the missing and discrepancy log and the need for a note to file to be indexed.
Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD - Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Renée Shotwell MD
Signature	PPD
Date	1-20-2011

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	ERIC A. SHELDON, MD
Signature	PPD
Date	5/6/11

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NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	Tdap 0.3-009 EXT:007 (Year 5)
E-Track Study Number (if applicable)	110084
Site ID (if applicable)	8 US Centers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	Contained in the Year 5 Regulatory Binders the Protocol Investigator Agreement Signature Page for Amendment 1 was issued to sites improperly missing the CARS Checksum for 8 US Centers.
Consequence(s) of Issue/incident	Signature Pages missing CARS checksum for 8 US centers was indexed into CARS causing a query on the missing and discrepancy log and the need for a note to file to be indexed.
Corrective Action(s) with justification and timeline(s) for completion	NTF
Outcome of Corrective Action(s)	N/A
Reference document(s)	None
Additional Information appended to this Note To File	This file note was created by GSK US Clinical Operations CSA PPD at the request of TCS for the CSR Study File. Original placed in US country Study File

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD - Clinical Study Assoc		12-Dec-2012
Co-Author (if applicable)			
Reviewed by (if applicable)			
Approved by (if applicable)			

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Marc Sheard
Signature	PPD
Date	11/8/11

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

cTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Gerald R. Shockey, MD
Signature	PPD
Date	5-2-11

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Donald R. Sisler
Signature	PPD
Date	5/16/11

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
Amendment 1

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	MARK TURNER
Signature	PPD
Date	5/12/11

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y10)
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IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Jonathan Paul Wilson, DO
Signature	PPD
Date	27- MAY- 2011

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IND number	BB-IND-8461
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Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	Phillip M. Green, MD
Signature	PPD
Date	5/16/11

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IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Investigator name	DUANE G. WOMBOLT, MD
Signature	PPD
Date	27 MAY 2011

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Sample Case Report Form

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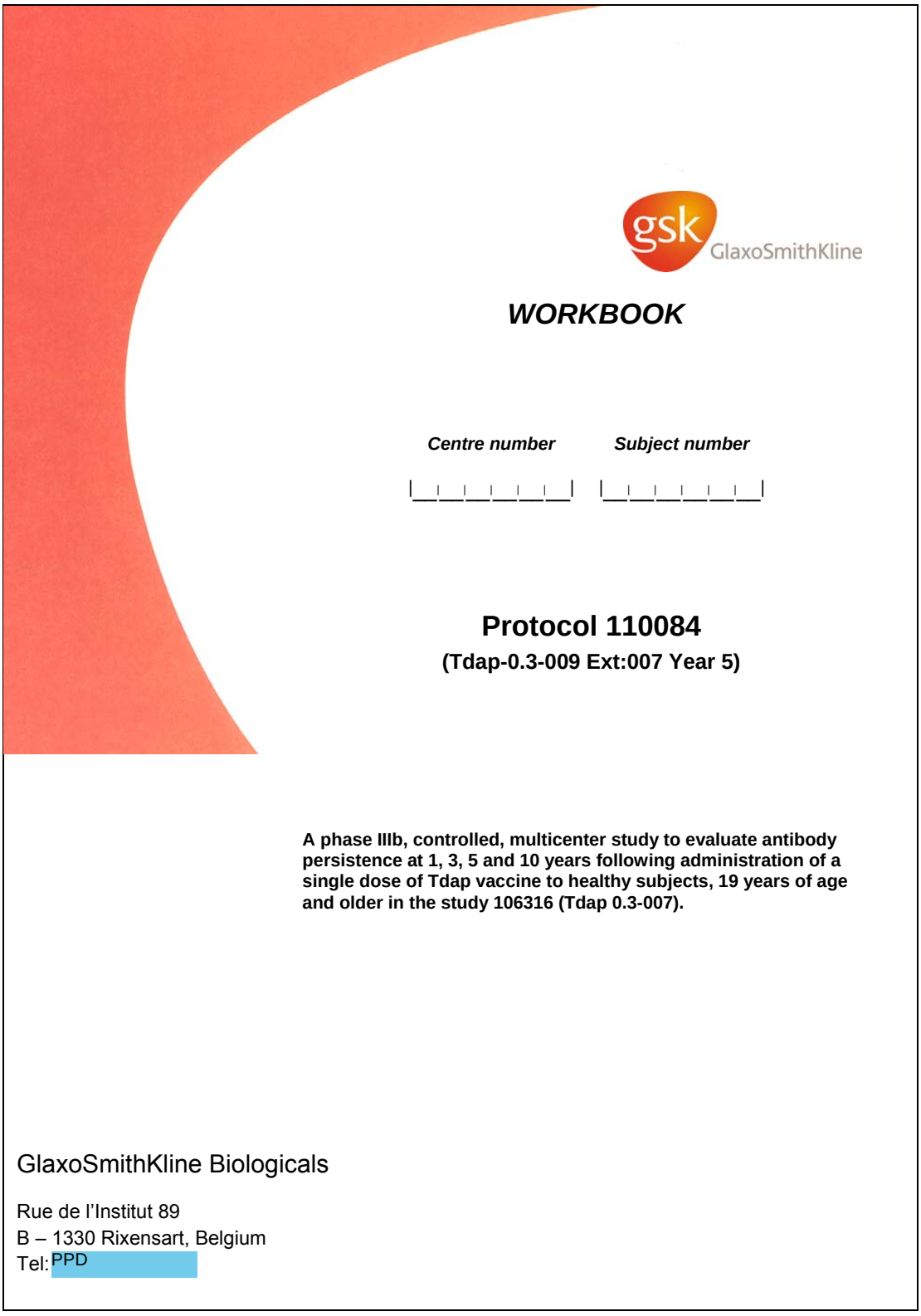

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WORKBOOK

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Protocol 110084

(Tdap-0.3-009 Ext:007 Year 5)

A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

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Rue de l'Institut 89
B – 1330 Rixensart, Belgium
Tel: PPD

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GENERAL INSTRUCTIONS

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

DATES

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example: | 0 1 | | J A N | | 2 0 0 6 | = 1st January 2006
day month year

The **Medication** and the **Concomitant Vaccination** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at each long-term follow-up study.

For all subjects enrolled, please complete the **Study Continuation** form**.**

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ADVERSE EVENT DEFINITIONS

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.

3: Severe: An adverse event which prevents normal, everyday activities
(In adults/ adolescents, such an adverse event would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO: The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1: Recovered / resolved.

2: Recovering / resolving: If the subject is recovering at the time the subject completes the study or at the time the subject dropped out.

3: Not recovered / not resolved: This means an AE ongoing at the time the subject completes the study or becomes lost to follow-up; if AE/SAE was ongoing at the time of death, but was not the cause of death.

4: Recovered with sequelae / Resolved with sequelae.

5: Fatal: AE is the cause of death (only applicable for SAE reports).

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death.
- is life threatening.
- results in persistent or significant disability / incapacity.
- requires in-patient hospitalization.
- prolongation of existing hospitalization.
- is a congenital anomaly / birth defect in the offspring of a study subject.
- In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

For each serious adverse event related to study participation or related to vaccination in the primary study the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

In case of pregnancy the investigator becomes aware of, please complete and submit a **Pregnancy Notification** form to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

FLOW SHEET

Visit Timing Sampling time point	VISIT 3 YEAR 1 1 year following Boostrix/ Adacel vaccination	VISIT 4 Year 3 3 years following Boostrix/ Adacel vaccination	VISIT 5 Year 5 5 years following Boostrix/ Adacel vaccination	VISIT 6 YEAR 10 10 years following Boostrix/ Adacel vaccination
Informed consent	●	●	●	●
Check inclusion criteria	●	●	●	●
Check elimination criteria	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●
Blood sampling for antibody determination	●	●	●	●
Study Continuation	●	●	●	
Study Conclusion				●

● is used to indicate a study procedure that requires documentation in the individual CRF.

Intervals between study visits

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	*1 year ±5 weeks*
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	*3 years ±5 weeks*
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	*5 years ±8 weeks*
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	*10 years ±8 weeks*

1. Whenever possible the investigator should arrange study visits within this interval
2. Subjects will not be eligible for inclusion in the ATP Year X cohort for analysis if they make the study visit outside this interval.

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VISIT 5

YEAR 5

Informed Consent has to be obtained prior to any study procedure

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each long-term visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. (See section 10.4 for definition of study cohorts to be evaluated.)

[A] Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.

[B] Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.

[C] Administration of immunoglobulins and/or any blood products within 90 days of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.

[D] Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, $\geq$ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).

[E] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol		Visit	Date of visit	Subject Number
110084		**VISIT 5**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__| day month year

Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study? ☐ Yes ☐ No ☐ NA

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender: [M] ☐ Male
[F] ☐ Female

LONG-TERM FOLLOW-UP

PREVIOUS STUDY

110082
(Tdap-0.3-009 EXT: 007 Year 3)

Subject number will be the same as in the previous study.

1.

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol		Visit		Subject Number
110084		**VISIT 5**		|__|__|__|__|__|__|

ELIGIBILITY CHECK

Did the subject meet all the entry criteria?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed

[1] ☐ All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.

[2] ☐ Written informed consent must be obtained from the subject prior to each study time point.

2.

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol		Visit		Subject Number
110084		**VISIT 5**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample for antibodies determination been taken?

☐ Yes → Date if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ No

3.

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CONCOMITANT VACCINATION

At each study visit/contact, the investigator should question the subject about any vaccination(s) administered.

- Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration.

110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol				Subject Number
110084				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any Td or Tdap Vaccine, or any registered or investigational vaccine utilizing a Diphtheria toxoïd or tetanus toxoïd vaccines been administered since the last visit performed?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** **day month year**
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
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For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

Route:			
ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

4.

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MEDICATION

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Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
IN	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject about any medication(s) taken.

- Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within 90 days prior to any study blood sampling are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, start and end dates of treatment)

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110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol				Subject Number
110084				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments specifically contraindicated in the protocol been administered?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

5.

CONFIDENTIAL

STUDY CONCLUSION

CONFIDENTIAL

GlaxoSmithKline

110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol				Subject Number
110084				|__|__|__|__|__|__|

FOLLOW-UP STUDIES

If a booster study or a follow-up study is offered in the future, would the subject or parents/guardians be willing to be contacted and learn more about it?

☐ Yes

☐ No, please specify the most appropriate reason:

→ ☐ Adverse Events, or Serious Adverse Events:

please specify: _____

→ ☐ Other:

please specify: _____

OCCURRENCE OF SERIOUS ADVERSE EVENT

Because subjects are not vaccinated as part of the study protocol, investigators are not required to specifically solicit SAE's.

However if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in the 106316 study, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations. SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

Did the subject experience any Serious Adverse Event during the study?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

6.

CONFIDENTIAL

GlaxoSmithKline

110084 (Tdap-0.3-009 EXT: 007 Year 5)

Protocol				Subject Number
110084				|__|__|__|__|__|__|

INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

7.

110084 (Tdap - 0.3-009 EXT:007 Year 5)

Protocol	**Previous study**	**Tracking Document Reason for non participation**	Center Number
110084	**110082** **(Tdap - 0.3-009 EXT:007 Year 3)**		|__|__|__|__|__|__|__|__|

Previous Subject Number	Date of Birth *(day month year)*	**Reason for non participation**	Date of Contact *(day month year)*
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: ___________________ [4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: ___________________ [4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: ___________________ [4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|	|__|__||__|__|__||__|__|__|__|
|__|__|__|__|__|__|__|	|__|__||__|__|__||__|__|__|__|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: ____________________ [2] ☐ Subject lost to follow-up or not reached. [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event; Please specify: __________________ ☐ Other; Please specify: ___________________ [4] ☐ Subject died on : |__|__| |__|__|__| |__|__|__|__|	|__|__||__|__|__||__|__|__|__|

Investigator name: (PRINT name)	**Signature**:	**Date:** *(day month year)*
		|__|__| |__|__|__| |__|__|__|__|

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GlaxoSmithKline

110084 (Tdap - 0.3-009 EXT:007 Year 5)

Protocol	Centre	
110084	|__|__|__|__|__|__|	

USE OF HUMAN SAMPLES BY GSK

In addition to the use of samples for the tests described in the protocol, samples might be used for other research by GSK (see protocol). Please tick what is also covered by the subject Informed Consent form of your center.

[2] ☐ **Quality Assurance of tests described in the protocol**

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in the protocol as well as making sure that new tests are comparable to previous methods and work reliably.

[3a] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study (Diphtheria Tetanus Pertussis). These investigations excludes genetics and HIV testing.**

[3b] ☐ **Further investigation by GSK Biologicals into the ability of Boostrix (Tdap,776423) to protect people if any findings from related studies require it and further research in the diseases under study(Diphtheria Tetanus Pertussis). These investigations excludes genetic and HIV testing. Investigator will always ask in advance the permission of the independent Ethics Committee/Institutional Review Board linked to the institution where this research is performed.**

[4] ☐ **Further research by GSK Biologicals that is NOT RELATED to Boostrix (Tdap,776423)or the diseases under study (Diphtheria Tetanus Pertussis) done on an anonymous basis (meaning that any identification linking the subject to the sample is destroyed). This research excludes genetic and HIV testing and does not affect subject participation in the study.**

Please tick below box if a 15 years GSK storage period is covered by the subject's Informed Consent form of your center.

☐ **At least 15 years storage period by GSK Biologicals**

☐ **Other, specify:** _____

ICF Effective date: |__|__| |__|__|__| |__|__|__|__|
day month year

! Complete and submit a new form for each change during the study.

INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

1.

Template CRF version 12.4 – January 06, 2011 - 14:30

List of Independent Ethics Committees /Institutional Review Boards

Center Number(s)*	Ethics Review Body	Location
PPD	Quorum IRB	1601 Fifth Ave Suite 1000 Seattle WA 98101 USA

* GSK Biologicals assigned center number

Representative written information for patient and sample consent forms

INFORMED CONSENT FORM

Study Identification: 110084 (Tdap-0.3-009 Ext:007 Year 5)

Study Title: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Version Number: 1 Date: 24 April 2007

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification:

This document should be presented to the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the subject.

What does giving consent for this study mean?

Consent means agreeing to take part in this clinical research study. You have the right to decide if you want to take part in the study or not. Please take time to read the following information carefully and discuss it if you wish with friends, relatives and your personal doctor. Ask us if there is anything that is not clear or if you would like more information.

Why is this study being carried out?

You were vaccinated with a Tdap (tetanus toxoid, diphtheria toxoid and acellular pertussis) vaccine in study 106316. Vaccines work by stimulating antibodies (substances that protect against diseases). This study is being conducted to find out how long information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens remain elevated following a single dose vaccination with GlaxoSmithKline Biologicals's Tdap vaccine (*Boostrix*).

What does this study involve?

In order to be included in this study, the following requirements must be met:

- You have signed this informed consent form.
- You have received a dose of Tdap vaccine (*Boostrix* or *Adacel*) as part of the 106316 study.

If you take part in the study, you will have the following tests and procedures:

- A blood sample of 5 ml will be taken from you.
- You should contact the health care provider immediately should you have any signs or symptoms you think may be serious, or if you are hospitalized during the study period.

How many other subjects are there in the study?

Total enrolment in the 106316 study was 2284 subjects, approximately 1522 of whom were vaccinated with *Boostrix*.

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will contact ALL subjects who received vaccination in study 106316. If at the time of initiation of the long-term study, you decline to participate in the study, your refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.

Do you have to stay in the study?

You may decide to stop participating in this study at any time without giving a reason. If you decide to stop participating in the study, you must notify the study doctor immediately. Your leaving the study will not have any effect on future medical care.

Your doctor for this study or GlaxoSmithKline Biologicals may also stop the study at any time before it is completed. If GlaxoSmithKline stops the study, the reason for that decision will be given to you.

If, during the time you are participating in the study, any new information becomes available that might affect whether you are willing to stay in the study, that information will be shared with you in a timely manner.

If you decide the stop participating in the study before it is completed, GlaxoSmithKline will still use the information and data they have collected about you up until that point, as part of the results of their research.

What are the foreseeable risks for taking part in the study?

Blood sampling may cause momentary discomfort, minor bruising or bleeding. The amount to be taken will not be harmful to your health.

Are there any benefits for taking part in the study?

Information from this study may help researchers understand more about protecting adults against tetanus, diphtheria and pertussis diseases in the future.

What payments will be made for the study?

You will receive the following payment for your participation in the study:

$ XXX for each completed scheduled visit, if you do not complete the entire study.

If you have to withdraw from the study for medical reasons related to the study, you will receive full payment.

Will you have to meet any cost/expenses for taking part in the study?

There will be no costs to you to participate in this study.

Who should you contact to answer any questions on the study?

You have the right to ask [**name**] at [**contact details**] any questions concerning this study at any time. This includes questions about your rights, study-related injuries, and the research study itself.

You may ask the study doctor questions about the study. If you have any questions, please contact:

Name of investigator:

Address of investigator:

Telephone number of investigator: _____Fax number _____:

In the event that you are injured in the study what compensation will be available?

If you are injured by any procedure that is done to you as specified by the study, GlaxoSmithKline will pay for reasonable and necessary medical expenses to treat the injury - as long as those expenses are not covered by your medical insurance or an alternative source such as the National Vaccine Injury Compensation Fund. GlaxoSmithKline is not offering to compensate you for any other expenses, but you keep all of your legal rights when you sign this form.

Who will have access to medical and personal information about you that is collected in this study?

If you decide to participate in the study, the study doctor and staff will collect medical and personal information about you as part of doing the study. People who work for or with GSK, and others like the independent ethics committee or the institutional review board (IEC/IRB) for the study or regulatory authorities responsible for approving medicines, will have access to this information at the site in order to check that the study is done properly. GSK staff who see this information at the site will keep it confidential.

The study site will also transfer to GSK some of the information it collects, in a coded form. The information transferred will not include your name, initials, address, or other direct identifiers. It will be assigned a code number that only the site can connect back to your name.

Your permission to the study doctor and staff to use this information or share it with GSK and others as described below for the study doesn't automatically end at a particular time.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

Medical information about you may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your medical care it will be given to the study doctor who will be encouraged to share it with you or your doctor. While you are in the study, however, the study site will not share certain new medical information about you that is created as part of the study (such as whether or not you are getting study drug, or the results of certain tests) unless the study doctor decides it is medically important to do so. This is done to stop the study results from being distorted. Once the study is over, you will be given access to medical information about you that you are entitled to see. You will be told if any of this medical information requires confirmation using a clinical test. This is important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment. At any time, you may ask your study doctor to let you see your personal information, e.g. name and address and to correct it if necessary

What will GlaxoSmithKline do with the information it gets?

- GSK may use the information that the study doctor gives it (i.e. the coded information):
- By storing and analyzing it electronically to find out what this study is telling us.
- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study (this will not include any information that directly identifies you)
- By sharing it as part of research with other companies or universities for the purpose of further understanding or developing this vaccine and with other GlaxoSmithKline offices in this country and in other countries. If the information is sent to another country, GSK will apply the same level of protection to your information, to the extent permitted by local law
- By using it to plan new studies or other types of research or other medical purposes related to the development of the vaccine.

What will happen to blood samples from this study?

- Samples will not be labelled with information that directly identifies you but will be coded with your study identification number.
- Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.
- By agreeing to take part in this study you will be allowing GSK Biologicals to use your samples for the following purposes:
- Testing to measure the immune response (e.g. amount of antibodies) to the vaccine(s) you received during the Study

- Testing to assure that the results from your sample are of good quality, for improvements of those tests or development of new test methods.
- If any findings from related studies require further investigation into the ability of the Boostrix vaccine to protect people or for further research in the diseases under study (diphtheria, tetanus and pertussis), additional testing on your collected samples may be performed by GSK Biologicals. This will, however, exclude testing related to your genes and HIV.

Collected samples will be stored for up to 15 years.

How is GlaxoSmithKline involved?

The study doctor and the institution are paid to conduct this research study by GSK.

The information and the materials that are given to you in relation to the study are confidential information belonging to GlaxoSmithKline and should be kept private. You can discuss this information in confidence with your doctor or friends and family to decide about taking part in this study and talking about your healthcare.

Consent statement

I, (Printed name of Subject)

confirm that I have read the written information (or have had the information read to me) for studies 110084 (Tdap-0.3-009 Ext-007 Year 5), Version 1, dated 24 April 2007, 6 pages and the study procedures have been explained to me by study staff during the consent process for this study.

- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data to authorised persons described in the information sheet
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my primary health care physician will be notified of my participation in this study.

Yes **No**

Tick as appropriate

I agree that my biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study. This will be done on an anonymous basis (meaning that any identification linking me to the sample is destroyed). Testing on my genes or testing for HIV will not be done. I understand that if I select "No", it will not affect my participation in the study.

Yes No

I agree to take part in this study.

Subject's Signature _____ **Date:** _____

Signature of Person conducting Consent _____ **Date:**

Printed Name of Person conducting Consent _____

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Sub-investigators	Centre number*	Investigational site	Location	Phone number Fax number	Number of Subjects	% of Subjects
Dr. PPD PPD	PPD			PPD	Phone: PPD Email: PPD	15	1.2%
Dr. PPD					Phone: PPD Email: PPD	57	4.5%
Dr. PPD PPD					Phone: PPD Email: PPD	88	7.0%
Dr. PPD PPD					Phone: PPD Email: PPD	66	5.3%
Dr. PPD PPD					Phone: PPD Email: PPD	27	2.1%
Dr. PPD PPD					Phone: PPD Email: PPD	23	1.8%
Dr. PPD				PPD United States PPD	Phone: PPD Email: PPD	14	1.1%

Investigator's name	Sub-investigators	Centre number*	Investigational site	Location	Phone number Fax number	Number of Subjects	% of Subjects
Dr. PPD PPD	PPD			PPD	Email: PPD	8	0.6%
Dr. PPD				PPD United States PPD	Phone: PPD Email: PPD	21	1.7%
Dr. PPD				PPD	Phone: PPD Email: PPD	9	0.7%
Dr. PPD					Phone: PPD Email: PPD	21	1.7%
Dr. PPD PPD					Phone: PPD Email: PPD	9	0.7%
Dr. PPD PPD					Phone: PPD PPD	3	0.2%
Dr. PPD PPD					Phone: PPD Email: PPD	31	2.5%
Dr. PPD PPD					Phone: PPD Email: PPD	40	3.2%

Investigator's name	Sub-investigators	Centre number*	Investigational site	Location	Phone number Fax number	Number of Subjects	% of Subjects
Dr. PPD	PPD			PPD	Phone: PPD Email: PPD	78	6.2%
Dr. PPD PPD				PPD United States PPD	Phone: PPD Email: PPD	31	2.5%
Dr. PPD PPD				PPD United States PPD	Phone: PPD Email: PPD	36	2.9%
Dr. PPD				PPD	Phone: PPD Email: PPD	16	1.3%
Dr. PPD PPD					Phone: PPD Email: PPD P P	75	6.0%
Dr. PPD					Phone: PPD Email: PPD	39	3.1%
Dr. PPD PPD				PPD PPD United States	Phone: PPD Email: PPD PPD	107	8.5%
Dr. PPD PPD				PPD PPD United States PPD	Phone: PPD Email: PPD	16	1.3%

Investigator's name	Sub-investigators	Centre number*	Investigational site	Location	Phone number Fax number	Number of Subjects	% of Subjects
Dr. PPD PPD	PPD			PPD	Phone: PPD Email: PPD	9	0.7%
Dr. PPD PPD					Phone: PPD Email: PPD	0	0%
Dr. PPD PPD				PPD	Phone: PPD Email: PPD	15	1.2%
Dr. PPD				PPD	Phone: PPD Email: PPD	69	5.5%
Dr. PPD					Phone: PPD Email: PPD	16	1.3%
Dr. PPD				PPD United States PPD	Phone: PPD Email: PPD	97	7.7%
Dr. PPD				PPD	Phone: PPD Email: PPD	15%	1.2%
Dr. PPD PPD					Phone: PPD Email: PPD	18	1.4%

Investigator's name	Sub-investigators	Centre number*	Investigational site	Location	Phone number Fax number	Number of Subjects	% of Subjects
Dr. PPD PPD	PPD			PPD	Phone: PPD Email: PPD	35	2.8%
Dr. PPD				PPD United States PPD	Phone: PPD Email: PPD	25	2.0%
Dr. PPD				PPD	Phone: PPD Email: PPD PPD	35	2.8%
Dr. PPD PPD				PPD United States PPD	Phone: PPD Email: PPD	57	4.5%
Dr. PPD				PPD United States PPD	Phone: PPD Email: PPD	21	1.7%
Dr. PPD PPD				PPD	Phone: PPD Email: PPD	15	1.2%

* GSK Biologicals assigned centre number

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Page(s) removed- Out of Scope of phase 1 of Policy 0070 – Investigator CVs

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007)

Study: 110084 (Tdap-0.3-009 Ext: 007 Y5) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Htay Htay Han
Title of Sponsor Signatory:	Director Lead, Clinical Development, Combination Vaccines-Infanrix, Boostrix, Hepatitis and Rotavirus Vaccines GlaxoSmithKline Biologicals
Signature:	
Date:	

For internal use only

- ----------Checksum----------!Ver.!Created On - -
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9f244b9032124a6f37f952bc5759217ee1a6e156 1.0 5/31/2013 8:10:15 AM - -
65838a114c79d0ba866a736aa0c398d460f4ac50 3.0 7/9/2013 8:13:36 AM - -
4ed5958a46f3d1202039103b02eed118af266f0a 1.0 5/31/2013 8:01:22 AM - -
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0980664cea34d6e924cd866efd0de8ecd5924cc3 2.0 5/31/2013 12:11:21 PM - -
f189ed5ef9115f6b5d3d2c1885f3d871c902b9e4 2.0 7/9/2013 7:26:10 AM - -
3b02fc9b9da6afeaa72ef9fcc01e1deb8ff4d4ff 1.0 7/4/2013 11:04:32 AM - -
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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not Applicable.

Randomization list

Not Applicable.

Audit certificates

Not Applicable.

Documentation of statistical methods

Refer to Section 5.9 of the Study Report.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not Applicable.

Publications based on the study

Publications based on the study

Blatter M, Friedland LR, Weston WM, et al. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine* 2009; 27(5): 765-72.

Weston W, Messier M, Friedland LR, et al. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. *Vaccine* 2011; 29(47): 8483-86.

CCI - This section contained journal publication(s), which are protected by third party copyright laws and therefore have been excluded.

Important publications referenced in the report

Blatter MM, Friedland LR, Weston WM, Li P, Howe B. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid, and 3-component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine* 2009; 27: 765–772.

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Individual Listings

NOTES TO APPENDIX TABLES

The following abbreviations are common throughout the Appendix tables:

Sub. No.		:	Subject number
Eli MA		:	Eligibility (MA: Main Analysis)
	E	:	Eliminated from reactogenicity and immunogenicity analyses
	I	:	Eliminated from immunogenicity analysis
	MC	:	Missing Confirmed
	N	:	No
	Y	:	Yes
	NA	:	Not Applicable

Abbreviations which are unique to a particular appendix are presented below.

Appendix Table IA - Individual subject data: Elimination codes

Elim Codes : Elimination codes

Appendix Table I.B - Individual subject data: Demography

Sex		:	Sex
	F	:	Female
	M	:	Male
Center		:	Study center

Appendix Table ICi - Individual subject data: Dates of Birth - vaccination - sampling - visits

Dates of vaccine administration,
Dates of sampling,
Dates of visits

VIS ND	:	Visit Not Done (the subject did not come)
VAC ND	:	Study vaccine administration not done
ND	:	Not Done

Appendix Table ICii - Individual subject data: Reason for visit not done

Reason		:	Reason for visit not done
	AEX	:	Non serious adverse event
	SAE	:	Serious adverse event
	OTH	:	Other
	SAM	:	Same reason and decision as previous visit

Appendix Table ID - Individual subject data: General medical history - Physical examination

Status

PAST	:	Medical history no more present at the physical examination
CURRENT	:	Medical history present at the physical examination
Both	:	Past and current

Appendix Table IE - Individual subject data: CONCLUSION

Elim Crit		:	Did any elimination criteria become applicable during the study?
	Y	:	Yes
	N	:	No
Link to AE		:	Is the withdrawal of the subject linked to an adverse event ?
	Yes	:	
	No	:	
Date of last contact			Date when last information was collected on subject's condition
Good Condition?			Was the subject in good condition at date of last contact?
SAE?		:	Did the subject experience any Serious Adverse Event during the
		:	study?
	Y	:	Yes
	N		No
Nb of SAE		:	Total number of SAE's recorded in SAE report.
Preg		:	Did the subject become pregnant during the study / since the end of the active phase?

Appendix Table IEii - Individual subject data: Subjects whose the code has been broken

Broken date	:	Unblinding treatment date

Appendix Table IEii - Individual subject data: Extensive safety follow-up

Contact date		:	Date of study conclusion extended safety follow-up contact
Sub Cont		:	Was the subject/subject's parents/guardian contacted after the end of the active phase?
Reason		:	Reason for not being contacted:
	Consent withdrawal / Lost to follow-up		
Non-Serious AE?		:	Did the subject experience any study relevant non-serious adverse event(s) since the end of the active phase?

Serious AE ?		:	Did the subject experience any serious adverse event(s) since the end of the active phase
	YES		
	NO		
	Subjects could not be contacted		
Other vaccine		:	Has the subject received any other investigational and/or non-registered vaccine and/or drug since the end of the active phase?
Other vaccine spec		:	Specification of the vaccine
Pregnant		:	Has the subject become pregnant since the end of the active phase?
	YES	:	Yes
	NO	:	No
	NA	:	Not applicable

Appendix table IF - Individual subject data : Notes RDE (sticky notes)

Tbl. Note			
	3	:	Sticky notes
	2	:	Notes data
	1	:	Force validation
Act		:	Activity
Scr Nb		:	Screen number
Screen		:	Screen name
Seq Nb		:	Sequence number
Note		:	Description of the note

Appendix Table IG - Individual subject data: Vaccination procedure for each subject: list of the administered vaccines and all related information

Trt. No.		:	Treatment number
According to Prot?		:	Is of the study vaccine be administered according to protocol in terms of side/site/route?
Injection?		:	Vaccine administration
Type of vacc.			
	1	:	Study vaccine not administered according to protocol: wrong side/site/route or replacement or wrong vial number
	2	:	Study vaccine planned but not administered for a given visit
	3	:	Administration of a study vaccine not planned in the group
Eff Vial Number		:	Effective vial number administered

Appendix Table IH - Individual subject data : Smoking history

Smoke now?		:	Does the subject smoke on a regular basis?
What?		:	What does the subject smoke?
	CIGARETTES		
	CIGARS		
	PIPE		
	CIGARILLOS		
Daily Average		:	How many cigarettes, cigars,… does the subject smoke on average?
	<= 10 DAILY		
	11-20 DAILY		
	21-40 DAILY		
	> 40 DAILY		
Start Date		:	Specification of the year the subject started smoking
Smoke past?		:	Did the subject smoke on a regular basis in the past?
Stop Date		:	Specification of the year the subject quit smoking

Appendix Table II - Individual subject data: Reason for vaccine not administered

Adm?		:	Study vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
Reason		:	Reason why the study vaccine was not administered:
	SAE	:	Serious adverse event
	AEX	:	Non serious adverse event
	OTH	:	Other

Appendix Table IJ - Individual subject data: Reason for non-Eligibility

Eligib.		:	Did the subject meet all the entry criteria?
	No	:	Some inclusion /exclusion criteria are not met
Study vacc.			
	Yes	:	The subject received at least one dose of study vaccine (study vaccine, Replacement or Wrong vial number)
	No	:	No vaccine received
Criterion number		:	Inclusion OR exclusion criteria number the subject failed
Reason of inclusion and exclusion criteria		:	Description of the criterion number: label from codelist or 'Cfr. description in CRF'

Appendix table IK - Individual subject data : Tracking Document Booster or Long Term Follow-up

Prev_sub		:	Previous PID number
Origin		:	Origin of the information
	Track.Doc	:	From TRACKDOC of the current study
	Demog	:	From DEMOG of the current study
	Err.Track	:	Inconsistensy between demog and trackdoc
	Prev.Study	:	From FU in Previous study
	No Track	:	Subject from primary without information
DOB		:	Date of birth
Crit_nb		:	Criteria number of the reason for non participation into an extension study
	1		
	2		
	3		
	4		
Comment for non eligibility		:	If the criteria for non participation into an extension study is 'Subject not eligible -Please specify criteria that are not fulfilled'?
Crit Description	-Subject not eligible -Please specify criteria that are not fulfilled -Subject lost to follow-up or not reached -Subject eligible but not willing to participate due to -Subject died		Label of the criteria number
Due to AE?		:	If subject is eligible but not willing to participate due to Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No
Due to Other?		:	If subject is eligible but not willing to participate due to Other reason that Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No

Appendix Table IIA - Individual subject data: Solicited local adverse events

L?		:	Has the subject experienced any local symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing
VACC CODE		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Table IIA)

VA		:	Vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
PA		:	Pain (empty or scored from 0 to 3)
RE		:	Redness (greatest diameter)
SW		:	Swelling (greatest diameter)
IN		:	Induration (greatest diameter)
EC		:	Ecchymosis (greatest diameter)
EXP		:	Has the subject experienced some symptoms?
	Y	:	Yes
	N	:	No
MA_TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIB - Individual subject data: Solicited general adverse events

G?		:	Has the subject experienced any general symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing
AC		:	General aches (empty or scored from 0 to 3)
AR		:	Arthralgia (empty or scored from 0 to 3)
DA		:	Diarrhoea (empty or scored from 0 to 3)
DR		:	Drowsiness (empty or scored from 0 to 3)
FA		:	Fatigue (empty or scored from 0 to 3)
FE		:	Fever = Body temperature in °Cs or °Fs
FU		:	Fussiness (empty or scored from 0 to 3)
GI		:	Gastrointestinal symptoms (empty or scored from 0 to 3)
HE		:	Headache (empty or scored from 0 to 3)
IR		:	Irritability/fussiness (empty or scored from 0 to 3)
LO		:	Loss of appetite (empty or scored from 0 to 3)
MA		:	Malaise (empty or scored from 0 to 3)
MY		:	Myalgia (empty or scored from 0 to 3)
NA		:	Nausea (empty or scored from 0 to 3)
SL		:	Sleeping less than usual (empty or scored from 0 to 3)
SH		:	Shivering (empty or scored from 0 to 3)
SW		:	Sweating (empty or scored from 0 to 3)

UC		:	Unusual crying (empty or scored from 0 to 3)
VO		:	Vomiting (empty or scored from 0 to 3)
TE		:	Temperature = Body temperature in °Cs or °Fs
	RTE	:	Route (for body temperature recording)
	O	:	Oral
	A	:	Axillary
	R	:	Rectal
	T	:	Tympanic
	X	:	Tympanic oral
	Y	:	Tympanic rectal
	Rte Pre	:	Route for pre-vaccination temperature recording
	Pre Vac	:	Pre-vaccination temperature
EXP		:	Symptom experienced
Caus		:	Causality
MA TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIC - Individual subject data: Unsolicited Adverse Event

Verbatim	:	Description of experience as recorded in the case report form
Keyword (MedDRA)	:	Specific identification terminology linked to MedDRA classification codes
LLT MedDRA code	:	Lower Level Term Code for MedDRA, Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym. (All PTs have an identical LLT).
Preferred term	:	Medical term assigned to the keyword/verbatim, Represents a single medical concept
SOC code	:	Primary System Organ Class code: Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
Chro	:	Chronic illness
Pr Do	:	Study vaccine dose given prior to the adverse event
M?	:	Medical advice sought for the symptom
Type	:	Type of medical advice
ER	:	Emergency room
HO	:	Hospitalization
MD	:	Medical doctor
Caus	:	Reasonable possibility that the AE have been caused by the investigational product?
Start date	:	Date of onset of adverse event
Imm Pst Vac	:	Adverse event starting during immediate post-vaccination period

Day onset		:	Number of days since last study vaccine dose
End date		:	Date of end of adverse event
Dur (d)		:	Duration (days) of adverse event
Int		:	Maximum intensity
	1	:	Mild
	2	:	Moderate
	3	:	Severe
L/G		:	Local or general symptom
Out		:	Outcome
	1	:	Recovered/Resolved
	2	:	Recovering/Resolving
	3	:	Not recovered/Not resolved
	4	:	Recovered with sequelae/Resolved with sequelae
	5	:	Died
Vacc Code		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Tables IIC)
Ser		:	Serious adverse event

Appendix tables IIDi - Individual subject data: Medication

Prev dose		:	Previous study vaccine dose
Rel. day of onset		:	Day of onset of medication, relative to previous study vaccine dose
Start date		:	Start date of medication
End date		:	End date of medication
Dur (day)		:	Duration (days) of medication
Trade-Generic name		:	Trade and/or generic name of medication
Medical indication		:	Medical indication for which medication was used
GSK Antibiot		:	Antibiotic
	Y	:	Yes
GSK Antipyr		:	Antipyretic
	Y	:	Yes
Proph		:	Prophylactic medication
	Y	:	Yes

Appendix table IIDii - Individual subject data: Concomitant Vaccination

Trade name	:	Trade name of concomitant vaccine administered
Admin. date	:	Date of administration of concomitant vaccine
Previous vaccination date	:	Date of administration of previous study vaccine dose
Prev dose	:	Previous study vaccine dose
Rel. day of onset	:	Day of onset of concomitant vaccination, relative to date of previous study vaccine dose

Appendix Tables IIE - Individual subject data: Extensive swelling limbs

Vac		: Vaccine administered for which the large swelling reaction is reported
Physexam		: Date of physical examination
Exam		: Was the examination performed by a member of study personnel during the large swelling reaction period?
	Y	: Yes
	N	: No
Ext. Swell Start		: Date when the swelling was first considered to be a large swelling reaction
H. advc		: Number of hours between last vaccination and large swelling reaction, if the swelling occured within 24 hours after vaccination
Pr Do		: Previous dose of vaccination
Day onset		: Number of days between the previous vaccination date and the onset date of large swelling reaction
Sw. size		: Measurement of the greatest diameter of swelling (mm)
Swe Typ		: Type of swelling
	LOC	: local swelling around injection site, not involving adjacent joint
	DIF	: diffuse swelling, not involving adjacent joint
	ADJ	: swelling, involving adjacent joint
Circum swo		: Circumference of swollen limb (at the site of max swelling) (mm)
Circum opp		: Circumference of the opposite limb (at the same level) (mm)
Val temp		: Temperature (maximum temperature if temperature has been taken more than once a day)
Rout		: Temperature measurement route
	A	: axilllary
	O	: oral
	R	:: Rectal
	X	tympanic
Red		: Symptom of redness occurring during the large swelling reaction
Red Dia		: Largest diameter of redness (mm)
Ind		: Symptom of induration occurring during the large swelling reaction
Ind Dia		: Largest diameter of induration (mm)
Pain		: Symptom of pain occurring during the large swelling reaction
Pain Int		: Pain intensity (at administration site)
	1	: Minor reaction to touch
	2	: cries/ protests on touch
	3	: cries when limb is moved / spontaneously painful
Func Imp		: Symptom of functional impairment occurring during the large swelling reaction
Imp Int		: Functional impairment intensity
	1	: easily tolerated, causing minimal discomfort and not interfering with everyday activities
	2	: sufficiently discomforting to interfere with normal everyday activities
	3	: prevents normal everyday activities
Ext. Swell. end		: Last date when the swelling was still considered to be large swelling reaction

H. dura		: Duration in hours, if the large swelling reaction lasted for less than 24 hours.
Out		: Outcome of the large swelling reaction
	1	: recovered/resolved
	2	: recovering/resolving
	3	: not recoverd / not resolved
	4	: recovered with sequelae / resolved with sequelae
Alt Expl		: Is there an alternative explanation for the swelling?
	Y	: Yes
	N	: No
Explanat		: Explanation of an alternative for the swelling

Appendix table IIIA - Individual subject data: IMMUNOGENICITY

cut	:	Cut-off of the laboratory assay
GSKBIO	:	GlaxoSmithKline Biologicals
AP	:	Absence of parallelism
BS ND	:	Blood sampling not done
IR	:	Invalid result
QNS	:	Quantity of serum not sufficient
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IIIB - Individual subject data: CMI

QCNF	:	Quality Criteria Not Fulfilled
TP	:	Technical Problem
NM	:	No Material
ND	:	Not Done
NR	:	Not recorded
IR	:	Invalid results
BSNA	:	Blood Sample Not Available

Appendix table IVA - Individual subject data: Haematology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVB - Individual subject data: Biochemistry

cut	:	Cut-off of the laboratory assay
INVESTIG		Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVC - Individual subject data: Urinology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
SBCODE/RES	:	SmithKline Beecham code/Result
VIS ND	:	Visit not done
ND	:	Not done
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IA - Elimination codes

SDD\RDE\ENABLE Appendix table IA - Individual subject data : Elimination codes (Eli_type : Y5)

Tdap-0.3-009 EXT:007 Year 5 (A.02JUL2012)

Pages 412 to 535 have been removed - Out of Scope of phase 1 of Policy 0070 - Individual Subject Data Listings

CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

Not Applicable.

GlaxoSmithKline Biologicals
Vaccine Value and Health Science
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007)

Study: 110084 (Tdap-0.3-009 Ext: 007 Y5) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Htay Htay Han
Title of Sponsor Signatory: Director
Lead, Clinical Development, Combination Vaccines-
Infanrix, Boostrix, Hepatitis and Rotavirus Vaccines
GlaxoSmithKline Biologicals

Signature: PPD

Date: July 12, 2013

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GlaxoSmithKline Biologicals, SA

Study detailed title

A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.

Clinical Study Report for Study 110086 (Tdap 0.3-009 Ext: 007 Year 9)

This clinical study report presents persistence data 1, 3, 5 and 9 years after vaccination with a single dose of Tdap vaccine in the study 106316 (Tdap 0.3-007). In addition, immunogenicity and safety data following a second dose of Tdap given at Year 9 are also presented in this clinical study report.

Development Phase III

IND Number: BB-IND-8461

Indication Studied: Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.

Study initiation date:	28 June 2007
First Subject First Visit (Year 9)	29 May 2015
Study completion date:	21 March 2016
Data lock point (Date of database freeze):	29 September 2017
Date of report:	Final: 19 December 2017
Earlier Study Reports	
Clinical study report 106316 (Tdap 0.3-007):	13 December 2007
Clinical study report 110080 (Tdap 0.3-009 EXT: 007 Year 1):	09 July 2008
Clinical study report 110082 (Tdap 0.3-009 EXT: 007 Year 3)	13 December 2010
Clinical study report 110082 (Tdap 0.3-009 EXT: 007 Year 5)	20 May 2013

Sponsor Signatory: Narcisa Elena Mesaros, MD,
Clinical and Epidemiology R&D Project Leader,
DTP, Polio and Hib containing vaccines – R&D Centre
Belgium, GlaxoSmithKline Biologicals.

This study was performed according to the principles of GCP including the archiving of essential documents.

Based on GSK Biologicals' Study Report INS-BIO-CLIN-1010 v05

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SYNOPSIS

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).
Study No.: 110086 (Tdap-0.3-009 Ext:007 Year 9)		
Title of the study: A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.		
Investigator(s) and study centre(s): This was a multicentre study conducted across 26 centres in the United States (US) by multiple investigators.		
Publication (reference): None at the time of this report.		
Study period: **Study initiation date:** 28 June 2007 **First Subject First Visit (Year 9):** 29 May 2015 **Study completion date:** 21 March 2016 **Data lock point (Date of database freeze):** 29 September 2017		**Phase:** III
Indication: Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.		

Objectives:

Co-Primary objectives:

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies[1]) and tetanus toxoid (anti-T antibodies[1]) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years.
- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control Group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

  The criteria for meeting the above objective are defined as:

  – One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between Groups in the seroprotection rate (a second dose of Tdap [Boostrix Group] minus the first dose of Tdap [Control Group]) against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

  – One month after vaccination, the lower limit of the 97.5% CIs for the difference between Groups in the seroprotection rate (a second dose of Tdap [Adacel Group] minus the first dose of Tdap [Control Group]) against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

[1] During the course of the study, the assays used to measure the anti-D, and anti-T IgG concentrations were re-developed and re-validated and both assay units and assay cut-off were adapted. The newly validated anti-D and anti-T IgG ELISA's have a lower assay cut-off as compared to the one described in the protocol and were used for the Year 9 pre and post vaccination blood samples. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for both the DI and TE response (0.1 IU/mL and 1.0 IU/mL).

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criteria for meeting the above objective are defined as:

  – One month after vaccination, the lower limits of the 97.5% CIs for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67[2].

  – One month after vaccination, the lower limits of the 97.5% CIs for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67[2].

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% CIs for the difference between Groups in the booster response rate (a second dose of Tdap [Boostrix Group] minus the first dose of Tdap [Control Group]) against diphtheria, tetanus and pertussis antigens (PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

Secondary objectives:

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-PT, -FHA and -PRN antibody concentrations ≥ the assay cut-off[3], 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.

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[2] For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the *Infanrix* Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of *Infanrix* for *Infanrix* Group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) to account heterogeneity of variance between this study and APV-039. Note that the APV-039 reference for this comparison was the results converted into the revalidated assays by using multiple imputation techniques (GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022).

[3] The assays used to measure the anti-PT, -FHA and -PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-off were adapted. The new ELISAs for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISAs in international units per milliliter (IU/mL) for the Year 9 blood samples instead of the formerly used ELISA units per milliliter (EL.U/mL) for the Year 1, 3 and 5 blood samples. The current assay cut-off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. The newly validated ELISA's were used for Year 9 pre and post vaccination blood samples.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.
- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination**.**
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of alternate booster response to D, T, PT, FHA and PRN antigens between Boostrix Group and Adacel Group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix Group and Adacel Group) and a first dose of Tdap vaccine (Control Group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix Group and Adacel Group) and a first dose of Tdap vaccine (Control Group), with respect to solicited symptoms (local and general), unsolicited adverse events and serious adverse events (SAEs).

Methodology:

- Experimental design: A phase III, parallel, open-label, interventional, multicentre study with the same two parallel Groups as in the 106316 (Tdap 0.3-007) study and one new Control Group receiving the first dose of Tdap vaccine *(Boostrix)*.
- Study groups:
  - **Boostrix Group**: Subjects who had received GSK Biologicals' Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and received a second dose of Tdap vaccine *(Boostrix)* in this study at Year 9 (Visit 6).
  - **Adacel Group**: Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and received a second dose of Tdap vaccine *(Boostrix)* in this study at Year 9 (Visit 6).
  - **Control Group**: Subjects in the Control Group received the first dose of Tdap vaccine *(Boostrix)* in this study at Year 9 (Visit 6).
- Blinding: This study was an open study since this was an extension of study 106316 (Tdap 0.3-007) which was unblinded at the time of primary analysis.
- Vaccination schedule: A single dose of *Boostrix* vaccine was administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9. For the Control Group, it was their first visit for this study, the first and second visits of the Control Group were named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel Groups. The study procedures were similar across all Groups at Visit 6 and Visit 7.
- Blood samples were collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who received vaccination in this study)].

Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule /site: Subjects received GSK Biologicals' *Boostrix* vaccine as an intramuscular (IM) injection administered at the non-dominant side of the upper deltoid at Visit 6.

Vaccine composition /dose /lot number: One single dose vial (0.5 mL) of GSK Biologicals' *Boostrix* (Lot Nos.: AC52VB151C, AC52VB117B, AC52VB118A, AC52VB172B) vaccine contained: diphtheria (D) toxoid: minimum 2.5 limit of flocculation (Lf), tetanus (T) toxoid: 5 Lf, pertussis toxoid (PT): 8 µg, filamentous hemagglutinin (FHA): 8 µg, pertactin (PRN): 2.5 µg, ≤0.39 mg aluminum and sodium chloride as salts.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Reference vaccine /Comparator, dose and mode of administration, lot no.:

Refer to the 106316 (Tdap 0.3-007) study report for details of the composition and administration of comparator vaccines.

Study Population: All subjects who had received the study vaccination (*Boostrix* or *Adacel*) in the study DTPA 0.3 (BOOSTRIX)-007 (106316) were considered eligible to participate at Year 9 persistence time point. They were assigned to Boostrix or Adacel Groups as per the previous vaccine received. Subjects newly recruited and who were not part of the 106316 (Tdap 0.3-007) study were part of the Control Group. Written informed consent was obtained from each subject prior to the enrolment in Year 9 study.

Duration of treatment: For Boostrix and Adacel Groups: Approximately 9 years for subjects who were enrolled in study 106316 (Tdap 0.3-007) and who participated at all persistence time points of the study including Year 9 time point.

Control Group: Approximately one month.

Criteria for evaluations:

Co-primary endpoints:

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the Boostrix and the Adacel Groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of *Infanrix* in Study APV-039
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination

Secondary endpoints:

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ assay cut-off in the Boostrix and Adacel Groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at the Year 9 time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ assay cut-off; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination
  - Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a VERO-cell neutralization assay.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4-day (Day 0–3) follow-up period after vaccination
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4-day (Day 0-3) follow-up period after vaccination
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs during the 31-day (Day 0-30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31-day (Day 0–30) follow-up period following vaccination

Statistical methods:

Analysis of demographics: Demographic characteristics (age in years at vaccination, gender, age stratum and visit at enrolment) of the ATP cohort for immunogenicity at Year 9 and for the Total Enrolled cohort were summarized using descriptive statistics.

The number of subjects included in each follow-up cohorts up to Year 9 and in the ATP Year 9 cohort were tabulated.

Time from the vaccination in 106316 (Tdap 0.3-007) study to the blood sampling at Year 9 (in years) was summarized using descriptive statistics.

Analysis of persistence: The primary analysis was based on the adapted ATP cohort for analysis of immunogenicity which integrated immunological summaries for time points from primary study (106316 [Tdap 0.3-007]), and at Year 1, Year 3, Year 5 and Year 9 follow up time points. It consisted of subjects who complied with protocol at the respective time points.

The following analyses were performed:

Within group assessment:

For each study group, at each time point for which a serological result was available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CIs were calculated by Group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by Vero cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, were calculated by Group. Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) were calculated by Group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated by Group.

In addition, at each persistence time point:

- Above summaries were provided for each level of the age stratum (Subjects age were classified as 28 – 38 years, 39 – 58 years and 59 – 73 years) and by gender. Age stratum was derived from the age stratum in study 106316 (Tdap 0.3-007) for subjects primed in 106316 (Tdap 0.3-007) study i.e. projected age at Year 9 and from the age at vaccination for subjects in the Control Group.
- Distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves (RCC) by Group at all persistence time points.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Comparability between groups - Exploratory analyses

At each persistence time point,

- For anti-D antibody response, the two-sided asymptotic 95% CIs for the group differences (Boostrix Group minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥ 0.016 IU/mL by VERO) were calculated using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].
- For anti-T antibody response, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix Group minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA were calculated.
- For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix Group minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ assay cut-off were also calculated.

Sensitivity analysis for persistence

A sensitivity analysis was performed to ensure that comparability between subjects in the Boostrix Group and Adacel Group was not biased by drop-out at the persistence time point.

Analysis of immunogenicity at booster dose: The following analyses were carried out after Year 9 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 9. If, in any study group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was 5% or more, a second analysis based on the Total Vaccinated Cohort (TVC) at Year 9 was to be performed to complement the ATP analysis.

Within groups assessment

For each group and each antigen:

- Seropositivity for anti-PT, anti-FHA and anti-PRN and seroprotection rate for anti-D and anti-T at pre-vaccination and one month post-vaccination was calculated with exact 95% CIs.
- GMCs or GMTs at pre-vaccination and one month post-vaccination was tabulated with 95% CIs.
- Booster response rate one month post-vaccination was calculated with exact 95% CIs.

In addition:

- The above summaries were provided for each level of the age stratum at Year 9 visit (28-38, 39-58 and 59-73 years old) and by gender.
- The distribution of antibody concentrations for each antigen at pre-vaccination and one month post-vaccination were displayed using RCCs by Group.

Comparability between groups – confirmatory analyses:

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CIs of the group difference in seroprotection rate one month after vaccination (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) was computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and for Boostrix and Adacel study groups, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix Group, one month after the third dose of *Infanrix* for Infanrix Group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CIs for the group differences (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) were calculated.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Comparability between groups – exploratory analyses:

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CIs for the group differences (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) were calculated.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody response respectively, the two-sided 95% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Adacel Group one month after vaccination were computed using an analysis of Co-variance (ANCOVA) model on the logarithm_{10} transformation of the concentrations. The pre-vaccination status in study 106316 (Tdap 0.3-007) was used as a co-variable.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Control Group and between the Adacel Group and (divided by) the Control Group one month after vaccination was computed using an ANOVA model on the logarithm10 transformation of the concentrations.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix Group – Adacel Group) were calculated.

Sensitivity analysis following the booster dose

A sensitivity analysis was performed to ensure that comparability between subjects in the Boostrix Group and Adacel Group was not biased by drop-out at the booster phase.

Analysis of safety:

Persistence follow-up phase up to Year 9 time point:

No safety analysis was performed at the persistence time points of this study. If GSK was informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 (Tdap 0.3-007), or to participation in this persistence study, the pertinent clinical details were summarized in this study report.

Vaccination phase at Year 9 time point:

The primary analysis was based on the TVC at Year 9. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 9 was more than 5%, a second analysis based on this ATP cohort was performed to complement the analysis of the TVC.

The incidence of solicited local and general symptoms occurring during the 4-day (Day 0-3) follow-up period after vaccination was tabulated with exact 95% CIs for each Group. The same calculations were performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity grade 3 (occurrence of fever was reported per 0.5°C cumulative increments), as well as for solicited general symptoms with relationship to vaccination. All solicited local adverse symptoms were causally related to vaccination.

The percentage of subjects who reported at least one unsolicited adverse event classified by MedDRA during the 31-day (Day 0-30) follow-up period after vaccination were tabulated with exact 95% CIs for each treatment Group. The same tabulation was performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that were considered by the investigator to be possibly related to vaccination.

Serious adverse events were summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse events were described in detail.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

In addition, the safety analysis of solicited symptoms was performed separately for each level of the age stratum (28-38, 39-58 and 59-73 years old) and by gender.

Study population

Number of subjects	**Boostrix**	**Adacel**	**Control**
Planned, N	1500	750	367
Total Enrolled Cohort*, N	1239	607	363
Completed the study at visit 6 without vaccination, n (%)	166(13.4)	94(15.5)	0(0.0)
Completed the study at visit 7 after vaccination, n (%)	306 (24.7)	136 (22.4)	357 (98.3)
Demographics	**Boostrix**	**Adacel**	**Control**
Females: Males	783:456	403:204	196:167
Mean age at enrolment, years (SD)	42.1 (13.5)	42.7 (13.4)	52.1 (13.6)
Mean age at Year 9 vaccination, years (SD)	44 (19, 72)	44 (19, 67)	54 (28, 73)
White - Caucasian / European Heritage, n (%)	1074 (86.7)	521 (85.8)	288 (79.3)

Boostrix Group= Subjects who had received GSK Biologicals' Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6

Adacel Group= Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6

Control Group= Subjects who had received the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6

*Total Enrolled Cohort included all subjects enrolled in the study regardless of the visit at enrolment.

Summary:

Immunogenicity results:

- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 95.7% of subjects at Year 1 to 91.1% of subjects at Year 9 (by ELISA) and from 98.3% of subjects at Year 1 to 99.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Boostrix Group. Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 98.6% of subjects at Year 1 to 98.1% of subjects at Year 9 in the Boostrix Group.
- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 97.0% of subjects at Year 1 to 95.8% of subjects at Year 9 (by ELISA) and from 98.2% of subjects at Year 1 to 98.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Adacel Group. Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 99.6% of subjects at Year 1 to 100% of subjects at Year 9 in the Adacel Group.
- The GMCs for antibodies against both diphtheria and tetanus antigens in both Groups reached a peak response post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1 and gradually kept decreasing until the Year 9 time point.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine*, Boostrix* (Boostrix Group and Adacel Group) was non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to seroprotection rate against diphtheria and tetanus antigens, was met, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group differences [Boostrix Group minus Control Group and Adacel Group minus Control Group] in the booster response to the diphtheria and tetanus antigens was above the pre-specified lower limit of -10%.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine*, Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to anti-PT, anti-FHA and anti-PRN antibody concentrations, was met, as, one month after the booster vaccination, the lower limit of the 97.5% CIs on the GMC ratios (Boostrix Group divided by Infanrix Group in APV-039 and Adacel Group divided by Infanrix Group in APV-039) for the PT, FHA and PRN antigens was above the pre-specified lower limit of 0.67.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met: for all antigens except PT, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Boostrix Group minus Control Group] in the booster response to the diphtheria, tetanus, FHA and PRN antigens was below the pre-specified lower limit of -10%.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met: for all antigens except FHA, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Adacel Group minus Control Group] in the booster response to the diphtheria, tetanus, PT and PRN antigens was below the pre-specified lower limit of - 10%.
- GMCs for anti-FHA, anti-PRN and anti-PT which reached a peak response at post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1, and continued the gradual decline at Year 3, Year 5 and Year 9 for both Groups. Note that the anti-FHA GMC decrease observed at Year 9 is largely due to pertussis assay revalidation which involved a calibration of approximately 2-fold.
- At least 98.8% of subjects were seropositive against PT, FHA and PRN antigens in all three Groups, one month after the booster vaccination. At least 97.9% of subjects were seroprotected against Diphtheria and at least 99.7% of subjects were seroprotected against Tetanus (antibody concentrations $\geq$ 0.1 IU/mL), one month after the booster vaccination.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 1: Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL and 1 IU/mL and GMCs at persistence time points (Adapted ATP cohort)

				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-D	Boostrix	Pre_bst_007	1439	1226	85.2	83.3	87.0	340	23.6	21.5	25.9	0.4	0.4	0.4
		Post_bst_007	1443	1417	98.2	97.4	98.8	1268	87.9	86.1	89.5	4.7	4.4	5.1
		Per(Yr1)	1010	967	95.7	94.3	96.9	673	66.6	63.6	69.5	1.4	1.3	1.6
		Per(Yr3)	914	857	93.8	92.0	95.2	478	52.3	49.0	55.6	0.9	0.8	1.0
		Per(Yr5)	789	735	93.2	91.2	94.8	377	47.8	44.2	51.3	0.8	0.7	0.9
		Pre_bst_009	269	245	91.1	87.0	94.2	114	42.4	36.4	48.5	0.7	0.6	0.8
	Adacel	Pre_bst_007	720	642	89.2	86.7	91.3	191	26.5	23.3	29.9	0.5	0.4	0.5
		Post_bst_007	727	717	98.6	97.5	99.3	669	92.0	89.8	93.9	5.0	4.6	5.4
		Per(Yr1)	504	489	97.0	95.1	98.3	351	69.6	65.4	73.6	1.4	1.3	1.6
		Per(Yr3)	442	425	96.2	93.9	97.7	247	55.9	51.1	60.6	1.0	0.9	1.1
		Per(Yr5)	372	359	96.5	94.1	98.1	190	51.1	45.9	56.3	0.9	0.8	1.0
		Pre_bst_009	118	113	95.8	90.4	98.6	54	45.8	36.6	55.2	0.8	0.6	0.9
ANTI-T	Boostrix	Pre_bst_007	1446	1387	95.9	94.8	96.9	1039	71.9	69.5	74.2	1.6	1.5	1.7
		Post_bst_007	1444	1438	99.6	99.1	99.8	1419	98.3	97.5	98.9	8.5	8.1	8.9
		Per(Yr1)	1014	1000	98.6	97.7	99.2	952	93.9	92.2	95.3	3.4	3.2	3.6
		Per(Yr3)	917	899	98.0	96.9	98.8	807	88.0	85.7	90.0	2.2	2.1	2.3
		Per(Yr5)	788	772	98.0	96.7	98.8	665	84.4	81.7	86.9	2.0	1.9	2.1
		Pre_bst_009	268	263	98.1	95.7	99.4	211	78.7	73.3	83.5	1.8	1.6	2.0
	Adacel	Pre_bst_007	727	707	97.2	95.8	98.3	543	74.7	71.4	77.8	1.7	1.6	1.8
		Post_bst_007	728	728	100	99.5	100	723	99.3	98.4	99.8	13.3	12.5	14.1
		Per(Yr1)	506	504	99.6	98.6	100	487	96.2	94.2	97.7	4.4	4.1	4.7
		Per(Yr3)	442	440	99.5	98.4	99.9	408	92.3	89.4	94.6	2.9	2.7	3.1
		Per(Yr5)	372	370	99.5	98.1	99.9	337	90.6	87.2	93.4	2.5	2.3	2.7
		Pre_bst_009	120	120	100	97.0	100	101	84.2	76.4	90.2	2.3	2.0	2.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_007 = blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
Post_bst_007 = blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1) = blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3) = blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5) = blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009 = blood sampling, 9 year post vaccination in Tdap 0.3-007 study

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 2: Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity at Year 9)

				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-D	Boostrix	Pre_bst_009	269	245	91.1	87.0	94.2	114	42.4	36.4	48.5	0.7	0.6	0.8
		Post_bst_009	271	269	99.3	97.4	99.9	249	91.9	88.0	94.8	4.1	3.6	4.7
	Adacel	Pre_bst_009	118	113	95.8	90.4	98.6	54	45.8	36.6	55.2	0.8	0.6	0.9
		Post_bst_009	121	120	99.2	95.5	100	113	93.4	87.4	97.1	4.7	3.9	5.7
	Control	Pre_bst_009	324	265	81.8	77.1	85.8	92	28.4	23.5	33.6	0.4	0.4	0.5
		Post_bst_009	326	319	97.9	95.6	99.1	282	86.5	82.3	90.0	4.0	3.4	4.6
ANTI-T	Boostrix	Pre_bst_009	268	263	98.1	95.7	99.4	211	78.7	73.3	83.5	1.8	1.6	2.0
		Post_bst_009	271	271	100	98.6	100	269	99.3	97.4	99.9	8.4	7.7	9.3
	Adacel	Pre_bst_009	120	120	100	97.0	100	101	84.2	76.4	90.2	2.3	2.0	2.7
		Post_bst_009	121	121	100	97.0	100	121	100	97.0	100	8.6	7.6	9.8
	Control	Pre_bst_009	324	304	93.8	90.6	96.2	231	71.3	66.0	76.2	1.5	1.3	1.7
		Post_bst_009	327	326	99.7	98.3	100	319	97.6	95.2	98.9	8.8	8.0	9.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 = Pre booster vaccination blood sampling time point
Post_bst_009 = Post booster vaccination blood sampling time point

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 3: Seroprotection status for anti-diphtheria antibody concentration by ELISA and VERO NEUTRALISATION at the persistence time points (Adapted ATP cohort)

			ELISA concentration <0.1 IU/ML		**VERO concentration < 0.016 for subjects with ELISA < 0.1 IU/ML**		**Estimated proportion of subjects with Vero concentration < 0.01 IU/ML**		**Estimated proportion of subjects with Vero concentration ≥ 0.016 IU/ML or ELISA ≥ 0.1 IU/ML**		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Boostrix	Pre_bst_007	1439	213/1439	14.8	100/212	47.2	213/1439 x 100/212	7.0	93.0	91.6	94.3
	Post_bst_007	1443	26/1443	1.8	9/26	34.6	26/1443 x 9/26	0.6	99.4	98.8	99.7
	Per(Yr1)	1012	45/1012	4.4	17/45	37.8	45/1012 x 17/45	1.7	98.3	97.3	99.0
	Per(Yr3)	914	57/914	6.2	28/57	49.1	57/914 x 28/57	3.1	96.9	95.6	98.0
	Per(Yr5)	789	54/789	6.8	13/54	24.1	54/789 x 13/54	1.6	98.4	97.2	99.1
	Pre_bst_009	269	24/269	8.9	2/24	8.3	24/269 x 2/24	0.7	99.3	97.3	99.9
Adacel	Pre_bst_007	720	78/720	10.8	28/77	36.4	78/720 x 28/77	3.9	96.1	94.5	97.3
	Post_bst_007	727	10/727	1.4	6/10	60.0	10/727 x 6/10	0.8	99.2	98.2	99.7
	Per(Yr1)	505	16/505	3.2	9/16	56.3	16/505 x 9/16	1.8	98.2	96.6	99.2
	Per(Yr3)	442	17/442	3.8	10/17	58.8	17/442 x 10/17	2.3	97.7	95.9	98.9
	Per(Yr5)	372	13/372	3.5	4/13	30.8	13/372 x 4/13	1.1	98.9	97.3	99.7
	Pre_bst_009	118	5/118	4.2	2/5	40.0	5/118 x 2/5	1.7	98.3	94.0	99.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/ml / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/ml / number of subjects tested by VERO neutralisation test for year x persistence time point
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/ml for ELISA and 0.016 IU/ml for VERO) for year x persistence time point
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 4: Number and percentage of subjects with an anti- PT, anti-FHA, anti- PRN antibody concentration ≥ Assay cut off and GMCs at persistence time points (Adapted ATP cohort)

				≥ Assay cut off				GMC		
					95% CI				95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-FHA	Boostrix	Pre_bst_007	1437	1393	96.9	95.9	97.8	31.6	29.9	33.5
		Post_bst_007	1442	1442	100	99.7	100	624.0	593.5	656.1
		Per(Yr1)	1014	1012	99.8	99.3	100	190.1	178.5	202.6
		Per(Yr3)	916	913	99.7	99.0	99.9	114.1	107.1	121.5
		Per(Yr5)	789	788	99.9	99.3	100	110.0	103.0	117.4
		Pre_bst_009	271	271	100	98.6	100	42.2	37.6	47.5
	Adacel	Pre_bst_007	717	691	96.4	94.7	97.6	34.8	32.0	37.8
		Post_bst_007	724	724	100	99.5	100	368.4	344.3	394.2
		Per(Yr1)	502	501	99.8	98.9	100	118.8	108.7	129.9
		Per(Yr3)	439	437	99.5	98.4	99.9	81.8	74.7	89.4
		Per(Yr5)	371	368	99.2	97.7	99.8	80.8	73.1	89.4
		Pre_bst_009	120	119	99.2	95.4	100	28.4	24.0	33.4
ANTI-PRN	Boostrix	Pre_bst_007	1444	1100	76.2	73.9	78.4	13.4	12.5	14.3
		Post_bst_007	1443	1426	98.8	98.1	99.3	401.0	368.5	436.3
		Per(Yr1)	1011	971	96.0	94.7	97.2	152.2	137.2	168.8
		Per(Yr3)	915	862	94.2	92.5	95.6	82.5	74.4	91.5
		Per(Yr5)	782	755	96.5	95.0	97.7	85.3	76.7	94.9
		Pre_bst_009	271	267	98.5	96.3	99.6	63.8	53.1	76.7
	Adacel	Pre_bst_007	727	555	76.3	73.1	79.4	14.3	12.9	15.7
		Post_bst_007	726	721	99.3	98.4	99.8	351.9	315.7	392.2
		Per(Yr1)	501	489	97.6	95.9	98.8	132.5	115.6	151.8
		Per(Yr3)	442	426	96.4	94.2	97.9	70.6	61.6	81.0
		Per(Yr5)	371	362	97.6	95.4	98.9	77.4	66.9	89.6
		Pre_bst_009	118	117	99.2	95.4	100	64.7	50.3	83.3
ANTI-PT	Boostrix	Pre_bst_007	1434	825	57.5	54.9	60.1	7.3	6.9	7.7
		Post_bst_007	1430	1388	97.1	96.1	97.9	63.6	60.1	67.3
		Per(Yr1)	1013	917	90.5	88.6	92.3	22.4	21.0	24.0
		Per(Yr3)	914	751	82.2	79.5	84.6	14.0	13.0	15.0
		Per(Yr5)	790	670	84.8	82.1	87.2	14.6	13.5	15.8
		Pre_bst_009	271	230	84.9	80.0	88.9	8.2	7.2	9.3
	Adacel	Pre_bst_007	722	444	61.5	57.8	65.1	8.1	7.5	8.8
		Post_bst_007	722	676	93.6	91.6	95.3	32.2	29.6	35.1
		Per(Yr1)	506	435	86.0	82.6	88.9	15.6	14.2	17.2
		Per(Yr3)	442	316	71.5	67.0	75.7	10.0	9.0	11.1
		Per(Yr5)	372	285	76.6	72.0	80.8	11.6	10.3	13.0
		Pre_bst_009	120	106	88.3	81.2	93.5	7.8	6.5	9.4

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1) = blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3) = blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5) = blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study
*Note: For the time points Pre-bst-007 to Yr5, the assay cut off and unit was 5 EL.U/ml, however the assay cut off and unit at Yr9 has changed to 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN

Synopsis Table 5: Number and percentage of subjects with an anti- PT, anti-FHA, anti- PRN antibody concentration ≥ Assay cut off and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity at Year 9)

				≥ Assay cut off				**GMC**		
					95% CI				**95% CI**	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-FHA	Boostrix	Pre_bst_009	271	271	100	98.6	100	42.2	37.6	47.5
		Post_bst_009	271	271	100	98.6	100	247.9	227.3	270.3
	Adacel	Pre_bst_009	120	119	99.2	95.4	100	28.4	24.0	33.4
		Post_bst_009	121	121	100	97.0	100	254.6	218.9	296.1
	Control	Pre_bst_009	327	322	98.5	96.5	99.5	23.6	20.6	27.1
		Post_bst_009	327	327	100	98.9	100	373.6	336.5	414.8
ANTI-PRN	Boostrix	Pre_bst_009	271	267	98.5	96.3	99.6	63.8	53.1	76.7
		Post_bst_009	271	271	100	98.6	100	405.4	359.3	457.5
	Adacel	Pre_bst_009	118	117	99.2	95.4	100	64.7	50.3	83.3
		Post_bst_009	121	121	100	97.0	100	511.8	427.8	612.2
	Control	Pre_bst_009	321	284	88.5	84.5	91.8	17.8	14.7	21.6
		Post_bst_009	326	326	100	98.9	100	336.4	283.3	399.4
ANTI-PT	Boostrix	Pre_bst_009	271	230	84.9	80.0	88.9	8.2	7.2	9.3
		Post_bst_009	271	268	98.9	96.8	99.8	64.1	56.8	72.3
	Adacel	Pre_bst_009	120	106	88.3	81.2	93.5	7.8	6.5	9.4
		Post_bst_009	121	120	99.2	95.5	100	70.4	58.6	84.5
	Control	Pre_bst_009	327	209	63.9	58.4	69.1	5.4	4.7	6.2
		Post_bst_009	326	322	98.8	96.9	99.7	66.2	58.5	74.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 = Pre booster vaccination blood sampling time point
Post_bst_009 = Post booster vaccination blood sampling time point
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 6: Booster response to anti-diphtheria and anti-tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
ANTI-D	Boostrix	S-	24	16	66.7	44.7	84.4
		S+	245	153	62.4	56.1	68.5
		Total	269	169	62.8	56.7	68.6
	Adacel	S-	5	3	60.0	14.7	94.7
		S+	113	68	60.2	50.5	69.3
		Total	118	71	60.2	50.7	69.1
	Control	S-	58	35	60.3	46.6	73.0
		S+	265	187	70.6	64.7	76.0
		Total	323	222	68.7	63.4	73.7
ANTI-T	Boostrix	S-	5	5	100	47.8	100
		S+	263	121	46.0	39.9	52.2
		Total	268	126	47.0	40.9	53.2
	Adacel	S-	0	-	-	-	-
		S+	120	44	36.7	28.1	45.9
		Total	120	44	36.7	28.1	45.9
	Control	S-	20	18	90.0	68.3	98.8
		S+	304	139	45.7	40.0	51.5
		Total	324	157	48.5	42.9	54.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
S- = Antibody concentration < 0.1 IU/mL
S+ = Antibody concentration ≥ 0.1 IU/mL
Total = subjects either seropositive or seronegative
Booster response to D and T antigens is defined as:
- For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 7: Booster response for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
ANTI-FHA	Boostrix	S-	0	-	-	-	-
		S+ (<4*cut_off)	16	16	100	79.4	100
		S+ (≥4*cut_off)	255	216	84.7	79.7	88.9
		Total	271	232	85.6	80.9	89.6
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	9	9	100	66.4	100
		S+ (≥4*cut_off)	110	106	96.4	91.0	99.0
		Total	120	116	96.7	91.7	99.1
	Control	S-	5	5	100	47.8	100
		S+ (<4*cut_off)	71	70	98.6	92.4	100
		S+ (≥4*cut_off)	251	228	90.8	86.6	94.1
		Total	327	303	92.7	89.3	95.2
ANTI-PRN	Boostrix	S-	4	4	100	39.8	100
		S+ (<4*cut_off)	29	27	93.1	77.2	99.2
		S+ (≥4*cut_off)	238	179	75.2	69.2	80.6
		Total	271	210	77.5	72.0	82.3
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	10	10	100	69.2	100
		S+ (≥4*cut_off)	107	87	81.3	72.6	88.2
		Total	118	98	83.1	75.0	89.3
	Control	S-	37	31	83.8	68.0	93.8
		S+ (<4*cut_off)	78	75	96.2	89.2	99.2
		S+ (≥4*cut_off)	205	175	85.4	79.8	89.9
		Total	320	281	87.8	83.7	91.2
ANTI-PT	Boostrix	S-	41	34	82.9	67.9	92.8
		S+ (<4*cut_off)	124	106	85.5	78.0	91.2
		S+ (≥4*cut_off)	106	95	89.6	82.2	94.7
		Total	271	235	86.7	82.1	90.5
	Adacel	S-	14	10	71.4	41.9	91.6
		S+ (<4*cut_off)	60	53	88.3	77.4	95.2
		S+ (≥4*cut_off)	46	43	93.5	82.1	98.6
		Total	120	106	88.3	81.2	93.5
	Control	S-	117	101	86.3	78.7	92.0
		S+ (<4*cut_off)	104	94	90.4	83.0	95.3
		S+ (≥4*cut_off)	105	97	92.4	85.5	96.7
		Total	326	292	89.6	85.7	92.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration above or equal to assay cut off for anti-PT, anti-FHA, anti-PRN)
Total = subjects either seropositive or seronegative

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN

Synopsis Table 8: Confirmatory objective: Group differences in the percentage of subjects with anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/mL [Boostrix Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

								Difference in percentage (Boostrix minus Control)		
		Boostrix			**Control**				**97.5% CI**	
Antibody	**Threshold**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-D	0.1 IU/mL	271	269	99.3	326	319	97.9	1.41	-1.16	4.17
ANTI-T	0.1 IU/mL	271	271	100	327	326	99.7	0.31	-1.52	2.07

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Synopsis Table 9: Confirmatory objective: Group differences in the percentage of subjects with anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/mL [Adacel Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

								Difference in percentage (Adacel minus Control)		
		Adacel			**Control**				**97.5% CI**	
Antibody	**Threshold**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-D	0.1 IU/mL	121	120	99.2	326	319	97.9	1.32	-3.41	4.15
ANTI-T	0.1 IU/mL	121	121	100	327	326	99.7	0.31	-3.69	2.07

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 Tdap 0.3-007 and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 10: Confirmatory objective: GMC ratio between Groups [Boostrix Group in this study divided by Infanrix Group in APV-039] and their 97.5% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC Ratio (Boostrix Group / Infanrix Group in APV-039)		
	Boostrix Group		**Infanrix Group in APV-039**			**97.5% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**GMC Ratio**	**LL**	**UL**
ANTI-PT	294	64.0	2884	41.7	1.53	1.31	1.79
ANTI-FHA	298	248.8	685	47.2	5.27	4.62	6.01
ANTI-PRN	298	408.7	631	113.0	3.62	3.07	4.25

Infanrix Group in APV-039 = Infanrix Group of the German household contact study APV-039
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
97.5% CI = 97.5% confidence interval for the GMC ratio LL = lower limit, UL = upper limit
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] GMC = geometric mean antibody concentration calculated on all subjects
The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Synopsis Table 11: Confirmatory objective: GMC ratio between Groups [Adacel Group in this study divided by Infanrix Group in APV-039] and their 97.5% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC Ratio (Adacel Group / Infanrix Group in APV-039)		
	Adacel Group		**Infanrix Group in APV-039**			**97.5% CI**	
Antibody	**N**	**GMC**	**N**	**GMC**	**GMC Ratio**	**LL**	**UL**
ANTI-PT	130	68.6	2884	41.7	1.64	1.33	2.03
ANTI-FHA	131	248.8	685	47.2	5.27	4.37	6.36
ANTI-PRN	131	504.8	631	113.0	4.47	3.58	5.57

Infanrix Group in APV-039 = Infanrix Group of the German household contact study APV-039
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
97.5% CI = 97.5% confidence interval for the GMC ratio LL = lower limit, UL = upper limit
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] GMC = geometric mean antibody concentration calculated on all subjects
The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 12: Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Boostrix Group minus Control Group], one month after booster vaccination and their standardised asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			**Control**				**97.5% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-D	269	169	62.8	323	222	68.7	-5.91	-14.67	2.85
ANTI-T	268	126	47.0	324	157	48.5	-1.44	-10.63	7.79

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Synopsis Table 13: Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Boostrix Group minus Control Group], one month after booster vaccination and their standardised asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			**Control**				**97.5% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-FHA	271	232	85.6	327	303	92.7	-7.05	-13.16	-1.40
ANTI-PRN	271	210	77.5	320	281	87.8	-10.32	-17.50	-3.38
ANTI-PT	271	235	86.7	326	292	89.6	-2.85	-9.09	3.08

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Synopsis Table 14: Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Adacel Group minus the Control Group], one month after booster vaccination and their standardised asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			**Control**				**97.5% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-D	118	71	60.2	323	222	68.7	-8.56	-20.33	2.73
ANTI-T	120	44	36.7	324	157	48.5	-11.79	-22.98	0.15

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Synopsis Table 15: Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Adacel Group minus the Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			**Control**				**97.5% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-FHA	120	116	96.7	327	303	92.7	4.01	-2.38	8.66
ANTI-PRN	118	98	83.1	320	281	87.8	-4.76	-14.53	3.18
ANTI-PT	120	106	88.3	326	292	89.6	-1.24	-10.03	5.57

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Safety results:

- *Any symptom (solicited and unsolicited):* Any symptom (solicited and unsolicited) was reported for 69.6% in the Boostrix Group, 70.1% in the Adacel Group and 48.3% of subjects in the Control Group. Any Grade 3 symptom (solicited and unsolicited) was reported for 3.3% in the Boostrix Group, 5.1% in the Adacel Group and 2.5% of subjects in the Control Group. Any symptom (solicited or unsolicited) that was considered by the investigator as being potentially causally related to vaccination, during the 4-day (Days 0-3) follow-up period was reported for 68.6% in the Boostrix Group, 68.6% in the Adacel Group and 45.5% of subjects in the Control Group. Majority of these symptoms were local symptoms.
- *Solicited local symptom:* During the 4-day (Days 0-3) post-vaccination period, higher incidences of local symptoms were observed in the Boostrix and Adacel groups as compared to the Control group. Pain was the most frequently reported solicited local symptom, reported for 58.8% in the Boostrix Group, 61.3% in the Adacel Group and 36.9% of subjects in the Control Group. In the Boostrix and Adacel Groups, redness was the most frequently reported Grade 3 solicited local symptom (1.6% of subjects in the Boostrix Group and 1.5% of subjects in the Adacel Group). None of the subjects in the Control Group reported redness of Grade 3 intensity; pain was the most frequently reported Grade 3 solicited local symptom in this group (for 1.1% of subjects).
- *Solicited general symptom:* Fatigue was the most frequently reported solicited general symptom in the Boostrix Group (for 23.2% of subjects) whereas in Adacel and Control Groups, headache was the most frequently reported solicited general symptom (for 18.2% and 14.8% of subjects, respectively). In the Boostrix Group, fatigue was also the most frequently reported Grade 3 solicited general symptom (for 1.0% of subjects) whereas in Adacel and Control Groups, headache was also the most frequently reported Grade 3 solicited general symptom (for 0.7% and 0.3% of subjects, respectively). Fever (≥37.5 C) was reported for less than 1% of subjects in all Groups (none in Adacel Group). No Grade 3 fever (>39) was reported for any of the subjects.
- *Unsolicited adverse events:* During the 31-day (Days 0-30) post-vaccination period, at least one Grade 3 unsolicited adverse event was reported for five subjects (1.6%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and nine subjects (2.5%) in the Control Group. At least one unsolicited adverse event with causal relationship to vaccination was reported for 14 subjects (4.5%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and four subjects (1.1%) in the Control Group.
- *SAEs:* One SAE (seizure) was reported in the Control Group during the study, which was considered by the investigator as not causally related to the vaccination. The SAE was of Grade 3 intensity and had resolved by the end of the study.
- *Withdrawals due to AEs/SAEs after vaccination at visit 6:* None of the subjects were withdrawn due to an AE or SAE, during the study period. There were also no large injection site reactions reported.
- *Pregnancy:* No pregnancies were reported in this study.

Name of company: **GlaxoSmithKline Biologicals, SA, Rixensart, Belgium**	**Name of finished product:** *Boostrix*	**Name of active substance:** Diphtheria (D) and tetanus (T) toxoids, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN).

Conclusion:

- In the Boostrix Group, persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 95.7% of subjects at Year 1 to 91.1% of subjects at Year 9 (by ELISA) and from 98.3% of subjects at Year 1 to 99.3% of subjects at Year 9 (by Vero cell neutralization assay). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 98.6% of subjects at Year 1 to 98.1% of subjects at Year 9 in the Boostrix Group. In the Adacel Group, persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 97.0% of subjects at Year 1 to 95.8% of subjects at Year 9 (by ELISA) and from 98.2% of subjects at Year 1 to 98.3% of subjects at Year 9 (by Vero cell neutralization assay). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 99.6% of subjects at Year 1 to 100% of subjects at Year 9 in the Adacel Group.
- The GMCs for antibodies against both diphtheria and tetanus antigens in both Groups reached a peak response post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1 and gradually kept decreasing till the Year 9 time point.
- The primary objectives of the study were partially met. Non-inferiority of the Boostrix Group to the Control Group was met for seroprotection for diphtheria and tetanus antigens, comparison with APV 039 with respect to pertussis antigens and was not met for the non-inferiority to the Control Group with respect to the booster response for diphtheria, tetanus and pertussis antigens. Non-inferiority of the Adacel Group to the Control Group was met for seroprotection for diphtheria and tetanus antigens, comparison with APV 039 with respect to pertussis antigens and was not met for the non-inferiority to the Control Group with respect to the booster response for diphtheria, tetanus and pertussis antigens.
- The GMCs for anti-FHA, anti-PRN and anti-PT which reached a peak response at post vaccination in study 106316 (Tdap 0.3-007) showed a sharp decrease at Year 1, continued the gradual decline at Year 3, Year 5 and Year 9 for both Groups.
- None of the subjects were withdrawn due to an AE or SAE, during the study period.
- One SAE (seizure) was reported in the Control Group during the study, which was considered by the investigator as not causally related to the vaccination. The SAE was of Grade 3 intensity and had resolved by the end of the study. There were no fatal SAEs reported in the study.

Discussion:

This section aims to put in perspective the failure to meet the primary confirmatory study objectives related to booster response for diphtheria, tetanus and pertussis antigens.

The study had less than 50% power to meet this objective due to low response rate expected in this older population.

The observed pre-booster GMC in the Boostrix and Adacel groups were higher than in the Control group. Considering that higher pre-vaccination titre is associated to a lower booster rate, this group unbalance favored the control group.

The other primary confirmatory objectives for anti-Diphtheria and anti-Tetanus demonstrated that non-inferiority was achieved in terms of seroprotection rate. In addition, comparably high GMC were observed post-vaccination in all groups for diphtheria and tetanus antigens.

The other primary confirmatory objectives for pertussis antigens demonstrated that non-inferiority was achieved in terms of GMC as compared to APV 039. In addition, comparably high GMC were observed post-vaccination in all groups for all pertussis antigens.

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TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF POST-TEXT TABLES DEMOGRAPHY

PAGE

LIST OF POST-TEXT TABLES IMMUNOGENICITY

PAGE

LIST OF POST-TEXT FIGURES IMMUNOGENICITY

PAGE

LIST OF POST-TEXT TABLES REACTOGENICITY

PAGE

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ATP	According-To-Protocol
ANCOVA	Analysis of Co-variance
BS	Blood Sample
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
D	Diphtheria
DTaP	Diphtheria, Tetanus, Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbant Assay
FHA	Filamentous Hemagglutinin from *Bordetella pertussis*
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary For Regulatory Activities
PRN	Pertactin from *Bordetella pertussis*
PT	Pertussis Toxoid from *Bordetella pertussis*
RCC	Reverse Cumulative distribution Curve
RDE	Remote Data Entry

SAE	Serious Adverse Event
SBIR	Randomization System on Internet
T	Tetanus
Td	Combined Tetanus-Diphtheria
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
TVC	Total Vaccinated Cohort
US	United States
Vacc	Vaccination
Yoa	Year of Age

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,

oral contraceptives, either combined or progestogen alone,

injectable progestogen,

implants of etonogestrel or levonorgestrel,

estrogenic vaginal ring,

percutaneous contraceptive patches,

intrauterine device or intrauterine system,

male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,

The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.

male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),

male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 5.2.4 and 5.8.5 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, the larche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present report.

Trademarks of the GSK group of companies	Generic description
Boostrix	Reduced antigen content diphtheria and tetanus toxoids and acellular Pertussis (Tdap) vaccine
Infanrix	Combined diphtheria, tetanus and acellular pertussis vaccine

Trademarks not owned by the GSK group of companies	Generic description
Adacel (Sanofi Pasteur)	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine Adsorbed (Tdap).

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, any amendments, the informed consent and other information that required pre-approval were reviewed and approved by a central IRB (Quorum Review IRB).

1.2. Ethical conduct of the study

This study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, the principles of "good clinical practice" (GCP) and all applicable regulatory requirements.

1.3. Subject information and consent

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures, in accordance with 21 CFR 50.25. Data collection was done by Remote Data Entry (RDE) using individual electronic case report forms (eCRFs).

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted by 35 investigators across multiple centres in the United States (US). GSK Biologicals, King of Prussia, PA, US was responsible for administration of the study including clinical trial supply management and laboratory facilities. There was a reduction in the number of participating centres at Year 9 (26 centres) when compared to the Year 5 (37 centres) and the 106316 (Tdap 0.3-007) study (45 centres) since several investigators declined to participate in this phase of the study.

3. INTRODUCTION

Diphtheria, tetanus toxoids and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Since the 1980s, there has been an increase in the number of reported cases of pertussis in the US, especially among 10-19 year olds and infants younger than six months of age. During 2015, 20,762 cases of pertussis were reported to Centers for Disease Control and Prevention (CDC) by state health departments. This represents a 37% decrease compared to 32,971 cases reported during 2014. CDC again observed increased rates in adolescents 13 through 15 years of age, as well as in 16 year olds [CDC, 2017].

Per the General Recommendations on Immunization, adolescents and adults 11-18 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults 19 years of age and older who have not received a dose of Tdap [ACIP, 2012]. Pregnant women should receive one dose of Tdap vaccine during each pregnancy, preferably during the early part of gestational weeks 27–36, regardless of prior history of receiving Tdap vaccine [CDC: Recommended Immunization Schedule for Adults, 2017].

Boostrix is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti, 2002; Greco, 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in *Boostrix* are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 mL dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. In 2005, *Boostrix* (0.3 mg) was approved in the US for use in 10-18 year olds. In December 2008, it was approved for use in adults 19-64 years of age and in 2011, it was approved in the US for use in adults 65 years of age and older.

The 106316 (Tdap 0.3-007) study was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age [Blatter MM, 2009]. The immunogenicity and reactogenicity of *Boostrix* was compared to that elicited by Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, *Adacel* vaccine, which is licensed in the US for individuals 11-64 years of age.

This current Phase III study demonstrated antibody persistence of the Tdap vaccine at three and five years in US adolescents and adults aged 19 to 64 years of age following booster vaccination (Weston, 2011; GlaxoSmithKline Biologicals Study Report 110084 [Tdap 0.3-009 EXT: 007 Year 5]). Immunogenicity results from Year 1, Year 3 and Year 5 showed that concentrations of antibodies to *Boostrix* antigens were lower than those observed 1 month post-vaccination but remained elevated relative to pre-vaccination levels.

This clinical study report describes persistence data 9 years after vaccination with a single dose of Tdap vaccine in the study 106316 (Tdap 0.3-007). In addition, immunogenicity and safety data following a second dose of Tdap given at Year 9 are also presented in this clinical study report.

4. STUDY OBJECTIVES

4.1. Co-primary objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years. Refer to Section 5.10.2 for the change in assay units and assay cut-off.
- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control Group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

  The criteria for meeting the above objective are defined as:

  – One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between Groups in the seroprotection rate (a second dose of Tdap [Boostrix Group] minus the first dose of Tdap [Control Group]) against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

  – One month after vaccination, the lower limit of the 97.5% CIs for the difference between Groups in the seroprotection rate (a second dose of Tdap [Adacel Group] minus the first dose of Tdap [Control Group]) against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).
- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criteria for meeting the above objective are defined as:

  – One month after vaccination, the lower limits of the 97.5% CIs for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

  – One month after vaccination, the lower limits of the 97.5% CIs for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel Group divided by Infanrix Group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% CIs for the difference between Groups in the booster response rate (a second dose of Tdap [Boostrix Group] minus the first dose of Tdap [Control Group]) against diphtheria, tetanus and pertussis antigens (PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

Refer to Section 5.8.1 for definition of the co-primary endpoints and Section 5.8.3 for the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.

4.2. Secondary objectives

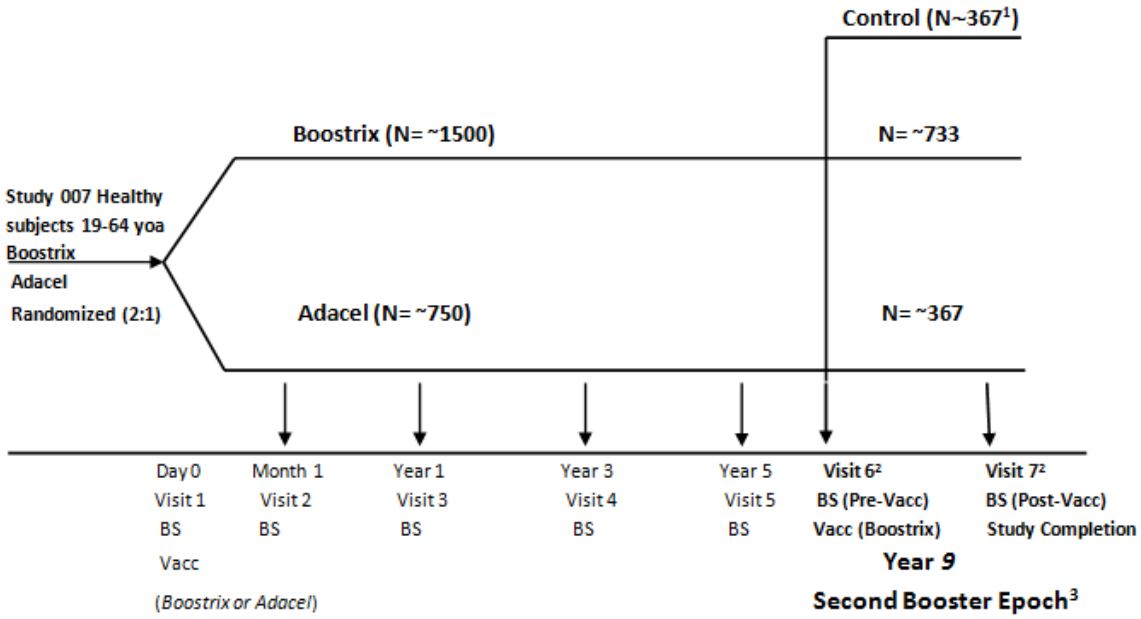
- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ the assay cut-off, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*. Refer to Section 5.10.2 for the change in assay units and assay cut-off.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.
- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination**.**
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of alternate booster response[1] to D, T, PT, FHA and PRN antigens between Boostrix Group and Adacel Group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix Group and Adacel Group) and a first dose of Tdap vaccine (Control Group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix Group and Adacel Group) and a first dose of Tdap vaccine (Control Group), with respect to solicited symptoms (local and general), unsolicited adverse events and serious adverse events (SAEs).

See Section 5.8.2 for details of the study endpoints and [1]Section 5.8.7 for the definition of the booster response.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overview



Yoa= Year of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch was a non-randomized study, for practical purposes group ratio of 1:2:1 was assigned for the Control, Boostrix and Adacel Groups respectively for the Year 9 time point.
[1]Subjects who were not part of the 106316 (Tdap 0.3-007) study were recruited as the Control Group.
[2]For the Control Group although it was their first and second visit for this study, the visits were named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel Groups. The study procedures were similar across all Groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch had been added for practical purposes and it had no relation to the number of epochs in this study.

5.1.2. Overall study design – Description

- Experimental design: A phase III, parallel, open-label, interventional, multicentre study with the same two parallel Groups as in the 106316 (Tdap 0.3-007) study and one new Control Group receiving the first dose of Tdap vaccine *(Boostrix)*.
- Study groups:
  - **Boostrix Group**: Subjects who had received GSK Biologicals' Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and received a second dose of Tdap vaccine *(Boostrix)* in the present study at Year 9 (Visit 6).

- **Adacel Group**: Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and received a second dose of Tdap vaccine *(Boostrix)* in the present study at Year 9 (Visit 6).
- **Control Group**: Subjects who received the first dose of Tdap vaccine *(Boostrix)* in the present study at Year 9 (Visit 6).

- Blinding: The present study was an open study as this was an extension of study 106316 (Tdap 0.3-007) which was unblinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 (Tdap 0.3-007) were analyzed as separate Groups. Subjects in the Control Group were also analyzed as a separate Group.
- Treatment allocation: Non-randomized, all the study groups received a single dose of *Boostrix* at Year 9 (Visit 6).
- Control: Active control (subjects who had received the first dose of Tdap vaccine [*Boostrix*] in this study at Year 9 [Visit 6]).
- Vaccination schedule: A single dose of *Boostrix* vaccine was administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9. For the Control Group, it was their first visit for this study, the first and second visits of the Control Group were named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel Groups. The study procedures were similar across all Groups at Visit 6 and Visit 7.
- Blood samples were collected at the following time points: 1 year, 3 years, 5 years and 9 years (Visit 6 [pre-vacc] and Visit 7 [post-vacc for subjects who received vaccination in this study]).
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 (Tdap 0.3-007) and who participated at all persistence time points of the study including Year 9 time point and approximately one month for the Control Group.Data collection: eCRF.

5.1.3. Discussion of study design

This study was designed as an open-label, non-randomized trial with two parallel Groups as in the 106316 (Tdap 0.3-007) study receiving the second dose of Tdap vaccine *(Boostrix)* and Control Group receiving the first dose of Tdap vaccine *(Boostrix)*. A single dose of *Boostrix* vaccine was administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9. Blood samples were collected at the following time points: 1 year, 3 years, 5 years and 9 years (Visit 6 [pre-vacc] and Visit 7 [post-vacc for subjects who received vaccination in this study]) for all the subjects.

5.2. Study procedures

Table 1 Outline of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 AND 7[1] Year *9* *9* years following *Boostrix/ Adacel* vaccination Administration of *Boostrix* vaccine	
				Visit 6	Visit 7
Informed consent for persistence follow-up	●	●	●	●[3]	
Informed consent for vaccination				●	
Check inclusion criteria	●	●	●	●[3]	
Check exclusion criteria				●	
Check elimination criteria	●	●	●	●[3]	●
Collect demographic data[2]				●	
Medical history				●	
Vaccination history				●[3]	
Pre-vaccination body temperature				●	
Recording of administered treatment number				●	
Urine Pregnancy test[4]				●	
Check contraindications to vaccination				O	
Check warnings and precautions				O	
Blood sampling (~5 mL) for antibody determination	●	●	●	●[3]	●
Vaccination				●	
Distribution of diary card				O	
Daily recording of solicited adverse events during the 4-day Day (0-3) follow-up period post-vaccination, by subjects				●	
Recording of non-serious adverse events during the 31-day Day (0-30) follow-up period post-vaccination, by subjects				●	●
Return of diary cards					O
Diary card transcription by investigator					●
Record concomitant medication/vaccination	●	●	●	●[3]	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●[3]	●

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 AND 7[1] Year *9* *9* years following *Boostrix/ Adacel* vaccination Administration of *Boostrix* vaccine	
				Visit 6	Visit 7
Recording of any large injection site reactions in the eCRF by the investigator[5]				●	
Reporting of SAEs				●[3]	●
Recording of pregnancies				●	●
Record any intercurrent medical conditions					●
Study Continuation	●	●	●	O (NA for Control Group)	●
Study conclusion for persistence follow-up				●[3]	
Study Conclusion for vaccinated Groups					●
Investigator sign-off on data for persistence follow-up				●[3]	
Investigator sign-off on data					●

● is used to indicate a study procedure that required documentation in the individual eCRF.
○ is used to indicate a study procedure that did not require documentation in the individual eCRF.
[1] Applicable to Control, Boostrix and Adacel Groups.
[2] Year of birth, gender, ethnicity and race for subjects in the Control Group.
[3] These were the only study procedures applicable for subjects who refused vaccination at Year 9 time point.
[4] Applicable to female subjects of childbearing potential only.
[5] Refer to Section 5.7.1.1 for detailed explanation on the reporting of large injection site reactions.
Note: Visit 1 and 2 were the vaccination visits in the 106316 (Tdap 0.3-007) study.
The grey shaded area represents the time point for which the analyses were presented in this report.

Table 2 Intervals between study visits

Intervals between study visits for subjects in Boostrix and Adacel Groups:

Visit	Optimum length of interval [1]	Maximum interval allowed [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	9 years – 3 months	9 years +6 months
Visit 7 (Visit 6→ Visit 7)	30-48 days (at least 30 days[3])	21-48[3] days

[1] Whenever possible the investigator should have arranged study visits within this interval.
[2] Subjects were not eligible for inclusion in the According-to-Protocol (ATP) Year 9 cohort for analysis if they made the study visit outside this interval.
[3] If subjects had returned for the visits prior to 30 days, they should have taken home the diary card and continued to record unsolicited safety information during the 31-day (Day 0-30) follow-up period post-vaccination and mailed/sent it upon completion. Investigators made an attempt to retrieve diary cards from subjects who did not mail/send them in.
The grey shaded area represents the time point for which the analyses were presented in this report.

Intervals between study visits for subjects in Control Group:

Visit	Optimum length of interval [1]	Maximum interval allowed[2]
Visit 6→Visit 7[3]	30-48 days (at least 30 days[4])	21-48 days

[1] Whenever possible the investigator should have arranged study visits within this interval.
[2] Subjects were not eligible for inclusion in the ATP Year 9 cohort for analysis if they made the study visit outside this interval.
[3] For the Control Group although it was their first and second visit for this study, the visits were named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel Groups. The study procedures were similar across all Groups at Visit 6 and Visit 7.
[4] If subjects had returned for the visits prior to 30 days, they should have taken home the diary card and continued to record unsolicited safety information during the 31-day (Day 0-30) follow-up period post-vaccination and mailed/sent it upon completion. Investigators made an attempt to retrieve diary cards from subjects who did not mail/send them in.

5.2.1. Selection of study population

A total of 26 centres in the US participated in this study at Year 9. The total number of subjects enrolled in the 106316 (Tdap 0.3-007) study was 2284, randomized into Boostrix or Adacel Groups in the ratio 2:1. The number of vaccinated subjects in the primary study 106316 (Tdap 0.3-007) was 1522 for Boostrix Group and 762 for Adacel Group. Around 476 subjects from Boostrix Group and 232 subjects from Adacel Group in the primary study returned at Year 9. Around 363 subjects were recruited for the Control Group to receive the first dose of Tdap vaccine *(Boostrix)*.

5.2.2. Inclusion criteria for enrolment

All subjects had to satisfy the following criteria at study entry.

Persistence follow-up phase up to Year 9 time point:

The following criteria were applicable to subjects who refused vaccination at Year 9 time point:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 (Tdap 0.3-007) were considered eligible to participate in this study.
- Written informed consent was obtained from the subject prior to each study time point.

Vaccination phase at Year 9 applicable for subjects in the Boostrix and Adacel Groups only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix and Adacel Groups only:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 (Tdap 0.3-007) were considered eligible to participate in this study.

Vaccination phase at Year 9 applicable for subjects in the Control Group only:

The following criterion was applicable to subjects willing to consent to vaccination at Year 9 time point in the Control Group only:

- Subjects within the age range of 28-73 years were considered eligible to participate in this study in the Control Group.

Vaccination phase at Year 9 applicable for ALL subjects (Control, Boostrix and Adacel Groups):

The following criteria were applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix, Adacel and Control Groups:

- Subjects who, in the opinion of the investigator, complied with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject for vaccination at Year 9 time point.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential were enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the GLOSSARY OF TERMS

Female subjects of child bearing potential were enrolled in the study, if the subject

- had practiced adequate contraception for 30 days prior to vaccination, and
- had a negative pregnancy test on the day of vaccination, and
- had agreed to continue adequate contraception for 1 month after completion of the vaccine dose.

Please refer to the GLOSSARY OF TERMS

5.2.3. Exclusion criteria

The following criteria had to be checked at the time of Year 9 vaccination time point. If any criteria were applicable, the subject had not to be vaccinated in the study:

For subjects in the Boostrix and Adacel Groups:

- Administration of Tdap vaccine since the last dose received in the study 106316.

For subjects in the Control Group:

- Administration of Tdap *(Boostrix or Adacel)* vaccine at any time prior to the administration of *Boostrix* vaccine in this study.

For ALL subjects (Control, Boostrix and Adacel Groups):

- Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of *Boostrix* vaccine in this study.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to Visit 6 (pre-vacc). For corticosteroids, this meant prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids were allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with the exception of inactivated Influenza vaccine which was allowed throughout the study period, 31 days (Day 0-30).
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would have been exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Hypersensitivity to latex.
- History of diphtheria, tetanus or pertussis diseases.
- Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of *Boostrix*.
- History of any neurological disorders or seizures.
- Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

- Acute disease and/or fever at the time of enrolment.
  - Fever was defined as temperature ≥ 100.4°F by any route. The preferred route for recording temperature in this study was oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever could have been enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31-day (Day 0-30) follow-up period post-vaccination.

5.2.4. Withdrawal criteria

The following criteria had to be checked at Visit 6 and were applicable to all subjects. If any became applicable during the study, from Visit 6, it did not require withdrawal of the subject from the study but could determine a subject's eligibility in the according-to protocol (ATP) analysis (see Section 5.8.5).

- Administration of a vaccine against diphtheria, tetanus or pertussis during the study period (Visit 6 through Visit 7).
- Administration of any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier during the study period (Visit 6 through Visit 7).
- Diphtheria and/or tetanus and/or pertussis disease diagnosed during the study period (Visit 6 through Visit 7).
- Administration of immunoglobulins and/or any blood products within three months of each study visit. Investigators could defer the blood draw for these subjects until such time as the criterion no longer applied.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this meant prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immuno-deficient condition based on medical history and physical examination (no laboratory testing was required) diagnosed during the study period (Visit 6 through Visit 7).

5.2.4.1. Subject completion

- A subject who returned for Visit 6 for persistence follow-up and refused vaccination is considered to have completed the study phase (Year 9) pertaining to that study visit.
- A subject who consented to vaccination and returned for Visit 7 as specified in the protocol is considered to have completed the study phase (Year 9) pertaining to that study visit.

5.2.4.2. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study was any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects could participate in each persistence time point independent of other persistence time points. For example, a subject who did not participate in the Year 1 antibody persistence analysis could be approached for participation in the 3, 5 and 9 year persistence analyses.

All data collected until the date of withdrawal/last contact of the subject was used for the analysis.

A subject qualified as a withdrawal from the study when no study procedure had occurred, no follow-up had been performed, and no further information had been collected for the subject since the last contact.

For subjects vaccinated at visit 6, information relative to the withdrawal of a subject was documented on the study continuation/conclusion pages of the eCRF. The investigator documented whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- SAE
- Non-SAE
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event (AE)*
- Moved from the study area
- Lost to follow-up
- Other (specify).

*In case a subject was withdrawn from the study because he/she had withdrawn consent, the investigator documented the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who were withdrawn from the study because of SAEs/AEs were clearly distinguished from subjects who were withdrawn for other reasons. Investigators would follow subjects who were withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 5.7.5).

5.2.4.3. Subject withdrawal from investigational vaccine

Subjects who were withdrawn because of AEs were clearly distinguished from subjects who were withdrawn for other reasons. Investigators would follow subjects who withdrawn as a result of an SAE/ AE until resolution of the event (see Section 5.7.1).

Withdrawals were not replaced.

5.3. Composition and administration of vaccines

5.3.1. Description of vaccine

Study vaccines administered during study 106316 (Tdap 0.3-007) were *Boostrix* and *Adacel*. Refer to the 106316 (Tdap 0.3-007) clinical study report for details of the composition of vaccines.

The study vaccine used at the Year 9 time point had been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the vaccines were described in separate release protocols and the required approvals were obtained.

Table 3 presents the composition of the study vaccine.

Table 3 Study vaccine administered at Year 9 time point

Treatment name	Vaccine/product name	Formulation	Presentation	Volume	Number of doses
Boostrix	Tdap	Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf , Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as $Al(OH)_3$:≤ 0.39 mg, Sodium chloride Lot numbers: AC52VB151C, AC52VB117B, AC52VB118A.	Pre-filled syringes, Homogeneous turbid white suspension	0.5 mL	1

5.3.2. Dosage and administration of study vaccines

Subjects were administered one dose of the study vaccine, as described in Table 4. Refer to the 106316 (Tdap 0.3-007) clinical study report for the dose and administration of *Boostrix* and *Adacel* at Visit 1 and 2.

Table 4 Dosage and Administration at Year 9 time point

Visit	Dose	Vaccine	Route	Site	Side
Visit 6[a]	1	Tdap	Intramuscular	Deltoid	Non-Dominant[b]

Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

a. Applicable to the Control, Boostrix and Adacel Groups. For the Control Group although it was their first and second visits for this study, the visits were named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel Groups.

b. Vaccination could be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

The vaccine recipients were to be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine(s)/product(s).

The contraindications and warnings/precautions to vaccination were specified in the protocol (see protocol for details).

5.3.3. Treatment allocation and randomization

There was no randomization of subjects into this study. The subjects in this study were allocated to the same Groups as in the primary vaccination study 106316. Subjects were allocated a new treatment number, but retained the same subject number as in the 106316 (Tdap 0.3-007) study (Boostrix and Adacel Groups), or subject numbers were assigned sequentially (for the subjects in the Control Group).

The central randomization system on internet (SBIR) was used at the investigator site to track enrolment at Year 9 i.e. to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration accessed SBIR. Upon identifying the subject identification number, the randomization system determined the study group and provided the treatment number to be used for the dose.

Enrolment of subjects in the Control Group was stratified by age to ensure age distribution was similar to that of Boostrix and Adacel Groups:

- 28-38 years: ~25.4%
- 39-58 years: ~35.5%
- 59-73 years: ~39.1%

5.4. Blinding

The study was an open study, since this was an extension of study 106316 (Tdap 0.3-007) which was un-blinded at the time of primary analysis. At Year 9 time point all the subjects received a single dose of *Boostrix*.

5.5. Prior and concomitant medication /vaccinations

5.5.1. Persistence follow-up phase up to Year 9 time point

The following criteria were applicable to subjects who refused vaccination at Year 9 time point:

At each study visit, the investigator questioned the subject about any medication /product taken and vaccination received by the subject.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to any study blood sampling) were to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 (Tdap 0.3-007) study, was to be recorded with the trade name, route of administration, and date of administration.

5.5.2. Vaccination phase at Year 9 time point

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of the dose of study vaccine and ending up to next study visit after the dose of study vaccine were recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to study vaccination or at any time during the study period were to be recorded with the generic name for the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding the dose of study vaccine and ending 31 days (Day 0-30) after the dose of study vaccine was recorded with trade name, route of administration and date(s) of administration.

A prophylactic medication was a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic was considered to be prophylactic when it was given in the absence of fever [temperature by any route < 100.4°F. The preferred route for recording temperature in this study was oral] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of a reaction to the vaccination was recorded in the eCRF with generic name of the medication (trade names were allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

During the period starting with administration of the dose of study vaccine and ending 31 (Day 0-30) days after the dose of study vaccine, concomitant medication administered for the treatment of an AE was recorded in the eCRF with generic name of the medication (trade names were allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, was recorded on the SAE Report Form/ SAE screens in the eCRF, as applicable.

Any investigational medication or vaccine administered throughout the study (i.e. from Visit 6 through Visit 7) was recorded in the eCRF.

5.6. Assessment of immunogenicity variables

5.6.1. Laboratory assays and time points

A blood sample was obtained from all subjects in the Boostrix and Adacel Groups at each of the following time points: 1 year, 3 years, 5 years and 9 years (at Visit 6 [persistence follow-up for subjects who refused vaccination and pre-vacc for subjects who consented to vaccination] and Visit 7 [post-vacc]) following study vaccination in 106316 (Tdap 0.3-007) study, and only at Year9, Visit 6 (pre-vacc) and Visit 7 (post-vacc) for subjects in the Control Group.

All serological assays were performed at GSK Biologicals' central laboratory using standardized, validated procedures with adequate controls. Refer to Section 5.10.2 for the change in assay units and assay cut-off.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus (anti-T and anti-D) were measured by enzyme-linked immunosorbent assay (ELISA). The assay cut-off for anti-diphtheria was set at 0.057 IU/mL and for anti-tetanus at 0.043 IU/mL. For both serology a threshold of 0.1 IU/mL provided a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL were re-tested using the neutralization assay on VERO cells, which was more sensitive for low antibody concentrations and had a cut-off of 0.016 IU/mL.

Antibodies against PT, FHA and PRN

No correlate of protection has been defined for the immune response to pertussis antigens. Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN were measured by ELISA technique. The assay cut-off for anti-PT was 2.693 IU/mL, for anti-FHA was 2.046 IU/mL and for anti-PRN was 2.187 IU/mL.

Table 5 Summary of immunogenicity assessments (humoral immunity - antibody determination)

Blood sample from Subjects	Marker	Assay	Assay cut-off (IU/mL)	Laboratory	Laboratory address
Serum	anti-D	ELISA	0.057	GSK Biologicals	GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium
Serum	anti-D	Neutralisation test on VERO cell	0.016*	GSK Biologicals	GSK Wavre Avenue Fleming, 20 B-1300 Wavre – Belgium
Serum	anti-T	ELISA	0.043	GSK Biologicals	GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium
Serum	anti-PT	ELISA	2.693	GSK Biologicals	GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium
Serum	anti-FHA	ELISA	2.046	GSK Biologicals	GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium
Serum	anti-PRN	ELISA	2.187	GSK Biologicals	GSK Rixensart Rue de l'Institut, 89 B-1330 Rixensart – Belgium

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
*VERO cut off at,
1 year persistence time point was 0.016 IU/ml
3 years persistence time point was 0.016 IU/ml
5 years persistence time point was 0.004 IU/ml
9 years persistence time point was 0.004 IU/ml

The investigator was encouraged to share the immunological assay results for low immunological assay results with the study subjects.

Low result was defined as:

- Antibody concentrations < 0.01 IU/mL for diphtheria antigen and,
- Antibody concentrations < 0.1 IU/mL for tetanus antigen.

For the study subjects identified as low-responders, it was the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

5.6.2. Immunological read-outs

The priority listing for antibody testing was as shown in Table 6

Table 6 Immunological read-outs for all subjects

Blood sampling time point		Marker
Timing	Visit no.	
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 9	6 and 7†	D*
		T
		PT
		FHA
		PRN

†Applicable to the Control, Boostrix and Adacel Groups. For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7, respectively to keep it consistent with the visit numbering of Boostrix and Adacel Groups. The study procedures will be similar across all Groups at Visit 6 and Visit 7.
*VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.

5.7. Assessment of safety variables

The investigator or site staff was/were responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in the protocol.

Each subject was instructed to contact the investigator immediately if he/she manifested any signs or symptoms they perceived as serious.

5.7.1. Adverse events

An AE was any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it could have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se was not reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action.
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Examples of an AE DID NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that lead to the procedure was an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- AEs included pre- or post-treatment events that occurred as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

5.7.1.1. Solicited adverse events

The following local (injection-site) AEs were solicited:

Table 7 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If subjects observed any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they were asked to contact study personnel and to visit the investigator's office for evaluation as soon as possible. The investigator recorded detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

Table 8 Solicited general adverse events

The following general AEs were solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache

†Gastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain.

N.B. Temperature was recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature was recorded.

5.7.1.2. Assessment of AEs

5.7.1.2.1. Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 9.

Table 9 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain that neither interfered with nor prevented normal every day activities.
	2	Moderate: Painful when limb was moved and interfered with every day activities.
	3	Severe: Significant pain at rest. Prevented normal every day activities.
Redness at injection site		Recorded greatest surface diameter in mm
Swelling at injection site		Recorded greatest surface diameter in mm
Fever*		Recorded temperature in °F
Headache	0	Normal
	1	Mild: Headache that was easily tolerated
	2	Moderate: Headache that interfered with normal activity
	3	Severe: Headache that prevented normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that was easily tolerated
	2	Moderate: Fatigue that interfered with normal activity
	3	Severe: Fatigue that prevented normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that were easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfered with normal activity
	3	Severe: Gastrointestinal symptoms that prevented normal activity

*Fever was defined as temperature ≥ 100.4 °F by any route. The preferred route for recording temperature in this study was oral.

The maximum intensity of local injection site redness/swelling was scored at GSK Biologicals as follows:

0	:	Absent
1	:	≤ 20 mm
2	:	> 20 mm and < 50 mm
3	:	≥ 50 mm

The maximum intensity of fever was scored at GSK Biologicals as follows:

0	:	<38°C
1	:	≥38°C to ≤ 39°C
2	:	>39°F to ≤ 40°C
3	:	> 40°C

The investigator made an assessment of the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment was based on the investigator's clinical judgment.

The intensity of each AE recorded in the eCRF or SAE Report Form, as applicable, was assigned to one of the following categories:

1 (mild)	=	An AE which was easily tolerated by the subject, causing minimal discomfort and did not interfere with everyday activities.
2 (moderate)	=	An AE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevented normal, everyday activities. (In a young child, such an AE would, for example, prevent attendance at a day-care centre and would cause the parents/ guardians to seek medical advice.)

An AE that was assessed as Grade 3 (severe) was not to be confused with a SAE. Grade 3 was a category utilized for rating the intensity of an event; and both AEs and SAEs could be assessed as Grade 3. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in Section 5.7.2.

5.7.1.2.2. Assessment of causality

The definitions for "NO" and "YES" were written in such a way that all events that were attributed a "NO" could be pooled with events which in the primary vaccination study were determined to be "not related" or "unlikely to be related" to vaccination. Those events that were attributed a "YES" were pooled with those events that in the past were determined to have a "suspected" or "probable" relationship to vaccination in the primary vaccination study.

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used his/her clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product was considered and investigated. The investigator also consulted the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There could be situations when a SAE had occurred and the investigator had minimal information to include in the initial report to GSK Biologicals. However, it was very important that the investigator always made an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may have changed his/her opinion of causality in light of follow-up information and amended the SAE information accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it was not possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator, therefore, assessed whether the AE was causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions were considered causally related to vaccination. Causality of all other AEs were assessed by the investigator using the following question:

Was there a reasonable possibility that the AE could have been caused by the investigational product?

NO	:	There was no reasonable possibility that the AE was causally related to the administration of the study vaccine. There were other, more likely causes and administration of the study vaccine was not suspected to have contributed to the AE.
YES	:	There was a reasonable possibility that the vaccine contributed to the AE.

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious" (see Section 5.7.2 for definition of SAE), additional examinations/tests were performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors included:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine(s), if applicable;
- Erroneous administration;
- Other cause (specify).

5.7.1.3. Assessment of outcomes

Outcome of any non-serious AE occurring during the 31-day (Day 0-30) follow-up period post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study was assessed as:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovering/resolving.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

5.7.1.4. Medically attended visits

For each solicited and unsolicited adverse event the subject experienced, the subject was asked if he/she received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information was recorded in the eCRF.

5.7.2. Serious adverse events

A SAE was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occurred during hospitalization were AEs. If a complication prolonged hospitalization or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE was considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

NOTE: The term disability meant a substantial disruption of a person's ability to conduct normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which could interfere or prevent everyday life functions but did not constitute a substantial disruption.

e. was a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgment should be exercised in deciding whether reporting was appropriate in other situations, such as important medical events that could not be immediately life-threatening or resulted in death or hospitalization but could jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization.

5.7.3. Pregnancy

Persistence follow-up phase up to Year 9 time point:

The following criterion was applicable to subjects who refused vaccination at Year 9 time point:

Because subjects were not being vaccinated as part of the time points at Year 1, 3 and 5, investigators were not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who were pregnant at the time of a study visit during the time points at Year 1, 3 and 5 were not excluded from the visit on the basis of their pregnancy.

Vaccination phase at Year 9 time point:

Female subjects who became pregnant after the vaccination could continue the study at the discretion of the investigator.

While pregnancy itself was not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons was recorded and reported as an AE or a SAE.

Note: The pregnancy itself was always recorded on an electronic pregnancy report.

The following should always be considered as SAE and was reported as described in protocol:

- Spontaneous pregnancy loss, included:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of fetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age was based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It was recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant that occurred within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus was delivered dead or alive. This included anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE that occurred as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine was reported to GSK Biologicals as described in protocol. While the investigator was not obligated to actively seek this information from former study participants, he/she could learn of a pregnancy through spontaneous reporting.

5.7.4. Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies

5.7.4.1. Persistence follow-up phase up to Year 9 time point:

The following criteria were applicable to subjects who refused vaccination at Year 9 time point:

Because subjects were not being vaccinated as part of the time points Year 1, 3 and 5, investigators were not required to specifically solicit SAEs. However, if an investigator became aware of an SAE that in his/her medical judgment was reasonably related to the study vaccine administered in study 106316, he/she did so within 24 hours of learning of the event. Additionally, in order to fulfil international reporting obligations, SAEs that were related to study participation (e.g. blood draws) were collected and recorded from the time the subject consented to participate in the study until she/he was discharged.

When an SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator then recorded all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It was not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there could be instances when copies of medical records for certain cases were requested by GSK Biologicals. In this instance, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF was the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs did not work or after removal of write access of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system was used to report SAEs.

5.7.4.2. Vaccination phase at Year 9 time point:

For subjects who received vaccination at the Year 9 time point: All AEs occurring within 31 days (Day 0-30) following administration of the dose of vaccine were recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they were considered vaccination-related.

The standard time period for collecting and recording SAEs began at the receipt of study vaccine and ended 31 days (Day 0-30) following administration of the dose of study vaccine for each subject.

In addition to the above-mentioned reporting requirements and in order to meet international reporting obligations, SAEs that were related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or were

related to a concurrent GSK medication/vaccine was collected and recorded from the time the subject consented to participate in the study until she/he was discharged from the study.

The time period for collecting and recording pregnancies began at the receipt of study vaccine and ended 31 days (Day 0-30) following administration of the dose of study vaccine for each subject.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 10.

Table 10 Reporting periods for adverse events, serious adverse events and pregnancies

Event	Pre-vacc (consent obtained)	Vaccination	4 days (Day 0-3) post-vacc	31 days (Day 0-30) post-vacc
				Study conclusion
Solicited local and general AEs including large injection site reactions				
Unsolicited AEs				
AEs/SAEs leading to withdrawal from the study				
SAEs				
SAEs related to study participation or concurrent GSK medication/vaccination				
Pregnancies				

Pre-vacc.: pre-vaccination; Post-vacc.: post-vaccination.

The investigator inquired about the occurrence of AEs/SAEs at every visit during the study and throughout the follow-up phase as appropriate.

All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question were evaluated by the investigator. AEs not previously documented in the study was recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where

appropriate) of onset, outcome, intensity and relationship to vaccination was established. Details of any corrective treatment was recorded on the appropriate page of the eCRF.

5.7.5. Follow-up of adverse events, serious adverse events and pregnancies

After the initial AE/SAE report, the investigator was required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving were reviewed at subsequent visit/contact until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving were reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Investigators followed-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE; until the event had resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up;

Clinically significant laboratory abnormalities were followed up until they had returned to normal, or a satisfactory explanation had been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject were made available to the Study Monitor.

If the investigator received additional relevant information on a previously reported SAE, he/she provided this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals requested that the investigator performed or arranged for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator was obliged to assist. If a subject died during participation in the study or during a recognized follow-up period, GSK Biologicals were provided with a copy of any available post-mortem findings, including histopathology.

New or updated information was recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF was resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in the protocol.

In case the electronic SAE reporting system did not work or the write access of the subject's eCRF was removed, paper SAE Report Forms and the facsimile (Fax) system was used to report SAEs. Refer to the protocol for details of the back-up reporting system.

Follow-up of pregnancies

Pregnant subjects were followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child was forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period was not longer than six to eight weeks after the estimated date of delivery. Regardless of the reporting period for SAEs for this study, if the pregnancy outcome was a SAE, it was always reported as SAE.

5.7.5.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting AEs, the subject was asked a non-leading question such as:

"Have you felt different in any way since receiving the vaccine or since the previous visit?"

When an AE/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator recorded all relevant information regarding an AE/SAE in the eCRF. The investigator was not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there could have been instances when copies of medical records for certain cases were requested by GSK Biologicals. In this instance, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator attempted to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as the AE/SAE and not the individual signs/symptoms.

5.8. Statistical methods

An analysis was performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 9) on cleaned data obtained through each respective Year.

For the current Year 9 persistence analysis, all previous time points including the initial study 106316 (Tdap 0.3-007), and follow up time points 110080 (Y1), 110082 (Y3), 110084 (Y5) were pooled together to generate some of the demography and immunogenicity tables.

The statistical analyses were performed using the Statistical Analysis Systems (SAS) version 9.

5.8.1. Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the Boostrix and the Adacel Groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of *Infanrix* in Study APV-039.
  - Booster response* to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.

*Refer to Section 5.8.7 for the definitions of booster response.

5.8.2. Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ assay cut-off in the Boostrix and Adacel Groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination. Refer to Section 5.10.2 for the change in assays.
- Immunogenicity with respect to components of the study vaccine at the Year 9 time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ assay cut-off; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination
  - Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 5.8.7 for the definitions of booster response and alternate booster response)

  *Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a VERO-cell neutralization assay.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4-day (Day 0–3) follow-up period after vaccination
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4-day (Day 0-3) follow-up period after vaccination

- Unsolicited AEs.
  - Occurrence of unsolicited AEs during the 31-day (Day 0-30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification
- SAEs.
  - Occurrence of SAEs from the administration of the vaccine dose and during the 31-day (Day 0–30) follow-up period following vaccination

5.8.3. Determination of sample size

No sample size was calculated for the time points at Year 1, 3 and 5. All subjects who received vaccination in study 106316 (Tdap 0.3-007) were eligible for enrolment in the present study.

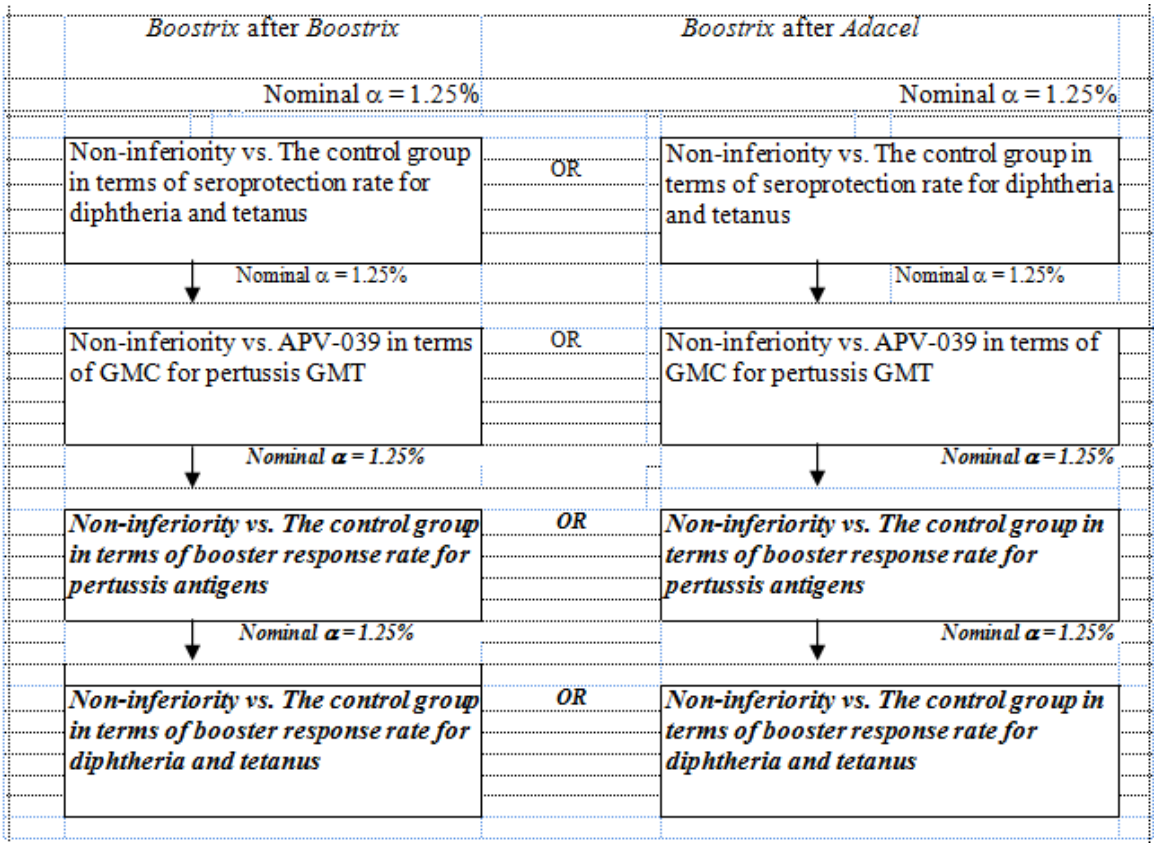
It was estimated that around 1100 subjects (733 subjects from Boostrix Group and 367 subjects from Adacel Group in the primary study) would return for Year 9 study. Around 367 subjects were to be recruited for the Control Group to receive the first dose of Tdap vaccine (*Boostrix*). Assuming 80% of enrolled subjects would be evaluable, the power in the study was based on 586 evaluable subjects in Boostrix Group, 293 evaluable subjects in Adacel Group and 293 evaluable subjects in the Control Group.

5.8.3.1. Control on type I error

This study was designed to assess independently non-inferiority of Boostrix Group to the Control Group, and non-inferiority of Adacel Group to the Control Group. To control the overall type I error below 2.5%, a Bonferroni adjustment was used, i.e., type I error allowed for each non-inferiority assessment was 1.25% (one-sided). In addition to further control misinterpretation related to multiple primary objectives, a hierarchy procedure was used as described in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%

An objective was reached if the associated criteria was met and the previous objectives were reached



5.8.4. Power computation

With 293 evaluable subjects in the Adacel Group and 293 evaluable subjects in the Control Group, the power to conclude non-inferiority of Adacel Group to the Control Group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Adacel Group to Infanrix Group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously was 88.91% (See Table 11 and Table 12 respectively).

As shown in Table 13, the power to demonstrate non-inferiority of Adacel Group to the Control Group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be very low (4%). In other words, there was a big chance that non-inferiority would not be demonstrated for one or more of the antibodies.

With 586 evaluable subjects in the Boostrix Group and 293 evaluable subjects in the Control Group, the power needed in order to conclude non-inferiority of the Boostrix Group to the Control Group in terms of anti-D, anti-T seroprotection rates and non-inferiority of the Boostrix Group to *Infanrix* in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 97.87 % (See Table 14 and Table 15 respectively).

As shown in Table 16, the power to demonstrate non-inferiority of the Boostrix Group to the Control Group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be 48%. It is likely that non-inferiority might not be demonstrated for one or more of the antibodies.

Table 11 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	**DTPA 0.3 *(Boostrix)*-007 (Boostrix Group)**	**Non-inferiority criterion Difference (2nd dose-1st dose)**	**293 (*Boostrix* following *Adacel)* 293 (First *Boostrix*)**
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both Groups; LL= lower limit.
**Overall power was the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 12 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 *(Boostrix)*-007 *(Boostrix)***	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =293 in Adacel+Boostrix**
Anti-PT	0.480	0.306	2884	99.99%
Anti-FHA	0.422	0.370	685	99.99%
Anti-PRN	0.710	0.413	631	88.93%
Overall power**				88.91%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 *(Boostrix)*-007 was considered as common variance for both Groups, power under alternative of equal means in both Groups; LL= lower limit.
**Overall power was the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 13 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to the first dose of *Boostrix* with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	Reference values		Power* to reject H0: LL of 97.5% of difference <-10%
	DTPA 0.3 *(Boostrix)*-007 (Boostrix Group)	Non-inferiority criterion Difference (2nd dose- 1st dose)	293 (Boostrix following Adacel) 293 (First Boostrix)
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	74.19%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	57.51%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	73.64%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	98.81%
		Overall power**	4.14%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both Groups; LL= lower limit.
**Overall power was the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

Table 14 Power to demonstrate non-inferiority of a second dose of *Boostrix* following the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 *(Boostrix)*-007 (Boostrix Group)	Non-inferiority criterion Difference (2nd dose- 1st dose)	586 (*Boostrix* following *Boostrix*) 293 (First *Boostrix*)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both Groups; LL= lower limit.
**Overall power was the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 15 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 *(Boostrix)*-007 *(Boostrix)***	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =586 in *Boostrix+Boostrix***
Anti-PT	0.480	0.306	2884	>99.99%
Anti-FHA	0.422	0.370	685	>99.99%
Anti-PRN	0.710	0.413	631	97.87%
Overall power**				97.87%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 *(Boostrix)*-007 was considered as common variance for both Groups, power under alternative of equal means in both Groups; LL= lower limit.
**Overall power was the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 16 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to the first dose of *Boostrix* with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	**Reference values**	**Non-inferiority criterion Difference(2nd dose- 1st dose)**	**Power* to reject H0: LL of 97.5%CI of difference <-10%**
	DTPA 0.3 *(Boostrix)*-007 (Boostrix Group)		**586 (*Boostrix* following *Boostrix*) 293 (First *Boostrix*)**
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	88.89%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	71.39%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	88.45%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	99.96%
Overall power**			48.69%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both Groups; LL= lower limit.
**Overall power was the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

5.8.5. Study cohorts /data sets analyzed

5.8.5.1. Year X (1, 3, 5, 9) cohort

The Year X cohort was a subset of the TVC in the 106316 (Tdap 0.3-007) study and was the cohort of subjects who participated at Year X visit.

The immunogenicity analysis of Year X blood sample based on the year X cohort included all subjects with immunogenicity results.

5.8.5.2. Total Enrolled Cohort

The Total Enrolled Cohort included all subjects enrolled in the study regardless of the visit at enrolment.

5.8.5.3. According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5) cohort

The ATP Year X (1, 3, 5) cohort included all subjects from the Year X (1, 3, 5) cohort who were in the ATP cohort for analysis of immunogenicity in the 106316 (Tdap 0.3-007) study and who did not meet the following elimination criteria:

- Without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 (Tdap 0.3-007) study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 (Tdap 0.3-007) study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this meant prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids were allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

This cohort was the primary cohort for the persistence analysis.

5.8.5.4. Additional cohorts defined for Year 9 analysis

Total Vaccinated Cohort (TVC) at Year 9

The TVC included all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC included all vaccinated subjects.
- An immunogenicity analysis based on the TVC included all vaccinated subjects for whom immunogenicity results were available.

ATP cohort for analysis of safety at Year 9

The ATP cohort for analysis of safety at Year 9 time point included all eligible and vaccinated subjects:

- Who received the dose of study vaccine.
- For whom administration site of study vaccine was known.
- Who did not receive a vaccine leading to elimination from an ATP analysis.

ATP cohort for analysis of immunogenicity at Year 9 (ATP Year 9)

The ATP cohort for analysis of immunogenicity included all evaluable subjects from the ATP cohort for analysis of safety:

- Who complied with the procedures and intervals defined in the protocol.
- Who did not meet any of the criteria for elimination from an ATP analysis.
- For whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after Year 9 vaccination.

5.8.6. Adapted ATP cohort

When presenting different time points, the Adapted ATP cohort was used to denote that for each time point, the corresponding ATP cohort for immunogenicity/persistence had been used.

More specifically,

- The analyses on the pre- and post-primary dose time points was based on the ATP cohort for immunogenicity in study 106316.
- The analysis on Year 1, 3, 5 time points was based on the ATP cohort for persistence Year 1, 3, 5, respectively.
- The analysis on Year 9 (pre-and post-Tdap vaccination) was based on the ATP cohort for immunogenicity at Year 9.

5.8.7. Derived and transformed data

- A seronegative subject was a subject whose antibody concentration was below the assay cut-off value.
- A seropositive subject was a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate was defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 5.8.10 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel Groups, 1 year, 3 years, 5 years, and 9 years following vaccination was derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥assay cut-off in the Boostrix and Adacel Groups, 1 year, 3 years, 5 years and 9 years following vaccination were derived to evaluate the first secondary objective.

- The GMC calculations were performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay were given an arbitrary value of half the assay cut-off for the purpose of GMC calculation.

- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 9 years after vaccination with *Boostrix* were derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

- The age stratum was derived, subjects classified as 28 – 38 years, 39 – 58 years and 59 – 73 years for primed subjects in the 106316 (Tdap 0.3-007) study and subjects were classified in to the following age stratum (28-38, 39-58 and 59-73 years old) at enrolment in 110086 (Tdap 0.3-009) for the Control Group.

Booster responses considered for Year 9 time point:

- Booster response to D and T antigens was defined as:
  - for subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
  - for subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
- Booster response to PT, FHA and PRN antigens was defined as:
  - for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration ≥ 4 times the assay cut-off,
  - for subjects with pre-vaccination antibody concentration between the assay cut-off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration,
  - for subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
- Alternative Booster response to D and T antigens is defined as:
  - for subjects with pre-vaccination concentration below 0.1 IU/mL: antibody concentration increases at least four times 0.1 IU/mL (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
  - for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.

- for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration ≥ 6.0 IU/mL were not evaluable for vaccine response.

- Alternative Booster response to PT, FHA and PRN antigens was defined as:
  - for initially seronegative subjects (pre-booster antibody concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination,
  - for initially seropositive subjects with pre-booster antibody concentration ≥ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.
  - for initially seropositive subjects with pre-booster antibody concentration ≥ 60 IU/mL: at least 1.5-fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

5.8.8. Handling of missing data:

5.8.8.1. Immunogenicity:

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced.

5.8.8.2. Reactogenicity and Safety:

- For a given subject and the analysis of solicited symptom during the 4-day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements were not replaced. Therefore, the analysis of the solicited symptoms based on the TVC included only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects were considered. Subjects who did not report the event or the concomitant medication were considered as subjects without the event or the concomitant medication respectively.
- For summaries reporting both solicited and unsolicited AEs, all vaccinated subjects were considered. Subjects who did not report the event or the concomitant medication were considered as subjects without the event or the concomitant medication respectively.

5.8.9. Analysis of demographics and other baseline characteristics

Demographic characteristics (age in years at vaccination, gender, age stratum and visit at enrolment) of the ATP cohort for immunogenicity at Year 9 and for the Total Enrolled cohort at Year 1 were summarized using descriptive statistics.

The number of subjects included in each follow-up cohorts up to Year 9 and in the ATP Year 9 cohort was tabulated.

Time from the vaccination in the 106316 (Tdap 0.3-007) study to the blood sampling at Year 9 (in years) was summarized using descriptive statistics.

5.8.10. Analysis of persistence

The primary analysis was based on the adapted ATP cohort for analysis of immunogenicity which integrated immunological summaries for time points from primary study (106316 [Tdap 0.3-007]), and at Year 1, Year 3, Year 5 and Year 9 follow up time points. It consisted of subjects who complied with protocol at the respective time points. The following analyses were performed:

Within Group assessment:

For each study group, at each time point for which a serological result was available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CIs were calculated by Group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, were calculated by Group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) were calculated by Group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) were tabulated by Group.

In addition, at each persistence time point:

- The above summaries were provided for each level of the age stratum (Subjects age were classified as 28 – 38 years, 39 – 58 years and 59 – 73 years) and by gender. Age stratum was derived from the age stratum in study 106316 (Tdap 0.3-007) for subjects primed in study 106316 (Tdap 0.3-007) i.e. projected age at Year 9 and from the age at vaccination for subjects in the Control Group.

- Distribution of antibody concentrations for each antigen was displayed using reverse cumulative distribution curves (RCC) by Group at all persistence time points.

Comparability between Groups - Exploratory analyses

At each persistence time point,

- For anti-D antibody response, the two-sided asymptotic 95% CIs for the group differences (Boostrix minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥ 0.016 IU/mL by VERO) were calculated using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].
- For anti-T antibody response, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA were calculated.
- For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix minus Adacel Group) in the percentage of subjects with antibody concentrations ≥ assay cut-off were also calculated.

Sensitivity analysis for persistence

A sensitivity analysis was performed to ensure that comparability between subjects in the Boostrix Group and Adacel Group was not biased by drop-out at the persistence time point.

The analysis used a repeated mixed model on log-transformed titre accounting for results one month post-vaccination in study 106316, Year 1, 3, 5, and 9 post-initial vaccination in study 106316. Analyses were based on adapted ATP cohorts. The model included the following fixed effects: the Group effect, the age strata effects (agestratum1, agestratum2 referred below as being the age indicator for 28 – 38 years and 39 – 58 years [Age stratum was derived from the age stratum in 106316 (Tdap 0.3-007) study for subjects primed in 106316 (Tdap 0.3-007) study i.e. projected age at Year 9]) and the pre-vaccination titre in study 106316 (Tdap 0.3-007), the activity effect and the fixed activity-by-Group effect. An unstructured covariance matrix was used.

5.8.11. Analysis of immunogenicity at booster dose

The following analyses were carried out after Year 9 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 9. If, in any study group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was 5% or more, a second analysis based on the TVC at Year 9 was to be performed to complement the ATP analysis.

Within groups assessment

For each group and each antigen:

- Seropositivity for anti-PT, anti-FHA and anti-PRN and seroprotection rate for anti-D and anti-T at pre-vaccination and one month post-vaccination was calculated with exact 95% CIs.

- GMCs or GMTs at pre-vaccination, one month post-vaccination was tabulated with 95% CIs.
- Booster response rate one month post-vaccination was calculated with exact 95% CIs.

In addition:

- The above summaries were provided for each level of the age stratum at Year 9 visit (28-38, 39-58 and 59-73 years old) and by gender.
- The distribution of antibody concentrations for each antigen at pre-vaccination and one month post-vaccination were displayed using RCCs by Group.

Comparability between groups – confirmatory analyses:

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CIs of the group difference in seroprotection rate one month after vaccination (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) was computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and for Boostrix and Adacel Groups, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix Group, one month after the third dose of Infanrix for Infanrix Group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008; Section 5.10.2).
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CIs for the group differences (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) were calculated.

Comparability between groups – exploratory analyses:

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CIs for the group differences (Boostrix Group minus Control Group and Adacel Group minus the Control Group, respectively) were calculated.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody response respectively, the two-sided 95% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Adacel Group one month after vaccination were computed using an analysis of Co-variance (ANCOVA) model on the logarithm10 transformation of the concentrations. The pre-vaccination status in study 106316 (Tdap 0.3-007) was used as a co-variable.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Control Group and between the Adacel Group and (divided by) the Control Group one month after vaccination was computed using an ANOVA model on the logarithm10 transformation of the concentrations.

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CIs for the group differences (Boostrix Group – Adacel Group) were calculated.

Sensitivity analysis following the booster dose

A sensitivity analysis was performed to ensure that comparability between subjects in the Boostrix Group and Adacel Group was not biased by drop-out at the booster phase.

The analysis used a repeated mixed model on log-transformed titre accounting for results one month post-vaccination in study 106316 (Tdap 0.3-007) and one month post-vaccination in study 110086 (Tdap 0.3-009). Analyses were based on adapted ATP cohorts. The model included the following fixed effects: the Group effect, the age strata effects (agestratum1, agestratum2 referred below as being the age indicator for 28 – 38 years and 39 – 58 years [Age stratum was derived from the age stratum in 106316 (Tdap 0.3-007) study for subjects primed in 106316 (Tdap 0.3-007) study i.e. projected age at Year 9 and from the age at vaccination for subjects in the Control Group])) and the pre-vaccination titre in study 106316 (Tdap 0.3-007), the activity effect and the fixed activity-by-Group effect. An unstructured covariance matrix was used.

5.8.12. Analysis of safety

Persistence follow-up phase up to Year 9 time point:

No safety analysis was performed at the persistence time points of this study. If GSK was informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 (Tdap 0.3-007), or to participation in this persistence study, the pertinent clinical details were summarized in this study report.

Vaccination phase at Year 9 time point:

The primary analysis was based on the TVC at Year 9. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 9 was more than 5%, a second analysis based on this ATP cohort was performed to complement the analysis of the TVC.

The incidence of solicited local and general symptoms occurring during the 4-day (Day 0-3) follow-up period after vaccination was tabulated with exact 95% CIs for each Group. The same calculations were performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity grade 3 (occurrence of fever was reported per 0.5°C cumulative increments), as well as for solicited general symptoms with relationship to vaccination. All solicited local symptoms were causally related to vaccination.

The percentage of subjects who reported at least one unsolicited AE classified by MedDRA during the 31-day (Day 0-30) follow-up period after vaccination were tabulated with exact 95% CIs for each treatment Group. The same tabulation was performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit and for unsolicited adverse events that were considered by the investigator to be possibly related to vaccination.

SAEs were summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse events were described in detail.

In addition, the safety analysis of solicited symptoms was performed separately for each level of the age stratum (28-38, 39-58 and 59-73 years old) and by gender.

5.8.13. Sequence of analyses

Persistence data was analysed at each time point (Year 1, Year 3, Year 5 and Year 9) as available and reported separately. At Year 9 time point, immunogenicity and safety of vaccine administration were reported.

5.8.14. Interim analysis

No interim analysis was planned for this persistence study.

5.9. Data quality assurance at study level

To ensure that the study procedures conformed across all investigator sites, the protocol, eCRF and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

All protocol deviations collected during the study were reviewed by the GSK study team in order to identify important protocol deviations. Consistent with ICH E3 guidance, important deviations are defined as deviations that were likely to affect the interpretation of the results and/or led to exclusion of any subject data from an analysis. Important deviations include, but are not limited to, those related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, subject management or subject assessment**.**

No CROs were employed in this study.

Independent Audit statement:

This study was subject to audit by GlaxoSmithKline's R&D Global Quality Compliance (GQC) - Clinical Development Quality Assurance. (CDQA) department.

During the course of the study/after study completion (at Year 9 time point), three major findings with regard to the conduct of the study were identified. These findings were investigated and where possible corrective and / preventive actions were taken.

5.10. Changes in the conduct of the study or planned analyses

5.10.1. Protocol amendments

There were three amendments and two administrative changes to the study protocol (dated 17 April 2007):

- **Administrative change 1** (dated 14 April 2009) was done to clarify the contact details for reporting of SAEs.
- **Amendment 1 (**dated 09 November 2010) was done to extend the window period allowed for the return of subjects, to clarify reporting of SAEs, to clarify reporting of spontaneous abortion and the number of attempts required to contact a subject.
- **Amendment 2** (dated 18 February 2014) was done for the following reasons:
  - To evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap vaccine when administered 8 years after an initial dose of Tdap. This study also evaluated the persistence of antibodies against diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, 8 years instead of 10 years after an initial dose of Tdap vaccine (*Boostrix* or *Adacel* [Sanofi-Pasteur]) administered in 106316 (Tdap 0.3-007) study. The Year 10 time point for evaluation of persistence had been cancelled because it was no longer feasible to conduct after a second dose of Tdap vaccine had been administered at Year 8.
  - As per advice from Centre for Biological Research and Evaluation (CBER), an additional treatment Group acting as control was also added and the subjects enrolled in the Control Group received *Boostrix* as a first dose of Tdap vaccine.
  - Alternative booster response definitions were given for diphtheria, tetanus and pertussis antigens since the traditional booster response definitions applied for evaluation of initial dose of *Boostrix* are based on the level of antibodies observed in subjects prior to the first dose of *Boostrix*. The definition of booster responses to D, T and pertussis antigens currently used may not accurately depict a true immunologic booster response of the vaccine in the context where subjects have high pre-vaccination concentrations (≥ 6.0 IU/mL for diphtheria and tetanus and ≥ 60 EL.U/mL for pertussis). Therefore, applying the traditional booster response definitions in such a context would lead to lower booster response rate despite a higher observed geometric mean antibody concentration (GMC) after the second booster dose.
  - The data from this study was planned to support the indication of Boostrix as a second dose of Tdap vaccine.

- **Amendment 3** (dated 10 December 2014) was done following CBER recommendation to add a co-primary objective to demonstrate the immune response elicited by a second dose of Tdap vaccine, amend the time point for the study from Year 8 to Year 9 to reflect the change in study start, update in the interval between study visits for Year 9 time point, update in the statistical section to include the power computation for the new objective, update to the exclusion criteria, removal of the text regarding documentation of non-participation of subjects who declined to participate in this long-term study and amendment in the measurement of temperature for fever.
- **Administrative change 2** (dated 03 February 2015): was done to add the collection of the SAEs occurring due to study related procedures for the Year 9 time point.

5.10.2. Changes from planned analyses

- For the within Group assessment, a sub-Group analysis for immunogenicity and reactogenicity by Gender was added to be consistent with Year 1, 3 and 5 analysis.
- For the sake of simplification, the adapted ATP cohort was introduced to present integrated immunological summaries for time points from study, and follow up time points 110080 (Y1), 110082 (Y3), 110084 (Y5).
- The ATP cohorts defined in previous analyses were revised for two reasons,
  - the age of one subject in study 106316 (Tdap 0.3-007 was modified leading to exclusion of the subject from all ATP analyses.
  - the previous ATP analyses at Year 3 did not exclude subjects eliminated from ATP in study 106316 (Tdap 0.3-007.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Tdap Group and (divided by) the *Infanrix* Group in APV-039 one month after vaccination (one month after vaccination for Tdap Group, one month after the third dose of *Infanrix* for *Infanrix* Group in APV-039) was computed using the method proposed by G.Y. Zou and A. Donner (Zou, 2008) in order to account heterogeneity of variance between this study and APV-039. Note that the APV-039 reference for this comparison was the results converted into the revalidated assays by using multiple imputation techniques (GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022).
- A sensitivity analysis was proposed in the protocol to compare immunogenicity post-vaccination in study 110086 (Tdap 0.3-009 EXT: 007 Year 9). The context of the sensitivity analysis was clarified to be limited to comparison between the Boostrix and Adacel Group as defined in study 106316 (Tdap 0.3-007). In addition, the imputation method proposed in the protocol was replaced by a mixed model which is direct and allows accounting for ANCOVA model covariates used in study 106316.
- During the course of the study, the assays used to measure the anti-D, -T, -PT, -FHA and -PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-off were adapted. The new ELISAs for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed

the expression of concentrations measured with the new ELISAs in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA's have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/mL for anti-D, 0.043 IU/mL for anti-T, 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. The newly validated DTPa ELISA's were used for the Year 9 pre and post vaccination blood samples. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) and therefore the clinical endpoints for anti-D and anti-T are unchanged. In the absence of a correlate of protection for the *B. pertussis* antigens, the pertussis endpoints were redefined based on the assay cut-off (see section 5.8.7 and section 5.8.2).

- In line with CBER request to use a standard threshold for seroprotection based on anti-Diphtheria by VERO and ELISA, the primary endpoint described in the protocol, namely the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ **0.01** IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA, was replaced by the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ **0.016** IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA.
- The enrolled cohort was redefined as the subject enrolled regardless of visit.
- For the difference between Groups in seroprotection status for anti-Diphtheria by ELISA and VERO neutralisation, the confidence limits for all persistence time points were computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].
- For anti-D, anti-T antibody response, the two-sided 95% CIs of the GMC ratios between subjects in the Boostrix Group and (divided by) the Control Group and between the Adacel Group and (divided by) the Control Group one month after vaccination was computed using an ANOVA model on the logarithm10 transformation of the concentrations.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject was enrolled in the study 110086 (Tdap 0.3-009 EXT: 007 Year 9) on 29 May 2015 and the last study visit was on 21 March 2016.

6.2. Subject disposition

The number of subjects by centre for the total enrolled cohort is presented in Table 6.1.

The number of subjects vaccinated, completed the study and number of subjects who were withdrawn from the study with reason for withdrawal for total enrolled cohort and TVC are presented in Table 17 and Table 18.

At Year 9, out of the total 809 vaccinated subjects (309 subjects from the Boostrix Group, 138 subjects from the Adacel Group and 362 subjects from the Control Group), ten subjects (three subjects from the Boostrix Group, two subjects from the Adacel Group and five subjects from the Control Group) were withdrawn from the study (Table 18).

Table 17 Number of subjects vaccinated completed and withdrawn with reason for withdrawal (Total enrolled cohort)

		Boostrix N = 1239		Adacel N = 607		Control N = 363		Total N = 2209	
Characteristics	**status**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
study disposition	drop-out before visit 6 at year 9	763	61.6	375	61.8	0	0.0	1138	51.5
	completed the study at visit 6 without vaccination	166	13.4	94	15.5	0	0.0	260	11.8
	drop-out after visit 6 vaccination	4	0.3	2	0.3	6	1.7	12	0.5
	completed the study at visit 7 after vaccination	306	24.7	136	22.4	357	98.3	799	36.2

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed the visit
Withdrawn = number of subjects who did not come for the visit

Table 18 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total Vaccinated Cohort at Year 9)

	Boostrix	Adacel	Control	Total
Number of subjects vaccinated	309	138	362	809
Number of subjects completed	306	136	357	799
Number of subjects withdrawn	3	2	5	10
Reasons for withdrawal				
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	0	0
Migrated/moved from study area	0	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	2	2	3	7
Others	1	0	2	3

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

6.3. Important Protocol deviations at subject level

6.3.1. Protocol Deviations leading to elimination from ATP analyses

The deviations from specifications for age and intervals between study visits for the Total Enrolled Cohort (Year 1, Year 3, Year 5 and Year 9) and TVC at Year 9 are presented in Table 6.6 and Table 6.7, respectively.

ATP cohort for previous time points for persistence have been revised due to database changes and to harmonise the elimination of subjects across time points. Refer to Section 5.10.2 for revision of ATP cohorts defined for previous time points. The number of subjects at each visit and the reasons for exclusion from ATP cohort of immunogenicity at Year 1, Year 3, Year 5 and Year 9 are presented in Table 6.2, Table 6.3, Table 6.4 and Table 6.5.

A total number of 809 subjects were vaccinated in the study and a total of 719 subjects were included in ATP cohort for immunogenicity at Year 9 (Table 19).

Table 19 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP for analysis of immunogenicity Year 9 cohort with reasons for exclusion (Total Vaccinated Cohort at Year 9)

	Total			Boostrix		Adacel		Control	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total Vaccinated Cohort at Year 9	809		100	309		138		362	
Administration of vaccine(s) forbidden in the protocol (code 1040)	27	27		11	11	2	2	14	14
Study vaccine dose not administered according to protocol (code 1070)	11	12		2	2	3	3	6	7
Administration of any medication forbidden by the protocol (code 2040)	4	5		2	3	0	0	2	2
Underlying medical condition forbidden by the protocol (code 2050	2	2		1	1	1	1	0	0
Non-compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	11	11		6	6	3	3	2	2
Essential serological data missing (code 2100)	27	29		10	11	6	7	11	11
Obvious incoherence or abnormality or error in data (code 2120)	2	2		1	1	1	1	0	0
Subjects eliminated from ATP cohort for immunogenicity in study Tdap 0.3-007 (code 2500)	6	7		5	6	1	1	0	0
ATP cohort for analysis of immunogenicity at Year 9	719		88.9	271		121		327	

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort

6.3.2. Protocol Deviations not leading to elimination from ATP analyses

The protocol deviations not leading to elimination from ATP analyses are mentioned below:

- **Study procedure**
  - The site administered the urine pregnancy test after the subject was vaccinated. The pregnancy test was negative. The site was aware of this deviation and has documented this in the source. All site staff is aware that this procedure is to be conducted prior to vaccination.
- **Informed consent:**
  - Two subjects were given the ICF for the Control Group instead of the Boostrix/Adacel Group ICF. These deviations were found on the 25th and 26th August, 2015 respectively during a routine monitoring visit. Re-consenting was not possible as the subjects had already completed the study. Site reported the deviation to IRB and the study manager on the 25th and 26th of August, 2015.
  - Two subjects were given the ICF for the Boostrix/Adacel Group ICF instead of the Control Group ICF. The deviations were found on the 25th and 26th of August, 2015 during a routine monitoring visit. Re-consenting was not possible as the subject had already completed the study. Site reported the deviations to IRB and the study manager on the 25th and 26th August, 2015.

– One subject signed on the subject line and the line for person obtaining consent on 05th February, 2016. The Clinical Research Associate (CRA) discovered this at the Interim Monitoring Visit (IMV) and the coordinator stated she did consent the subject and reviewed it with the subject in length, and inadvertently did not sign the ICF. A note to file was created and the ICF was signed/dated on 09th February, 2016 by the coordinator.

6.4. Demographic characteristics and other baseline characteristics

The summary of demographic characteristics for the total enrolled cohort and ATP cohort for immunogenicity at Year 9 cohort are presented in Table 20 and Table 21.

Most of the subjects having participated in study 106316 (Tdap 0.3-007) were enrolled at visit 3 (Year 1 visit) while the subjects from the Control Group were enrolled at visit 6 (Year 9 visit). Accordingly, a group difference was seen in the age at enrolment between Groups (Boostrix, Adacel and Control Groups). Despite age stratification at enrolment for the Control Group, slight differences were observed between Groups in term of age at vaccination, race and gender.

Table 20 Summary of demographic characteristics (Total enrolled cohort)

		Boostrix N = 1239		Adacel N = 607		Control N = 363		Total N = 2209	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Enrolment visit	Year 1 visit	1069	86.3	523	86.2	0	0.0	1592	72.1
	Year 3 visit	142	11.5	73	12.0	0	0.0	215	9.7
	Year 5 visit	24	1.9	8	1.3	0	0.0	32	1.4
	Year 9 visit	4	0.3	3	0.5	363	100	370	16.7
Age [Years] at enrolment	Mean	42.1	-	42.7	-	52.1	-	43.9	-
	SD	13.5	-	13.4	-	13.6	-	14.0	-
	Median	44.0	-	44.0	-	54.0	-	45.0	-
	Minimum	19.0	-	19.0	-	28.0	-	19.0	-
	Maximum	72.0	-	67.0	-	73.0	-	73.0	-
	Missing	0	-	0	-	0	-	0	-
Age [Years] at Year 9 blood sample	Mean	52.6	-	52.0	-	52.1	-	52.3	-
	SD	13.3	-	12.7	-	13.6	-	13.3	-
	Median	56.0	-	54.0	-	54.0	-	55.0	-
	Minimum	27.0	-	28.0	-	28.0	-	27.0	-
	Maximum	73.0	-	73.0	-	73.0	-	73.0	-
	Missing	763	-	375	-	0	-	1138	-
Age [Years] at Year 9 vaccination	Mean	52.7	-	51.0	-	52.0	-	52.1	-
	SD	13.1	-	12.4	-	13.6	-	13.2	-
	Median	56.0	-	52.0	-	54.0	-	54.0	-
	Minimum	28.0	-	28.0	-	28.0	-	28.0	-
	Maximum	73.0	-	73.0	-	73.0	-	73.0	-
	Missing	930	-	469	-	1	-	1400	-
Age stratum	28-38 year	375	30.3	174	28.7	85	23.4	634	28.7
	39-58 year	418	33.7	210	34.6	134	36.9	762	34.5
	59-73 year	446	36.0	223	36.7	144	39.7	813	36.8
Gender	Female	783	63.2	403	66.4	196	54.0	1382	62.6
	Male	456	36.8	204	33.6	167	46.0	827	37.4
Race	African Heritage / African American	82	6.6	44	7.2	64	17.6	190	8.6
	American Indian or Alaskan Native	3	0.2	3	0.5	3	0.8	9	0.4
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	1	0.3	1	0.0
	Asian - East Asian Heritage	2	0.2	1	0.2	1	0.3	4	0.2
	Asian - Japanese Heritage	3	0.2	0	0.0	0	0.0	3	0.1
	Asian - South East Asian Heritage	5	0.4	2	0.3	1	0.3	8	0.4
	Native Hawaiian or Other Pacific Islander	6	0.5	3	0.5	0	0.0	9	0.4
	White - Arabic / North African Heritage	17	1.4	10	1.6	3	0.8	30	1.4
	White - Caucasian / European Heritage	1074	86.7	521	85.8	288	79.3	1883	85.2
	Other	47	3.8	23	3.8	2	0.6	72	3.3

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter

SD = standard deviation
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control Group

Table 21 Summary of demographic characteristics (ATP cohort for analysis of immunogenicity at Year 9)

		Boostrix N = 271		Adacel N = 121		Control N = 327		Total N = 719	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age [Years] at Year 9 vaccination	Mean	53.0	-	51.4	-	52.1	-	52.3	-
	SD	13.2	-	12.3	-	13.5	-	13.2	-
	Median	56.0	-	53.0	-	54.0	-	55.0	-
	Minimum	28.0	-	28.0	-	28.0	-	28.0	-
	Maximum	73.0	-	73.0	-	73.0	-	73.0	-
	Missing	0	-	0	-	0	-	0	-
Gender	Female	182	67.2	84	69.4	179	54.7	445	61.9
	Male	89	32.8	37	30.6	148	45.3	274	38.1
Age stratum	28-38 year	60	22.1	22	18.2	75	22.9	157	21.8
	39-58 year	88	32.5	55	45.5	122	37.3	265	36.9
	59-73 year	123	45.4	44	36.4	130	39.8	297	41.3
Race	African Heritage / African American	6	2.2	4	3.3	58	17.7	68	9.5
	American Indian or Alaskan Native	0	0.0	1	0.8	3	0.9	4	0.6
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	1	0.3	1	0.1
	Asian - East Asian Heritage	1	0.4	0	0.0	0	0.0	1	0.1
	Asian - Japanese Heritage	2	0.7	0	0.0	0	0.0	2	0.3
	Asian - South East Asian Heritage	1	0.4	0	0.0	1	0.3	2	0.3
	Native Hawaiian or Other Pacific Islander	0	0.0	1	0.8	0	0.0	1	0.1
	White - Arabic / North African Heritage	7	2.6	2	1.7	3	0.9	12	1.7
	White - Caucasian / European Heritage	252	93.0	111	91.7	259	79.2	622	86.5
	Other	2	0.7	2	1.7	2	0.6	6	0.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control Group

7. IMMUNOGENICITY RESULTS

7.1. Data sets analysed

The primary analysis was based on the adapted ATP cohort for analysis of immunogenicity for persistence and was based on the ATP cohort for analysis of immunogenicity at Year 9. A second analysis based on the TVC at Year 9 was performed to complement the primary analysis.

Refer to Section 5.8.5 for the definition of the cohorts identified for analyses.

7.2. According-to-protocol analysis

7.2.1. Persistence of antibodies to diphtheria and tetanus toxoids

- The number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentrations ≥ 0.1 IU/mL and 1 IU/mL and GMCs at persistence time points for the Adapted ATP cohort is presented in Table 22.
- The seroprotection status for anti-Diphtheria antibody concentration by ELISA and VERO neutralisation at the persistence time points for adapted ATP cohort is presented in Table 23.
- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 95.7% of subjects at Year 1 to 91.1% of subjects at Year 9 (by ELISA; Table 22) and from 98.3% of subjects at Year 1 to 99.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Boostrix Group (Table 23). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 98.6% of subjects at Year 1 to 98.1% of subjects at Year 9 in the Boostrix Group (Table 22).
- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 97.0% of subjects at Year 1 to 95.8% of subjects at Year 9 (by ELISA; Table 22) and from 98.2% of subjects at Year 1 to 98.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Adacel Group (Table 23). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 99.6% of subjects at Year 1 to 100% of subjects at Year 9 in the Adacel Group (Table 22).
- The GMCs for antibodies against both diphtheria and tetanus antigens in both Groups reached a peak response post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1 and gradually kept decreasing till the Year 9 time point (Table 22).
- The seroprotection status for anti-Diphtheria antibody concentration by ELISA and VERO neutralisation at the persistence time points for the ATP cohort for analysis of immunogenicity at Year 9 and total enrolled cohort are presented in Table 7.1 and Table 7.46.

- The persistence of anti-Diphtheria and anti-Tetanus antibodies and GMCs at persistence time points for adapted ATP cohort (by age stratum and gender) and for total enrolled cohort are presented in Table 7.27, Table 7.33 and Table 7.45.

RCCs of anti-Diphtheria and anti-Tetanus antibody concentrations per Group at the persistence time point are presented in Figure 7.1 and Figure 7.3, respectively.

- The GMCs for antibodies against both diphtheria and tetanus antigens in both groups at persistence time points predicted by modelling are presented in Table 7.17 and Table 7.18 and Figure 7.11 to Figure 7.12.

Table 22 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at persistence time points (Adapted ATP cohort)

				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	Pre_bst_007	1439	1226	85.2	83.3	87.0	340	23.6	21.5	25.9	0.4	0.4	0.4
		Post_bst_007	1443	1417	98.2	97.4	98.8	1268	87.9	86.1	89.5	4.7	4.4	5.1
		Per(Yr1)	1010	967	95.7	94.3	96.9	673	66.6	63.6	69.5	1.4	1.3	1.6
		Per(Yr3)	914	857	93.8	92.0	95.2	478	52.3	49.0	55.6	0.9	0.8	1.0
		Per(Yr5)	789	735	93.2	91.2	94.8	377	47.8	44.2	51.3	0.8	0.7	0.9
		Pre_bst_009	269	245	91.1	87.0	94.2	114	42.4	36.4	48.5	0.7	0.6	0.8
	Adacel	Pre_bst_007	720	642	89.2	86.7	91.3	191	26.5	23.3	29.9	0.5	0.4	0.5
		Post_bst_007	727	717	98.6	97.5	99.3	669	92.0	89.8	93.9	5.0	4.6	5.4
		Per(Yr1)	504	489	97.0	95.1	98.3	351	69.6	65.4	73.6	1.4	1.3	1.6
		Per(Yr3)	442	425	96.2	93.9	97.7	247	55.9	51.1	60.6	1.0	0.9	1.1
		Per(Yr5)	372	359	96.5	94.1	98.1	190	51.1	45.9	56.3	0.9	0.8	1.0
		Pre_bst_009	118	113	95.8	90.4	98.6	54	45.8	36.6	55.2	0.8	0.6	0.9
ANTI-T	Boostrix	Pre_bst_007	1446	1387	95.9	94.8	96.9	1039	71.9	69.5	74.2	1.6	1.5	1.7
		Post_bst_007	1444	1438	99.6	99.1	99.8	1419	98.3	97.5	98.9	8.5	8.1	8.9
		Per(Yr1)	1014	1000	98.6	97.7	99.2	952	93.9	92.2	95.3	3.4	3.2	3.6
		Per(Yr3)	917	899	98.0	96.9	98.8	807	88.0	85.7	90.0	2.2	2.1	2.3
		Per(Yr5)	788	772	98.0	96.7	98.8	665	84.4	81.7	86.9	2.0	1.9	2.1
		Pre_bst_009	268	263	98.1	95.7	99.4	211	78.7	73.3	83.5	1.8	1.6	2.0
	Adacel	Pre_bst_007	727	707	97.2	95.8	98.3	543	74.7	71.4	77.8	1.7	1.6	1.8
		Post_bst_007	728	728	100	99.5	100	723	99.3	98.4	99.8	13.3	12.5	14.1
		Per(Yr1)	506	504	99.6	98.6	100	487	96.2	94.2	97.7	4.4	4.1	4.7
		Per(Yr3)	442	440	99.5	98.4	99.9	408	92.3	89.4	94.6	2.9	2.7	3.1
		Per(Yr5)	372	370	99.5	98.1	99.9	337	90.6	87.2	93.4	2.5	2.3	2.7
		Pre_bst_009	120	120	100	97.0	100	101	84.2	76.4	90.2	2.3	2.0	2.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study

Table 23 Seroprotection status for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION at the persistence time points (Adapted ATP cohort)

			ELISA concentration <0.1 IU/mL		VERO concentration < 0.016 for subjects with ELISA < 0.1 IU/ML		Estimated proportion of subjects with Vero concentration < 0.016 IU/ML		Estimated proportion of subjects with Vero concentration ≥ 0.016 IU/ml or ELISA ≥ 0.1 IU/ML		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Boostrix	Pre_bst_007	1439	213/1439	14.8	100/212	47.2	213/1439 x 100/212	7.0	93.0	91.6	94.3
	Post_bst_007	1443	26/1443	1.8	9/26	34.6	26/1443 x 9/26	0.6	99.4	98.8	99.7
	Per(Yr1)	1012	45/1012	4.4	17/45	37.8	45/1012 x 17/45	1.7	98.3	97.3	99.0
	Per(Yr3)	914	57/914	6.2	28/57	49.1	57/914 x 28/57	3.1	96.9	95.6	98.0
	Per(Yr5)	789	54/789	6.8	13/54	24.1	54/789 x 13/54	1.6	98.4	97.2	99.1
	Pre_bst_009	269	24/269	8.9	2/24	8.3	24/269 x 2/24	0.7	99.3	97.3	99.9
Adacel	Pre_bst_007	720	78/720	10.8	28/77	36.4	78/720 x 28/77	3.9	96.1	94.5	97.3
	Post_bst_007	727	10/727	1.4	6/10	60.0	10/727 x 6/10	0.8	99.2	98.2	99.7
	Per(Yr1)	505	16/505	3.2	9/16	56.3	16/505 x 9/16	1.8	98.2	96.6	99.2
	Per(Yr3)	442	17/442	3.8	10/17	58.8	17/442 x 10/17	2.3	97.7	95.9	98.9
	Per(Yr5)	372	13/372	3.5	4/13	30.8	13/372 x 4/13	1.1	98.9	97.3	99.7
	Pre_bst_009	118	5/118	4.2	2/5	40.0	5/118 x 2/5	1.7	98.3	94.0	99.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralisation test for year x persistence time point
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO) for year x persistence time point
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study

7.2.2. Non-inferiority of second dose of *Boostrix* to first dose of *Boostrix* with respect to percentages of subjects with defined concentrations of anti-D and anti-T antibodies

The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix Group and Adacel Group) was non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to seroprotection rate against diphtheria and tetanus antigens, was met, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group differences [Boostrix Group minus Control Group and Adacel Group minus Control Group] in the booster response to the diphtheria and tetanus antigens was above the pre-specified lower limit of -10% (Table 24 and Table 25).

The results for the group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL for TVC cohort at Year 9 are presented in Table 7.39 and Table 7.40.

Table 24 Confirmatory objective: Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL [Boostrix Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

								Difference in percentage (Boostrix minus Control)		
		Boostrix			Control				97.5% CI	
Antibody	Threshold	N	n	%	N	n	%	%	LL	UL
ANTI-D	0.1 IU/mL	271	269	99.3	326	319	97.9	1.41	-1.16	4.17
ANTI-T	0.1 IU/mL	271	271	100	327	326	99.7	0.31	-1.52	2.07

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 25 Confirmatory objective: Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL [Adacel Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

								Difference in percentage (Adacel minus Control)		
		Adacel			Control				97.5% CI	
Antibody	Threshold	N	n	%	N	n	%	%	LL	UL
ANTI-D	0.1 IU/mL	121	120	99.2	326	319	97.9	1.32	-3.41	4.15
ANTI-T	0.1 IU/mL	121	121	100	327	326	99.7	0.31	-3.69	2.07

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

7.2.3. Non-inferiority of a second dose of *Boostrix* to *Infanrix* with respect to GMCs for antibodies to acellular pertussis antigens

The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to anti-PT, anti-FHA and anti-PRN antibody concentrations, was met, as, one month after the booster vaccination, the lower limit of the 97.5% CIs on the GMC ratios (Boostrix Group divided by Infanrix Group in APV-039 and Adacel Group divided by Infanrix Group in APV-039) for the PT, FHA and PRN antigens was above the pre-specified lower limit of 0.67 (Table 26 and Table 27).

Table 26 Confirmatory objective: GMC ratio between Groups [Boostrix Group divided by Infanrix Group in APV-039] and their 97.5% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC Ratio (Boostrix Group / Infanrix Group in APV-039)		
	Boostrix Group		Infanrix Group in APV-039			97.5% CI	
Antibody	N	GMC	N	GMC	GMC Ratio	LL	UL
ANTI-PT	294	64.0	2884	41.7	1.53	1.31	1.79
ANTI-FHA	298	248.8	685	47.2	5.27	4.62	6.01
ANTI-PRN	298	408.7	631	113.0	3.62	3.07	4.25

Infanrix Group in APV-039 = Infanrix Group of the German household contact study APV-039
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
97.5% CI = 97.5% confidence interval for the GMC ratio LL = lower limit, UL = upper limit
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] GMC = geometric mean antibody concentration calculated on all subjects
The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 27 Confirmatory objective: GMC ratio between Groups [Adacel Group divided by Infanrix Group in APV-039] and their 97.5% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC Ratio (Adacel Group / Infanrix Group in APV-039)		
	Adacel Group		Infanrix Group in APV-039			97.5% CI	
Antibody	N	GMC	N	GMC	GMC Ratio	LL	UL
ANTI-PT	130	68.6	2884	41.7	1.64	1.33	2.03
ANTI-FHA	131	248.8	685	47.2	5.27	4.37	6.36
ANTI-PRN	131	504.8	631	113.0	4.47	3.58	5.57

Infanrix Group in APV-039 = Infanrix Group of the German household contact study APV-039
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
97.5% CI = 97.5% confidence interval for the GMC ratio LL = lower limit, UL = upper limit
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] GMC = geometric mean antibody concentration calculated on all subjects
The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

7.2.4. Non-inferiority of booster responses to diphtheria, tetanus and pertussis antigens after receiving second dose of *Boostrix* in comparison to the first dose of *Boostrix*)

The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met: for all antigens except PT, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Boostrix Group minus Control Group] in the booster response to the diphtheria, tetanus, FHA and PRN antigens was below the pre-specified lower limit of -10% (Table 28 and Table 29).

The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met: for all antigens except FHA, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Adacel Group minus Control Group] in the booster response to the diphtheria, tetanus, PT, FHA and PRN antigens was below the pre-specified lower limit of - 10% (Table 30 and Table 31).

The results for the group differences in booster response to diphtheria, tetanus and pertussis antigens for TVC cohort at Year 9 are presented in Table 7.41 to Table 7.44.

Table 28 Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Boostrix Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	269	169	62.8	323	222	68.7	-5.91	-14.67	2.85
ANTI-T	268	126	47.0	324	157	48.5	-1.44	-10.63	7.79

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 29 Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Boostrix Group minus Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-FHA	271	232	85.6	327	303	92.7	-7.05	-13.16	-1.40
ANTI-PRN	271	210	77.5	320	281	87.8	-10.32	-17.50	-3.38
ANTI-PT	271	235	86.7	326	292	89.6	-2.85	-9.09	3.08

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 30 Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Adacel Group minus the Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
ANTI-D	118	71	60.2	323	222	68.7	-8.56	-20.33	2.73
ANTI-T	120	44	36.7	324	157	48.5	-11.79	-22.98	0.15

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and
- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 31 Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Adacel Group minus the Control Group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	120	116	96.7	327	303	92.7	4.01	-2.38	8.66
ANTI-PRN	118	98	83.1	320	281	87.8	-4.76	-14.53	3.18
ANTI-PT	120	106	88.3	326	292	89.6	-1.24	-10.03	5.57

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
- For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

7.3. Secondary analyses

7.3.1. Persistence of antibodies to PT, FHA, and PRN antigens at all Year 1, Year 3, Year 5 and Year 9 time points

- In the Boostrix Group, at Year 9 pre-vaccination, 100% of subjects had anti-FHA antibodies, 98.5% of subjects had anti-PRN antibodies and 84.9% of subjects had anti-PT antibodies ≥ assay cut off. In the Adacel Group, at Year 9 pre-vaccination, 99.2% of subjects had anti-FHA and anti-PRN antibodies, and 88.3% of subjects had anti-PT antibodies ≥ assay cut off (Table 32).
- GMCs for anti-FHA, anti-PRN and anti-PT which reached a peak response at post vaccination in study 106316 (Tdap 0.3-007) showed a sharp decrease at Year 1, and continued the gradual decline at Year 3, Year 5 and Year 9 for both Groups. Note that the anti-FHA GMC decrease observed at Year 9 is largely due to pertussis assay revalidation which involved a calibration of approximately 2-fold (Table 32).
- The persistence of anti- PT, anti-FHA, anti- PRN antibody concentrations and GMCs at persistence time points for adapted ATP cohort (by age stratum and gender) and for total enrolled cohort are presented in Table 7.28, Table 7.34 and Table 7.47.

RCCs of anti- PT, anti-FHA, anti- PRN antibody concentrations per Group at the persistence time point are presented in Figure 7.5, Figure 7.7 and Figure 7.9, respectively.

- The GMCs for antibodies against the pertussis antigens in both groups at persistence time points predicted by modelling are presented in Table 7.19 to Table 7.21 and Figure 7.13 to Figure 7.15.

Table 32 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at persistence time points (Adapted ATP cohort)

				≥ Assay cut off				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	Pre_bst_007	1437	1393	96.9	95.9	97.8	31.6	29.9	33.5
		Post_bst_007	1442	1442	100	99.7	100	624.0	593.5	656.1
		Per(Yr1)	1014	1012	99.8	99.3	100	190.1	178.5	202.6
		Per(Yr3)	916	913	99.7	99.0	99.9	114.1	107.1	121.5
		Per(Yr5)	789	788	99.9	99.3	100	110.0	103.0	117.4
		Pre_bst_009	271	271	100	98.6	100	42.2	37.6	47.5
	Adacel	Pre_bst_007	717	691	96.4	94.7	97.6	34.8	32.0	37.8
		Post_bst_007	724	724	100	99.5	100	368.4	344.3	394.2
		Per(Yr1)	502	501	99.8	98.9	100	118.8	108.7	129.9
		Per(Yr3)	439	437	99.5	98.4	99.9	81.8	74.7	89.4
		Per(Yr5)	371	368	99.2	97.7	99.8	80.8	73.1	89.4
		Pre_bst_009	120	119	99.2	95.4	100	28.4	24.0	33.4
ANTI-PRN	Boostrix	Pre_bst_007	1444	1100	76.2	73.9	78.4	13.4	12.5	14.3
		Post_bst_007	1443	1426	98.8	98.1	99.3	401.0	368.5	436.3
		Per(Yr1)	1011	971	96.0	94.7	97.2	152.2	137.2	168.8
		Per(Yr3)	915	862	94.2	92.5	95.6	82.5	74.4	91.5
		Per(Yr5)	782	755	96.5	95.0	97.7	85.3	76.7	94.9
		Pre_bst_009	271	267	98.5	96.3	99.6	63.8	53.1	76.7
	Adacel	Pre_bst_007	727	555	76.3	73.1	79.4	14.3	12.9	15.7
		Post_bst_007	726	721	99.3	98.4	99.8	351.9	315.7	392.2
		Per(Yr1)	501	489	97.6	95.9	98.8	132.5	115.6	151.8
		Per(Yr3)	442	426	96.4	94.2	97.9	70.6	61.6	81.0
		Per(Yr5)	371	362	97.6	95.4	98.9	77.4	66.9	89.6
		Pre_bst_009	118	117	99.2	95.4	100	64.7	50.3	83.3
ANTI-PT	Boostrix	Pre_bst_007	1434	825	57.5	54.9	60.1	7.3	6.9	7.7
		Post_bst_007	1430	1388	97.1	96.1	97.9	63.6	60.1	67.3
		Per(Yr1)	1013	917	90.5	88.6	92.3	22.4	21.0	24.0
		Per(Yr3)	914	751	82.2	79.5	84.6	14.0	13.0	15.0
		Per(Yr5)	790	670	84.8	82.1	87.2	14.6	13.5	15.8
		Pre_bst_009	271	230	84.9	80.0	88.9	8.2	7.2	9.3
	Adacel	Pre_bst_007	722	444	61.5	57.8	65.1	8.1	7.5	8.8
		Post_bst_007	722	676	93.6	91.6	95.3	32.2	29.6	35.1
		Per(Yr1)	506	435	86.0	82.6	88.9	15.6	14.2	17.2
		Per(Yr3)	442	316	71.5	67.0	75.7	10.0	9.0	11.1
		Per(Yr5)	372	285	76.6	72.0	80.8	11.6	10.3	13.0
		Pre_bst_009	120	106	88.3	81.2	93.5	7.8	6.5	9.4

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study
*Note: For the time points Pre-bst-007 to Yr5, the assay cut off and unit was 5 EL.U/ml, however the assay cut off and unit at Yr9 has changed to 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN

7.3.2. Immunogenicity of *Boostrix*

One month after booster vaccination,

- All subjects in three Groups were seropositive against FHA and PRN antigens and 98.9% of subjects in the Boostrix Group, 99.2% of subjects in the Adacel Group and 98.8% of subjects in the Control Group were seropositive against PT antigen (Table 33).
- Anti-Diphtheria antibody concentrations ≥ 0.1 IU/mL was observed in at least 99.2% of subjects in the Boostrix and Adacel Groups and 97.9% of subjects in the Control Group. Anti-Diphtheria antibody concentrations ≥ 1 IU/mL was observed in 91.9%, 93.4% and 86.5% of subjects in the Boostrix, Adacel and Control Groups, respectively (Table 34).
- Anti-Tetanus antibody concentrations ≥ 0.1 IU/mL was observed in all subjects (100%) in the Boostrix and Adacel Groups and 99.7% of subjects in the Control Group. Anti-Tetanus antibody concentrations ≥ 1 IU/mL was observed in all subjects in the Adacel Group and 99.3% and 97.6% of subjects in the Boostrix, Adacel and Control Groups, respectively (Table 34).

The results for the percentage of subjects with anti-Diphtheria, anti-Tetanus, anti- PT, anti-FHA, anti- PRN antibody concentrations at pre and post booster vaccination time points by age stratum and gender are presented Table 7.29, Table 7.30, Table 7.35 and Table 7.36.

RCCs of anti-Diphtheria, anti-Tetanus anti- PT, anti-FHA and anti- PRN, antibody concentrations per Group at pre and post booster vaccination time point are presented in Figure 7.2, Figure 7.4, Figure 7.6, Figure 7.8 and Figure 7.10, respectively. Despite the lower booster response observed in the Boostrix and Adacel Groups, the distribution of titre post vaccination was similar to the Control Group as shown by the RCCs.

- The GMCs for antibodies against diphtheria, tetanus and pertussis antigens in both groups one month after the first and second booster vaccination predicted by modelling are presented in Table 7.22 to Table 7.26 and Figure 7.16 to Figure 7.20.

Table 33 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity at Year 9)

				≥ Assay cut off				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-FHA	Boostrix	Pre_bst_009	271	271	100	98.6	100	42.2	37.6	47.5
		Post_bst_009	271	271	100	98.6	100	247.9	227.3	270.3
	Adacel	Pre_bst_009	120	119	99.2	95.4	100	28.4	24.0	33.4
		Post_bst_009	121	121	100	97.0	100	254.6	218.9	296.1
	Control	Pre_bst_009	327	322	98.5	96.5	99.5	23.6	20.6	27.1
		Post_bst_009	327	327	100	98.9	100	373.6	336.5	414.8
ANTI-PRN	Boostrix	Pre_bst_009	271	267	98.5	96.3	99.6	63.8	53.1	76.7
		Post_bst_009	271	271	100	98.6	100	405.4	359.3	457.5
	Adacel	Pre_bst_009	118	117	99.2	95.4	100	64.7	50.3	83.3
		Post_bst_009	121	121	100	97.0	100	511.8	427.8	612.2
	Control	Pre_bst_009	321	284	88.5	84.5	91.8	17.8	14.7	21.6
		Post_bst_009	326	326	100	98.9	100	336.4	283.3	399.4
ANTI-PT	Boostrix	Pre_bst_009	271	230	84.9	80.0	88.9	8.2	7.2	9.3
		Post_bst_009	271	268	98.9	96.8	99.8	64.1	56.8	72.3
	Adacel	Pre_bst_009	120	106	88.3	81.2	93.5	7.8	6.5	9.4
		Post_bst_009	121	120	99.2	95.5	100	70.4	58.6	84.5
	Control	Pre_bst_009	327	209	63.9	58.4	69.1	5.4	4.7	6.2
		Post_bst_009	326	322	98.8	96.9	99.7	66.2	58.5	74.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 =Pre booster vaccination blood sampling time point
Post_bst_009 = Post booster vaccination blood sampling time point
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 34 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at pre and post booster vaccination time points (ATP cohort for analysis of immunogenicity at Year 9)

				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	Pre_bst_009	269	245	91.1	87.0	94.2	114	42.4	36.4	48.5	0.7	0.6	0.8
		Post_bst_009	271	269	99.3	97.4	99.9	249	91.9	88.0	94.8	4.1	3.6	4.7
	Adacel	Pre_bst_009	118	113	95.8	90.4	98.6	54	45.8	36.6	55.2	0.8	0.6	0.9
		Post_bst_009	121	120	99.2	95.5	100	113	93.4	87.4	97.1	4.7	3.9	5.7
	Control	Pre_bst_009	324	265	81.8	77.1	85.8	92	28.4	23.5	33.6	0.4	0.4	0.5
		Post_bst_009	326	319	97.9	95.6	99.1	282	86.5	82.3	90.0	4.0	3.4	4.6
ANTI-T	Boostrix	Pre_bst_009	268	263	98.1	95.7	99.4	211	78.7	73.3	83.5	1.8	1.6	2.0
		Post_bst_009	271	271	100	98.6	100	269	99.3	97.4	99.9	8.4	7.7	9.3
	Adacel	Pre_bst_009	120	120	100	97.0	100	101	84.2	76.4	90.2	2.3	2.0	2.7
		Post_bst_009	121	121	100	97.0	100	121	100	97.0	100	8.6	7.6	9.8
	Control	Pre_bst_009	324	304	93.8	90.6	96.2	231	71.3	66.0	76.2	1.5	1.3	1.7
		Post_bst_009	327	326	99.7	98.3	100	319	97.6	95.2	98.9	8.8	8.0	9.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 =Pre booster vaccination blood sampling time point
Post_bst_009 = Post booster vaccination blood sampling time point

7.3.3. Booster response to diphtheria, tetanus and pertussis

One month after booster vaccination,

- At least 60.2% of subjects in all Groups showed a booster response to diphtheria antigen in the ATP cohort for analysis of immunogenicity at Year 9. At least 47.0% of subjects in the Boostrix and Control Groups, 36.7% of subjects in the Adacel Group showed a booster response to tetanus antigen (Table 35).
- Booster response to FHA antigen was observed in 85.6%, 96.7% and 92.7% of subjects in Boostrix Group, Adacel Group and Control Group, respectively (Table 36).
- Booster response to PRN antigen was observed in 77.5%, 83.1% and 87.8% of subjects in Boostrix Group, Adacel Group and Control Group, respectively (Table 36).
- Booster response to PT antigen was observed in 86.7%, 88.3% and 89.6% of subjects in Boostrix Group, Adacel Group and Control Group, respectively (Table 36).

The alternative booster responses to anti-Diphtheria and anti-Tetanus, anti-PT, anti-FHA and anti-PRN antigens are presented in Table 7.2 and Table 7.3. The booster responses to anti-Diphtheria and anti-Tetanus, anti-PT, anti-FHA and anti-PRN antigens ATP cohort for analysis of immunogenicity at Year 9 by age stratum and for TVC cohort at Year 9 are presented in Table 7.31, Table 7.32. Table 7.48 and Table 7.49.

Table 35 Booster response to anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
ANTI-D	Boostrix	S-	24	16	66.7	44.7	84.4
		S+	245	153	62.4	56.1	68.5
		Total	269	169	62.8	56.7	68.6
	Adacel	S-	5	3	60.0	14.7	94.7
		S+	113	68	60.2	50.5	69.3
		Total	118	71	60.2	50.7	69.1
	Control	S-	58	35	60.3	46.6	73.0
		S+	265	187	70.6	64.7	76.0
		Total	323	222	68.7	63.4	73.7
ANTI-T	Boostrix	S-	5	5	100	47.8	100
		S+	263	121	46.0	39.9	52.2
		Total	268	126	47.0	40.9	53.2
	Adacel	S-	0	-	-	-	-
		S+	120	44	36.7	28.1	45.9
		Total	120	44	36.7	28.1	45.9
	Control	S-	20	18	90.0	68.3	98.8
		S+	304	139	45.7	40.0	51.5
		Total	324	157	48.5	42.9	54.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
S- = Antibody concentration < 0.1 IU/mL
S+ = Antibody concentration ≥ 0.1 IU/mL
Total = subjects either seropositive or seronegative
Booster response to D and T antigens is defined as:
-For subjects with pre-vaccination concentration < 0.1 IU/ml (i.e. below the seroprotection cut-off), antibody concentrations at least ≥ 0.4 IU/ml one month after vaccination, and- For subjects with pre-vaccination concentration ≥ 0.1 IU/ml (i.e. equal or above the seroprotection cut-off), an increase in antibody concentrations of at least four times the pre-vaccination concentration one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 36 Booster response for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

				Booster response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
ANTI-FHA	Boostrix	S-	0	-	-	-	-
		S+ (<4*cut_off)	16	16	100	79.4	100
		S+ (≥4*cut_off)	255	216	84.7	79.7	88.9
		Total	271	232	85.6	80.9	89.6
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	9	9	100	66.4	100
		S+ (≥4*cut_off)	110	106	96.4	91.0	99.0
		Total	120	116	96.7	91.7	99.1
	Control	S-	5	5	100	47.8	100
		S+ (<4*cut_off)	71	70	98.6	92.4	100
		S+ (≥4*cut_off)	251	228	90.8	86.6	94.1
		Total	327	303	92.7	89.3	95.2
ANTI-PRN	Boostrix	S-	4	4	100	39.8	100
		S+ (<4*cut_off)	29	27	93.1	77.2	99.2
		S+ (≥4*cut_off)	238	179	75.2	69.2	80.6
		Total	271	210	77.5	72.0	82.3
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	10	10	100	69.2	100
		S+ (≥4*cut_off)	107	87	81.3	72.6	88.2
		Total	118	98	83.1	75.0	89.3
	Control	S-	37	31	83.8	68.0	93.8
		S+ (<4*cut_off)	78	75	96.2	89.2	99.2
		S+ (≥4*cut_off)	205	175	85.4	79.8	89.9
		Total	320	281	87.8	83.7	91.2
ANTI-PT	Boostrix	S-	41	34	82.9	67.9	92.8
		S+ (<4*cut_off)	124	106	85.5	78.0	91.2
		S+ (≥4*cut_off)	106	95	89.6	82.2	94.7
		Total	271	235	86.7	82.1	90.5
	Adacel	S-	14	10	71.4	41.9	91.6
		S+ (<4*cut_off)	60	53	88.3	77.4	95.2
		S+ (≥4*cut_off)	46	43	93.5	82.1	98.6
		Total	120	106	88.3	81.2	93.5
	Control	S-	117	101	86.3	78.7	92.0
		S+ (<4*cut_off)	104	94	90.4	83.0	95.3
		S+ (≥4*cut_off)	105	97	92.4	85.5	96.7
		Total	326	292	89.6	85.7	92.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration above or equal to assay cut off for anti-PT, anti-FHA, anti-PRN)
Total = subjects either seropositive or seronegative
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,

For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

7.3.4. Exploratory Analyses

The results for the exploratory analyses one month after the booster vaccination are presented from Table 37 to Table 40.

The results for the exploratory analyses one month after the booster vaccination and alternative booster response to the diphtheria, tetanus and pertussis antigens are presented in Table 7.4 to Table 7.14, Table 7.37 to Table 7.38 and Table 7.50 to Table 7.54.

Table 37 Exploratory comparison: GMC ratio between Groups [Boostrix Group divided by Control Group] and their 95% CIs for anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					GMC ratio (Boostrix / Control)		
	Boostrix		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-D	271	4.1	326	4.0	1.03	0.83	1.26
ANTI-T	271	8.4	327	8.8	0.96	0.84	1.10

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 38 Exploratory comparison: GMC ratio between Groups [Boostrix Group divided by Control Group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					GMC ratio (Boostrix / Control)		
	Boostrix		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-FHA	271	247.9	327	373.6	0.66	0.58	0.76
ANTI-PRN	271	405.4	326	336.4	1.21	0.97	1.50
ANTI-PT	271	64.1	326	66.2	0.97	0.81	1.15

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 39 Exploratory comparison: GMC ratio between Groups [Adacel Group divided by Control Group] and their 95% CIs for anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					GMC ratio (Adacel / Control)		
	Adacel		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-D	121	4.7	326	4.0	1.18	0.89	1.56
ANTI-T	121	8.6	327	8.8	0.98	0.82	1.17

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 40 Exploratory comparison: GMC ratio between Groups [Adacel Group divided by Control Group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					GMC ratio (Adacel / Control)		
	Adacel		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-FHA	121	254.6	327	373.6	0.68	0.56	0.83
ANTI-PRN	121	511.8	326	336.4	1.52	1.13	2.06
ANTI-PT	121	70.4	326	66.2	1.06	0.85	1.34

Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model).

7.4. Total vaccinated cohort analysis

Since more than 5% (11.1%; Table 19) of the subjects with available immunogenicity data were eliminated from analysis for the ATP cohort for immunogenicity, an analysis based on the TVC was performed to complement the ATP analysis.

The immunogenicity results based on TVC are comparable to the ATP cohorts and are presented from Table 7.39 to Table 7.44 and Table 7.48 to Table 7.49.

7.5. Immunogenicity summary

- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 95.7% of subjects at Year 1 to 91.1% of subjects at Year 9 (by ELISA) and from 98.3% of subjects at Year 1 to 99.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Boostrix Group. Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 98.6% of subjects at Year 1 to 98.1% of subjects at Year 9 in the Boostrix Group.

- Persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 97.0% of subjects at Year 1 to 95.8% of subjects at Year 9 (by ELISA) and from 98.2% of subjects at Year 1 to 98.3% of subjects at Year 9 (by Vero cell neutralization assay) in the Adacel Group. Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 99.6% of subjects at Year 1 to 100% of subjects at Year 9 in the Adacel Group.
- The GMCs for antibodies against both diphtheria and tetanus antigens in both Groups reached a peak response post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1 and gradually kept decreasing till the Year 9 time point.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) was non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to seroprotection rate against diphtheria and tetanus antigens, was met, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group differences [Boostrix Group minus Control Group and Adacel Group minus Control Group] in the booster response to the diphtheria and tetanus antigens was above the pre-specified lower limit of -10%.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group and Adacel Group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to anti-PT, anti-FHA and anti-PRN antibody concentrations, was met, as, one month after the booster vaccination, the lower limit of the 97.5% CIs on the GMC ratios (Boostrix Group divided by Infanrix Group in APV-039 and Adacel Group divided by Infanrix Group in APV-039) for the PT, FHA and PRN antigens was above the pre-specified lower limit of 0.67.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met for all antigens except PT, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Boostrix Group minus Control Group] in the booster response to the diphtheria, tetanus, FHA and PRN antigens was below the pre-specified lower limit of -10%.
- The co-primary objective to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Adacel Group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine, *Boostrix* (Control Group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens was not met for all antigens except FHA, as one month after the booster vaccination, the lower limit of the standardised asymptotic 97.5% CIs on the group difference [Adacel Group minus Control Group] in the booster response to the diphtheria, tetanus, PT and PRN antigens was below the pre-specified lower limit of - 10%.

- GMCs for anti-FHA, anti-PRN and anti-PT which reached a peak response at post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1, and continued the gradual decline at Year 3, Year 5 and Year 9 for both Groups. Due to pertussis assay revalidation, the calibration performed led to a decrease in GMC by approximately 2-fold for FHA antigen results.
- At least 98.8% of subjects were seropositive against PT, FHA and PRN antigens in all three Groups, one month after the booster vaccination. At least 97.9% of subjects were seroprotected against diphtheria antigens (antibody concentrations ≥ 0.1 IU/mL), one month after the booster vaccination. At least 99.7% of subjects were seroprotected against tetanus antigens (antibody concentrations ≥ 0.1 IU/mL).

8. SAFETY RESULTS

8.1. Total vaccinated cohort analysis

The analysis of safety was performed on TVC at Year 9.

The number and percentage of subjects who received vaccine doses are reported in Table 8.1. The compliance in returning symptom sheets are reported in Table 8.2, respectively.

8.1.1. Overall incidence of adverse events

During the 4-day (Days 0-3) post-vaccination period:

- Any symptom (solicited and unsolicited) was reported for 69.6% in the Boostrix Group, 70.1% in the Adacel Group and 48.3% of subjects in the Control Group (Table 8.4).
- Any Grade 3 symptom (solicited and unsolicited) was reported for 3.3% in the Boostrix Group, 5.1% in the Adacel Group and 2.5% of subjects in the Control Group (Table 8.5).
- Any symptom (solicited or unsolicited) that was considered by the investigator as being potentially causally related to vaccination was reported for 68.6% in the Boostrix Group, 68.6% in the Adacel Group and 45.5% of subjects in the Control Group. Majority of these symptoms were local symptoms (Table 8.6).
- Any symptom (solicited or unsolicited) that required medical attention during the 4-day (Days 0-3) follow-up period was reported for 0.7% in the Boostrix Group, 2.9% in the Adacel Group and 0.8% of subjects in the Control Group (Table 8.7).

8.1.2. Solicited local adverse events

The incidence of solicited local symptoms reported during the 4-day (Days 0-3) post vaccination period for TVC at Year 9 are presented in Table 41.

The incidence of solicited local symptoms reported during the 4-day (Days 0-3) post vaccination period by age stratum and by gender for TVC at Year 9 are presented in Table 8.13 and Table 8.15.

- Higher incidences of local symptoms were observed in the Boostrix and Adacel groups as compared to the Control group. Pain was the most frequently reported solicited local symptom, reported for 58.8% in the Boostrix Group, 61.3% in the Adacel Group and 36.9% of subjects in the Control Group (Table 41).
- In the Boostrix and Adacel Groups, redness was the most frequently reported Grade 3 solicited local symptom (1.6% of subjects in the Boostrix Group and 1.5% of subjects in the Adacel Group). None of the subjects in the Control Group reported redness of Grade 3 intensity; pain was the most frequently reported Grade 3 solicited local symptom in this group (for 1.1% of subjects; Table 41).

Table 41 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix					Adacel					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	306	180	58.8	53.1	64.4	137	84	61.3	52.6	69.5	358	132	36.9	31.9	42.1
	Grade 2 or 3	306	51	16.7	12.7	21.3	137	21	15.3	9.7	22.5	358	31	8.7	6.0	12.1
	Grade 3	306	3	1.0	0.2	2.8	137	1	0.7	0.0	4.0	358	4	1.1	0.3	2.8
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
Redness (mm)	All	306	74	24.2	19.5	29.4	137	32	23.4	16.6	31.3	358	53	14.8	11.3	18.9
	>20	306	17	5.6	3.3	8.7	137	5	3.6	1.2	8.3	358	4	1.1	0.3	2.8
	≥50mm	306	5	1.6	0.5	3.8	137	2	1.5	0.2	5.2	358	0	0.0	0.0	1.0
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
Swelling (mm)	All	306	57	18.6	14.4	23.4	137	26	19.0	12.8	26.6	358	41	11.5	8.3	15.2
	>20	306	8	2.6	1.1	5.1	137	4	2.9	0.8	7.3	358	10	2.8	1.3	5.1
	≥50mm	306	4	1.3	0.4	3.3	137	2	1.5	0.2	5.2	358	2	0.6	0.1	2.0
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

8.1.3. Solicited general adverse events

The incidence of solicited general symptoms reported during the 4-day (Days 0-3) post vaccination period for Total vaccinated cohort at Year 9 is presented in Table 42.

The incidence of solicited general symptoms reported during the 4-day (Days 0-3) post vaccination period by age stratum and by gender for TVC at Year 9 are presented in Table 8.14 and Table 8.16.

- Fatigue was the most frequently reported solicited general symptom in the Boostrix Group (for 23.2% of subjects) whereas in Adacel and Control Groups, headache was the most frequently reported solicited general symptom (for 18.2% and 14.8% of subjects, respectively; Table 42).

- In the Boostrix Group, fatigue was also the most frequently reported Grade 3 solicited general symptom (for 1.0% of subjects) whereas in Adacel and Control Groups, headache was the most frequently reported Grade 3 solicited general symptom (for 0.7% and 0.3% of subjects, respectively; Table 42).
- Fever (≥37.5 C) was reported for less than 1% of subjects in all Groups (none in Adacel Group). No Grade 3 fever (>39) was reported for any of the subjects (Table 42).

Table 42 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix					Adacel					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	All	306	71	23.2	18.6	28.3	137	23	16.8	11.0	24.1	358	51	14.2	10.8	18.3
	Grade 2 or 3	306	23	7.5	4.8	11.1	137	10	7.3	3.6	13.0	358	9	2.5	1.2	4.7
	Grade 3	306	3	1.0	0.2	2.8	137	1	0.7	0.0	4.0	358	0	0.0	0.0	1.0
	Related	306	57	18.6	14.4	23.4	137	21	15.3	9.7	22.5	358	34	9.5	6.7	13.0
	Grade 3 Related	306	3	1.0	0.2	2.8	137	1	0.7	0.0	4.0	358	0	0.0	0.0	1.0
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
Gastrointestinal symptoms	All	306	27	8.8	5.9	12.6	137	4	2.9	0.8	7.3	358	29	8.1	5.5	11.4
	Grade 2 or 3	306	6	2.0	0.7	4.2	137	0	0.0	0.0	2.7	358	9	2.5	1.2	4.7
	Grade 3	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	Related	306	18	5.9	3.5	9.1	137	4	2.9	0.8	7.3	358	17	4.7	2.8	7.5
	Grade 3 Related	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
Headache	All	306	52	17.0	13.0	21.7	137	25	18.2	12.2	25.7	358	53	14.8	11.3	18.9
	Grade 2 or 3	306	12	3.9	2.0	6.7	137	6	4.4	1.6	9.3	358	8	2.2	1.0	4.4
	Grade 3	306	0	0.0	0.0	1.2	137	1	0.7	0.0	4.0	358	1	0.3	0.0	1.5
	Related	306	37	12.1	8.7	16.3	137	19	13.9	8.6	20.8	358	28	7.8	5.3	11.1
	Grade 3 Related	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	Medical advice	306	1	0.3	0.0	1.8	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
Temperature (°C)	All	306	2	0.7	0.1	2.3	137	0	0.0	0.0	2.7	358	2	0.6	0.1	2.0
	>38.5	306	1	0.3	0.0	1.8	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	>39.0	306	1	0.3	0.0	1.8	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	>39.5	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	>40.0	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	Related	306	2	0.7	0.1	2.3	137	0	0.0	0.0	2.7	358	2	0.6	0.1	2.0
	>40.0 Related	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0
	Medical advice	306	0	0.0	0.0	1.2	137	0	0.0	0.0	2.7	358	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

8.1.4. Unsolicited adverse events

The percentage of subjects reporting the occurrence of Grade 3 unsolicited adverse events and unsolicited adverse events with causal relationship to vaccination classified by MedDRA Primary System Organ Class and Preferred Term occurring within the 31-days (Day 0-30) post-vaccination period and with causal relationship to vaccination, occurring within 31 days (Day 0-30) post vaccination period for Total vaccinated cohort are presented in Table 43 and Table 44.

The percentage of subjects reporting the occurrence of unsolicited adverse events and occurrence of unsolicited adverse events medically attended visit classified by MedDRA Primary System Organ Class and Preferred Term occurring within the 31-days (Day 0-30) post-vaccination period for Total vaccinated cohort are presented in Table 8.8 and Table 8.9.

- At least one Grade 3 unsolicited adverse event was reported for five subjects (1.6%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and nine subjects (2.5%) in the Control Group (Table 43).
- At least one unsolicited adverse event with causal relationship to vaccination was reported for 14 subjects (4.5%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and four subjects (1.1%) in the Control Group (Table 44).

Table 43 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Days 0-30) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		5	1.6	0.5	3.7	3	2.2	0.5	6.2	9	2.5	1.1	4.7
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Abdominal pain upper (10000087)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Diarrhoea (10012735)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Immune system disorders (10021428)	Food allergy (10016946)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
Infections and infestations (10021881)	Influenza (10022000)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Tonsillitis (10044008)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Viral upper respiratory tract infection (10047482)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	2	0.6	0.1	2.0
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Muscle strain (10050031)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Skin abrasion (10064990)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Sunburn (10042496)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Musculoskeletal and connective tissue disorders (10028395)	Back pain (10003988)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Musculoskeletal pain (10028391)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Neck pain (10028836)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Pain in extremity (10033425)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
Nervous system disorders (10029205)	Headache (10019211)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Seizure (10039906)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Urticaria (10046735)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 44 Percentage of subjects reporting the occurrence of unsolicited symptoms with causal relationship to vaccination classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Days 0-30) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		14	4.5	2.5	7.5	3	2.2	0.5	6.2	4	1.1	0.3	2.8
Gastrointestinal disorders (10017947)	Gastrointestinal disorder (10017944)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
General disorders and administration site conditions (10018065)	Axillary pain (10048750)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Influenza like illness (10022004)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Injection site bruising (10022052)	3	1.0	0.2	2.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Injection site erythema (10022061)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site induration (10022075)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site joint pain (10049261)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site pain (10022086)	1	0.3	0.0	1.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Injection site pruritus (10022093)	4	1.3	0.4	3.3	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Injection site swelling (10053425)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Malaise (10025482)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Pain (10033371)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Vaccination site reaction (10059080)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Musculoskeletal and connective tissue disorders (10028395)	Arthralgia (10003239)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
Nervous system disorders (10029205)	Aura (10003791)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Dizziness (10013573)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Dysgeusia (10013911)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Psychiatric disorders (10037175)	Anxiety (10002855)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Respiratory, thoracic and mediastinal disorders (10038738)	Dry throat (10013789)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Dysphonia (10013952)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Vocal cord dysfunction (10047671)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

8.2. Serious adverse events

One SAE was reported during the study (nervous system disorders) in the Control Group (Table 45).

The serious adverse event (SAE) Listing Table(s) are in Section 13.1 and the SAE clinical narratives are in Section 13.2.

Table 45 Number (%) of subjects with serious adverse events reported during the entire study period including number of events reported (Total Vaccinated Cohort at Year 9)

			Boostrix N = 309			Adacel N = 138			Control N = 362		
Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**n***	**n**	**%**	**n***	**n**	**%**	**n***	**n**	**%**
SAE	At least one symptom		0	0	0.0	0	0	0.0	1	1	0.3
	Nervous system disorders (10029205)	Seizure (10039906)	0	0	0.0	0	0	0.0	1	1	0.3
Related SAE	At least one symptom		0	0	0.0	0	0	0.0	0	0	0.0
Fatal SAE	At least one symptom		0	0	0.0	0	0	0.0	0	0	0.0
Related fatal SAE	At least one symptom		0	0	0.0	0	0	0.0	0	0	0.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

8.2.1. Fatal events

No fatal events were reported during the study period.

8.2.2. Non-fatal events

The SAE Listing Table is presented in Section 13.1.

One SAE (nervous system disorders) was reported in the Control Group during the study, which was considered by the investigator as not causally related to the vaccination. The SAE was of Grade 3 intensity and had resolved by the end of the study.

8.3. Adverse events leading to premature discontinuation of study vaccine and/or study

No AEs leading to premature discontinuation of the study vaccine and/or study were reported.

8.4. Other significant adverse events

No other significant AEs were reported in the study.

8.5. Concomitant medications /vaccinations

The results of concomitant medications over the 4-day and 31-day follow-up periods are detailed in Table 8.10 and Table 8.11, respectively.

During the 4-day (Days 0-3) post-vaccination period:

- Any concomitant medication was administered to 11.0% of subjects in the Boostrix Group, 15.2% of subjects in the Adacel Group and 6.6% of subjects in the Control Group.
- Any antipyretic medication was administered to 7.4% of subjects in the Boostrix Group, 11.6% of subjects in the Adacel Group and 4.7% of subjects in the Control Group.
- Prophylactic antipyretic medication was not administered to any subject Group.

During the 31-day (Days 0-30) post-vaccination period:

- Any concomitant medication was administered to 18.1% of subjects in the Boostrix Group, 21.7% of subjects in the Adacel Group and 14.6% of subjects in the Control Group, respectively.
- Any antipyretic medication was administered to 12.0% of subjects in the Boostrix Group, 15.9% of subjects in the Adacel Group and 9.1% of subjects in the Control Group.
- *Prophylactic* antipyretic medication was not administered to any subject Group.

8.6. Pregnancy

No pregnancy was reported in this study.

8.7. Safety summary

- *Any symptom (solicited and unsolicited)*: Any symptom (solicited and unsolicited) was reported for 69.6% in the Boostrix Group, 70.1% in the Adacel Group and 48.3% of subjects in the Control Group. Any Grade 3 symptom (solicited and unsolicited) was reported for 3.3% in the Boostrix Group, 5.1% in the Adacel Group and 2.5% of subjects in the Control Group. Any symptom (solicited or unsolicited) that was considered by the investigator as being potentially causally related to vaccination, during the 4-day (Days 0-3) follow-up period was reported for 68.6% in the Boostrix Group, 68.6% in the Adacel Group and 45.5% of subjects in the Control Group. Majority of these symptoms were local symptoms.
- *Solicited local symptom*: During the 4-day (Days 0-3) post-vaccination period, higher incidences of local symptoms were observed in the Boostrix and Adacel groups as compared to the Control group. Pain was the most frequently reported solicited local symptom, reported for 58.8% in the Boostrix Group, 61.3% in the Adacel Group and 36.9% of subjects in the Control Group. In the Boostrix and Adacel Groups, redness was the most frequently reported Grade 3 solicited local

symptom (1.6% of subjects in the Boostrix Group and 1.5% of subjects in the Adacel Group). None of the subjects in the Control Group reported redness of Grade 3 intensity; pain was the most frequently reported Grade 3 solicited local symptom (for 1.1% of subjects) in this group.

- *Solicited general symptom*: Fatigue was the most frequently reported solicited general symptom in the Boostrix Group (for 23.2% of subjects) whereas in Adacel and Control Groups, headache was the most frequently reported solicited general symptom (for 18.2% and 14.8% of subjects, respectively). In the Boostrix Group, fatigue was also the most frequently reported Grade 3 solicited general symptom (for 1.0% of subjects) whereas in Adacel and Control Groups, headache was also the most frequently reported Grade 3 solicited general symptom (for 0.7% and 0.3% of subjects, respectively). Fever (≥37.5 C) was reported for less than 1% of subjects in all Groups (none in Adacel Group). No Grade 3 fever (>39) was reported for any of the subjects.
- *Unsolicited adverse events*: During the 31-day (Days 0-30) post-vaccination period, at least one Grade 3 unsolicited adverse event was reported for five subjects (1.6%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and nine subjects (2.5%) in the Control Group. At least one unsolicited adverse event with causal relationship to vaccination was reported for 14 subjects (4.5%) in the Boostrix Group, three subjects (2.2%) in the Adacel Group and four subjects (1.1%) in the Control Group.
- *SAEs*: One SAE (seizure) was reported in the Control Group during the study, which was considered by the investigator as not causally related to the vaccination. The SAE was of Grade 3 intensity and had resolved by the end of the study.
- *Withdrawals due to AEs/SAEs:* None of the subjects were withdrawn due to an AE or SAE, during the study period. There were also no large injection site reactions reported.
- *Pregnancy:* No pregnancies were reported in this study.

9. OVERALL CONCLUSIONS

- In the Boostrix Group, persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 95.7% of subjects at Year 1 to 91.1% of subjects at Year 9 (by ELISA) and from 98.3% of subjects at Year 1 to 99.3% of subjects at Year 9 (by Vero cell neutralization assay). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 98.6% of subjects at Year 1 to 98.1% of subjects at Year 9 in the Boostrix Group. In the Adacel Group, persistence of anti-Diphtheria antibodies (≥ 0.1 IU/mL) ranged from 97.0% of subjects at Year 1 to 95.8% of subjects at Year 9 (by ELISA) and from 98.2% of subjects at Year 1 to 98.3% of subjects at Year 9 (by Vero cell neutralization assay). Persistence of anti-Tetanus antibodies (≥ 0.1 IU/mL) ranged from 99.6% of subjects at Year 1 to 100% of subjects at Year 9 in the Adacel Group.
- The GMCs for antibodies against both diphtheria and tetanus antigens in both Groups reached a peak response post vaccination in study 106316 (Tdap 0.3-007), showed a sharp decrease at Year 1 and gradually kept decreasing till the Year 9 time point.
- The primary objectives of the study were partially met. Non-inferiority of the Boostrix Group to the Control Group was met for seroprotection for diphtheria and tetanus antigens, comparison with APV 039 with respect to pertussis antigens and was not met for the non-inferiority to the Control Group with respect to the booster response for diphtheria, tetanus and pertussis antigens. Non-inferiority of the Adacel Group to the Control Group was met for seroprotection for diphtheria and tetanus antigens, comparison with APV 039 with respect to pertussis antigens and was not met for the non-inferiority to the Control Group with respect to the booster response for diphtheria, tetanus and pertussis antigens.
- The GMCs for anti-FHA, anti-PRN and anti-PT which reached a peak response at post vaccination in study 106316 (Tdap 0.3-007) showed a sharp decrease at Year 1, continued the gradual decline at Year 3, Year 5 and Year 9 for both Groups.
- None of the subjects were withdrawn due to an AE or SAE, during the study period.
- One SAE (seizure) was reported in the Control Group during the study, which was considered by the investigator as not causally related to the vaccination. The SAE was of Grade 3 intensity and had resolved by the end of the study. There were no fatal SAEs reported in the study.

10. DISCUSSION

This section aims to put in perspective the failure to meet the primary confirmatory study objectives related to booster response for diphtheria, tetanus and pertussis antigens.

The study had less than 50% power to meet this objective due to low response rate expected in this older population.

The observed pre-booster GMC in the Boostrix and Adacel groups were higher than in the Control group. Considering that higher pre-vaccination titre is associated to a lower booster rate, this group unbalance favored the control group.

The other primary confirmatory objectives for anti-Diphtheria and anti-Tetanus demonstrated that non-inferiority was achieved in terms of seroprotection rate. In addition, comparably high GMC were observed post-vaccination in all groups for diphtheria and tetanus antigens.

The other primary confirmatory objectives for pertussis antigens demonstrated that non-inferiority was achieved in terms of GMC as compared to APV 039. In addition, comparably high GMC were observed post-vaccination in all groups for all pertussis antigens.

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12. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Clinical and Epidemiology Project Lead: PPD

13. SERIOUS ADVERSE EVENTS / OTHER SIGNIFICANT ADVERSE EVENTS / PREGNANCY

13.1. SAE Listing (Total Vaccinated Cohort at Year 9)

Group	Sub. No.	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MA type	Day of onset	Duration	Intensity	Causality	Outcome
Control	PPD	F	United States	White - Caucasian / European Heritage	50	seizure	Seizure	Nervous system disorders	HO	23	1	3	N	Recovered/resolved

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine *(Boostrix)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteur's Tdap vaccine *(Adacel)* in study 106316 (Tdap 0.3-007) and a second dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine *(Boostrix)* at Year 9 Visit 6
HO = Hospitalisation

13.2. Clinical narratives for SAEs and Pregnancy Case Narratives

Confidential
Unblinded Report – With Suspect Products and Serious and Non-Serious Events

Study Number: 110086

Study Center ID: PPD

Subject ID: PPD

Randomization Number: UNKNOWN

Case ID: PPD

Suspect Products: dTpa vaccine.

Serious Events: Seizure

Non-Serious Events:

Narrative: This 50-year-old female subject was enrolled in an open label study titled A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9. The subject received the 1st dose of dTpa vaccine (intramuscular) on 9th December 2015, for prophylaxis.

The subject's past medical history included syncopal attack.

On PPD 23 days after receiving dTpa vaccine, the subject developed severe - grade 3 seizure. Serious criteria included hospitalization and GSK medically significant. The outcome of seizure was recovered/resolved on 1st January 2016.

The investigator considered that there was no reasonable possibility that the seizure may have been caused by dTpa vaccine.

Relevant Tests: electroencephalogram

INVESTIGATOR TEXT
pt was awoken in early am of 1/1/16 with leg cramps, felt spinning sensation and lost consciousness which resulted in a fall where her left mandibular fracture. Pt was hospitalized 1/1/16-1/3/16 with episode felt to be due to seizure as eeg was abnormal.

14. POST-TEXT TABLES AND FIGURES

Table 6.1 Number of subjects by center (Total enrolled cohort)

	Boostrix	Adacel	Control	Total	
Center	n	n	n	n	%
PPD	55	23	0	78	3.5
	10	4	0	14	0.6
	21	10	0	31	1.4
	13	8	0	21	1.0
	17	8	0	25	1.1
	19	9	0	28	1.3
	18	7	0	25	1.1
	37	15	0	52	2.4
	27	16	0	43	1.9
	12	6	0	18	0.8
	20	9	0	29	1.3
	11	7	0	18	0.8
	12	5	0	17	0.8
	52	22	24	98	4.4
	8	2	0	10	0.5
	7	4	34	45	2.0
	31	14	0	45	2.0
	83	41	18	142	6.4
	53	27	25	105	4.8
	57	29	0	86	3.9
	17	7	19	43	1.9
	60	26	6	92	4.2
	75	39	10	124	5.6
	33	18	14	65	2.9
	12	7	40	59	2.7
	24	12	0	36	1.6
	59	30	7	96	4.3
	23	15	3	41	1.9
	30	15	14	59	2.7
	13	3	27	43	1.9
	28	13	6	47	2.1
	20	9	40	69	3.1
	81	39	1	121	5.5
	19	10	0	29	1.3
	10	7	14	31	1.4
	23	12	40	75	3.4
	37	23	0	60	2.7
	62	32	7	101	4.6
	50	24	14	88	4.0
All	1239	607	363	2209	100

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Table 6.2 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP for analysis of immunogenicity Year 1 cohort with reasons for exclusion (subset of subjects participating at year 1)

	Total			Boostrix		Adacel	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled Cohort at Year 1	1592		100	1069		523	
Administration of vaccine(s) forbidden in the protocol (code 1040)	8	8		6	6	2	2
Protocol violation (inclusion/exclusion criteria) (code 2010)	2	2		2	2	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	31	31		22	22	9	9
Essential serological data missing (code 2100)	4	5		4	5	0	0
Subjects eliminated from ATP cohort for immunogenicity in study Tdap 0.3-007 (code 2500)	26	28		20	22	6	6
ATP cohort for analysis of immunogenicity at Year 1	1521		95.5	1015		506	

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort

Table 6.3 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP for analysis of immunogenicity Year 3 cohort with reasons for exclusion (subset of subjects participating at year 3)

	Total			Boostrix		Adacel	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled Cohort at Year 3	1505		100	1019		486	
Administration of vaccine(s) forbidden in the protocol (code 1040)	39	39		28	28	11	11
Protocol violation (inclusion/exclusion criteria) (code 2010)	7	8		6	6	1	2
Administration of any medication forbidden by the protocol (code 2040)	0	8		0	6	0	2
Underlying medical condition forbidden by the protocol (code 2050)	0	4		0	2	0	2
Essential serological data missing (code 2100)	61	64		40	43	21	21
Subjects eliminated from ATP cohort for immunogenicity in study Tdap 0.3-007 (code 2500)	39	41		28	30	11	11
ATP cohort for analysis of immunogenicity at Year 3	1359		90.3	917		442	

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort

Table 6.4 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP for analysis of immunogenicity Year 5 cohort with reasons for exclusion (subset of subjects participating at year 5)

	Total			Boostrix		Adacel	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled Cohort at Year 5	1262		100	860		402	
Administration of vaccine(s) forbidden in the protocol (code 1040)	64	64		40	40	24	24
Administration of any medication forbidden by the protocol (code 2040)	11	12		9	9	2	3
Underlying medical condition forbidden by the protocol (code 2050)	2	6		2	4	0	2
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	1	1		1	1	0	0
Essential serological data missing (code 2100)	0	5		0	4	0	1
Subjects eliminated from ATP cohort for immunogenicity in study Tdap 0.3-007 (code 2500)	22	24		18	20	4	4
ATP cohort for analysis of immunogenicity at Year 5	1162		92.1	790		372	

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort

Table 6.5 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP for analysis of immunogenicity Year 9 cohort with reasons for exclusion(Total Vaccinated Cohort at Year 9)

	Total			Boostrix		Adacel		Control	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total Vaccinated Cohort at Year 9	809		100	309		138		362	
Administration of vaccine(s) forbidden in the protocol (code 1040)	27	27		11	11	2	2	14	14
Study vaccine dose not administered according to protocol (code 1070)	11	12		2	2	3	3	6	7
Administration of any medication forbidden by the protocol (code 2040)	4	5		2	3	0	0	2	2
Underlying medical condition forbidden by the protocol (code 2050)	2	2		1	1	1	1	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	11	11		6	6	3	3	2	2
Essential serological data missing (code 2100)	27	29		10	11	6	7	11	11
Obvious incoherence or abnormality or error in data (code 2120)	2	2		1	1	1	1	0	0
Subjects eliminated from atp cohort for immunogenicity in study tdap 0.3-007 (code 2500)	6	7		5	6	1	1	0	0
ATP cohort for analysis of immunogenicity at Year 9	719		88.9	271		121		327	

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort

Table 6.6 Deviations from specifications for age and intervals between study visits (Total enrolled cohort)

		Dose:1-Per(Yr1)	Dose:1-Per(Yr3)	Dose:1-Per(Yr5)		Dose:1-Pre_bst_009	
Group		**Protocol**	**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 47 to 57 weeks	from 151 to 161 weeks	from 255 to 265 weeks	from 252 to 268 weeks	from 105 to 111 months	from 102 to 114 months
Boostrix	N	1065	1017	856	856	476	476
	n	22	17	168	0	18	0
	%	2.1	1.7	19.6	0.0	3.8	0.0
	range	45 to 58	150 to 163	252 to 268	252 to 268	105 to 113	105 to 113
Adacel	N	523	484	401	401	232	232
	n	9	5	69	0	6	0
	%	1.7	1.0	17.2	0.0	2.6	0.0
	range	46 to 58	150 to 164	252 to 267	252 to 267	105 to 113	105 to 113

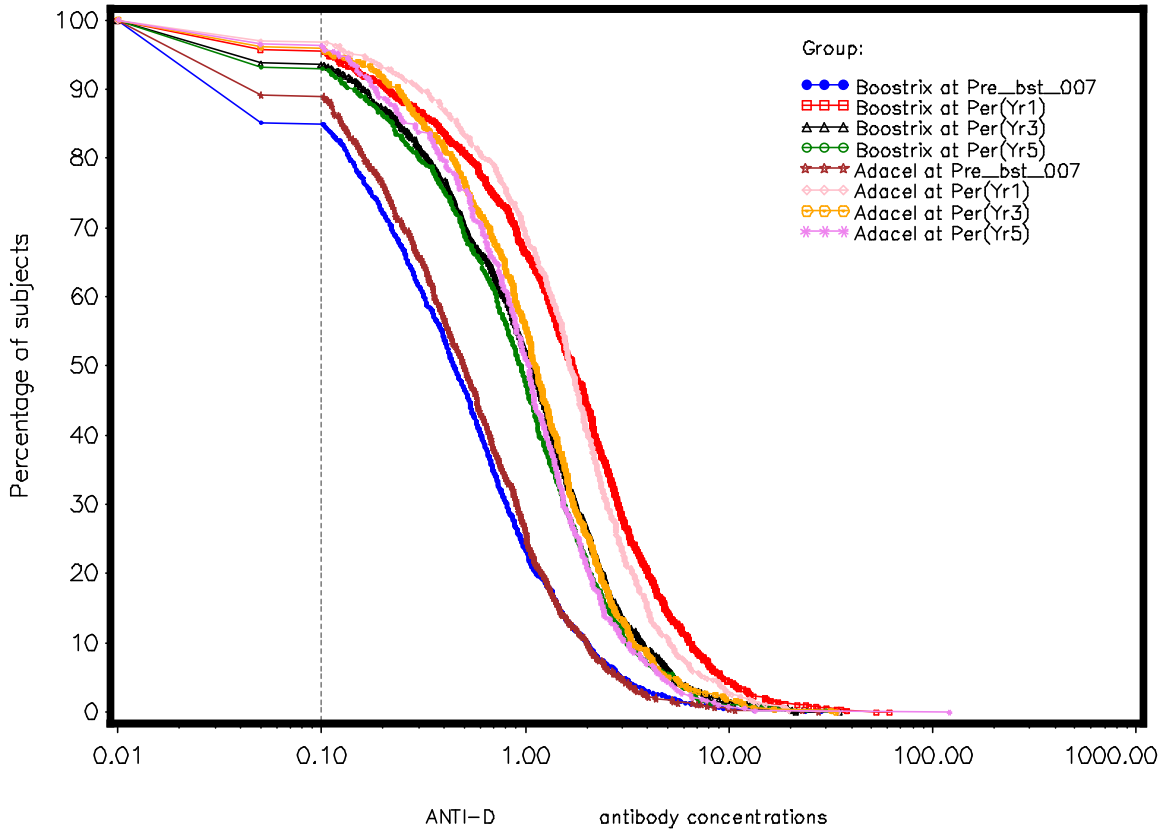
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for intervals
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study

Table 6.7 Deviations from specifications for age and intervals between study visits at Year 9 vaccination and one month post vaccination (Total Vaccinated Cohort at Year 9)

		Dose:2-Post_bst_009	
Group		**Protocol**	**Adapted**
		from 30 to 48 days	from 21 to 48 days
Boostrix	N	298	298
	n	23	6
	%	7.7	2.0
	range	21 to 72	21 to 72
Adacel	N	131	131
	n	9	3
	%	6.9	2.3
	range	21 to 71	21 to 71
Control	N	352	352
	n	9	2
	%	2.6	0.6
	range	21 to 56	21 to 56

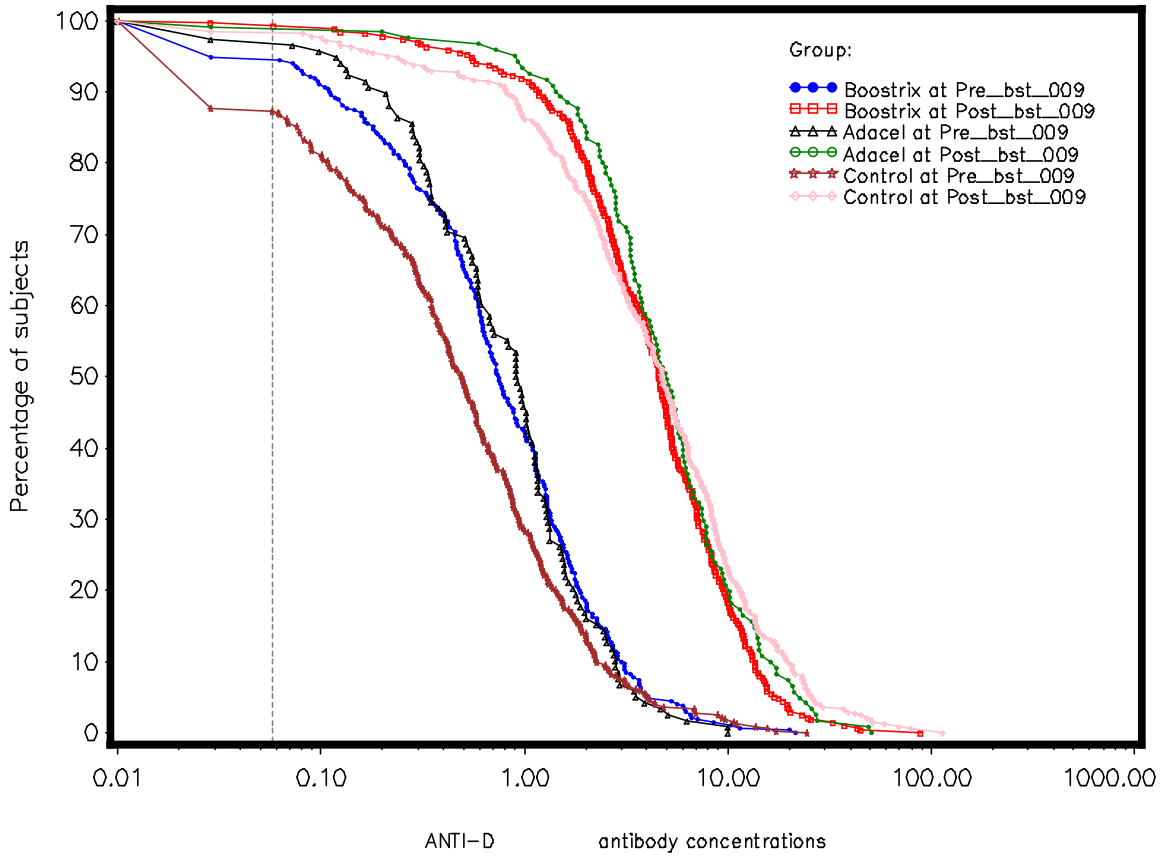
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for intervals
Post_bst_009 = Post booster vaccination blood sampling time-point

Figure 7.1 Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at the persistence time point (Adapted ATP cohort)



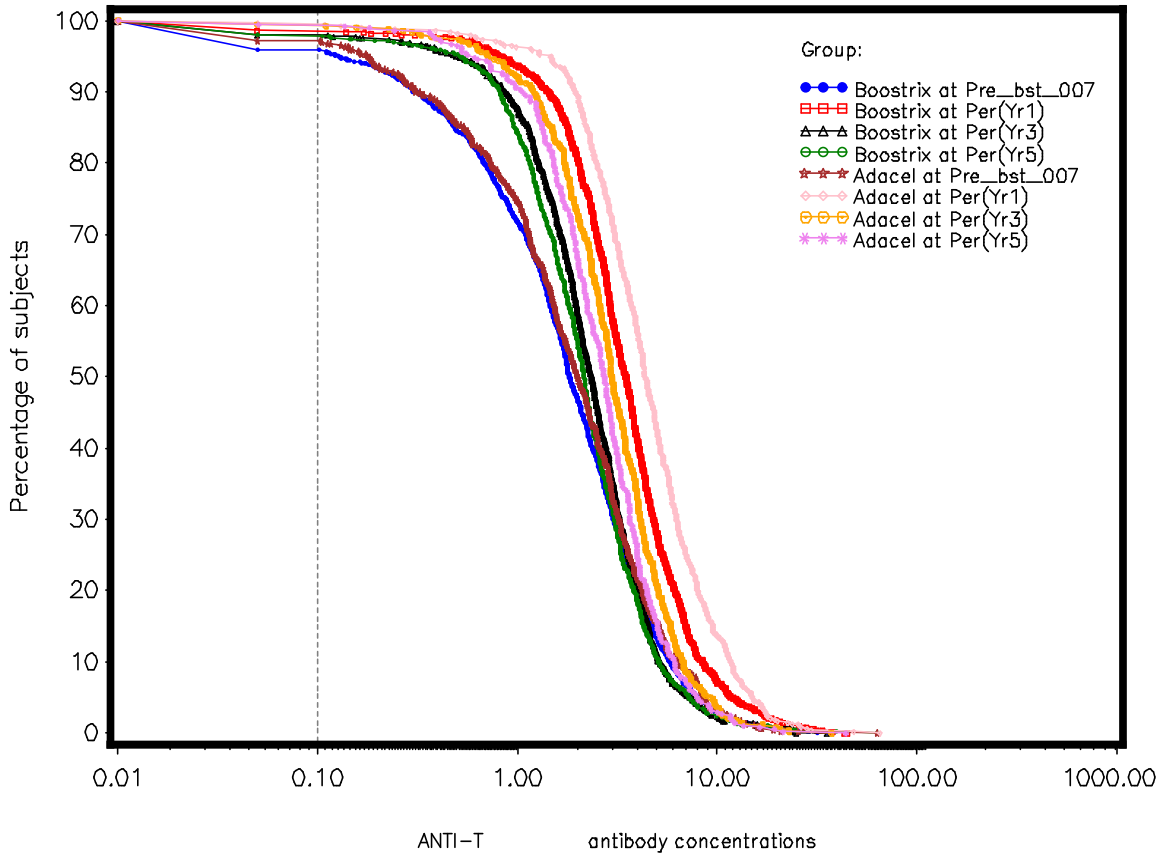
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-D antibody concentration (0.1 IU/mL)

Figure 7.2 Reverse cumulative distribution curve for anti-Diphtheria antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity at Year9)



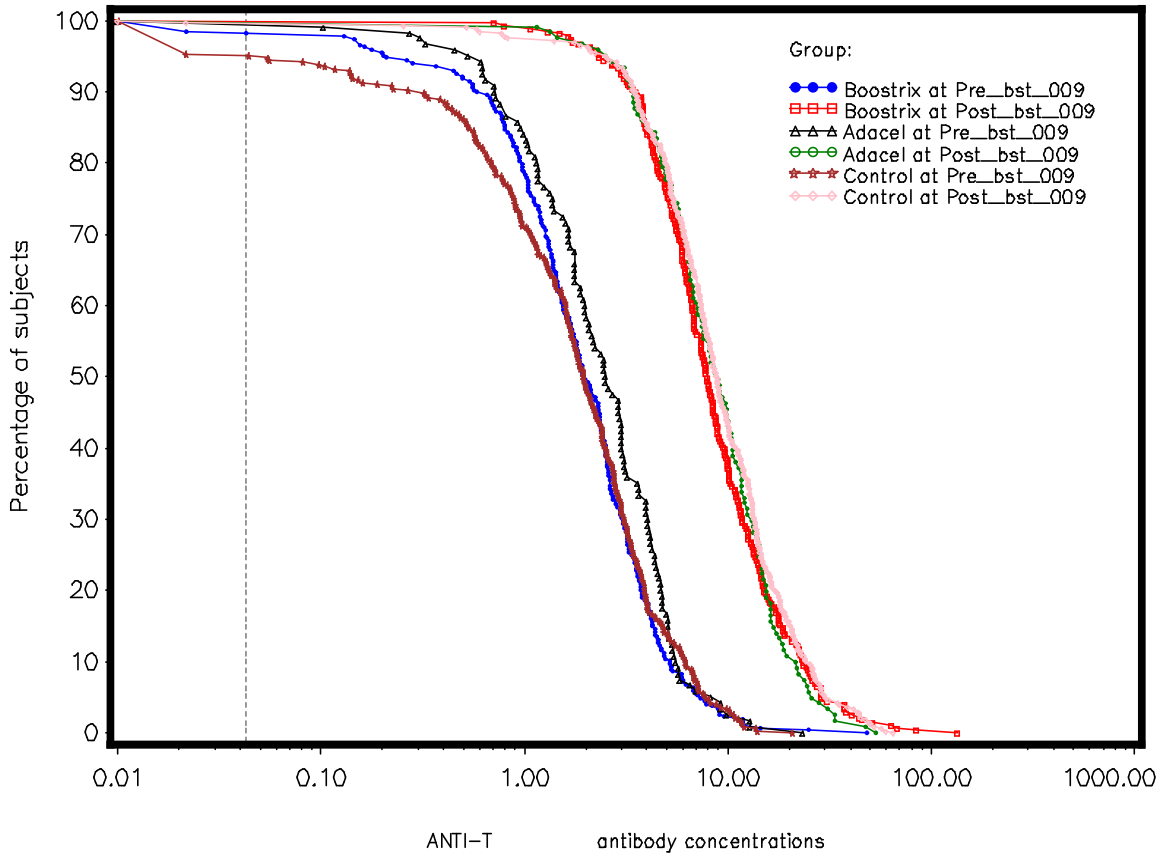
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-D antibody concentration (0.057 IU/mL)

Figure 7.3 Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at the persistence time point (Adapted ATP cohort)



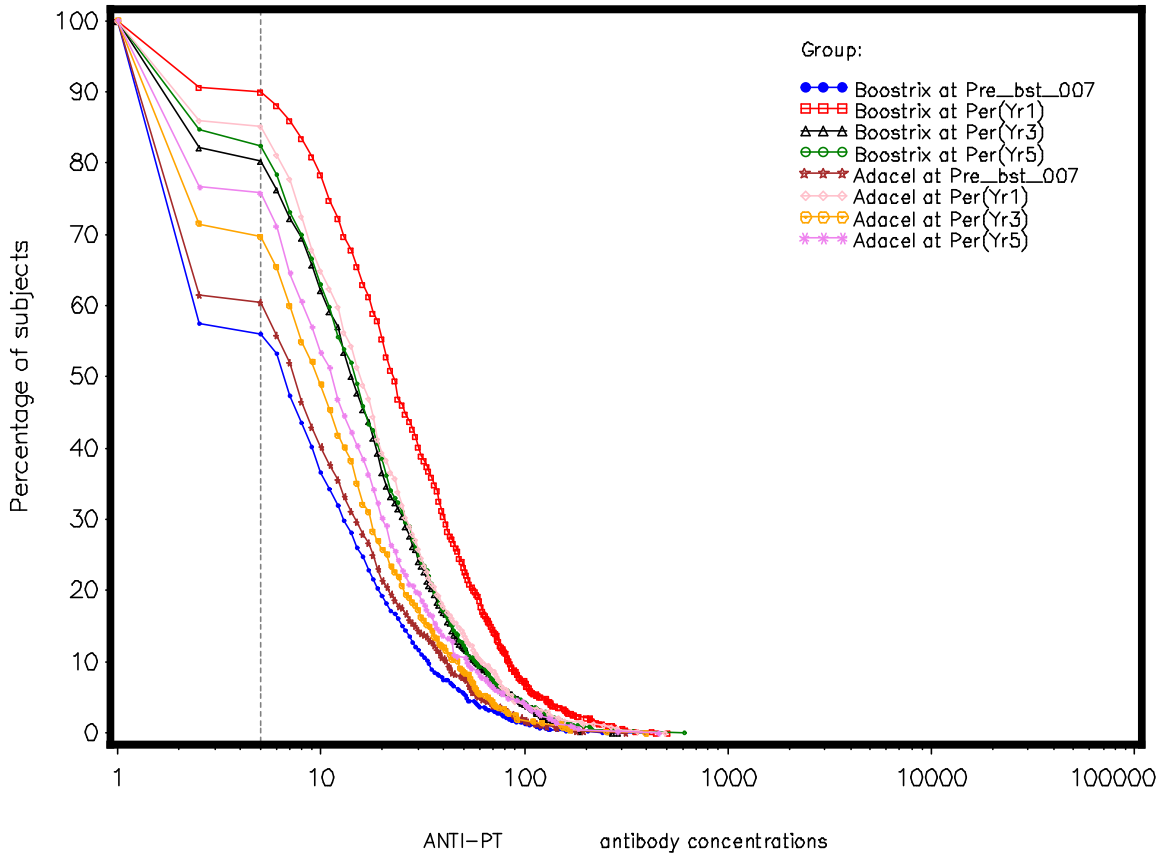
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-T antibody concentration (0.1 IU/mL)

Figure 7.4 Reverse cumulative distribution curve for anti-Tetanus antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity at Year 9)



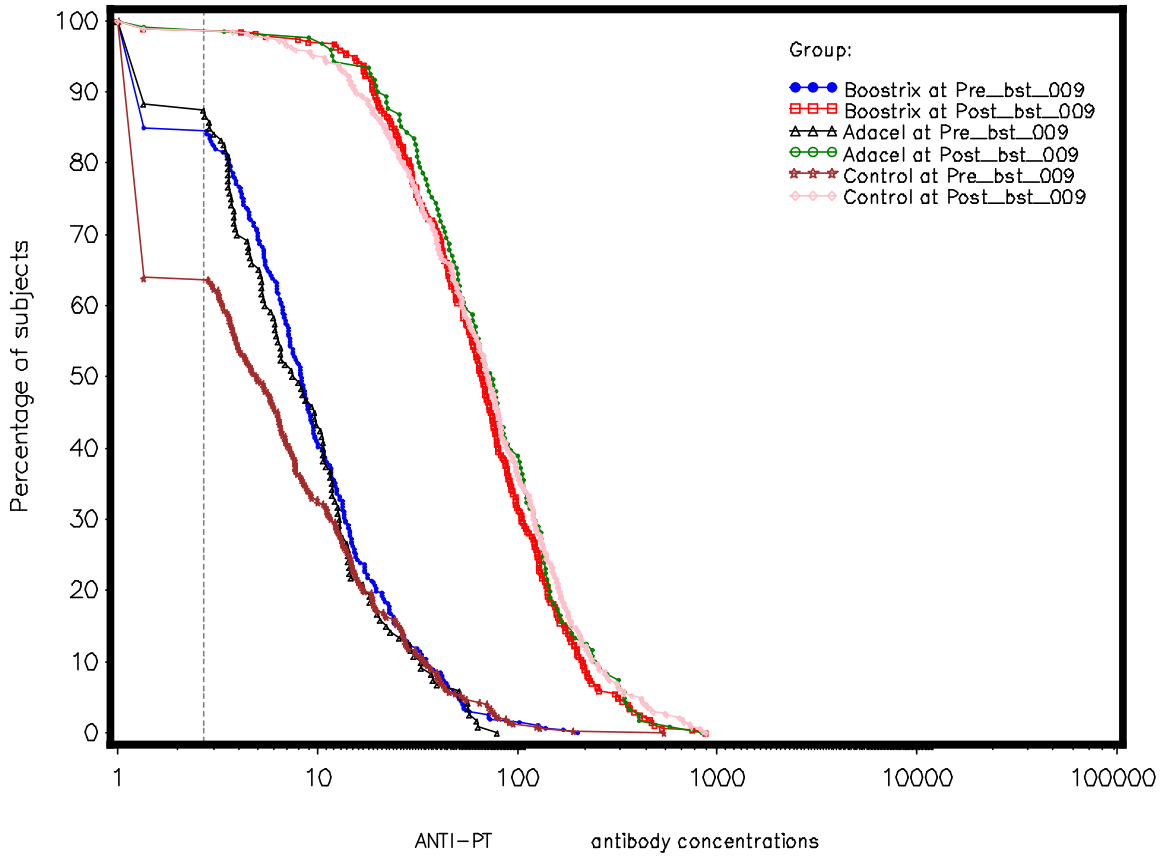
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-T antibody concentration (0.043 IU/mL)

Figure 7.5 Reverse cumulative distribution curve for anti-PT antibody concentrations per group at the persistence time point (Adapted ATP cohort)



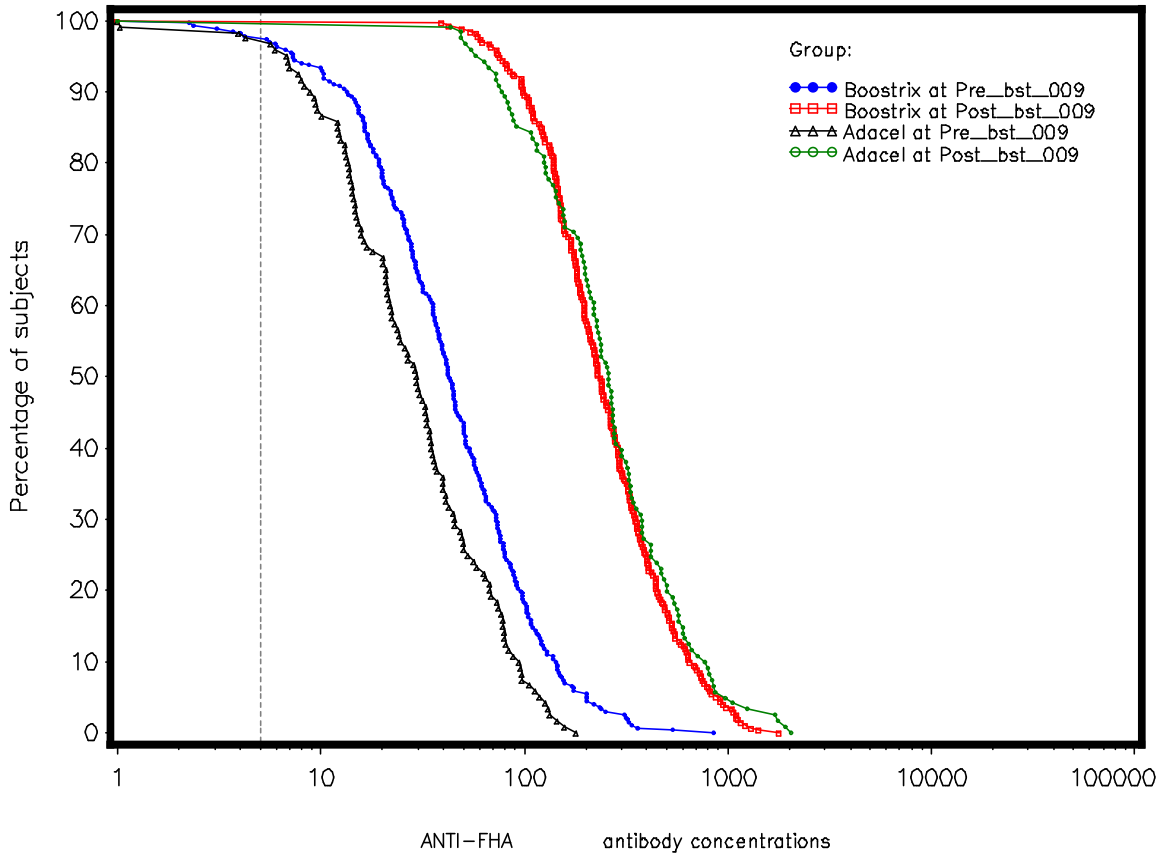
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-PT antibody concentration (5 ELU/mL)

Figure 7.6 Reverse cumulative distribution curve for anti-PT antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity at Year 9)



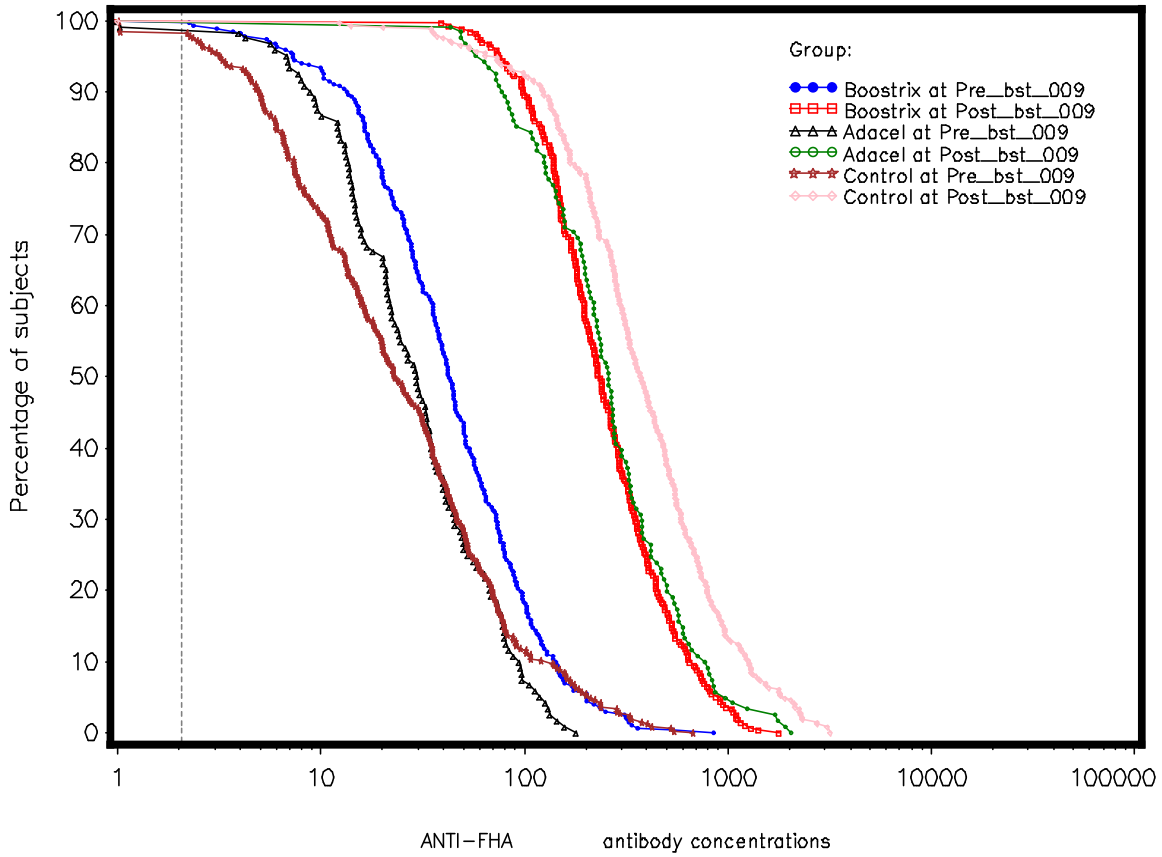
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-PT antibody concentration (2.693 IU/mL)

Figure 7.7 Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at the persistence time point (Adapted ATP cohort)



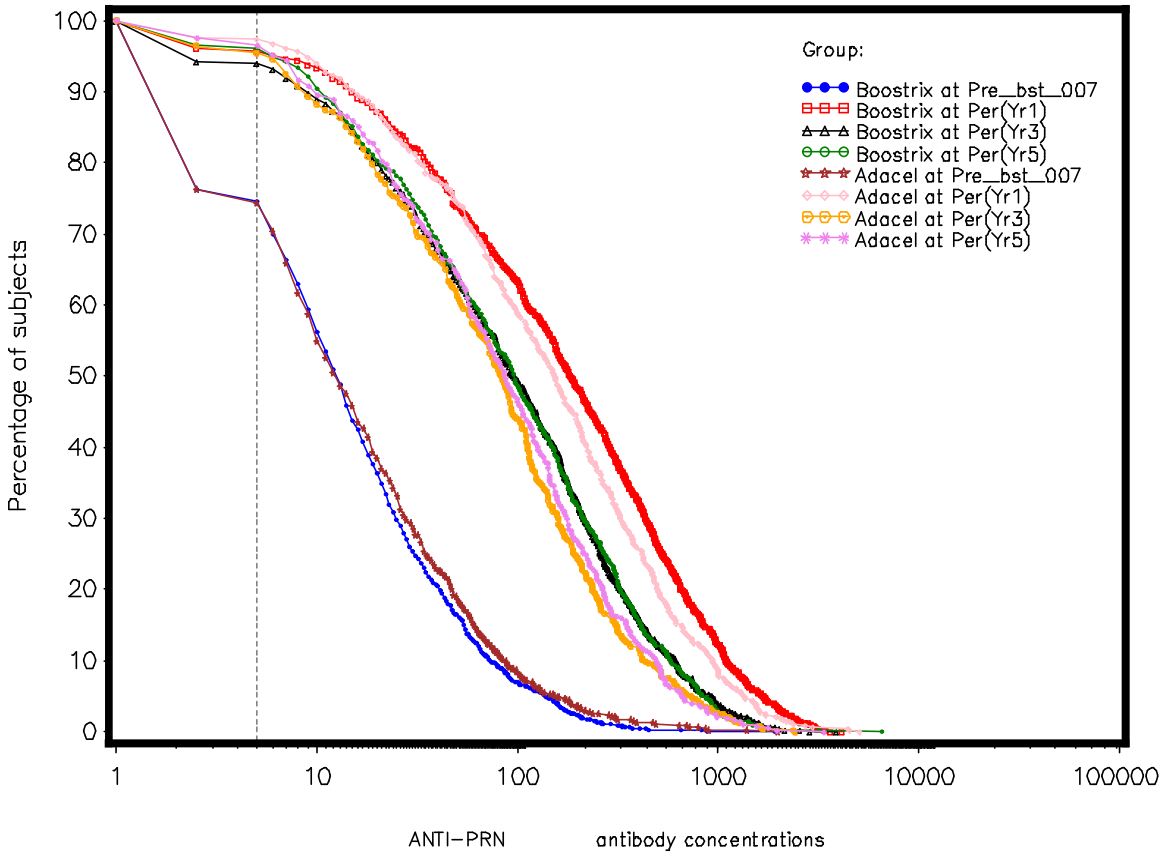
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-FHA antibody concentration (5 ELU/mL)

Figure 7.8 Reverse cumulative distribution curve for anti-FHA antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity at Year 9)



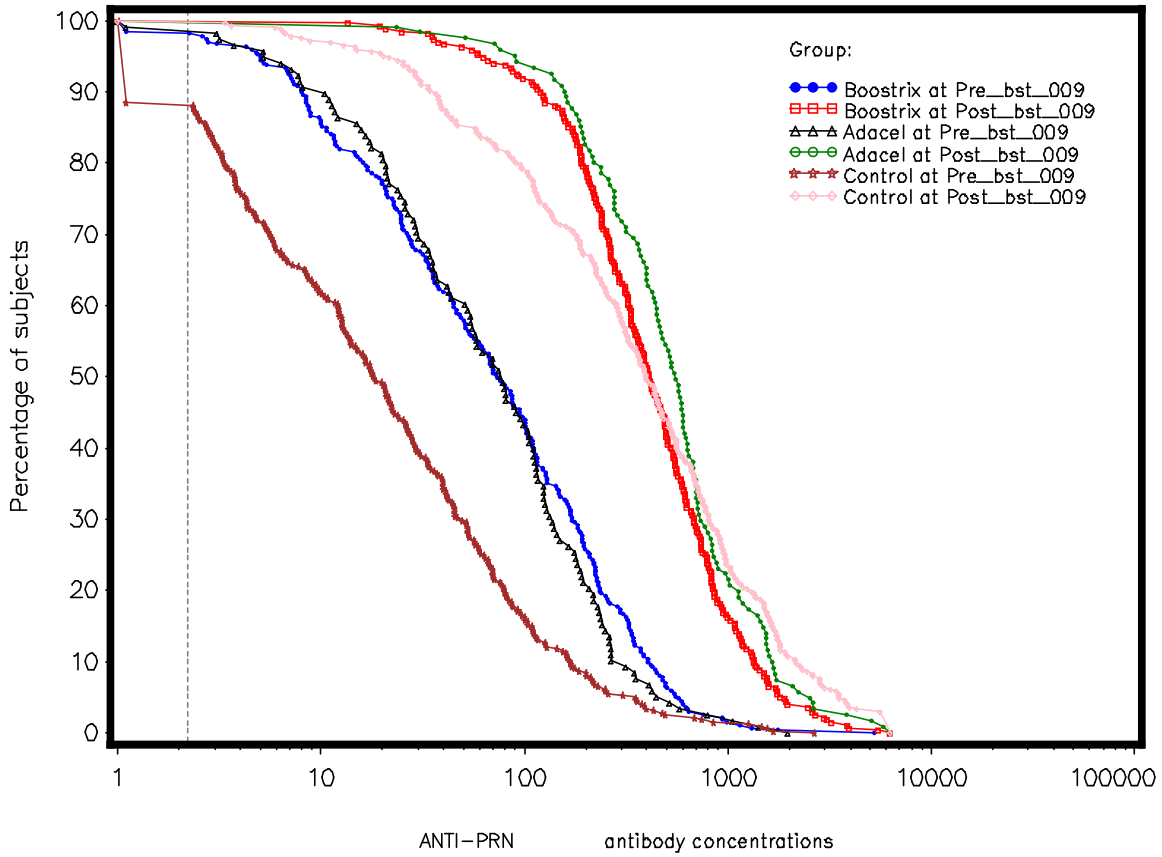
Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-FHA antibody concentration (2.046 IU/mL)

Figure 7.9 Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at the persistence time point (Adapted ATP cohort)



Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-PRN antibody concentration (5 ELU/mL)

Figure 7.10 Reverse cumulative distribution curve for anti-PRN antibody concentrations per group at pre and post booster vaccination time point (ATP cohort for analysis of immunogenicity at Year 9)



Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
ANTI-PRN antibody concentration (2.187 IU/mL)

Table 7.1 Seroprotection status for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION, at pre and post booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

			ELISA concentration <0.1 IU/ML		VERO concentration < 0.016 for subjects with ELISA < 0.1 IU/ML		Estimated proportion of subjects with Vero concentration < 0.016 IU/ML		Estimated proportion of subjects with Vero concentration ≥ 0.016 IU/ML or ELISA >=0.1 IU/ML		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Boostrix	Pre_bst_009	269	24/269	8.9	2/24	8.3	24/269 x 2/24	0.7	99.3	97.3	99.9
	Post_bst_009	271	2/271	0.7	1/2	50.0	2/271 x 1/2	0.4	99.6	98.0	100
Adacel	Pre_bst_009	118	5/118	4.2	2/5	40.0	5/118 x 2/5	1.7	98.3	94.0	99.8
	Post_bst_009	121	1/121	0.8	0/1	0.0	1/121 x 0/1	0.0	100	97.0	100
Control	Pre_bst_009	324	59/324	18.2	16/58	27.6	59/324 x 16/58	5.0	95.0	92.2	97.0
	Post_bst_009	326	7/326	2.1	1/7	14.3	7/326 x 1/7	0.3	99.7	98.3	100

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralisation test for year x persistence time point
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO) for year x persistence time point
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 7.2 Alternative booster response to anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9 - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

				Booster response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
ANTI-D	Boostrix	S-	24	16	66.7	44.7	84.4
		S+ (<1 IU/ML)	131	103	78.6	70.6	85.3
		S+ (≥1 IU/ML)	104	84	80.8	71.9	87.8
		Total	259	203	78.4	72.9	83.2
	Adacel	S-	5	3	60.0	14.7	94.7
		S+ (<1 IU/ML)	59	45	76.3	63.4	86.4
		S+ (≥1 IU/ML)	51	40	78.4	64.7	88.7
		Total	115	88	76.5	67.7	83.9
	Control	S-	58	35	60.3	46.6	73.0
		S+ (<1 IU/ML)	173	148	85.5	79.4	90.4
		S+ (≥1 IU/ML)	80	65	81.3	71.0	89.1
		Total	311	248	79.7	74.8	84.1
ANTI-T	Boostrix	S-	5	5	100	47.8	100
		S+ (<1 IU/ML)	52	46	88.5	76.6	95.6
		S+ (≥1 IU/ML)	191	151	79.1	72.6	84.6
		Total	248	202	81.5	76.0	86.1
	Adacel	S-	0	-	-	-	-
		S+ (<1 IU/ML)	19	14	73.7	48.8	90.9
		S+ (≥1 IU/ML)	92	74	80.4	70.9	88.0
		Total	111	88	79.3	70.5	86.4
	Control	S-	20	18	90.0	68.3	98.8
		S+ (<1 IU/ML)	73	65	89.0	79.5	95.1
		S+ (≥1 IU/ML)	196	159	81.1	74.9	86.3
		Total	289	242	83.7	79.0	87.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
S- = Antibody concentration < 0.1 IU/mL
S+ = Antibody concentration ≥ 0.1 IU/mL
Total = subjects either seropositive or seronegative
Alternative Booster response to D and T antigens is defined as:
- For subjects with pre-booster antibody concentration below 0.1 IU/mL: antibody concentrations at least four times the 0.1IU/ML, one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- Subjects with pre-booster antibody concentration ≥6.0 IU/mL are not evaluable for booster response.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.3 Alternative booster responses to anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

				Booster response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
ANTI-FHA	Boostrix	S-	0	-	-	-	-
		≥ assay Cut-off and < 60 IU/ML	174	171	98.3	95.0	99.6
		≥ 60 IU/ML	97	82	84.5	75.8	91.1
		Total	271	253	93.4	89.7	96.0
	Adacel	S-	1	1	100	2.5	100
		≥ assay Cut-off and < 60 IU/ML	91	91	100	96.0	100
		≥ 60 IU/ML	28	27	96.4	81.7	99.9
		Total	120	119	99.2	95.4	100
	Control	S-	5	5	100	47.8	100
		≥ assay Cut-off and < 60 IU/ML	245	241	98.4	95.9	99.6
		≥ 60 IU/ML	77	64	83.1	72.9	90.7
		Total	327	310	94.8	91.8	96.9
ANTI-PRN	Boostrix	S-	4	4	100	39.8	100
		≥ assay Cut-off and < 60 IU/ML	118	115	97.5	92.7	99.5
		≥ 60 IU/ML	149	111	74.5	66.7	81.3
		Total	271	230	84.9	80.0	88.9
	Adacel	S-	1	1	100	2.5	100
		≥ assay Cut-off and < 60 IU/ML	53	52	98.1	89.9	100
		≥ 60 IU/ML	64	53	82.8	71.3	91.1
		Total	118	106	89.8	82.9	94.6
	Control	S-	37	31	83.8	68.0	93.8
		≥ assay Cut-off and < 60 IU/ML	200	185	92.5	87.9	95.7
		≥ 60 IU/ML	83	62	74.7	64.0	83.6
		Total	320	278	86.9	82.7	90.4
ANTI-PT	Boostrix	S-	41	34	82.9	67.9	92.8
		≥ assay Cut-off and < 60 IU/ML	222	169	76.1	70.0	81.6
		≥ 60 IU/ML	8	7	87.5	47.3	99.7
		Total	271	210	77.5	72.0	82.3
	Adacel	S-	14	10	71.4	41.9	91.6
		≥ assay Cut-off and < 60 IU/ML	103	83	80.6	71.6	87.7
		≥ 60 IU/ML	3	3	100	29.2	100
		Total	120	96	80.0	71.7	86.7
	Control	S-	117	101	86.3	78.7	92.0
		≥ assay Cut-off and < 60 IU/ML	194	166	85.6	79.8	90.2
		≥ 60 IU/ML	15	10	66.7	38.4	88.2
		Total	326	277	85.0	80.6	88.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
Total = subjects either seropositive or seronegative
Alternative Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-booster antibody concentration below the assay cut off: antibody concentrations at least four times the assay cut off one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥ assay cut off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.

- For subjects with pre-booster antibody concentration ≥ 60 IU/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.4 Exploratory comparison: Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL [Boostrix group minus Adacel group] at persistence time points and their standardized asymptotic 95% CIs (Adapted ATP cohort)

								Difference in percentage			
										95 % CI	
Antibody	Timing	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
ANTI-D	Per(Yr1)	Adacel	504	97.0	Boostrix	1010	95.7	Boostrix - Adacel	-1.28	-3.15	0.87
	Per(Yr3)	Adacel	442	96.2	Boostrix	914	93.8	Boostrix - Adacel	-2.39	-4.69	0.21
	Per(Yr5)	Adacel	372	96.5	Boostrix	789	93.2	Boostrix - Adacel	-3.35	-5.85	-0.53
	Per(Yr9)	Adacel	118	95.8	Boostrix	269	91.1	Boostrix - Adacel	-4.68	-9.51	1.24
ANTI-T	Per(Yr1)	Adacel	506	99.6	Boostrix	1014	98.6	Boostrix - Adacel	-0.99	-1.98	0.14
	Per(Yr3)	Adacel	442	99.5	Boostrix	917	98.0	Boostrix - Adacel	-1.51	-2.71	-0.19
	Per(Yr5)	Adacel	372	99.5	Boostrix	788	98.0	Boostrix - Adacel	-1.49	-2.83	0.04
	Per(Yr9)	Adacel	120	100.0	Boostrix	268	98.1	Boostrix - Adacel	-1.87	-4.30	1.26

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.5 Exploratory comparison: Group differences in the percentage of subjects with anti-Diphtheria antibody concentrations ≥ 0.1 IU/mL by ELISA or at least 0.016 IU/mL by VERO cell assay (when anti-Diphtheria concentrations < 0.1 IU/mL by ELISA) between Boostrix group and Adacel group, at persistence time point and their standardized asymptotic 95% CIs (Adapted ATP cohort)

					Difference in seroprotection rate (Boostrix group minus Adacel group)		
						95 % CI	
Timing	Boostrix Group		Adacel Group		Difference	LL	UL
	N	%	N	%			
Per(Yr1)	1012	98.3	505	98.2	0.1	-1.3	1.8
Per(Yr3)	914	96.9	442	97.7	-0.8	-2.6	1.3
Per(Yr5)	789	98.4	372	98.9	-0.5	-1.9	1.2
Per(Yr9)	269	99.3	118	98.3	1.0	-1.5	5.3

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
% = percentage of subjects with ANTI-DIPHTHERIA concentration ≥ 0.1 IU/mL by ELISA or ≥ 0.016 IU/mL by VERO
The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008]
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.6 Exploratory comparison: Group differences in the percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥Assay cut off [Boostrix group minus Adacel group] at persistence time points and their standardized asymptotic 95% CIs (Adapted ATP cohort)

								Difference in percentage			
										95 % CI	
Antibody	Timing	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
ANTI-FHA	Per(Yr1)	Adacel	502	99.8	Boostrix	1014	99.8	Boostrix - Adacel	0.00	-0.55	0.93
	Per(Yr3)	Adacel	439	99.5	Boostrix	916	99.7	Boostrix - Adacel	0.13	-0.58	1.34
	Per(Yr5)	Adacel	371	99.2	Boostrix	789	99.9	Boostrix - Adacel	0.68	-0.05	2.23
	Per(Yr9)	Adacel	120	99.2	Boostrix	271	100.0	Boostrix - Adacel	0.83	-0.58	4.58
ANTI-PRN	Per(Yr1)	Adacel	501	97.6	Boostrix	1011	96.0	Boostrix - Adacel	-1.56	-3.31	0.45
	Per(Yr3)	Adacel	442	96.4	Boostrix	915	94.2	Boostrix - Adacel	-2.17	-4.40	0.36
	Per(Yr5)	Adacel	371	97.6	Boostrix	782	96.5	Boostrix - Adacel	-1.03	-2.97	1.33
	Per(Yr9)	Adacel	118	99.2	Boostrix	271	98.5	Boostrix - Adacel	-0.63	-3.05	3.25
ANTI-PT	Per(Yr1)	Adacel	506	86.0	Boostrix	1013	90.5	Boostrix - Adacel	4.55	1.17	8.25
	Per(Yr3)	Adacel	442	71.5	Boostrix	914	82.2	Boostrix - Adacel	10.67	5.89	15.66
	Per(Yr5)	Adacel	372	76.6	Boostrix	790	84.8	Boostrix - Adacel	8.20	3.38	13.34
	Per(Yr9)	Adacel	120	88.3	Boostrix	271	84.9	Boostrix - Adacel	-3.46	-10.18	4.45

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.7 Exploratory comparison: Group difference in alternative booster response to the diphtheria and tetanus antigens [Boostrix group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9 - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	259	203	78.4	311	248	79.7	-1.36	-9.17	6.26
ANTI-T	248	202	81.5	289	242	83.7	-2.29	-9.82	5.05

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to D and T antigens is defined as:
- For subjects with pre-booster antibody concentration below 0.1 IU/mL: antibody concentrations at least four times the 0.1IU/ML, one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- Subjects with pre-booster antibody concentration ≥6.0 IU/mL are not evaluable for booster response.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.8 Exploratory comparison: Group difference in alternative booster response to the PT, FHA and PRN antigens [Boostrix group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	271	253	93.4	327	310	94.8	-1.44	-6.23	2.95
ANTI-PRN	271	230	84.9	320	278	86.9	-2.00	-8.66	4.43
ANTI-PT	271	210	77.5	326	277	85.0	-7.48	-14.84	-0.33

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-booster antibody concentration below the assay cut off: antibody concentrations at least four times the assay cut off one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥ assay cut off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥ 60 IU/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available; n/% = number/percentage of subjects with booster response; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.9 Exploratory comparison: Group difference in alternative booster response to the diphtheria and tetanus antigens [Adacel group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9 - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	115	88	76.5	311	248	79.7	-3.22	-14.16	6.30
ANTI-T	111	88	79.3	289	242	83.7	-4.46	-15.21	4.68

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to D and T antigens is defined as:
- For subjects with pre-booster antibody concentration below 0.1 IU/mL: antibody concentrations at least four times the 0.1IU/ML, one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- Subjects with pre-booster antibody concentration ≥6.0 IU/mL are not evaluable for booster response.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.10 Exploratory comparison: Group difference in alternative booster response to the PT, FHA and PRN antigens [Adacel group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	120	119	99.2	327	310	94.8	4.37	-0.54	8.04
ANTI-PRN	118	106	89.8	320	278	86.9	2.96	-5.78	9.82
ANTI-PT	120	96	80.0	326	277	85.0	-4.97	-15.12	3.59

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-booster antibody concentration below the assay cut off: antibody concentrations at least four times the assay cut off one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥ assay cut off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥ 60 IU/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.11 Exploratory comparison: Adjusted GMC ratio between groups [Boostrix group divided by Adacel group] and their 95% CIs for anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					Adjusted GMC ratio (Boostrix / Adacel)		
	Boostrix		Adacel			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
ANTI-D	268	4.3	116	4.4	0.98	0.80	1.20
ANTI-T	270	8.5	120	8.4	1.01	0.86	1.19

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N= Number of subjects with available results
95% CI = 95% confidence interval for the adjusted GMC ratio LL = lower limit, UL = upper limit (ANCOVA model)
N = Number of subjects with both pre- and post-vaccination results available
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 106316 study
Note: The pre-vaccination status in study 106316 will be used as co-variable
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit

Table 7.12 Exploratory comparison: Adjusted GMC ratio between groups [Boostrix group divided by Adacel group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (ATP cohort for analysis of immunogenicity at Year 9)

					Adjusted GMC ratio (Boostrix / Adacel)		
	Boostrix		Adacel			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
ANTI-FHA	265	250.2	119	253.2	0.99	0.84	1.16
ANTI-PRN	269	401.0	120	524.7	0.76	0.63	0.93
ANTI-PT	266	65.6	119	65.7	1.00	0.82	1.22

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N= Number of subjects with available results
95% CI = 95% confidence interval for the adjusted GMC ratio LL = lower limit, UL = upper limit (ANCOVA model)
N = Number of subjects with both pre- and post-vaccination results available
Adjusted GMC = geometric mean antibody concentration adjusted for baseline of 106316 study
Note: The pre-vaccination status in study 106316 will be used as co-variable
95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit

Table 7.13 Exploratory comparison: Group difference in booster response to the diphtheria and tetanus antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	269	169	62.8	118	71	60.2	2.66	-7.66	13.31
ANTI-T	268	126	47.0	120	44	36.7	10.35	-0.35	20.52

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination.
- For initially seropositive subjects with pre-booster antibody concentration ≥0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.14 Exploratory comparison: Group difference in booster response to the PT, FHA and PRN antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 95% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	271	232	85.6	120	116	96.7	-11.06	-16.34	-5.14
ANTI-PRN	271	210	77.5	118	98	83.1	-5.56	-13.49	3.46
ANTI-PT	271	235	86.7	120	106	88.3	-1.62	-8.18	6.19

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.15 Number of months since the vaccination in primary study DTPA0.3-007(106316) and subsequent blood samples (Adapted ATP cohort)

		Boostrix	Adacel	Total
Timing	**Parameters**	**Value**	**Value**	**Value**
Post_bst_007(M1)	N	1447	728	2175
	Mean	0.99	0.98	0.99
	Median	1.00	1.00	1.00
	SD	0.12	0.12	0.12
	Minimum	0.00	0.00	0.00
	Maximum	1.00	1.00	1.00
Per(Yr1)	N	1015	506	1521
	Mean	11.49	11.51	11.50
	Median	11.00	11.50	11.00
	SD	0.60	0.60	0.60
	Minimum	10.00	10.00	10.00
	Maximum	13.00	13.00	13.00
Per(Yr3)	N	917	442	1359
	Mean	35.07	35.04	35.06
	Median	35.00	35.00	35.00
	SD	0.64	0.65	0.64
	Minimum	34.00	34.00	34.00
	Maximum	37.00	37.00	37.00
Per(Yr5)	N	790	372	1162
	Mean	58.78	58.82	58.79
	Median	59.00	59.00	59.00
	SD	0.77	0.79	0.78
	Minimum	58.00	57.00	57.00
	Maximum	61.00	61.00	61.00
Pre_bst_009	N	271	120	391
	Mean	106.82	106.92	106.85
	Median	106.00	106.00	106.00
	SD	1.47	1.53	1.49
	Minimum	105.00	105.00	105.00
	Maximum	113.00	113.00	113.00
Post_bst_009	N	271	121	392
	Mean	107.91	108.12	107.98
	Median	107.00	108.00	107.00
	SD	1.45	1.54	1.48
	Minimum	106.00	106.00	106.00
	Maximum	114.00	114.00	114.00

N = number of subject number
Value = value of the considered parameter
SD = Standard deviation
Boostrix group= Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel group= Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Post_bst_007= blood sampling, one motnh after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 years post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 years post vaccination in Tdap 0.3-007 study
Post_bst_009 = Post booster vaccination blood sampling time-point in current study

Table 7.16 Number of months since the vaccination in primary study DTPA0.3-007(106316) and subsequent blood samples (Total enrolled cohort)

		Boostrix	Adacel	Total
Timing	**Parameters**	**Value**	**Value**	**Value**
Post_bst_007(M1)	N	1477	736	2213
	Mean	0.99	0.99	0.99
	Median	1.00	1.00	1.00
	SD	0.13	0.14	0.13
	Minimum	0.00	0.00	0.00
	Maximum	2.00	2.00	2.00
Per(Yr1)	N	1064	523	1587
	Mean	11.48	11.49	11.48
	Median	11.00	11.00	11.00
	SD	0.63	0.63	0.63
	Minimum	10.00	10.00	10.00
	Maximum	13.00	13.00	13.00
Per(Yr3)	N	976	465	1441
	Mean	35.07	35.05	35.06
	Median	35.00	35.00	35.00
	SD	0.64	0.65	0.64
	Minimum	34.00	34.00	34.00
	Maximum	37.00	37.00	37.00
Per(Yr5)	N	856	401	1257
	Mean	58.79	58.80	58.79
	Median	59.00	59.00	59.00
	SD	0.78	0.78	0.78
	Minimum	58.00	57.00	57.00
	Maximum	61.00	61.00	61.00
Pre_bst_009	N	476	230	706
	Mean	107.14	107.18	107.15
	Median	106.00	106.00	106.00
	SD	1.87	1.80	1.85
	Minimum	105.00	105.00	105.00
	Maximum	113.00	113.00	113.00
Post_bst_009	N	298	131	429
	Mean	107.95	108.24	108.03
	Median	107.00	108.00	107.00
	SD	1.50	1.70	1.57
	Minimum	106.00	106.00	106.00
	Maximum	114.00	114.00	114.00

N = number of subject number
Value = value of the considered parameter
SD = Standard deviation
Boostrix group= Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel group= Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Post_bst_007= blood sampling, one motnh after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 years post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 years post vaccination in Tdap 0.3-007 study
Post_bst_009 = Post booster vaccination blood sampling time-point in current study

Table 7.17 ANTI-D GMCs at persistence time points, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-D	Boostrix	Post_bst_007	4.72	4.50	4.96
		Per(Yr1)	1.42	1.34	1.51
		Per(Yr3)	0.93	0.88	0.99
		Per(Yr5)	0.83	0.78	0.89
		Per(Yr9)	0.73	0.66	0.82
	Adacel	Post_bst_007	4.68	4.37	5.01
		Per(Yr1)	1.39	1.28	1.51
		Per(Yr3)	0.97	0.89	1.06
		Per(Yr5)	0.89	0.81	0.98
		Per(Yr9)	0.75	0.63	0.89

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study

Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study

Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study

Per(Yr9) = blood sampling, 9 years post vaccination in Tdap 0.3-007 study

Figure 7.11 Observed and predicted geometric mean antibody concentration for Anti-D (Adapted ATP cohort)

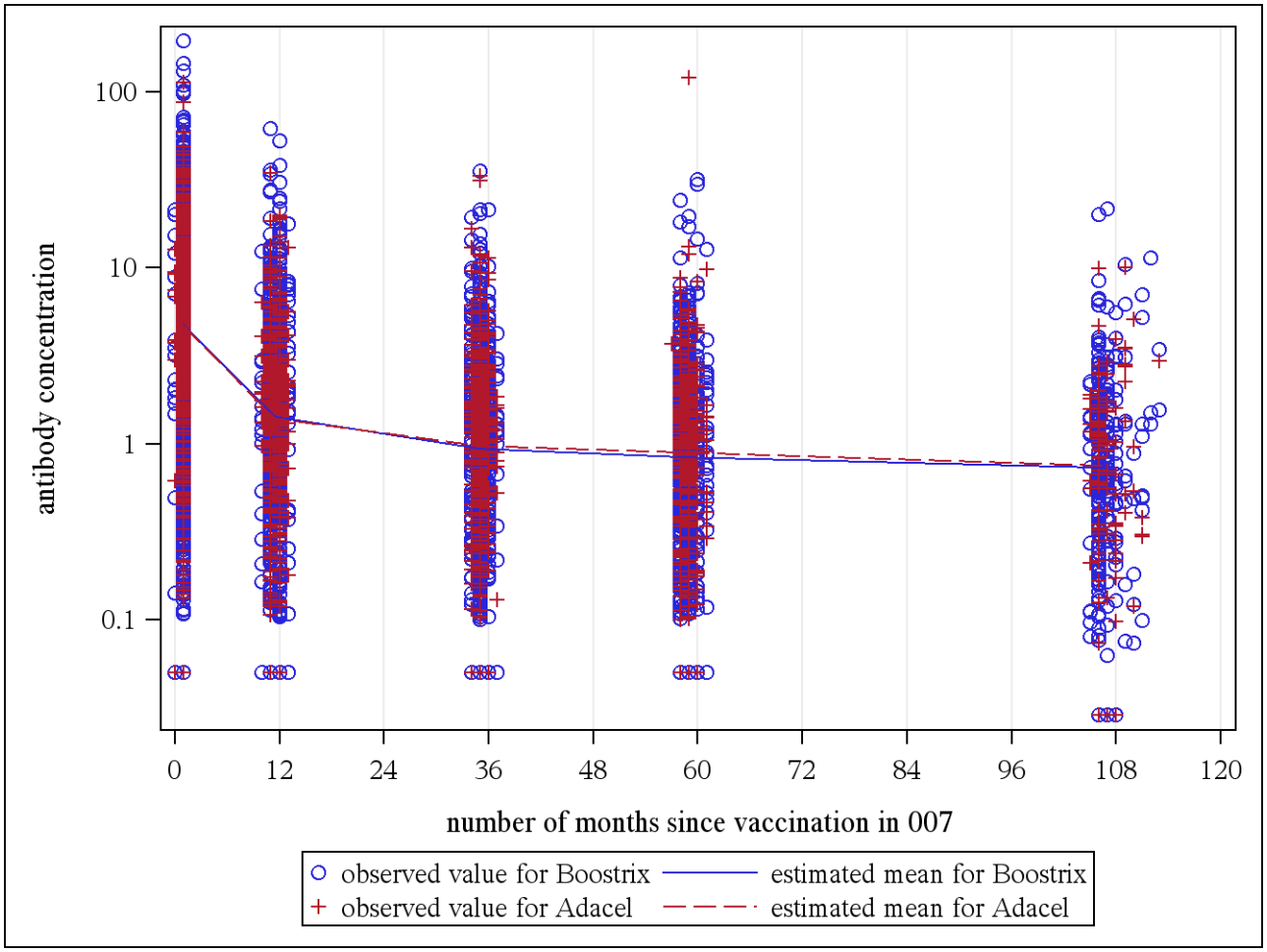


Table 7.18 ANTI-T GMCs at persistence time points, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-T	Boostrix	Post_bst_007	8.52	8.18	8.88
		Per(Yr1)	3.37	3.21	3.54
		Per(Yr3)	2.23	2.12	2.35
		Per(Yr5)	2.04	1.93	2.15
		Per(Yr9)	1.88	1.71	2.06
	Adacel	Post_bst_007	12.90	12.19	13.66
		Per(Yr1)	4.31	4.02	4.61
		Per(Yr3)	2.80	2.60	3.01
		Per(Yr5)	2.47	2.28	2.68
		Per(Yr9)	2.26	1.96	2.60

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study

Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study

Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study

Per(Yr9) = blood sampling, 9 years post vaccination in Tdap 0.3-007 study

Figure 7.12 Observed and predicted geometric mean antibody concentration for Anti-T (Adapted ATP cohort)

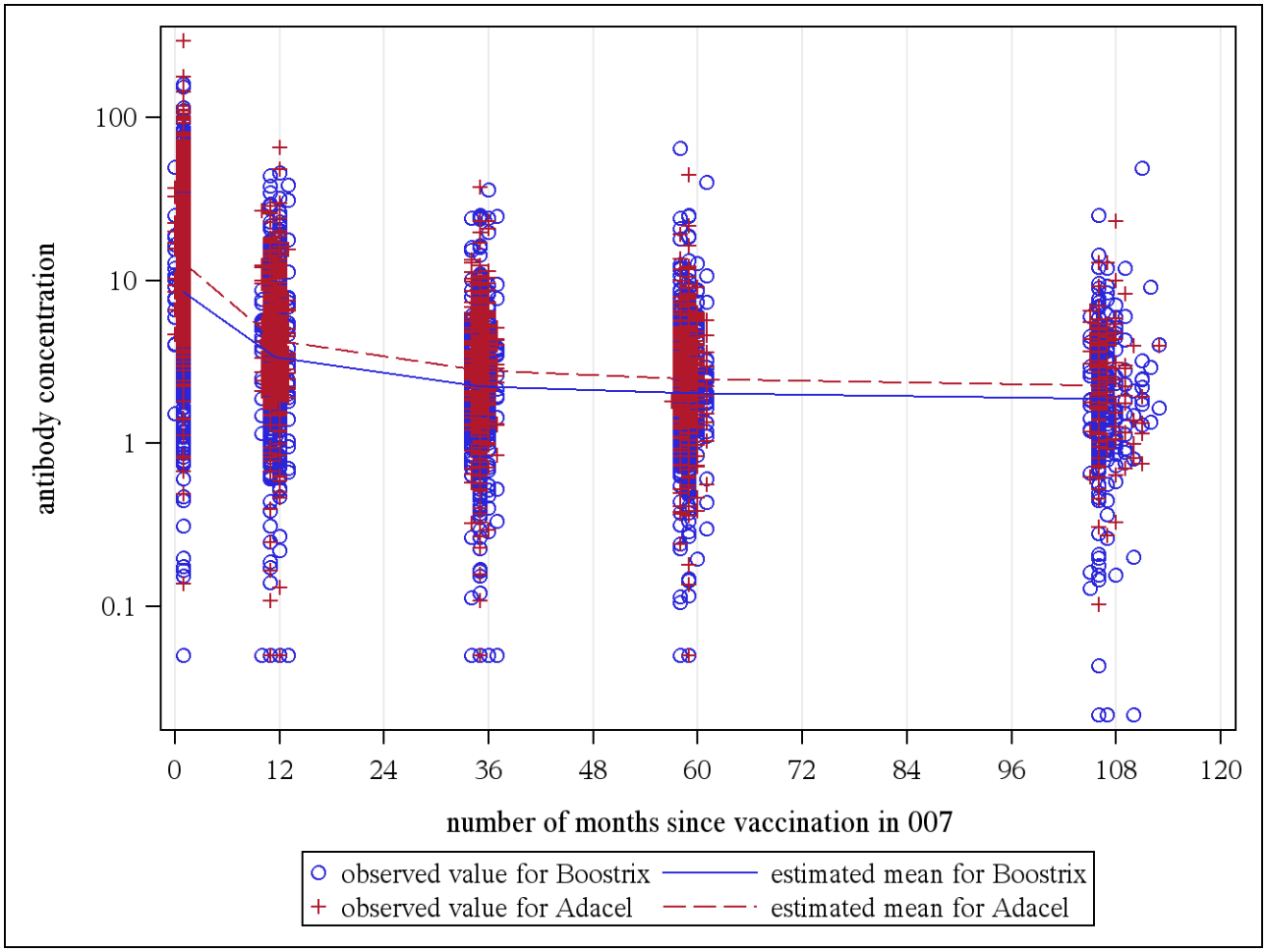


Table 7.19 ANTI-PT GMCs at persistence time points, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	**Group**	**Timing**	**value**	**LL**	**UL**
ANTI-PT	Boostrix	Post_bst_007	63.67	60.96	66.50
		Per(Yr1)	22.97	21.82	24.19
		Per(Yr3)	14.39	13.63	15.20
		Per(Yr5)	15.04	14.19	15.95
		Per(Yr9)	8.97	8.11	9.91
	Adacel	Post_bst_007	30.07	28.29	31.97
		Per(Yr1)	14.47	13.45	15.57
		Per(Yr3)	9.13	8.44	9.87
		Per(Yr5)	10.90	10.01	11.88
		Per(Yr9)	6.98	6.00	8.11

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model
LL = Lower Limit, UL = Upper Limit
Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects
Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study
Per(Yr9) = blood sampling, 9 years post vaccination in Tdap 0.3-007 study

Figure 7.13 Observed and predicted geometric mean antibody concentration for Anti-PT (Adapted ATP cohort)

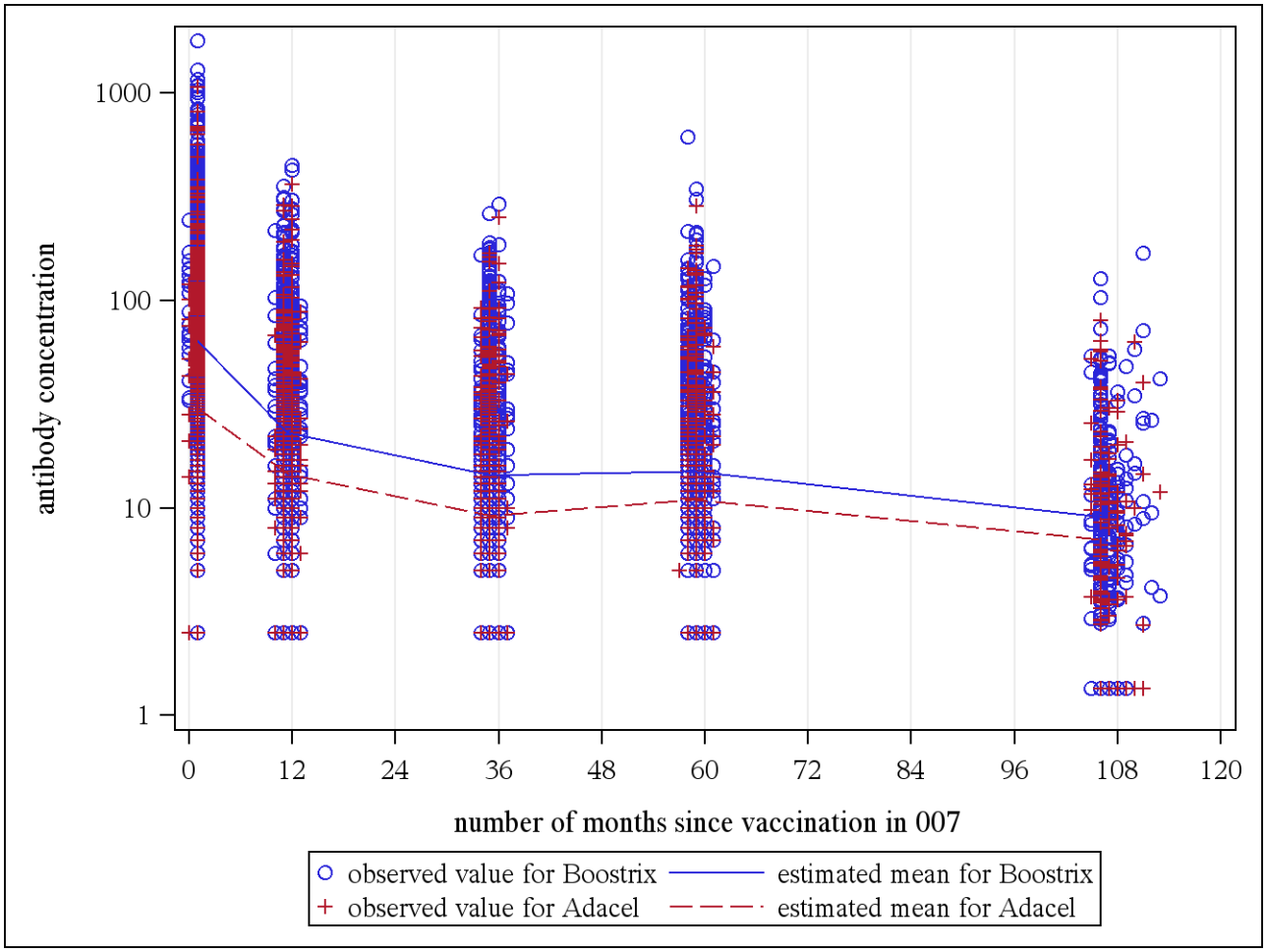


Table 7.20 ANTI-PRN GMCs at persistence time points, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-PRN	Boostrix	Post_bst_007	406.48	381.14	433.50
		Per(Yr1)	152.64	141.35	164.84
		Per(Yr3)	84.19	77.66	91.27
		Per(Yr5)	86.51	79.27	94.41
		Per(Yr9)	66.01	56.88	76.61
	Adacel	Post_bst_007	339.03	309.65	371.20
		Per(Yr1)	128.25	114.99	143.04
		Per(Yr3)	68.05	60.58	76.43
		Per(Yr5)	74.77	65.86	84.89
		Per(Yr9)	67.08	53.53	84.07

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study

Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study

Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study

Per(Yr9) = blood sampling, 9 years post vaccination in Tdap 0.3-007 study

Per(Yr1)= blood sampling, 1 years post vaccination in Tdap 0.3-007 study

Figure 7.14 Observed and predicted geometric mean antibody concentration for Anti-PRN (Adapted ATP cohort)

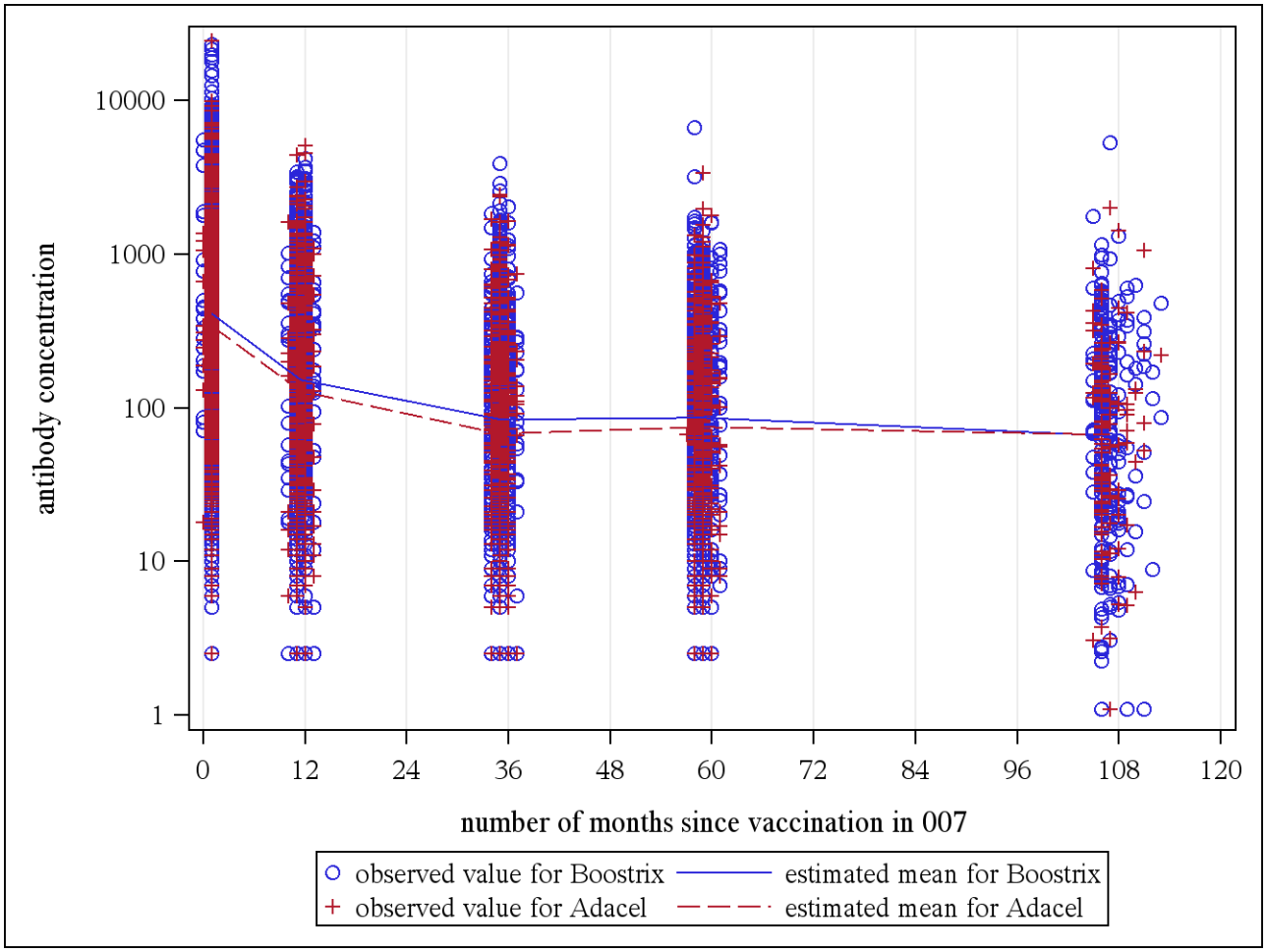


Table 7.21 ANTI-FHA GMCs at persistence time points, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-FHA	Boostrix	Post_bst_007	622.92	595.83	651.24
		Per(Yr1)	191.70	181.81	202.13
		Per(Yr3)	116.52	110.20	123.21
		Per(Yr5)	113.32	106.70	120.34
		Per(Yr9)	45.38	40.93	50.33
	Adacel	Post_bst_007	353.65	332.07	376.63
		Per(Yr1)	115.45	107.04	124.52
		Per(Yr3)	78.85	72.72	85.49
		Per(Yr5)	78.50	71.87	85.73
		Per(Yr9)	28.65	24.54	33.44

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study

Per(Yr3)= blood sampling, 3 years post vaccination in Tdap 0.3-007 study

Per(Yr5)= blood sampling, 5 years post vaccination in Tdap 0.3-007 study

Per(Yr9) = blood sampling, 9 years post vaccination in Tdap 0.3-007 study

Figure 7.15 Observed and predicted geometric mean antibody concentration for Anti-FHA (Adapted ATP cohort)

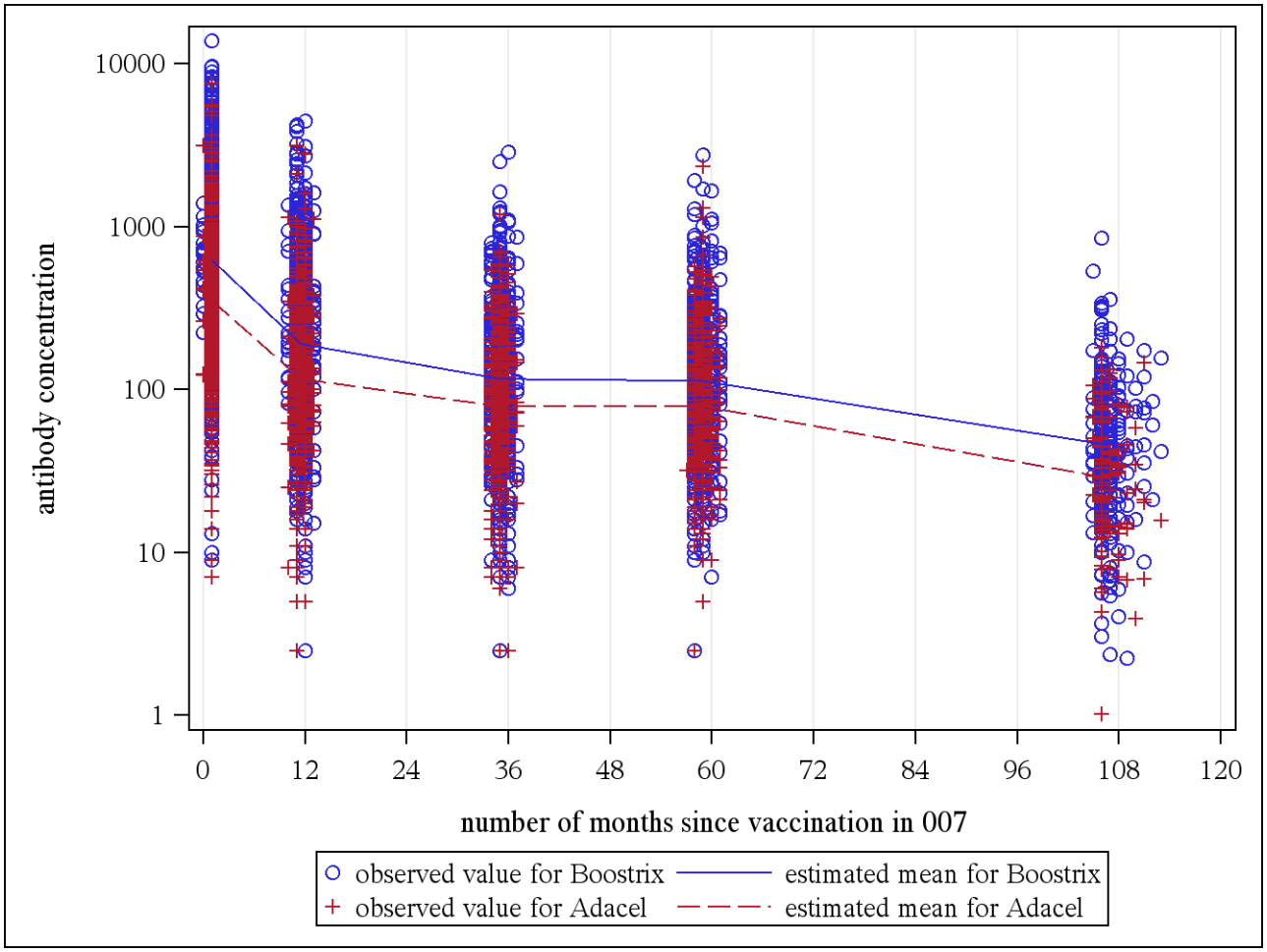


Table 7.22 ANTI-D GMCs, one month after the first and second booster vaccination, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-D	Boostrix	Post_bst_007	4.76	4.51	5.03
		Post_bst_009	4.57	4.03	5.18
	Adacel	Post_bst_007	4.77	4.42	5.15
		Post_bst_009	4.51	3.73	5.45

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Post_bst_009 = Post booster vaccination blood sampling timepoint, one month after the booster dose in the current study blood sampling

Figure 7.16 Observed and predicted geometric mean antibody concentration for Anti-D, one month after the first and second booster vaccination (Adapted ATP cohort)

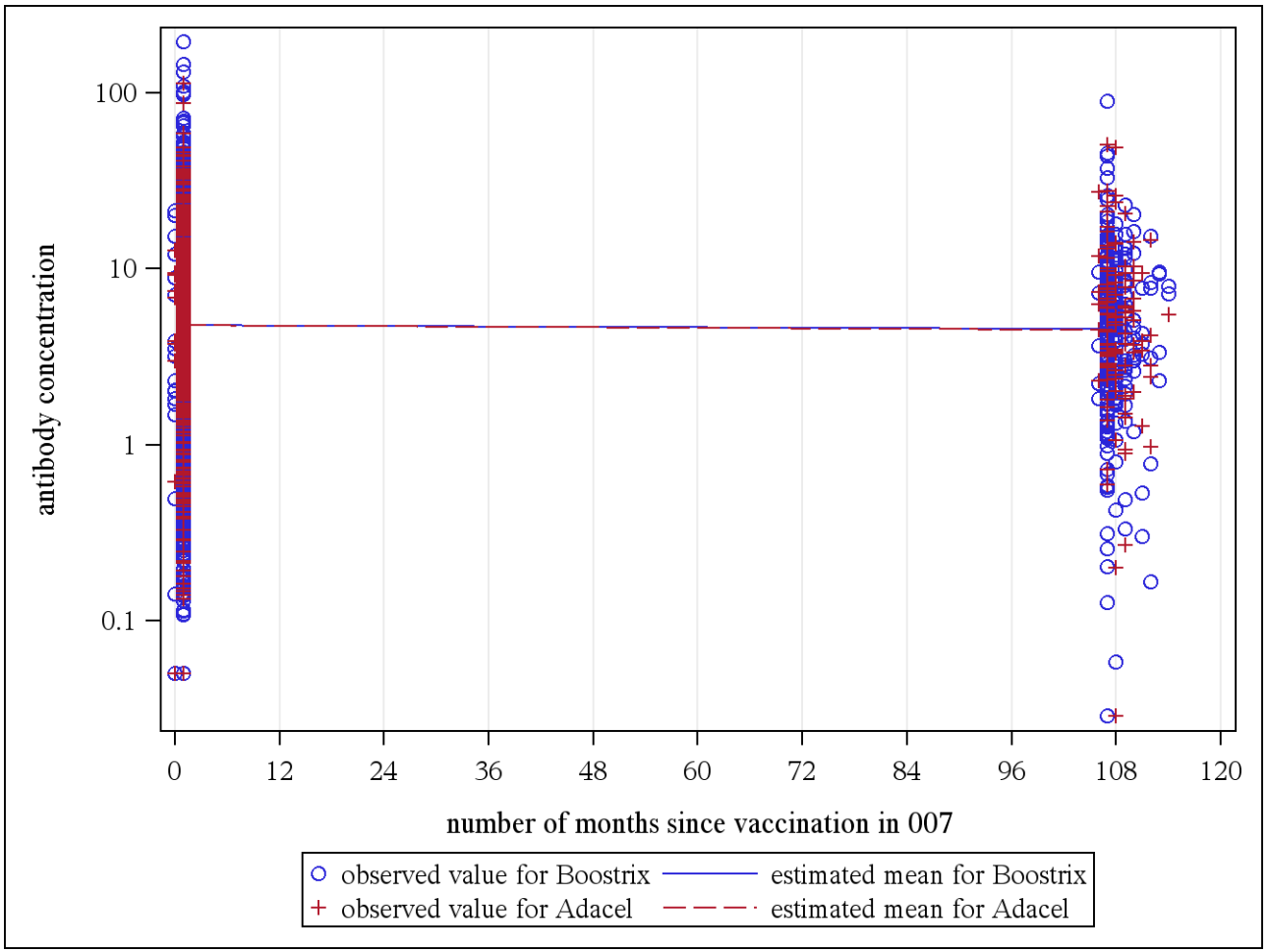


Table 7.23 ANTI-T GMCs, one month after the first and second booster vaccination, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	**Group**	**Timing**	**value**	**LL**	**UL**
ANTI-T	Boostrix	Post_bst_007	8.51	8.15	8.89
		Post_bst_009	8.69	7.85	9.61
	Adacel	Post_bst_007	13.13	12.35	13.97
		Post_bst_009	8.58	7.38	9.98

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Post_bst_009 = Post booster vaccination blood sampling timepoint, one month after the booster dose in the current Tdap 0.3-009 study

Figure 7.17 Observed and predicted geometric mean antibody concentration for Anti-T, one month after the first and second booster vaccination (Adapted ATP cohort)

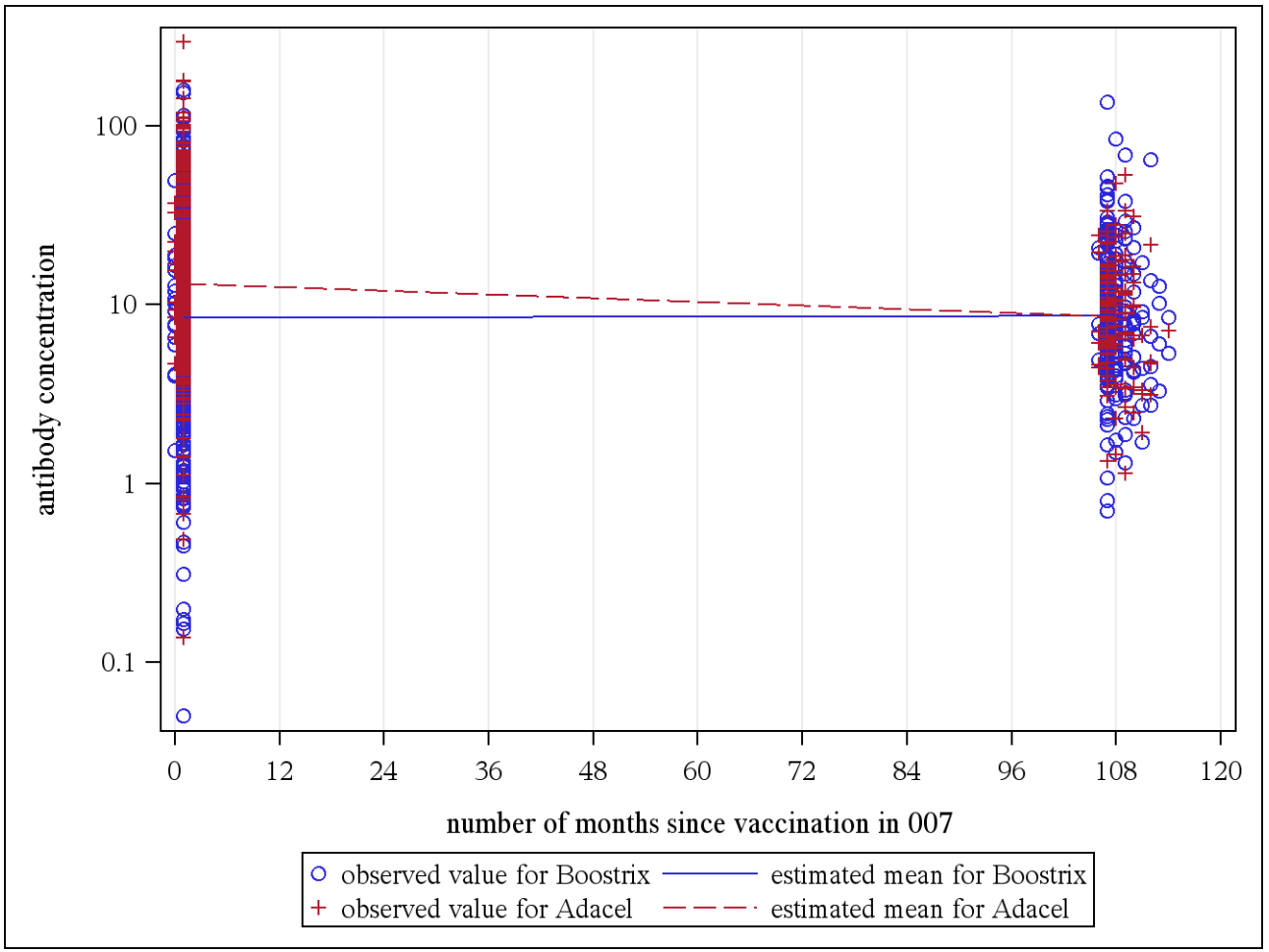


Table 7.24 ANTI-PT GMCs, one month after the first and second booster vaccination, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-PT	Boostrix	Post_bst_007	63.65	60.65	66.80
		Post_bst_009	70.42	62.96	78.75
	Adacel	Post_bst_007	30.51	28.51	32.66
		Post_bst_009	65.76	55.64	77.72

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Post_bst_009 = Post booster vaccination blood sampling timepoint, one month after the booster dose in the current study blood sampling

Figure 7.18 Observed and predicted geometric mean antibody concentration for Anti-PT, one month after the first and second booster vaccination (Adapted ATP cohort)

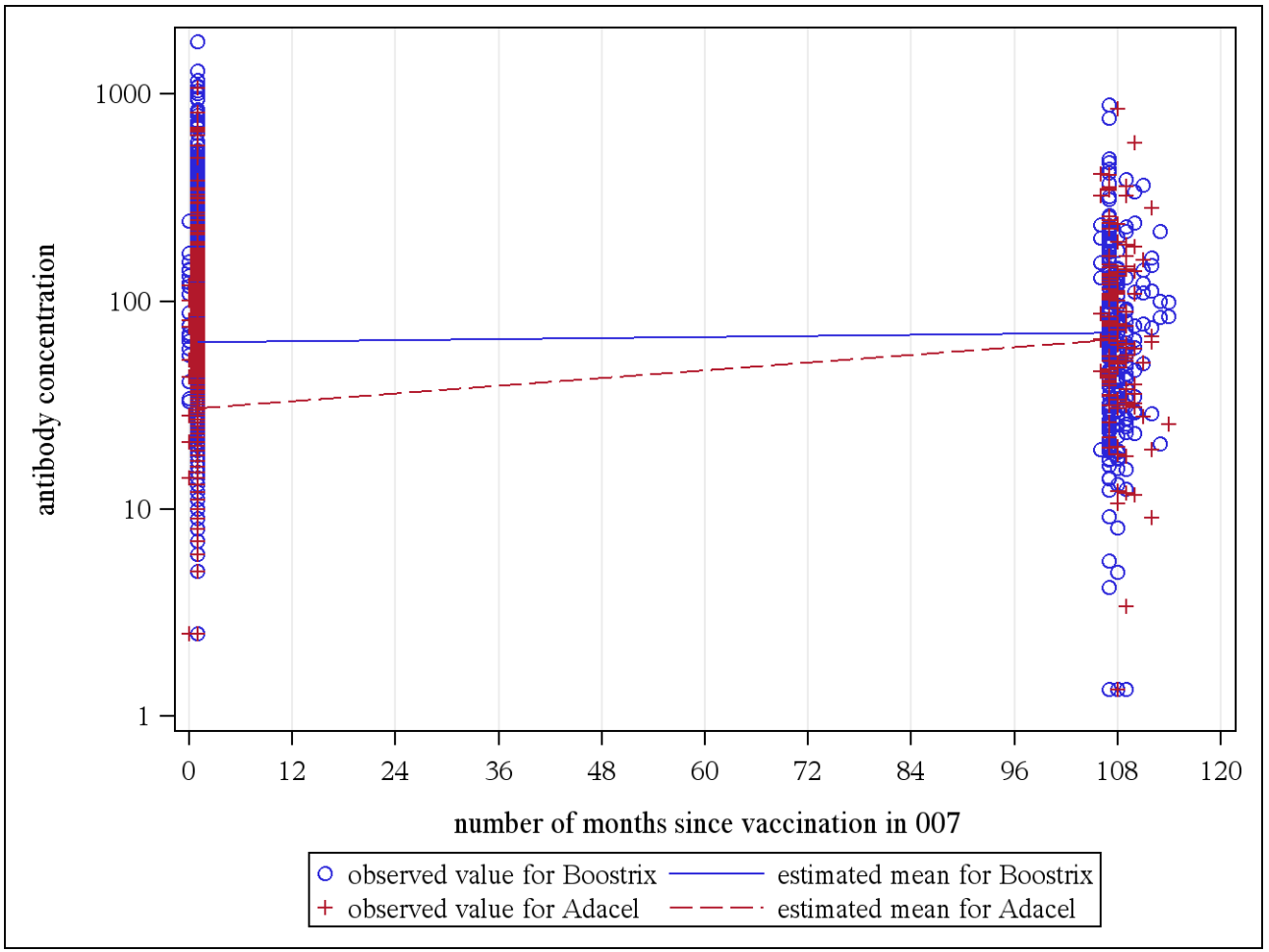


Table 7.25 ANTI-PRN GMCs, one month after the first and second booster vaccination, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	Group	Timing	value	LL	UL
ANTI-PRN	Boostrix	Post_bst_007	403.82	377.56	431.91
		Post_bst_009	416.94	356.74	487.30
	Adacel	Post_bst_007	339.72	309.01	373.49
		Post_bst_009	543.71	430.55	686.61

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Post_bst_009 = Post booster vaccination blood sampling timepoint, one month after the booster dose in the current study blood sampling

Figure 7.19 Observed and predicted geometric mean antibody concentration for Anti-PRN, one month after the first and second booster vaccination (Adapted ATP cohort)

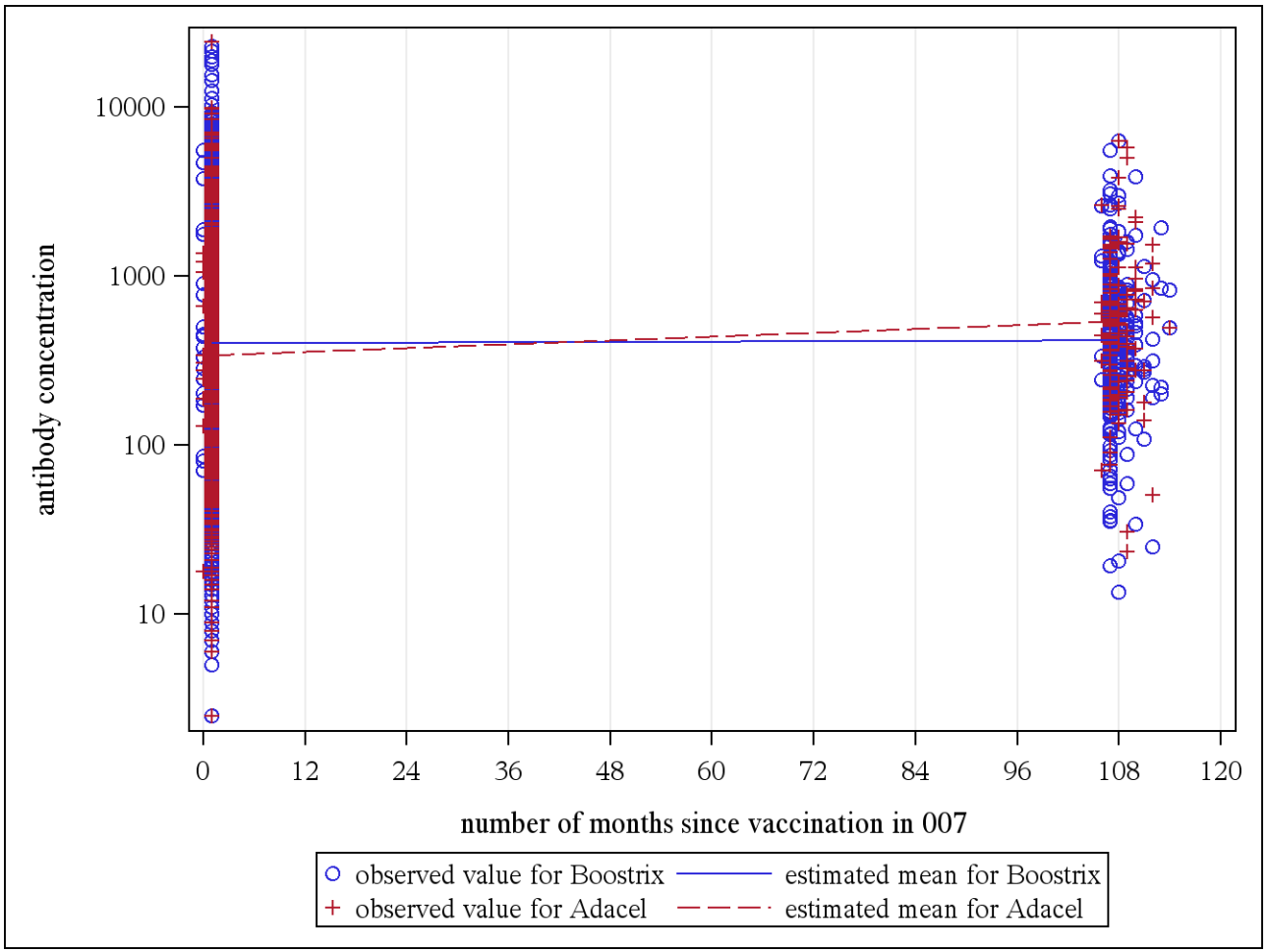


Table 7.26 ANTI-FHA GMCs, one month after the first and second booster vaccination, predicted by modelling (Adapted ATP cohort)

			GMC		
				95% CI	
Antibody	**Group**	**Timing**	**value**	**LL**	**UL**
ANTI-FHA	Boostrix	Post_bst_007	625.56	597.51	654.93
		Post_bst_009	262.36	235.73	291.99
	Adacel	Post_bst_007	360.50	337.81	384.72
		Post_bst_009	259.60	221.34	304.47

GMC = corrected geometric mean antibody concentration for missing data estimated using a repeated nonlinear mixed model

LL = Lower Limit, UL = Upper Limit

Prediction and CI from repeated mixed model with group*timepoint pre-vaccination and age strata as fixed effects

Post_bst_007 = Post booster blood sampling time point, one month after the booster dose in Tdap 0.3-007 study

Post_bst_009 = Post booster vaccination blood sampling timepoint, one month after the booster dose in the current study blood sampling

Figure 7.20 Observed and predicted geometric mean antibody concentration for Anti-FHA, one month after the first and second booster vaccination(Adapted ATP cohort)

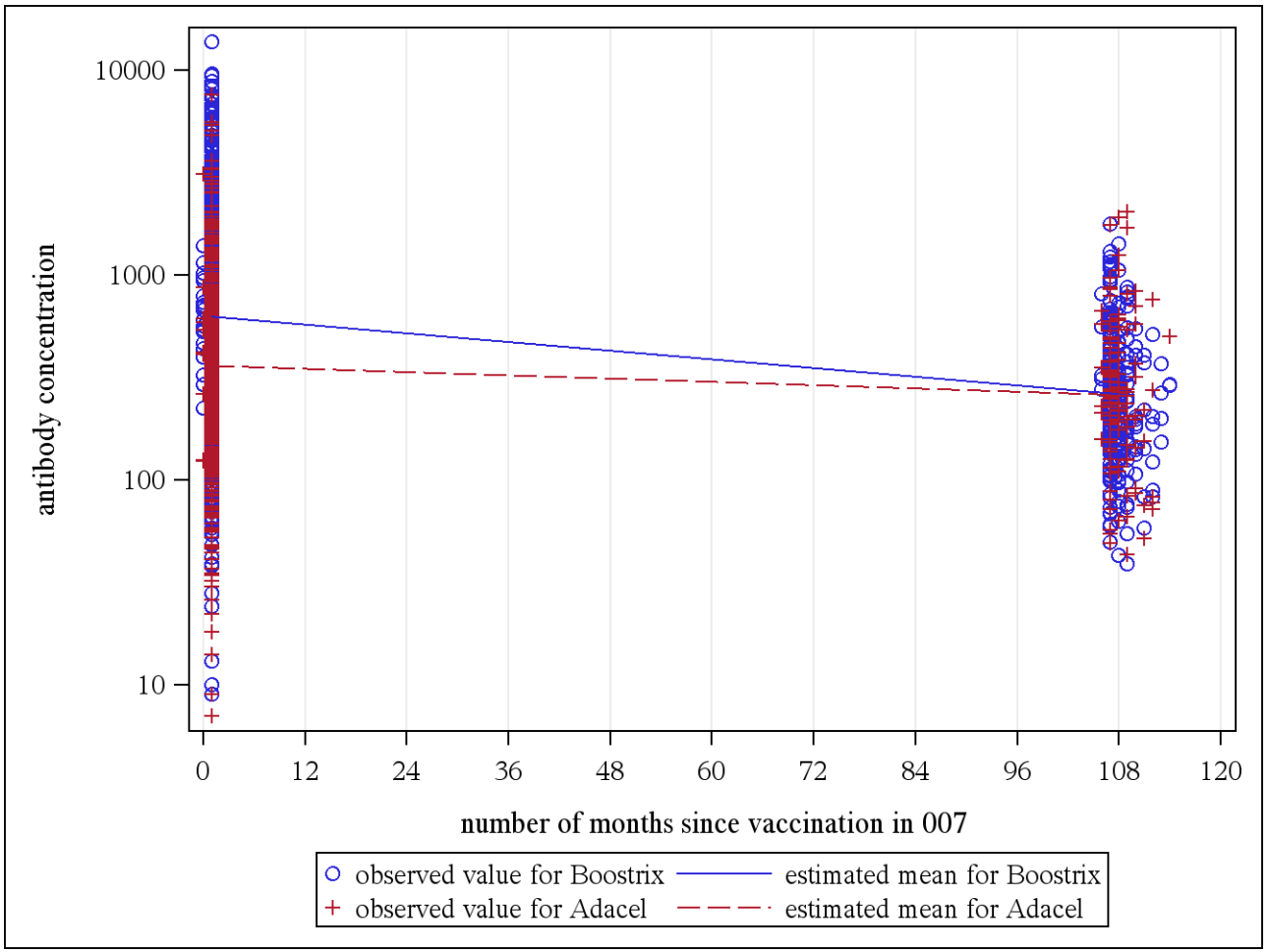


Table 7.27 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at persistence time points by age stratum (Adapted ATP cohort)

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	28-38	Pre_bst_007	470	427	90.9	87.9	93.3	127	27.0	23.1	31.3	0.5	0.4	0.5
			Post_bst_007	470	467	99.4	98.1	99.9	457	97.2	95.3	98.5	7.6	7.0	8.4
			Per(Yr1)	301	300	99.7	98.2	100	250	83.1	78.3	87.1	2.4	2.1	2.7
			Per(Yr3)	252	249	98.8	96.6	99.8	169	67.1	60.9	72.8	1.4	1.2	1.6
			Per(Yr5)	204	200	98.0	95.1	99.5	128	62.7	55.7	69.4	1.2	1.0	1.3
			Pre_bst_009	59	57	96.6	88.3	99.6	27	45.8	32.7	59.2	0.8	0.7	1.0
		39-58	Pre_bst_007	472	424	89.8	86.7	92.4	123	26.1	22.2	30.3	0.5	0.4	0.5
			Post_bst_007	475	471	99.2	97.9	99.8	440	92.6	89.9	94.8	5.6	5.1	6.2
			Per(Yr1)	349	341	97.7	95.5	99.0	247	70.8	65.7	75.5	1.6	1.4	1.8
			Per(Yr3)	306	298	97.4	94.9	98.9	169	55.2	49.5	60.9	1.1	0.9	1.2
			Per(Yr5)	275	267	97.1	94.3	98.7	139	50.5	44.5	56.6	1.0	0.8	1.1
			Pre_bst_009	88	83	94.3	87.2	98.1	40	45.5	34.8	56.4	0.7	0.6	1.0
		59-73	Pre_bst_007	497	375	75.5	71.4	79.2	90	18.1	14.8	21.8	0.3	0.3	0.3
			Post_bst_007	498	479	96.2	94.1	97.7	371	74.5	70.4	78.3	2.5	2.2	2.9
			Per(Yr1)	360	326	90.6	87.1	93.4	176	48.9	43.6	54.2	0.8	0.7	1.0
			Per(Yr3)	356	310	87.1	83.1	90.4	140	39.3	34.2	44.6	0.6	0.5	0.6
			Per(Yr5)	310	268	86.5	82.1	90.1	110	35.5	30.2	41.1	0.5	0.5	0.6
			Pre_bst_009	122	105	86.1	78.6	91.7	47	38.5	29.9	47.8	0.6	0.4	0.8
	Adacel	28-38	Pre_bst_007	236	215	91.1	86.7	94.4	75	31.8	25.9	38.1	0.5	0.5	0.6
			Post_bst_007	236	235	99.6	97.7	100	229	97.0	94.0	98.8	6.9	6.2	7.7
			Per(Yr1)	141	140	99.3	96.1	100	119	84.4	77.3	90.0	2.0	1.7	2.3
			Per(Yr3)	110	106	96.4	91.0	99.0	74	67.3	57.7	75.9	1.3	1.0	1.5
			Per(Yr5)	79	77	97.5	91.2	99.7	51	64.6	53.0	75.0	1.2	0.9	1.5
			Pre_bst_009	21	20	95.2	76.2	99.9	10	47.6	25.7	70.2	0.8	0.5	1.3
		39-58	Pre_bst_007	238	218	91.6	87.3	94.8	58	24.4	19.1	30.3	0.5	0.4	0.6
			Post_bst_007	243	239	98.4	95.8	99.5	227	93.4	89.5	96.2	5.5	4.7	6.4
			Per(Yr1)	176	173	98.3	95.1	99.6	128	72.7	65.5	79.2	1.7	1.4	2.0
			Per(Yr3)	159	156	98.1	94.6	99.6	93	58.5	50.4	66.2	1.2	1.0	1.4
			Per(Yr5)	140	137	97.9	93.9	99.6	71	50.7	42.1	59.3	1.0	0.9	1.2
			Pre_bst_009	55	52	94.5	84.9	98.9	27	49.1	35.4	62.9	0.8	0.6	1.1
		59-73	Pre_bst_007	246	209	85.0	79.9	89.2	58	23.6	18.4	29.4	0.4	0.3	0.4
			Post_bst_007	248	243	98.0	95.4	99.3	213	85.9	80.9	90.0	3.3	2.8	3.9
			Per(Yr1)	187	176	94.1	89.7	97.0	104	55.6	48.2	62.9	1.0	0.8	1.2
			Per(Yr3)	173	163	94.2	89.6	97.2	80	46.2	38.6	54.0	0.7	0.6	0.9
			Per(Yr5)	153	145	94.8	90.0	97.7	68	44.4	36.4	52.7	0.7	0.6	0.8
			Pre_bst_009	42	41	97.6	87.4	99.9	17	40.5	25.6	56.7	0.8	0.5	1.1
ANTI-T	Boostrix	28-38	Pre_bst_007	471	455	96.6	94.5	98.0	342	72.6	68.3	76.6	1.7	1.5	1.9
			Post_bst_007	471	470	99.8	98.8	100	465	98.7	97.2	99.5	9.5	8.8	10.2
			Per(Yr1)	301	301	100	98.8	100	297	98.7	96.6	99.6	4.3	4.0	4.6
			Per(Yr3)	252	251	99.6	97.8	100	234	92.9	88.9	95.7	2.4	2.2	2.7
			Per(Yr5)	204	203	99.5	97.3	100	178	87.3	81.9	91.5	2.1	1.9	2.4
			Pre_bst_009	60	60	100	94.0	100	47	78.3	65.8	87.9	1.8	1.5	2.1
		39-58	Pre_bst_007	475	466	98.1	96.4	99.1	356	74.9	70.8	78.8	1.7	1.6	1.9
			Post_bst_007	476	476	100	99.2	100	476	100	99.2	100	9.2	8.6	9.9
			Per(Yr1)	350	348	99.4	98.0	99.9	335	95.7	93.0	97.6	3.5	3.3	3.8
			Per(Yr3)	307	307	100	98.8	100	284	92.5	89.0	95.2	2.5	2.3	2.6
			Per(Yr5)	275	275	100	98.7	100	243	88.4	84.0	91.9	2.2	2.0	2.4
			Pre_bst_009	87	87	100	95.8	100	72	82.8	73.2	90.0	2.1	1.8	2.5
		59-73	Pre_bst_007	500	466	93.2	90.6	95.2	341	68.2	63.9	72.3	1.4	1.2	1.5

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
			Post_bst_007	497	492	99.0	97.7	99.7	478	96.2	94.1	97.7	7.1	6.5	7.8
			Per(Yr1)	363	351	96.7	94.3	98.3	320	88.2	84.4	91.3	2.7	2.4	3.0
			Per(Yr3)	358	341	95.3	92.5	97.2	289	80.7	76.3	84.7	1.8	1.6	2.0
			Per(Yr5)	309	294	95.1	92.1	97.3	244	79.0	74.0	83.4	1.7	1.5	2.0
			Pre_bst_009	121	116	95.9	90.6	98.6	92	76.0	67.4	83.3	1.6	1.2	2.0
	Adacel	28-38	Pre_bst_007	236	229	97.0	94.0	98.8	183	77.5	71.7	82.7	1.9	1.6	2.2
			Post_bst_007	236	236	100	98.4	100	236	100	98.4	100	14.1	12.8	15.6
			Per(Yr1)	141	141	100	97.4	100	139	98.6	95.0	99.8	5.1	4.4	5.8
			Per(Yr3)	110	110	100	96.7	100	104	94.5	88.5	98.0	3.0	2.5	3.5
			Per(Yr5)	79	79	100	95.4	100	72	91.1	82.6	96.4	2.8	2.3	3.3
			Pre_bst_009	22	22	100	84.6	100	20	90.9	70.8	98.9	2.4	1.6	3.7
		39-58	Pre_bst_007	242	238	98.3	95.8	99.5	181	74.8	68.8	80.1	1.7	1.5	2.0
			Post_bst_007	243	243	100	98.5	100	240	98.8	96.4	99.7	13.7	12.3	15.3
			Per(Yr1)	177	176	99.4	96.9	100	172	97.2	93.5	99.1	4.9	4.4	5.5
			Per(Yr3)	159	158	99.4	96.5	100	152	95.6	91.1	98.2	3.1	2.8	3.5
			Per(Yr5)	140	139	99.3	96.1	100	131	93.6	88.1	97.0	2.7	2.4	3.1
			Pre_bst_009	55	55	100	93.5	100	46	83.6	71.2	92.2	2.3	1.8	2.8
		59-73	Pre_bst_007	249	240	96.4	93.2	98.3	179	71.9	65.9	77.4	1.5	1.3	1.8
			Post_bst_007	249	249	100	98.5	100	247	99.2	97.1	99.9	12.1	10.9	13.4
			Per(Yr1)	188	187	99.5	97.1	100	176	93.6	89.1	96.7	3.6	3.2	4.1
			Per(Yr3)	173	172	99.4	96.8	100	152	87.9	82.0	92.3	2.6	2.3	2.9
			Per(Yr5)	153	152	99.3	96.4	100	134	87.6	81.3	92.4	2.3	2.0	2.6
			Pre_bst_009	43	43	100	91.8	100	35	81.4	66.6	91.6	2.4	1.8	3.1

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
n/% = number/percentage of subjects with concentration equal to or above specified value
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control group

Table 7.28 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at persistence time points by age stratum (Adapted ATP cohort)

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	28-38	Pre_bst_007	468	458	97.9	96.1	99.0	30.6	27.8	33.7
			Post_bst_007	471	471	100	99.2	100	665.5	615.6	719.4
			Per(Yr1)	301	300	99.7	98.2	100	211.0	189.3	235.1
			Per(Yr3)	252	251	99.6	97.8	100	121.0	108.0	135.6
			Per(Yr5)	204	204	100	98.2	100	113.7	101.5	127.5
			Pre_bst_009	60	60	100	94.0	100	38.4	30.7	48.0
		39-58	Pre_bst_007	472	462	97.9	96.1	99.0	32.3	29.5	35.5
			Post_bst_007	476	476	100	99.2	100	687.2	631.8	747.4
			Per(Yr1)	350	349	99.7	98.4	100	203.8	183.1	226.8
			Per(Yr3)	307	306	99.7	98.2	100	127.0	114.5	140.7
			Per(Yr5)	275	274	99.6	98.0	100	118.5	105.8	132.6
			Pre_bst_009	88	88	100	95.9	100	48.3	39.6	58.9
		59-73	Pre_bst_007	497	473	95.2	92.9	96.9	32.0	28.8	35.5
			Post_bst_007	495	495	100	99.3	100	535.0	486.1	588.8
			Per(Yr1)	363	363	100	99.0	100	163.1	145.9	182.4
			Per(Yr3)	357	356	99.7	98.4	100	99.8	89.6	111.2
			Per(Yr5)	310	310	100	98.8	100	100.7	90.2	112.4
			Pre_bst_009	123	123	100	97.0	100	40.2	33.3	48.5
	Adacel	28-38	Pre_bst_007	234	226	96.6	93.4	98.5	36.3	31.2	42.2
			Post_bst_007	236	236	100	98.4	100	404.2	362.5	450.7
			Per(Yr1)	140	140	100	97.4	100	142.9	121.2	168.5
			Per(Yr3)	110	110	100	96.7	100	85.2	71.0	102.2
			Per(Yr5)	79	79	100	95.4	100	88.8	71.8	109.9
			Pre_bst_009	22	22	100	84.6	100	40.4	27.8	58.7
		39-58	Pre_bst_007	238	231	97.1	94.0	98.8	35.5	30.7	41.0
			Post_bst_007	243	243	100	98.5	100	383.8	340.7	432.3
			Per(Yr1)	176	176	100	97.9	100	117.6	100.8	137.0
			Per(Yr3)	158	157	99.4	96.5	100	87.2	74.4	102.3
			Per(Yr5)	140	138	98.6	94.9	99.8	77.8	65.1	92.9
			Pre_bst_009	55	54	98.2	90.3	100	27.0	20.5	35.5
		59-73	Pre_bst_007	245	234	95.5	92.1	97.7	32.8	28.6	37.7
			Post_bst_007	245	245	100	98.5	100	323.5	286.3	365.6
			Per(Yr1)	186	185	99.5	97.0	100	104.4	90.3	120.9
			Per(Yr3)	171	170	99.4	96.8	100	75.0	65.4	85.9
			Per(Yr5)	152	151	99.3	96.4	100	79.7	68.6	92.7
			Pre_bst_009	43	43	100	91.8	100	25.2	19.9	32.0
ANTI-PRN	Boostrix	28-38	Pre_bst_007	471	357	75.8	71.7	79.6	12.7	11.3	14.2
			Post_bst_007	471	467	99.2	97.8	99.8	469.0	409.9	536.6
			Per(Yr1)	301	294	97.7	95.3	99.1	180.9	152.7	214.3
			Per(Yr3)	252	242	96.0	92.8	98.1	100.3	83.0	121.1
			Per(Yr5)	204	202	99.0	96.5	99.9	103.3	85.3	125.0
			Pre_bst_009	60	60	100	94.0	100	69.6	47.8	101.4
		39-58	Pre_bst_007	473	380	80.3	76.5	83.8	15.7	14.0	17.6
			Post_bst_007	474	469	98.9	97.6	99.7	512.2	443.9	591.0
			Per(Yr1)	350	342	97.7	95.5	99.0	213.1	180.3	251.8
			Per(Yr3)	307	296	96.4	93.7	98.2	108.1	91.1	128.2
			Per(Yr5)	272	267	98.2	95.8	99.4	111.7	94.1	132.6
			Pre_bst_009	88	88	100	95.9	100	89.0	65.9	120.2
		59-73	Pre_bst_007	500	363	72.6	68.5	76.5	12.0	10.7	13.5

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
			Post_bst_007	498	490	98.4	96.9	99.3	273.9	234.8	319.5
			Per(Yr1)	360	335	93.1	89.9	95.5	95.0	78.8	114.4
			Per(Yr3)	356	324	91.0	87.5	93.8	56.9	48.0	67.6
			Per(Yr5)	306	286	93.5	90.1	96.0	59.1	49.4	70.7
			Pre_bst_009	123	119	96.7	91.9	99.1	48.2	36.1	64.3
	Adacel	28-38	Pre_bst_007	236	199	84.3	79.0	88.7	16.9	14.2	20.0
			Post_bst_007	236	235	99.6	97.7	100	460.0	388.9	544.1
			Per(Yr1)	139	136	97.8	93.8	99.6	185.1	145.4	235.8
			Per(Yr3)	110	106	96.4	91.0	99.0	81.2	62.7	105.2
			Per(Yr5)	79	79	100	95.4	100	99.4	75.3	131.4
			Pre_bst_009	22	22	100	84.6	100	123.7	72.8	210.2
		39-58	Pre_bst_007	242	186	76.9	71.0	82.0	14.8	12.4	17.7
			Post_bst_007	242	240	99.2	97.0	99.9	390.6	326.2	467.6
			Per(Yr1)	175	172	98.3	95.1	99.6	151.5	121.9	188.2
			Per(Yr3)	159	153	96.2	92.0	98.6	85.7	68.5	107.2
			Per(Yr5)	140	136	97.1	92.8	99.2	86.7	68.5	109.6
			Pre_bst_009	55	54	98.2	90.3	100	73.6	50.4	107.6
		59-73	Pre_bst_007	249	170	68.3	62.1	74.0	11.7	9.8	13.9
			Post_bst_007	248	246	99.2	97.1	99.9	246.3	200.5	302.5
			Per(Yr1)	187	181	96.8	93.1	98.8	91.2	71.9	115.5
			Per(Yr3)	173	167	96.5	92.6	98.7	54.2	43.1	68.1
			Per(Yr5)	152	147	96.7	92.5	98.9	61.3	48.1	78.2
			Pre_bst_009	41	41	100	91.4	100	38.4	25.5	57.8
ANTI-PT	Boostrix	28-38	Pre_bst_007	468	291	62.2	57.6	66.6	8.0	7.3	8.9
			Post_bst_007	467	454	97.2	95.3	98.5	71.9	65.2	79.2
			Per(Yr1)	300	280	93.3	89.9	95.9	25.2	22.4	28.4
			Per(Yr3)	251	209	83.3	78.1	87.7	15.3	13.3	17.7
			Per(Yr5)	204	177	86.8	81.3	91.1	16.1	13.8	18.8
			Pre_bst_009	60	52	86.7	75.4	94.1	8.3	6.2	11.0
		39-58	Pre_bst_007	469	264	56.3	51.7	60.8	7.2	6.5	7.9
			Post_bst_007	471	464	98.5	97.0	99.4	70.7	64.5	77.4
			Per(Yr1)	349	325	93.1	89.9	95.5	25.5	22.8	28.6
			Per(Yr3)	305	266	87.2	82.9	90.7	16.1	14.3	18.1
			Per(Yr5)	275	241	87.6	83.2	91.3	15.5	13.7	17.6
			Pre_bst_009	88	77	87.5	78.7	93.6	9.0	7.1	11.4
		59-73	Pre_bst_007	497	270	54.3	49.8	58.8	6.8	6.1	7.4
			Post_bst_007	492	470	95.5	93.3	97.2	51.2	46.2	56.7
			Per(Yr1)	364	312	85.7	81.7	89.1	18.0	16.0	20.2
			Per(Yr3)	358	276	77.1	72.4	81.3	11.7	10.4	13.1
			Per(Yr5)	311	252	81.0	76.2	85.2	13.0	11.5	14.7
			Pre_bst_009	123	101	82.1	74.2	88.4	7.7	6.3	9.3
	Adacel	28-38	Pre_bst_007	234	153	65.4	58.9	71.5	9.1	7.9	10.6
			Post_bst_007	234	223	95.3	91.7	97.6	38.3	33.4	44.1
			Per(Yr1)	141	121	85.8	78.9	91.1	16.6	13.8	20.0
			Per(Yr3)	110	77	70.0	60.5	78.4	10.5	8.4	12.9
			Per(Yr5)	79	60	75.9	65.0	84.9	12.4	9.5	16.3
			Pre_bst_009	22	21	95.5	77.2	99.9	11.2	7.6	16.5
		39-58	Pre_bst_007	240	147	61.3	54.8	67.4	8.1	7.0	9.3
			Post_bst_007	241	229	95.0	91.5	97.4	32.2	27.9	37.2
			Per(Yr1)	177	154	87.0	81.1	91.6	15.4	13.2	17.9
			Per(Yr3)	159	119	74.8	67.4	81.4	10.2	8.7	12.1
			Per(Yr5)	140	108	77.1	69.3	83.8	11.0	9.2	13.2
			Pre_bst_009	55	46	83.6	71.2	92.2	6.2	4.7	8.2

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
		59-73	Pre_bst_007	248	144	58.1	51.7	64.3	7.4	6.4	8.4
			Post_bst_007	247	224	90.7	86.4	94.0	27.3	23.3	32.0
			Per(Yr1)	188	160	85.1	79.2	89.9	15.1	12.8	17.7
			Per(Yr3)	173	120	69.4	61.9	76.1	9.4	7.9	11.2
			Per(Yr5)	153	117	76.5	68.9	82.9	11.7	9.7	14.1
			Pre_bst_009	43	39	90.7	77.9	97.4	8.8	6.3	12.3

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
N = number of subjects with available results
GMC = geometric mean antibody concentration calculated on all subjects
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control group
*Note: For the time points Pre-bst-007 to Yr5, the assay cut off and unit was 5 EL.U/ml, however the assay cut off and unit at Yr9 has changed to 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN

Table 7.29 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at pre and post booster vaccination time points by age stratum (ATP cohort for analysis of immunogenicity at Year 9)

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	28-38	Pre_bst_009	59	57	96.6	88.3	99.6	27	45.8	32.7	59.2	0.8	0.7	1.0
			Post_bst_009	60	60	100	94.0	100	60	100	94.0	100	5.3	4.6	6.1
		39-58	Pre_bst_009	88	83	94.3	87.2	98.1	40	45.5	34.8	56.4	0.7	0.6	1.0
			Post_bst_009	88	88	100	95.9	100	82	93.2	85.7	97.5	4.8	3.9	6.0
		59-73	Pre_bst_009	122	105	86.1	78.6	91.7	47	38.5	29.9	47.8	0.6	0.4	0.8
			Post_bst_009	123	121	98.4	94.2	99.8	107	87.0	79.7	92.4	3.2	2.5	4.0
	Adacel	28-38	Pre_bst_009	21	20	95.2	76.2	99.9	10	47.6	25.7	70.2	0.8	0.5	1.3
			Post_bst_009	22	22	100	84.6	100	21	95.5	77.2	99.9	4.3	3.1	6.0
		39-58	Pre_bst_009	55	52	94.5	84.9	98.9	27	49.1	35.4	62.9	0.8	0.6	1.1
			Post_bst_009	55	54	98.2	90.3	100	51	92.7	82.4	98.0	4.4	3.2	6.1
		59-73	Pre_bst_009	42	41	97.6	87.4	99.9	17	40.5	25.6	56.7	0.8	0.5	1.1
			Post_bst_009	44	44	100	92.0	100	41	93.2	81.3	98.6	5.3	3.9	7.2
	Control	28-38	Pre_bst_009	73	64	87.7	77.9	94.2	22	30.1	19.9	42.0	0.5	0.3	0.6
			Post_bst_009	75	73	97.3	90.7	99.7	72	96.0	88.8	99.2	5.9	4.4	7.8
		39-58	Pre_bst_009	122	100	82.0	74.0	88.3	35	28.7	20.9	37.6	0.4	0.3	0.6
			Post_bst_009	122	121	99.2	95.5	100	107	87.7	80.5	93.0	4.1	3.2	5.2
		59-73	Pre_bst_009	129	101	78.3	70.2	85.1	35	27.1	19.7	35.7	0.4	0.3	0.5
			Post_bst_009	129	125	96.9	92.3	99.1	103	79.8	71.9	86.4	3.1	2.4	4.1
ANTI-T	Boostrix	28-38	Pre_bst_009	60	60	100	94.0	100	47	78.3	65.8	87.9	1.8	1.5	2.1
			Post_bst_009	60	60	100	94.0	100	60	100	94.0	100	8.7	7.6	10.1
		39-58	Pre_bst_009	87	87	100	95.8	100	72	82.8	73.2	90.0	2.1	1.8	2.5
			Post_bst_009	88	88	100	95.9	100	88	100	95.9	100	9.5	8.0	11.1
		59-73	Pre_bst_009	121	116	95.9	90.6	98.6	92	76.0	67.4	83.3	1.6	1.2	2.0
			Post_bst_009	123	123	100	97.0	100	121	98.4	94.2	99.8	7.6	6.5	8.9
	Adacel	28-38	Pre_bst_009	22	22	100	84.6	100	20	90.9	70.8	98.9	2.4	1.6	3.7
			Post_bst_009	22	22	100	84.6	100	22	100	84.6	100	7.0	5.7	8.6
		39-58	Pre_bst_009	55	55	100	93.5	100	46	83.6	71.2	92.2	2.3	1.8	2.8
			Post_bst_009	55	55	100	93.5	100	55	100	93.5	100	8.6	7.0	10.6
		59-73	Pre_bst_009	43	43	100	91.8	100	35	81.4	66.6	91.6	2.4	1.8	3.1
			Post_bst_009	44	44	100	92.0	100	44	100	92.0	100	9.6	7.5	12.1
	Control	28-38	Pre_bst_009	75	73	97.3	90.7	99.7	52	69.3	57.6	79.5	1.6	1.2	2.1
			Post_bst_009	75	75	100	95.2	100	75	100	95.2	100	9.5	8.2	11.1
		39-58	Pre_bst_009	120	116	96.7	91.7	99.1	91	75.8	67.2	83.2	1.8	1.4	2.2
			Post_bst_009	122	122	100	97.0	100	120	98.4	94.2	99.8	10.1	8.7	11.7
		59-73	Pre_bst_009	129	115	89.1	82.5	93.9	88	68.2	59.4	76.1	1.2	0.9	1.6
			Post_bst_009	130	129	99.2	95.8	100	124	95.4	90.2	98.3	7.3	6.2	8.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pre_bst_009 =Pre booster vaccination blood sampling time-point
Post_bst_009 = Post booster vaccination blood sampling time-point
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control group

Table 7.30 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at pre and post booster vaccination time points by age stratum (ATP cohort for analysis of immunogenicity at Year 9)

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	28-38	Pre_bst_009	60	60	100	94.0	100	38.4	30.7	48.0
			Post_bst_009	60	60	100	94.0	100	257.0	217.6	303.6
		39-58	Pre_bst_009	88	88	100	95.9	100	48.3	39.6	58.9
			Post_bst_009	88	88	100	95.9	100	263.4	227.0	305.6
		59-73	Pre_bst_009	123	123	100	97.0	100	40.2	33.3	48.5
			Post_bst_009	123	123	100	97.0	100	233.2	203.1	267.9
	Adacel	28-38	Pre_bst_009	22	22	100	84.6	100	40.4	27.8	58.7
			Post_bst_009	22	22	100	84.6	100	225.3	172.6	294.2
		39-58	Pre_bst_009	55	54	98.2	90.3	100	27.0	20.5	35.5
			Post_bst_009	55	55	100	93.5	100	276.1	217.3	350.8
		59-73	Pre_bst_009	43	43	100	91.8	100	25.2	19.9	32.0
			Post_bst_009	44	44	100	92.0	100	244.5	186.9	320.0
	Control	28-38	Pre_bst_009	75	75	100	95.2	100	28.0	20.7	37.8
			Post_bst_009	75	75	100	95.2	100	415.5	349.8	493.4
		39-58	Pre_bst_009	122	120	98.4	94.2	99.8	22.0	17.3	27.9
			Post_bst_009	122	122	100	97.0	100	365.3	305.2	437.2
		59-73	Pre_bst_009	130	127	97.7	93.4	99.5	22.9	18.6	28.3
			Post_bst_009	130	130	100	97.2	100	359.0	300.2	429.3
ANTI-PRN	Boostrix	28-38	Pre_bst_009	60	60	100	94.0	100	69.6	47.8	101.4
			Post_bst_009	60	60	100	94.0	100	441.8	369.7	528.1
		39-58	Pre_bst_009	88	88	100	95.9	100	89.0	65.9	120.2
			Post_bst_009	88	88	100	95.9	100	445.4	361.2	549.3
		59-73	Pre_bst_009	123	119	96.7	91.9	99.1	48.2	36.1	64.3
			Post_bst_009	123	123	100	97.0	100	363.5	296.4	445.7
	Adacel	28-38	Pre_bst_009	22	22	100	84.6	100	123.7	72.8	210.2
			Post_bst_009	22	22	100	84.6	100	495.0	357.7	685.0
		39-58	Pre_bst_009	55	54	98.2	90.3	100	73.6	50.4	107.6
			Post_bst_009	55	55	100	93.5	100	555.5	425.3	725.6
		59-73	Pre_bst_009	41	41	100	91.4	100	38.4	25.5	57.8
			Post_bst_009	44	44	100	92.0	100	469.7	333.9	660.6
	Control	28-38	Pre_bst_009	72	71	98.6	92.5	100	21.5	14.8	31.3
			Post_bst_009	75	75	100	95.2	100	457.1	336.1	621.6
		39-58	Pre_bst_009	120	107	89.2	82.2	94.1	20.5	14.9	28.3
			Post_bst_009	122	122	100	97.0	100	397.1	300.5	524.6
		59-73	Pre_bst_009	129	106	82.2	74.5	88.3	14.1	10.3	19.2
			Post_bst_009	129	129	100	97.2	100	240.5	179.8	321.9
ANTI-PT	Boostrix	28-38	Pre_bst_009	60	52	86.7	75.4	94.1	8.3	6.2	11.0
			Post_bst_009	60	60	100	94.0	100	86.8	70.7	106.6
		39-58	Pre_bst_009	88	77	87.5	78.7	93.6	9.0	7.1	11.4
			Post_bst_009	88	88	100	95.9	100	74.5	60.7	91.3
		59-73	Pre_bst_009	123	101	82.1	74.2	88.4	7.7	6.3	9.3
			Post_bst_009	123	120	97.6	93.0	99.5	49.6	41.0	60.1
	Adacel	28-38	Pre_bst_009	22	21	95.5	77.2	99.9	11.2	7.6	16.5

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
			Post_bst_009	22	22	100	84.6	100	91.4	70.2	118.9
		39-58	Pre_bst_009	55	46	83.6	71.2	92.2	6.2	4.7	8.2
			Post_bst_009	55	54	98.2	90.3	100	66.8	49.6	89.9
		59-73	Pre_bst_009	43	39	90.7	77.9	97.4	8.8	6.3	12.3
			Post_bst_009	44	44	100	92.0	100	66.0	47.7	91.3
	Control	28-38	Pre_bst_009	75	52	69.3	57.6	79.5	6.7	4.9	9.1
			Post_bst_009	75	75	100	95.2	100	83.5	66.2	105.5
		39-58	Pre_bst_009	122	76	62.3	53.1	70.9	5.1	4.0	6.3
			Post_bst_009	122	120	98.4	94.2	99.8	67.5	54.7	83.4
		59-73	Pre_bst_009	130	81	62.3	53.4	70.7	5.1	4.1	6.4
			Post_bst_009	129	127	98.4	94.5	99.8	56.6	46.5	69.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 =Pre booster vaccination blood sampling time-point
Post_bst_009 = Post booster vaccination blood sampling time-point
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.31 Booster response to anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination by age stratum (ATP cohort for analysis of immunogenicity at Year 9)

					Booster response			
							95% CI	
Antibody	Group	Sub-group	Pre-vaccination status	N	n	%	LL	UL
ANTI-D	Boostrix	28-38	S-	2	2	100	15.8	100
			S+	57	39	68.4	54.8	80.1
			Total	59	41	69.5	56.1	80.8
		39-58	S-	5	5	100	47.8	100
			S+	83	49	59.0	47.7	69.7
			Total	88	54	61.4	50.4	71.6
		59-73	S-	17	9	52.9	27.8	77.0
			S+	105	65	61.9	51.9	71.2
			Total	122	74	60.7	51.4	69.4
	Adacel	28-38	S-	1	1	100	2.5	100
			S+	20	11	55.0	31.5	76.9
			Total	21	12	57.1	34.0	78.2
		39-58	S-	3	1	33.3	0.8	90.6
			S+	52	33	63.5	49.0	76.4
			Total	55	34	61.8	47.7	74.6
		59-73	S-	1	1	100	2.5	100
			S+	41	24	58.5	42.1	73.7
			Total	42	25	59.5	43.3	74.4
ANTI-T	Boostrix	28-38	S-	0	-	-	-	-
			S+	60	26	43.3	30.6	56.8
			Total	60	26	43.3	30.6	56.8
		39-58	S-	0	-	-	-	-
			S+	87	42	48.3	37.4	59.2
			Total	87	42	48.3	37.4	59.2
		59-73	S-	5	5	100	47.8	100
			S+	116	53	45.7	36.4	55.2
			Total	121	58	47.9	38.8	57.2
	Adacel	28-38	S-	0	-	-	-	-
			S+	22	5	22.7	7.8	45.4
			Total	22	5	22.7	7.8	45.4
		39-58	S-	0	-	-	-	-
			S+	55	22	40.0	27.0	54.1
			Total	55	22	40.0	27.0	54.1
		59-73	S-	0	-	-	-	-
			S+	43	17	39.5	25.0	55.6
			Total	43	17	39.5	25.0	55.6

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
S- = Antibody concentration < 0.1 IU/mL
S+ = Antibody concentration ≥ 0.1 IU/mL
Total = subjects either seropositive or seronegative
Booster response to D and T antigens is defined as:

- For initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination.
- For initially seropositive subjects with pre-booster antibody concentration ≥0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Age stratum is derived from the age stratum in study 106316 for subjects primed in 106316 study (ie projected age at year 9) and from the age at vaccination for subjects in the control group

Table 7.32 Booster response for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination by age stratum (ATP cohort for analysis of immunogenicity at Year 9)

					Booster response			
							95% CI	
Antibody	Group	Sub-group	Pre-vaccination status	N	n	%	LL	UL
ANTI-FHA	Boostrix	28-38	S-	0	-	-	-	-
			S+ (<4*cut_off)	2	2	100	15.8	100
			S+ (≥4*cut_off)	58	52	89.7	78.8	96.1
			Total	60	54	90.0	79.5	96.2
		39-58	S-	0	-	-	-	-
			S+ (<4*cut_off)	3	3	100	29.2	100
			S+ (≥4*cut_off)	85	70	82.4	72.6	89.8
			Total	88	73	83.0	73.4	90.1
		59-73	S-	0	-	-	-	-
			S+ (<4*cut_off)	11	11	100	71.5	100
			S+ (≥4*cut_off)	112	94	83.9	75.8	90.2
			Total	123	105	85.4	77.9	91.1
	Adacel	28-38	S-	0	-	-	-	-
			S+ (<4*cut_off)	1	1	100	2.5	100
			S+ (≥4*cut_off)	21	19	90.5	69.6	98.8
			Total	22	20	90.9	70.8	98.9
		39-58	S-	1	1	100	2.5	100
			S+ (<4*cut_off)	5	5	100	47.8	100
			S+ (≥4*cut_off)	49	48	98.0	89.1	99.9
			Total	55	54	98.2	90.3	100
		59-73	S-	0	-	-	-	-
			S+ (<4*cut_off)	3	3	100	29.2	100
			S+ (≥4*cut_off)	40	39	97.5	86.8	99.9
			Total	43	42	97.7	87.7	99.9
ANTI-PRN	Boostrix	28-38	S-	0	-	-	-	-
			S+ (<4*cut_off)	7	7	100	59.0	100
			S+ (≥4*cut_off)	53	38	71.7	57.7	83.2
			Total	60	45	75.0	62.1	85.3
		39-58	S-	0	-	-	-	-
			S+ (<4*cut_off)	7	6	85.7	42.1	99.6
			S+ (≥4*cut_off)	81	62	76.5	65.8	85.2
			Total	88	68	77.3	67.1	85.5
		59-73	S-	4	4	100	39.8	100
			S+ (<4*cut_off)	15	14	93.3	68.1	99.8
			S+ (≥4*cut_off)	104	79	76.0	66.6	83.8
			Total	123	97	78.9	70.6	85.7
	Adacel	28-38	S-	0	-	-	-	-
			S+ (<4*cut_off)	0	-	-	-	-
			S+ (≥4*cut_off)	22	13	59.1	36.4	79.3

					Booster response			
							95% CI	
Antibody	**Group**	**Sub-group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
			Total	22	13	59.1	36.4	79.3
		39-58	S-	1	1	100	2.5	100
			S+ (<4*cut_off)	4	4	100	39.8	100
			S+ (≥4*cut_off)	50	42	84.0	70.9	92.8
			Total	55	47	85.5	73.3	93.5
		59-73	S-	0	-	-	-	-
			S+ (<4*cut_off)	6	6	100	54.1	100
			S+ (≥4*cut_off)	35	32	91.4	76.9	98.2
			Total	41	38	92.7	80.1	98.5
ANTI-PT	Boostrix	28-38	S-	8	8	100	63.1	100
			S+ (<4*cut_off)	30	28	93.3	77.9	99.2
			S+ (≥4*cut_off)	22	21	95.5	77.2	99.9
			Total	60	57	95.0	86.1	99.0
		39-58	S-	11	10	90.9	58.7	99.8
			S+ (<4*cut_off)	43	38	88.4	74.9	96.1
			S+ (≥4*cut_off)	34	29	85.3	68.9	95.0
			Total	88	77	87.5	78.7	93.6
		59-73	S-	22	16	72.7	49.8	89.3
			S+ (<4*cut_off)	51	40	78.4	64.7	88.7
			S+ (≥4*cut_off)	50	45	90.0	78.2	96.7
			Total	123	101	82.1	74.2	88.4
	Adacel	28-38	S-	1	1	100	2.5	100
			S+ (<4*cut_off)	8	8	100	63.1	100
			S+ (≥4*cut_off)	13	13	100	75.3	100
			Total	22	22	100	84.6	100
		39-58	S-	9	6	66.7	29.9	92.5
			S+ (<4*cut_off)	30	28	93.3	77.9	99.2
			S+ (≥4*cut_off)	16	16	100	79.4	100
			Total	55	50	90.9	80.0	97.0
		59-73	S-	4	3	75.0	19.4	99.4
			S+ (<4*cut_off)	22	17	77.3	54.6	92.2
			S+ (≥4*cut_off)	17	14	82.4	56.6	96.2
			Total	43	34	79.1	64.0	90.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
Total = subjects either seropositive or seronegative
Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
- For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
- For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.
(each age strata)= subjects age strata classified as 19 – 29 years, 30 – 49 years and 50-64 years based on the enrolment in the 106316 study

Table 7.33 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at persistence time points by gender (Adapted ATP cohort)

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	Male	Pre_bst_007	529	464	87.7	84.6	90.4	151	28.5	24.7	32.6	0.5	0.4	0.5
			Post_bst_007	530	523	98.7	97.3	99.5	472	89.1	86.1	91.6	5.1	4.6	5.7
			Per(Yr1)	364	349	95.9	93.3	97.7	241	66.2	61.1	71.1	1.4	1.3	1.6
			Per(Yr3)	309	295	95.5	92.5	97.5	176	57.0	51.2	62.6	1.0	0.9	1.2
			Per(Yr5)	284	270	95.1	91.9	97.3	143	50.4	44.4	56.3	0.9	0.8	1.0
			Pre_bst_009	88	85	96.6	90.4	99.3	45	51.1	40.2	61.9	0.9	0.7	1.1
		Female	Pre_bst_007	910	762	83.7	81.2	86.1	189	20.8	18.2	23.6	0.4	0.3	0.4
			Post_bst_007	913	894	97.9	96.8	98.7	796	87.2	84.8	89.3	4.5	4.1	4.9
			Per(Yr1)	646	618	95.7	93.8	97.1	432	66.9	63.1	70.5	1.4	1.3	1.6
			Per(Yr3)	605	562	92.9	90.5	94.8	302	49.9	45.9	54.0	0.8	0.8	0.9
			Per(Yr5)	505	465	92.1	89.4	94.3	234	46.3	41.9	50.8	0.7	0.7	0.8
			Pre_bst_009	181	160	88.4	82.8	92.7	69	38.1	31.0	45.6	0.6	0.5	0.7
	Adacel	Male	Pre_bst_007	264	250	94.7	91.3	97.1	79	29.9	24.5	35.8	0.6	0.5	0.6
			Post_bst_007	266	266	100	98.6	100	254	95.5	92.3	97.6	5.5	4.9	6.1
			Per(Yr1)	160	159	99.4	96.6	100	115	71.9	64.2	78.7	1.6	1.3	1.9
			Per(Yr3)	142	136	95.8	91.0	98.4	82	57.7	49.2	66.0	1.0	0.8	1.2
			Per(Yr5)	114	111	97.4	92.5	99.5	69	60.5	50.9	69.6	1.0	0.8	1.3
			Pre_bst_009	36	35	97.2	85.5	99.9	17	47.2	30.4	64.5	0.9	0.6	1.1
		Female	Pre_bst_007	456	392	86.0	82.4	89.0	112	24.6	20.7	28.8	0.4	0.4	0.5
			Post_bst_007	461	451	97.8	96.0	99.0	415	90.0	86.9	92.6	4.7	4.2	5.3
			Per(Yr1)	344	330	95.9	93.3	97.8	236	68.6	63.4	73.5	1.4	1.2	1.6
			Per(Yr3)	300	289	96.3	93.5	98.2	165	55.0	49.2	60.7	1.0	0.9	1.1
			Per(Yr5)	258	248	96.1	93.0	98.1	121	46.9	40.7	53.2	0.8	0.7	1.0
			Pre_bst_009	82	78	95.1	88.0	98.7	37	45.1	34.1	56.5	0.7	0.6	1.0
ANTI-T	Boostrix	Male	Pre_bst_007	531	515	97.0	95.2	98.3	418	78.7	75.0	82.1	1.9	1.7	2.1
			Post_bst_007	530	530	100	99.3	100	522	98.5	97.0	99.3	8.1	7.6	8.6
			Per(Yr1)	366	362	98.9	97.2	99.7	345	94.3	91.4	96.4	3.4	3.1	3.7
			Per(Yr3)	310	306	98.7	96.7	99.6	280	90.3	86.5	93.4	2.3	2.1	2.5
			Per(Yr5)	284	281	98.9	96.9	99.8	249	87.7	83.3	91.3	2.2	2.0	2.5
			Pre_bst_009	88	87	98.9	93.8	100	75	85.2	76.1	91.9	2.1	1.7	2.6
		Female	Pre_bst_007	915	872	95.3	93.7	96.6	621	67.9	64.7	70.9	1.4	1.3	1.5
			Post_bst_007	914	908	99.3	98.6	99.8	897	98.1	97.0	98.9	8.8	8.2	9.3
			Per(Yr1)	648	638	98.5	97.2	99.3	607	93.7	91.5	95.4	3.4	3.1	3.6
			Per(Yr3)	607	593	97.7	96.2	98.7	527	86.8	83.9	89.4	2.1	2.0	2.3
			Per(Yr5)	504	491	97.4	95.6	98.6	416	82.5	78.9	85.8	1.9	1.7	2.0
			Pre_bst_009	180	176	97.8	94.4	99.4	136	75.6	68.6	81.6	1.6	1.4	1.9
	Adacel	Male	Pre_bst_007	267	265	99.3	97.3	99.9	209	78.3	72.8	83.1	2.1	1.8	2.4
			Post_bst_007	267	267	100	98.6	100	266	99.6	97.9	100	12.8	11.6	14.0
			Per(Yr1)	161	161	100	97.7	100	156	96.9	92.9	99.0	4.9	4.3	5.5
			Per(Yr3)	142	142	100	97.4	100	132	93.0	87.4	96.6	3.2	2.8	3.6
			Per(Yr5)	114	114	100	96.8	100	106	93.0	86.6	96.9	2.8	2.5	3.3
			Pre_bst_009	37	37	100	90.5	100	33	89.2	74.6	97.0	2.7	2.0	3.6
		Female	Pre_bst_007	460	442	96.1	93.9	97.7	334	72.6	68.3	76.6	1.5	1.3	1.7
			Post_bst_007	461	461	100	99.2	100	457	99.1	97.8	99.8	13.5	12.5	14.6
			Per(Yr1)	345	343	99.4	97.9	99.9	331	95.9	93.3	97.8	4.2	3.8	4.6

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
			Per(Yr3)	300	298	99.3	97.6	99.9	276	92.0	88.3	94.8	2.7	2.5	3.0
			Per(Yr5)	258	256	99.2	97.2	99.9	231	89.5	85.1	93.0	2.4	2.2	2.7
			Pre_bst_009	83	83	100	95.7	100	68	81.9	72.0	89.5	2.2	1.8	2.6

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
n/% = number/percentage of subjects with concentration equal to or above specified value
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study

Table 7.34 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at persistence time points by gender (Adapted ATP cohort)

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	Male	Pre_bst_007	527	521	98.9	97.5	99.6	38.5	35.1	42.1
			Post_bst_007	529	529	100	99.3	100	678.9	628.0	733.9
			Per(Yr1)	366	366	100	99.0	100	220.7	200.0	243.7
			Per(Yr3)	310	310	100	98.8	100	134.4	121.9	148.1
			Per(Yr5)	283	283	100	98.7	100	131.8	119.2	145.6
			Pre_bst_009	89	89	100	95.9	100	51.1	42.6	61.2
		Female	Pre_bst_007	910	872	95.8	94.3	97.0	28.3	26.3	30.3
			Post_bst_007	913	913	100	99.6	100	594.3	556.8	634.2
			Per(Yr1)	648	646	99.7	98.9	100	174.8	161.1	189.6
			Per(Yr3)	606	603	99.5	98.6	99.9	104.9	96.8	113.7
			Per(Yr5)	506	505	99.8	98.9	100	99.4	91.3	108.1
			Pre_bst_009	182	182	100	98.0	100	38.5	33.1	44.7
	Adacel	Male	Pre_bst_007	264	257	97.3	94.6	98.9	38.9	34.1	44.4
			Post_bst_007	265	265	100	98.6	100	410.3	369.2	455.9
			Per(Yr1)	160	159	99.4	96.6	100	138.8	119.2	161.7
			Per(Yr3)	142	142	100	97.4	100	102.3	88.4	118.4
			Per(Yr5)	113	113	100	96.8	100	100.8	86.1	118.0
			Pre_bst_009	37	37	100	90.5	100	38.2	29.5	49.4
		Female	Pre_bst_007	453	434	95.8	93.5	97.5	32.6	29.3	36.3
			Post_bst_007	459	459	100	99.2	100	346.2	317.2	377.8
			Per(Yr1)	342	342	100	98.9	100	110.5	99.0	123.2
			Per(Yr3)	297	295	99.3	97.6	99.9	73.4	65.7	82.1
			Per(Yr5)	258	255	98.8	96.6	99.8	73.4	64.7	83.3
			Pre_bst_009	83	82	98.8	93.5	100	24.8	20.2	30.5
ANTI-PRN	Boostrix	Male	Pre_bst_007	530	433	81.7	78.1	84.9	15.6	14.0	17.4

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
			Post_bst_007	529	526	99.4	98.4	99.9	513.3	450.1	585.4
			Per(Yr1)	366	355	97.0	94.7	98.5	199.9	169.6	235.7
			Per(Yr3)	309	298	96.4	93.7	98.2	113.3	95.4	134.6
			Per(Yr5)	278	272	97.8	95.4	99.2	120.1	100.9	142.9
			Pre_bst_009	89	89	100	95.9	100	103.9	78.5	137.6
		Female	Pre_bst_007	914	667	73.0	70.0	75.8	12.2	11.2	13.3
			Post_bst_007	914	900	98.5	97.4	99.2	347.6	311.7	387.5
			Per(Yr1)	645	616	95.5	93.6	97.0	130.4	114.3	148.6
			Per(Yr3)	606	564	93.1	90.7	95.0	70.2	61.8	79.8
			Per(Yr5)	504	483	95.8	93.7	97.4	70.6	61.9	80.6
			Pre_bst_009	182	178	97.8	94.5	99.4	50.3	39.9	63.3
	Adacel	Male	Pre_bst_007	267	218	81.6	76.5	86.1	16.7	14.1	19.7
			Post_bst_007	265	263	99.2	97.3	99.9	399.5	337.0	473.8
			Per(Yr1)	159	158	99.4	96.5	100	162.5	127.9	206.3
			Per(Yr3)	142	140	98.6	95.0	99.8	96.6	76.6	121.8
			Per(Yr5)	114	113	99.1	95.2	100	111.9	87.7	142.8
			Pre_bst_009	36	36	100	90.3	100	108.4	74.9	157.0
		Female	Pre_bst_007	460	337	73.3	69.0	77.3	13.0	11.5	14.7
			Post_bst_007	461	458	99.3	98.1	99.9	327.1	284.4	376.3
			Per(Yr1)	342	331	96.8	94.3	98.4	120.5	102.1	142.2
			Per(Yr3)	300	286	95.3	92.3	97.4	60.9	51.5	72.0
			Per(Yr5)	257	249	96.9	94.0	98.6	65.8	55.0	78.6
			Pre_bst_009	82	81	98.8	93.4	100	51.6	37.5	70.8
ANTI-PT	Boostrix	Male	Pre_bst_007	527	333	63.2	58.9	67.3	8.2	7.4	9.0
			Post_bst_007	524	513	97.9	96.3	98.9	73.8	67.2	81.1
			Per(Yr1)	366	339	92.6	89.4	95.1	26.4	23.5	29.6
			Per(Yr3)	310	268	86.5	82.1	90.1	16.5	14.6	18.7
			Per(Yr5)	284	251	88.4	84.1	91.9	17.3	15.2	19.6
			Pre_bst_009	89	81	91.0	83.1	96.0	10.2	8.1	12.9
		Female	Pre_bst_007	907	492	54.2	50.9	57.5	6.8	6.4	7.3
			Post_bst_007	906	875	96.6	95.2	97.7	58.4	54.4	62.6
			Per(Yr1)	647	578	89.3	86.7	91.6	20.5	18.8	22.3
			Per(Yr3)	604	483	80.0	76.5	83.1	12.9	11.8	14.0
			Per(Yr5)	506	419	82.8	79.2	86.0	13.3	12.1	14.6
			Pre_bst_009	182	149	81.9	75.5	87.2	7.3	6.3	8.6
	Adacel	Male	Pre_bst_007	264	164	62.1	56.0	68.0	8.5	7.4	9.9
			Post_bst_007	264	251	95.1	91.7	97.4	34.9	30.4	40.2
			Per(Yr1)	161	140	87.0	80.8	91.7	16.7	14.0	19.9
			Per(Yr3)	142	110	77.5	69.7	84.0	11.5	9.5	13.8
			Per(Yr5)	114	93	81.6	73.2	88.2	13.5	10.9	16.7
			Pre_bst_009	37	34	91.9	78.1	98.3	9.0	6.4	12.6
		Female	Pre_bst_007	458	280	61.1	56.5	65.6	7.9	7.1	8.8
			Post_bst_007	458	425	92.8	90.0	95.0	30.7	27.6	34.2
			Per(Yr1)	345	295	85.5	81.3	89.0	15.1	13.5	16.9
			Per(Yr3)	300	206	68.7	63.1	73.9	9.3	8.2	10.6
			Per(Yr5)	258	192	74.4	68.6	79.6	10.9	9.5	12.5
			Pre_bst_009	83	72	86.7	77.5	93.2	7.4	5.9	9.2

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results

n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_007= blood sampling, at Month 0 before vaccination in Tdap 0.3-007 study
n/% = number/percentage of subjects with concentration equal to or above specified value
Post_bst_007= blood sampling, one Month after vaccination in Tdap 0.3-007 study
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Per(Yr1)= blood sampling, 1 year post vaccination in Tdap 0.3-007 study
Per(Yr3)= blood sampling, 3 year post vaccination in Tdap 0.3-007 study
Per(Yr5)= blood sampling, 5 year post vaccination in Tdap 0.3-007 study
Pre_bst_009= blood sampling, 9 year post vaccination in Tdap 0.3-007 study
*Note: For the time points Pre-bst-007 to Yr5, the assay cut off and unit was 5 EL.U/ml, however the assay cut off and unit at Yr9 has changed to 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN

Table 7.35 Number and percentage of subjects with an anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/mL and 1 IU/mL and GMCs at pre and post booster vaccination time points by gender (ATP cohort for analysis of immunogenicity at Year 9)

					≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
							95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	Male	Pre_bst_009	88	85	96.6	90.4	99.3	45	51.1	40.2	61.9	0.9	0.7	1.1
			Post_bst_009	89	89	100	95.9	100	83	93.3	85.9	97.5	4.4	3.6	5.3
		Female	Pre_bst_009	181	160	88.4	82.8	92.7	69	38.1	31.0	45.6	0.6	0.5	0.7
			Post_bst_009	182	180	98.9	96.1	99.9	166	91.2	86.1	94.9	4.0	3.3	4.7
	Adacel	Male	Pre_bst_009	36	35	97.2	85.5	99.9	17	47.2	30.4	64.5	0.9	0.6	1.1
			Post_bst_009	37	37	100	90.5	100	34	91.9	78.1	98.3	4.5	3.3	6.2
		Female	Pre_bst_009	82	78	95.1	88.0	98.7	37	45.1	34.1	56.5	0.7	0.6	1.0
			Post_bst_009	84	83	98.8	93.5	100	79	94.0	86.7	98.0	4.8	3.8	6.1
	Control	Male	Pre_bst_009	147	119	81.0	73.7	87.0	48	32.7	25.2	40.9	0.4	0.3	0.6
			Post_bst_009	148	143	96.6	92.3	98.9	126	85.1	78.4	90.4	3.5	2.8	4.4
		Female	Pre_bst_009	177	146	82.5	76.1	87.8	44	24.9	18.7	31.9	0.4	0.3	0.5
			Post_bst_009	178	176	98.9	96.0	99.9	156	87.6	81.9	92.1	4.4	3.6	5.4
ANTI-T	Boostrix	Male	Pre_bst_009	88	87	98.9	93.8	100	75	85.2	76.1	91.9	2.1	1.7	2.6
			Post_bst_009	89	89	100	95.9	100	87	97.8	92.1	99.7	7.7	6.7	9.0
		Female	Pre_bst_009	180	176	97.8	94.4	99.4	136	75.6	68.6	81.6	1.6	1.4	1.9
			Post_bst_009	182	182	100	98.0	100	182	100	98.0	100	8.8	7.8	9.9
	Adacel	Male	Pre_bst_009	37	37	100	90.5	100	33	89.2	74.6	97.0	2.7	2.0	3.6
			Post_bst_009	37	37	100	90.5	100	37	100	90.5	100	7.3	5.6	9.5
		Female	Pre_bst_009	83	83	100	95.7	100	68	81.9	72.0	89.5	2.2	1.8	2.6
			Post_bst_009	84	84	100	95.7	100	84	100	95.7	100	9.3	8.0	10.7
	Control	Male	Pre_bst_009	147	143	97.3	93.2	99.3	117	79.6	72.2	85.8	2.0	1.6	2.4
			Post_bst_009	148	148	100	97.5	100	145	98.0	94.2	99.6	9.0	7.9	10.3
		Female	Pre_bst_009	177	161	91.0	85.7	94.7	114	64.4	56.9	71.4	1.2	0.9	1.5
			Post_bst_009	179	178	99.4	96.9	100	174	97.2	93.6	99.1	8.6	7.5	9.8

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre_bst_009 =Pre booster vaccination blood sampling time-point
Post_bst_009 = Post booster vaccination blood sampling time-point

Table 7.36 Number and percentage of subjects with an anti- PT, anti-FHA, anti-PRN antibody concentration ≥ Assay cut off and GMCs at pre and post booster vaccination time points by gender (ATP cohort for analysis of immunogenicity at Year 9)

					≥ Assay cut off				GMC		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	Male	Pre_bst_009	89	89	100	95.9	100	51.1	42.6	61.2
			Post_bst_009	89	89	100	95.9	100	235.0	204.8	269.6
		Female	Pre_bst_009	182	182	100	98.0	100	38.5	33.1	44.7
			Post_bst_009	182	182	100	98.0	100	254.5	227.8	284.3
	Adacel	Male	Pre_bst_009	37	37	100	90.5	100	38.2	29.5	49.4
			Post_bst_009	37	37	100	90.5	100	272.9	212.4	350.8
		Female	Pre_bst_009	83	82	98.8	93.5	100	24.8	20.2	30.5
			Post_bst_009	84	84	100	95.7	100	246.9	204.1	298.6
	Control	Male	Pre_bst_009	148	146	98.6	95.2	99.8	27.2	22.2	33.3
			Post_bst_009	148	148	100	97.5	100	386.8	332.1	450.5
		Female	Pre_bst_009	179	176	98.3	95.2	99.7	21.0	17.4	25.5
			Post_bst_009	179	179	100	98.0	100	363.1	314.2	419.6
ANTI-PRN	Boostrix	Male	Pre_bst_009	89	89	100	95.9	100	103.9	78.5	137.6
			Post_bst_009	89	89	100	95.9	100	422.3	349.8	509.8
		Female	Pre_bst_009	182	178	97.8	94.5	99.4	50.3	39.9	63.3
			Post_bst_009	182	182	100	98.0	100	397.4	340.2	464.3
	Adacel	Male	Pre_bst_009	36	36	100	90.3	100	108.4	74.9	157.0
			Post_bst_009	37	37	100	90.5	100	620.3	462.1	832.6
		Female	Pre_bst_009	82	81	98.8	93.4	100	51.6	37.5	70.8
			Post_bst_009	84	84	100	95.7	100	470.2	375.7	588.5
	Control	Male	Pre_bst_009	143	129	90.2	84.1	94.5	18.2	13.8	24.1
			Post_bst_009	147	147	100	97.5	100	391.7	311.4	492.9
		Female	Pre_bst_009	178	155	87.1	81.2	91.6	17.5	13.4	22.8
			Post_bst_009	179	179	100	98.0	100	296.8	231.1	381.0
ANTI-PT	Boostrix	Male	Pre_bst_009	89	81	91.0	83.1	96.0	10.2	8.1	12.9
			Post_bst_009	89	88	98.9	93.9	100	66.6	53.8	82.4
		Female	Pre_bst_009	182	149	81.9	75.5	87.2	7.3	6.3	8.6
			Post_bst_009	182	180	98.9	96.1	99.9	62.9	54.2	72.8
	Adacel	Male	Pre_bst_009	37	34	91.9	78.1	98.3	9.0	6.4	12.6
			Post_bst_009	37	36	97.3	85.8	99.9	74.5	51.7	107.3
		Female	Pre_bst_009	83	72	86.7	77.5	93.2	7.4	5.9	9.2
			Post_bst_009	84	84	100	95.7	100	68.7	55.5	85.0
	Control	Male	Pre_bst_009	148	99	66.9	58.7	74.4	5.8	4.7	7.2
			Post_bst_009	147	144	98.0	94.2	99.6	62.3	51.3	75.7
		Female	Pre_bst_009	179	110	61.5	53.9	68.6	5.1	4.2	6.2
			Post_bst_009	179	178	99.4	96.9	100	69.5	59.2	81.4

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above the specified cut off
GMC = geometric mean antibody concentration calculated on all subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper LimitPre_bst_009 =Pre booster vaccination blood sampling time-point
Post_bst_009 = Post booster vaccination blood sampling time-point
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.37 Exploratory comparison: Group difference in alternative booster response to the diphtheria and tetanus antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9 - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	259	203	78.4	115	88	76.5	1.86	-8.10	13.05
ANTI-T	248	202	81.5	111	88	79.3	2.17	-7.43	13.19

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to D and T antigens is defined as:
- For subjects with pre-booster antibody concentration below 0.1 IU/mL: antibody concentrations at least four times the 0.1IU/ML, one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- Subjects with pre-booster antibody concentration ≥6.0 IU/mL are not evaluable for booster response.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.38 Exploratory comparison: Group difference in alternative booster response to the PT, FHA and PRN antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (ATP cohort for analysis of immunogenicity at Year 9)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	271	253	93.4	120	119	99.2	-5.81	-10.22	-0.77
ANTI-PRN	271	230	84.9	118	106	89.8	-4.96	-12.37	4.01
ANTI-PT	271	210	77.5	120	96	80.0	-2.51	-11.89	8.16

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-booster antibody concentration below the assay cut off: antibody concentrations at least four times the assay cut off one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥ assay cut off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥ 60 IU/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.39 Confirmatory objective: Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL [Boostrix group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

								Difference in percentage (Boostrix minus Control)		
		Boostrix			Control				97.5% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
ANTI-D	0.1 IU/ML	298	296	99.3	350	343	98.0	1.33	-1.02	3.90
ANTI-T	0.1 IU/ML	298	298	100	351	350	99.7	0.28	-1.38	1.93

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.40 Confirmatory objective: Group differences in the percentage of subjects with anti-Diphtheria and anti-Tetanus antibody concentrations ≥0.1 IU/mL [Adacel group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

								Difference in percentage (Adacel minus Control)		
		Adacel			Control				97.5% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
ANTI-D	0.1 IU/ML	131	130	99.2	350	343	98.0	1.24	-3.15	3.88
ANTI-T	0.1 IU/ML	131	131	100	351	350	99.7	0.28	-3.42	1.93

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut off (≥0.1 IU/mL)
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.41 Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Boostrix group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	296	184	62.2	347	238	68.6	-6.43	-14.84	2.00
ANTI-T	295	134	45.4	348	169	48.6	-3.14	-11.93	5.71

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination.
- For initially seropositive subjects with pre-booster antibody concentration ≥0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.42 Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Boostrix group minus Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

							Difference in booster response rate (Boostrix minus Control)		
	Boostrix			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	298	254	85.2	351	324	92.3	-7.07	-12.96	-1.57
ANTI-PRN	297	230	77.4	344	302	87.8	-10.35	-17.22	-3.69
ANTI-PT	298	254	85.2	350	312	89.1	-3.91	-10.05	1.97

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.

Table 7.43 Confirmatory objective: Group difference in booster response to the diphtheria and tetanus antigens [Adacel group minus the Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	118	71	60.2	323	222	68.7	-8.56	-20.33	2.73
ANTI-T	120	44	36.7	324	157	48.5	-11.79	-22.98	0.15

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to D and T antigens is defined as:
- For initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination.
- For initially seropositive subjects with pre-booster antibody concentration ≥0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.44 Confirmatory objective: Group difference in booster response to the PT, FHA and PRN antigens [Adacel group minus the Control group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated Cohort at Year 9)

							Difference in booster response rate (Adacel minus Control)		
	Adacel			Control				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	130	125	96.2	351	324	92.3	3.85	-2.44	8.50
ANTI-PRN	128	107	83.6	344	302	87.8	-4.20	-13.48	3.39
ANTI-PT	130	113	86.9	350	312	89.1	-2.22	-10.88	4.64

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Booster response to PT, FHA and PRN antigens is defined as:
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,
For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.

Table 7.45 Number and percentage of subjects with an ANTI-D or ANTI-T concentration equal to or above 0.1 and 1 IU/mL and GMCs (Total enrolled cohort)

				≥ 0.1 IU/ML				≥ 1 IU/ML				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-D	Boostrix	Pre_bst_007	1514	1297	85.7	83.8	87.4	359	23.7	21.6	25.9	0.4	0.4	0.4
		Post_bst_007	1473	1446	98.2	97.3	98.8	1297	88.1	86.3	89.7	4.7	4.4	5.0
		Per(Yr1)	1059	1014	95.8	94.4	96.9	707	66.8	63.8	69.6	1.4	1.3	1.6
		Per(Yr3)	973	914	93.9	92.2	95.4	522	53.6	50.5	56.8	0.9	0.9	1.0
		Per(Yr5)	855	798	93.3	91.4	94.9	417	48.8	45.4	52.2	0.8	0.8	0.9
		Pre_bst_009	471	432	91.7	88.9	94.0	215	45.6	41.1	50.3	0.8	0.7	0.9
	Adacel	Pre_bst_007	754	676	89.7	87.3	91.7	201	26.7	23.5	30.0	0.5	0.4	0.5
		Post_bst_007	735	725	98.6	97.5	99.3	677	92.1	89.9	94.0	5.0	4.6	5.4
		Per(Yr1)	521	504	96.7	94.8	98.1	361	69.3	65.1	73.2	1.4	1.3	1.6
		Per(Yr3)	465	448	96.3	94.2	97.9	264	56.8	52.1	61.3	1.0	0.9	1.1
		Per(Yr5)	401	387	96.5	94.2	98.1	210	52.4	47.4	57.3	0.9	0.8	1.0
		Pre_bst_009	228	218	95.6	92.1	97.9	115	50.4	43.8	57.1	0.9	0.8	1.0
ANTI-T	Boostrix	Pre_bst_007	1521	1462	96.1	95.0	97.0	1101	72.4	70.1	74.6	1.6	1.5	1.7
		Post_bst_007	1474	1468	99.6	99.1	99.9	1449	98.3	97.5	98.9	8.5	8.1	8.9
		Per(Yr1)	1063	1049	98.7	97.8	99.3	999	94.0	92.4	95.3	3.4	3.2	3.6
		Per(Yr3)	976	958	98.2	97.1	98.9	863	88.4	86.2	90.4	2.2	2.1	2.4
		Per(Yr5)	854	837	98.0	96.8	98.8	724	84.8	82.2	87.1	2.0	1.9	2.2
		Pre_bst_009	473	464	98.1	96.4	99.1	390	82.5	78.7	85.8	2.1	1.9	2.3
	Adacel	Pre_bst_007	761	741	97.4	96.0	98.4	571	75.0	71.8	78.1	1.7	1.6	1.9
		Post_bst_007	736	736	100	99.5	100	731	99.3	98.4	99.8	13.2	12.4	14.0
		Per(Yr1)	523	521	99.6	98.6	100	503	96.2	94.2	97.6	4.4	4.1	4.7
		Per(Yr3)	465	463	99.6	98.5	99.9	429	92.3	89.4	94.5	2.9	2.7	3.1
		Per(Yr5)	401	399	99.5	98.2	99.9	366	91.3	88.1	93.8	2.6	2.4	2.9
		Pre_bst_009	230	230	100	98.4	100	206	89.6	84.9	93.2	2.7	2.4	3.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.46 Seroprotection status for anti-Diphtheria antibody concentration by ELISA and VERO NEUTRALISATION at the persistence time points (Total enrolled cohort)

			ELISA concentration <0.1 IU/ML		VERO concentration < 0.016 for subjects with ELISA < 0.1 IU/ML		Estimated proportion of subjects with Vero concentration < 0.01 IU/ML		Estimated proportion of subjects with Vero concentration ≥ 0.016 IU/ML or ELISA >=0.1 IU/ML		
Group	**Timing**	**N**	**n/N**	**%**	**n'/N'**	**%**	**n/N x n'/N'**	**%**	**SP**	**LL**	**UL**
Boostrix	Pre_bst_007	1514	217/1514	14.3	102/216	47.2	217/1514 x 102/216	6.8	93.2	91.9	94.4
	Post_bst_007	1473	27/1473	1.8	9/27	33.3	27/1473 x 9/27	0.6	99.4	98.8	99.7
	Per(Yr1)	1061	47/1061	4.4	17/47	36.2	47/1061 x 17/47	1.6	98.4	97.4	99.1
	Per(Yr3)	973	59/973	6.1	30/59	50.8	59/973 x 30/59	3.1	96.9	95.6	97.9
	Per(Yr5)	855	57/855	6.7	13/57	22.8	57/855 x 13/57	1.5	98.5	97.4	99.2
	Pre_bst_009	471	39/471	8.3	6/39	15.4	39/471 x 6/39	1.3	98.7	97.2	99.5
Adacel	Pre_bst_007	754	78/754	10.3	28/77	36.4	78/754 x 28/77	3.8	96.2	94.7	97.4
	Post_bst_007	735	10/735	1.4	6/10	60.0	10/735 x 6/10	0.8	99.2	98.2	99.7
	Per(Yr1)	522	18/522	3.4	11/18	61.1	18/522 x 11/18	2.1	97.9	96.3	98.9
	Per(Yr3)	465	17/465	3.7	10/17	58.8	17/465 x 10/17	2.2	97.8	96.1	99.0
	Per(Yr5)	401	14/401	3.5	4/14	28.6	14/401 x 4/14	1.0	99.0	97.5	99.7
	Pre_bst_009	228	10/228	4.4	3/10	30.0	10/228 x 3/10	1.3	98.7	96.2	99.7

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects tested by ELISA
n/N = number of subjects with concentrations below the 0.1 IU/mL / number of subjects tested by ELISA
n'/N' = number of subjects with concentrations below the 0.016 IU/mL / number of subjects tested by VERO neutralisation test for year x persistence time point
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for VERO) for year x persistence time point
n/N x n'/N' = the multiplication of the two proportions = overall seronegativity for anti-Diphtheria
Overall = based on both the ELISA and the Vero-cell neutralisation testing
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 7.47 Number and percentage of subjects with an ANTI-FHA , ANTI-PRN , or ANTI-PT concentration ≥ Assay cut off and GMCs (Total Enrolled Cohort)

				≥ Assay cut off				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-FHA	Boostrix	Pre_bst_007	1512	1467	97.0	96.0	97.8	32.1	30.3	33.9
		Post_bst_007	1472	1472	100	99.7	100	624.0	593.7	655.7
		Per(Yr1)	1063	1061	99.8	99.3	100	191.3	179.8	203.4
		Per(Yr3)	974	971	99.7	99.1	99.9	116.3	109.4	123.6
		Per(Yr5)	855	854	99.9	99.4	100	112.0	105.1	119.4
		Pre_bst_009	476	476	100	99.2	100	45.9	42.1	50.1
	Adacel	Pre_bst_007	751	725	96.5	95.0	97.7	34.8	32.1	37.7
		Post_bst_007	732	732	100	99.5	100	365.7	341.9	391.1
		Per(Yr1)	519	518	99.8	98.9	100	118.8	109.0	129.6
		Per(Yr3)	462	460	99.6	98.4	99.9	81.4	74.6	88.8
		Per(Yr5)	400	397	99.3	97.8	99.8	81.3	73.9	89.5
		Pre_bst_009	230	229	99.6	97.6	100	37.3	32.7	42.6
ANTI-PRN	Boostrix	Pre_bst_007	1519	1161	76.4	74.2	78.5	13.4	12.6	14.3
		Post_bst_007	1473	1456	98.8	98.2	99.3	399.7	367.6	434.6
		Per(Yr1)	1060	1020	96.2	94.9	97.3	154.3	139.6	170.6
		Per(Yr3)	974	921	94.6	92.9	95.9	84.9	76.9	93.8
		Per(Yr5)	848	821	96.8	95.4	97.9	87.7	79.2	97.0
		Pre_bst_009	474	469	98.9	97.6	99.7	70.2	61.4	80.2
	Adacel	Pre_bst_007	761	581	76.3	73.2	79.3	14.1	12.8	15.6
		Post_bst_007	734	729	99.3	98.4	99.8	349.9	314.2	389.7
		Per(Yr1)	518	506	97.7	96.0	98.8	131.7	115.1	150.5
		Per(Yr3)	465	449	96.6	94.5	98.0	70.8	62.1	80.9
		Per(Yr5)	400	391	97.8	95.8	99.0	78.6	68.4	90.2
		Pre_bst_009	226	224	99.1	96.8	99.9	76.1	63.3	91.5
ANTI-PT	Boostrix	Pre_bst_007	1509	876	58.1	55.5	60.6	7.4	7.0	7.8
		Post_bst_007	1460	1418	97.1	96.1	97.9	63.6	60.1	67.2
		Per(Yr1)	1062	964	90.8	88.9	92.4	22.6	21.1	24.1
		Per(Yr3)	973	803	82.5	80.0	84.9	14.3	13.3	15.3
		Per(Yr5)	856	730	85.3	82.7	87.6	14.9	13.9	16.1
		Pre_bst_009	476	412	86.6	83.2	89.5	9.5	8.6	10.6
	Adacel	Pre_bst_007	756	463	61.2	57.7	64.7	8.1	7.5	8.8
		Post_bst_007	730	684	93.7	91.7	95.4	32.2	29.6	35.0
		Per(Yr1)	523	449	85.9	82.6	88.7	15.6	14.2	17.2
		Per(Yr3)	465	335	72.0	67.7	76.1	10.2	9.2	11.3
		Per(Yr5)	401	307	76.6	72.1	80.6	11.7	10.5	13.1
		Pre_bst_009	230	206	89.6	84.9	93.2	9.5	8.2	11.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.48 Booster response to anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

				Booster response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
ANTI-D	Boostrix	S-	24	16	66.7	44.7	84.4
		S+	272	168	61.8	55.7	67.6
		Total	296	184	62.2	56.4	67.7
	Adacel	S-	5	3	60.0	14.7	94.7
		S+	123	73	59.3	50.1	68.1
		Total	128	76	59.4	50.3	68.0
	Control	S-	58	35	60.3	46.6	73.0
		S+	289	203	70.2	64.6	75.5
		Total	347	238	68.6	63.4	73.4
ANTI-T	Boostrix	S-	5	5	100	47.8	100
		S+	290	129	44.5	38.7	50.4
		Total	295	134	45.4	39.6	51.3
	Adacel	S-	0	-	-	-	-
		S+	130	46	35.4	27.2	44.2
		Total	130	46	35.4	27.2	44.2
	Control	S-	21	19	90.5	69.6	98.8
		S+	327	150	45.9	40.4	51.4
		Total	348	169	48.6	43.2	54.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
S- = Antibody concentration < 0.1 IU/mL
S+ = Antibody concentration ≥ 0.1 IU/mL
Total = subjects either seropositive or seronegative
Booster response to D and T antigens is defined as:
- For initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination.
- For initially seropositive subjects with pre-booster antibody concentration ≥0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 7.49 Booster response for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

				Booster response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
ANTI-FHA	Boostrix	S-	0	-	-	-	-
		S+ (<4*cut_off)	16	16	100	79.4	100
		S+ (≥4*cut_off)	282	238	84.4	79.6	88.4
		Total	298	254	85.2	80.7	89.1
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	10	10	100	69.2	100
		S+ (≥4*cut_off)	119	114	95.8	90.5	98.6
		Total	130	125	96.2	91.3	98.7
	Control	S-	6	6	100	54.1	100
		S+ (<4*cut_off)	75	74	98.7	92.8	100
		S+ (≥4*cut_off)	270	244	90.4	86.2	93.6
		Total	351	324	92.3	89.0	94.9
ANTI-PRN	Boostrix	S-	4	4	100	39.8	100
		S+ (<4*cut_off)	30	28	93.3	77.9	99.2
		S+ (≥4*cut_off)	263	198	75.3	69.6	80.4
		Total	297	230	77.4	72.3	82.1
	Adacel	S-	1	1	100	2.5	100
		S+ (<4*cut_off)	11	11	100	71.5	100
		S+ (≥4*cut_off)	116	95	81.9	73.7	88.4
		Total	128	107	83.6	76.0	89.5
	Control	S-	41	33	80.5	65.1	91.2
		S+ (<4*cut_off)	82	79	96.3	89.7	99.2
		S+ (≥4*cut_off)	221	190	86.0	80.7	90.3
		Total	344	302	87.8	83.9	91.1
ANTI-PT	Boostrix	S-	46	37	80.4	66.1	90.6
		S+ (<4*cut_off)	129	107	82.9	75.3	89.0
		S+ (≥4*cut_off)	123	110	89.4	82.6	94.3
		Total	298	254	85.2	80.7	89.1
	Adacel	S-	17	13	76.5	50.1	93.2
		S+ (<4*cut_off)	63	55	87.3	76.5	94.4
		S+ (≥4*cut_off)	50	45	90.0	78.2	96.7
		Total	130	113	86.9	79.9	92.2
	Control	S-	125	108	86.4	79.1	91.9
		S+ (<4*cut_off)	112	101	90.2	83.1	95.0
		S+ (≥4*cut_off)	113	103	91.2	84.3	95.7
		Total	350	312	89.1	85.4	92.2

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Total = subjects either seropositive or seronegative at pre-vaccination
S- = seronegative subjects (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
S+ = seropositive (antibody concentration below assay cut off for anti-PT, anti-FHA, anti-PRN)
Total = subjects either seropositive or seronegative
Booster response to PT, FHA and PRN antigens is defined as:
For subjects with pre-vaccination antibody concentration below the assay cut off, post-vaccination antibody concentration ≥4 times the assay cut-off,

For subjects with pre-vaccination antibody concentration between the assay cut off and below 4 times the assay cut-off, post-vaccination antibody concentration ≥4 times the pre-vaccination antibody concentration,
For subjects with pre-vaccination antibody concentration ≥4 times the assay cut off, post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.50 Exploratory comparison: Group difference in alternative booster response to the diphtheria and tetanus antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated cohort at Year 9 - excluding subjects with pre-vaccination concentration greater than or equal to 6 IU/mL)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-D	284	222	78.2	125	95	76.0	2.17	-7.46	12.92
ANTI-T	273	220	80.6	118	93	78.8	1.77	-7.60	12.48

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to D and T antigens is defined as:
- For subjects with pre-booster antibody concentration below 0.1 IU/mL: antibody concentrations at least four times the 0.1 IU/mL, one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
- Subjects with pre-booster antibody concentration ≥6.0 IU/mL are not evaluable for booster response.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 7.51 Exploratory comparison: Group difference in alternative booster response to the anti-PT, FHA and PRN antigens [Boostrix group minus Adacel group], one month after booster vaccination and their standardized asymptotic 97.5% CIs (Total Vaccinated cohort at Year 9)

							Difference in booster response rate (Boostrix minus Adacel)		
	Boostrix			Adacel				97.5% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
ANTI-FHA	298	279	93.6	130	128	98.5	-4.84	-9.10	0.36
ANTI-PRN	297	252	84.8	128	115	89.8	-5.00	-12.10	3.56
ANTI-PT	298	227	76.2	130	103	79.2	-3.06	-12.21	7.28

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Alternative Booster response to PT, FHA and PRN antigens is defined as:
- For subjects with pre-booster antibody concentration below the assay cut off: antibody concentrations at least four times the assay cut off one month after vaccination, and
- For subjects with pre-booster antibody concentration ≥ assay cut off and < 60 IU/mL: antibody concentration increase of at least 30 IU/mL from the pre-booster antibody concentration, one month after vaccination.
- For subjects with pre-booster antibody concentration ≥ 60 IU/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with booster response
97.5% CI = 97.5% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Note: The assay cut off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

Table 7.52 Exploratory comparison: GMC ratio between groups [Boostrix group divided by Control group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9

					GMC ratio (Boostrix / Control)		
	Boostrix		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-FHA	298	248.8	351	360.3	0.69	0.60	0.79
ANTI-PRN	298	408.7	350	327.2	1.25	1.01	1.54
ANTI-PT	298	64.0	350	64.8	0.99	0.83	1.17

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N= Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 7.53 Exploratory comparison: GMC ratio between groups [Adacel group divided by Control group] and their 95% CIs for anti-Diphtheria and anti-Tetanus antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC ratio (Adacel / Control)		
	Adacel		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-D	131	4.6	350	4.0	1.16	0.89	1.51
ANTI-T	131	8.5	351	8.7	0.98	0.82	1.15

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N= Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 7.54 Exploratory comparison: GMC ratio between groups [Adacel group divided by Control group] and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens one month after booster vaccination (Total Vaccinated Cohort at Year 9)

					GMC ratio (Adacel / Control)		
	Adacel		Control			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-FHA	131	248.8	351	360.3	0.69	0.57	0.83
ANTI-PRN	131	504.8	350	327.2	1.54	1.15	2.07
ANTI-PT	131	68.6	350	64.8	1.06	0.85	1.32

Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N= Number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio LL = lower limit, UL = upper limit (ANOVA model)

Table 8.1 Number and percentage of subjects who received the study vaccine dose (Total Vaccinated Cohort at Year 9)

	Boostrix N = 309		Adacel N = 138		Control N = 362	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	309	100	138	100	362	100
Total number of doses	309	-	138	-	362	-

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the dose

Table 8.2 Compliance in returning symptom sheets (Total Vaccinated Cohort at Year 9)

Group	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS	Number of local SS	Compliance % local SS
Boostrix	309	2	306	99.0	306	99.0
Adacel	138	3	137	99.3	137	99.3
Control	362	7	358	98.9	358	98.9

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
SS = Symptom screens/sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom screen/sheet return / number of administered doses) X 100

Table 8.3 Large Injection Site Reaction Summary (>100 mm) (Total Vaccinated Cohort at Year 9)

No records exist in this table

Table 8.4 Incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Boostrix	306	213	69.6	64.1	74.7	306	106	34.6	29.3	40.3	306	198	64.7	59.1	70.1
Adacel	137	96	70.1	61.7	77.6	137	40	29.2	21.7	37.6	137	88	64.2	55.6	72.2
Control	358	173	48.3	43.0	53.6	358	92	25.7	21.2	30.6	358	144	40.2	35.1	45.5

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.5 Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Boostrix	306	10	3.3	1.6	5.9	306	3	1.0	0.2	2.8	306	8	2.6	1.1	5.1
Adacel	137	7	5.1	2.1	10.2	137	4	2.9	0.8	7.3	137	4	2.9	0.8	7.3
Control	358	9	2.5	1.2	4.7	358	3	0.8	0.2	2.4	358	6	1.7	0.6	3.6

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.6 Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Boostrix	306	210	68.6	63.1	73.8	306	76	24.8	20.1	30.1	306	198	64.7	59.1	70.1
Adacel	137	94	68.6	60.1	76.3	137	31	22.6	15.9	30.6	137	88	64.2	55.6	72.2
Control	358	163	45.5	40.3	50.8	358	51	14.2	10.8	18.3	358	144	40.2	35.1	45.5

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.7 Incidence and nature of symptoms (solicited and unsolicited) with medically attended visit, reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Boostrix	306	2	0.7	0.1	2.3	306	2	0.7	0.1	2.3	306	0	0.0	0.0	1.2
Adacel	137	4	2.9	0.8	7.3	137	4	2.9	0.8	7.3	137	0	0.0	0.0	2.7
Control	358	3	0.8	0.2	2.4	358	3	0.8	0.2	2.4	358	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.8 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Days 0-30) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		42	13.6	10.0	17.9	23	16.7	10.9	24.0	37	10.2	7.3	13.8
Ear and labyrinth disorders (10013993)	Vertigo (10047340)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Eye disorders (10015919)	Eyelid pain (10059208)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Abdominal pain (10000081)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Abdominal pain upper (10000087)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Constipation (10010774)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Diarrhoea (10012735)	1	0.3	0.0	1.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Gastrointestinal disorder (10017944)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Gastrooesophageal reflux disease (10017885)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Nausea (10028813)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Toothache (10044055)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Vomiting (10047700)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	2	0.6	0.1	2.0
General disorders and administration site conditions (10018065)	Axillary pain (10048750)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Fatigue (10016256)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Gravitational oedema (10018713)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Influenza like illness (10022004)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Injection site bruising (10022052)	3	1.0	0.2	2.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Injection site erythema (10022061)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site induration (10022075)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site joint pain (10049261)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site pain (10022086)	1	0.3	0.0	1.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Injection site pruritus (10022093)	4	1.3	0.4	3.3	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Injection site swelling (10053425)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Malaise (10025482)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Pain (10033371)	3	1.0	0.2	2.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Peripheral swelling (10048959)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Pyrexia (10037660)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Vaccination site reaction (10059080)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Immune system disorders (10021428)	Food allergy (10016946)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Hypersensitivity (10020751)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Seasonal allergy (10048908)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Infections and infestations (10021881)	Bacterial vaginosis (10004055)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Bronchitis (10006451)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Fungal infection (10017533)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	1	0.3	0.0	1.5
	Furuncle (10017553)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Gastroenteritis (10017888)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Gastrointestinal candidiasis (10017938)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Herpes zoster (10019974)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Influenza (10022000)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Otitis externa (10033072)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Sinusitis (10040753)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	2	0.6	0.1	2.0
	Tonsillitis (10044008)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Upper respiratory tract infection (10046306)	2	0.6	0.1	2.3	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Urinary tract infection (10046571)	2	0.6	0.1	2.3	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Viral upper respiratory tract infection (10047482)	2	0.6	0.1	2.3	0	0.0	0.0	2.6	3	0.8	0.2	2.4
Injury, poisoning and procedural complications (10022117)	Arthropod sting (10003402)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Concussion (10010254)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Contusion (10050584)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Jaw fracture (10023149)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Laceration (10023572)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Ligament sprain (10024453)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Muscle injury (10028314)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Muscle strain (10050031)	1	0.3	0.0	1.8	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Procedural nausea (10066962)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Procedural pain (10064882)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Skin abrasion (10064990)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Sunburn (10042496)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Musculoskeletal and connective tissue disorders (10028395)	Arthralgia (10003239)	1	0.3	0.0	1.8	2	1.4	0.2	5.1	0	0.0	0.0	1.0

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Back pain (10003988)	3	1.0	0.2	2.8	1	0.7	0.0	4.0	1	0.3	0.0	1.5
	Muscle spasms (10028334)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Musculoskeletal pain (10028391)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Musculoskeletal stiffness (10052904)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Myalgia (10028411)	0	0.0	0.0	1.2	2	1.4	0.2	5.1	0	0.0	0.0	1.0
	Neck pain (10028836)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Osteoarthritis (10031161)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Pain in extremity (10033425)	0	0.0	0.0	1.2	2	1.4	0.2	5.1	3	0.8	0.2	2.4
	Tendonitis (10043255)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Lipoma (10024612)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Seborrhoeic keratosis (10039796)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Nervous system disorders (10029205)	Aura (10003791)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Dizziness (10013573)	2	0.6	0.1	2.3	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Dysgeusia (10013911)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Headache (10019211)	2	0.6	0.1	2.3	4	2.9	0.8	7.3	5	1.4	0.4	3.2
	Migraine (10027599)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Sciatica (10039674)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Seizure (10039906)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Psychiatric disorders (10037175)	Anxiety (10002855)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Cough (10011224)	2	0.6	0.1	2.3	2	1.4	0.2	5.1	3	0.8	0.2	2.4
	Dry throat (10013789)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Dysphonia (10013952)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Oropharyngeal pain (10068319)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	1	0.3	0.0	1.5
	Sinus congestion (10040742)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Vocal cord dysfunction (10047671)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Skin and subcutaneous tissue disorders (10040785)	Dermatitis contact (10012442)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Rash (10037844)	1	0.3	0.0	1.8	1	0.7	0.0	4.0	2	0.6	0.1	2.0
	Urticaria (10046735)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6

Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 8.9 Percentage of subjects reporting the occurrence of unsolicited symptoms medically attended visit classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Days 0-30) post-vaccination period (Total Vaccinated Cohort at Year 9)

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		9	2.9	1.3	5.5	9	6.5	3.0	12.0	14	3.9	2.1	6.4
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Gastrooesophageal reflux disease (10017885)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Toothache (10044055)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Immune system disorders (10021428)	Food allergy (10016946)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
Infections and infestations (10021881)	Bronchitis (10006451)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Furuncle (10017553)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Gastrointestinal candidiasis (10017938)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Herpes zoster (10019974)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Sinusitis (10040753)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Tonsillitis (10044008)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Urinary tract infection (10046571)	2	0.6	0.1	2.3	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Viral upper respiratory tract infection (10047482)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Injury, poisoning and procedural complications (10022117)	Arthropod sting (10003402)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Concussion (10010254)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Contusion (10050584)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Jaw fracture (10023149)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Laceration (10023572)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Muscle injury (10028314)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Procedural nausea (10066962)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Procedural pain (10064882)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Skin abrasion (10064990)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5

		Boostrix N = 309				Adacel N = 138				Control N = 362			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Musculoskeletal and connective tissue disorders (10028395)	Arthralgia (10003239)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Musculoskeletal pain (10028391)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	2	0.6	0.1	2.0
	Neck pain (10028836)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Osteoarthritis (10031161)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
	Pain in extremity (10033425)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	1	0.3	0.0	1.5
	Tendonitis (10043255)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Lipoma (10024612)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	0	0.0	0.0	1.0
Nervous system disorders (10029205)	Dizziness (10013573)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Seizure (10039906)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	0	0.0	0.0	1.2	0	0.0	0.0	2.6	1	0.3	0.0	1.5
	Cough (10011224)	1	0.3	0.0	1.8	0	0.0	0.0	2.6	1	0.3	0.0	1.5
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0
	Urticaria (10046735)	0	0.0	0.0	1.2	1	0.7	0.0	4.0	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 8.10 Percentage of subjects with concomitant medication during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Boostrix					Adacel					Control				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Any	309	34	11.0	7.7	15.0	138	21	15.2	9.7	22.3	362	24	6.6	4.3	9.7
Any antipyretic	309	23	7.4	4.8	11.0	138	16	11.6	6.8	18.1	362	17	4.7	2.8	7.4
Prophylactic antipyretic	309	0	0.0	0.0	1.2	138	0	0.0	0.0	2.6	362	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the administered dose
n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.11 Percentage of subjects with concomitant medication during the 31-day (Days 0-30) post-vaccination period (Total Vaccinated Cohort at Year 9)

	Boostrix					Adacel					Control				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Any	309	56	18.1	14.0	22.9	138	30	21.7	15.2	29.6	362	53	14.6	11.2	18.7
Any antipyretic	309	37	12.0	8.6	16.1	138	22	15.9	10.3	23.1	362	33	9.1	6.4	12.6
Prophylactic antipyretic	309	0	0.0	0.0	1.2	138	0	0.0	0.0	2.6	362	0	0.0	0.0	1.0

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the administered dose
n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 8.12 Listing of SAEs (Total Vaccinated Cohort at Year 9)

Group	Sub. No.	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MA type	Day of onset	Duration	Intensity	Causality	Outcome
Control	PPD	F	United States	White - Caucasian / European Heritage	50	seizure	Seizure	Nervous system disorders	HO	23	1	3	N	Recovered/resolved

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
HO=Hospitalisation

Table 8.13 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period by age stratum (Total Vaccinated Cohort at Year 9)

		Boostrix														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	67	50	74.6	62.5	84.5	104	69	66.3	56.4	75.3	135	61	45.2	36.6	54.0
	Grade 2 or 3	67	17	25.4	15.5	37.5	104	19	18.3	11.4	27.1	135	15	11.1	6.4	17.7
	Grade 3	67	1	1.5	0.0	8.0	104	0	0.0	0.0	3.5	135	2	1.5	0.2	5.2
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
Redness (mm)	All	67	20	29.9	19.3	42.3	104	27	26.0	17.9	35.5	135	27	20.0	13.6	27.7
	>20	67	3	4.5	0.9	12.5	104	8	7.7	3.4	14.6	135	6	4.4	1.6	9.4
	≥50mm	67	0	0.0	0.0	5.4	104	3	2.9	0.6	8.2	135	2	1.5	0.2	5.2
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
Swelling (mm)	All	67	10	14.9	7.4	25.7	104	23	22.1	14.6	31.3	135	24	17.8	11.7	25.3
	>20	67	2	3.0	0.4	10.4	104	4	3.8	1.1	9.6	135	2	1.5	0.2	5.2
	≥50mm	67	0	0.0	0.0	5.4	104	2	1.9	0.2	6.8	135	2	1.5	0.2	5.2
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
		Adacel														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	27	17	63.0	42.4	80.6	61	41	67.2	54.0	78.7	49	26	53.1	38.3	67.5
	Grade 2 or 3	27	3	11.1	2.4	29.2	61	13	21.3	11.9	33.7	49	5	10.2	3.4	22.2
	Grade 3	27	1	3.7	0.1	19.0	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
Redness (mm)	All	27	5	18.5	6.3	38.1	61	19	31.1	19.9	44.3	49	8	16.3	7.3	29.7
	>20	27	1	3.7	0.1	19.0	61	3	4.9	1.0	13.7	49	1	2.0	0.1	10.9
	≥50mm	27	0	0.0	0.0	12.8	61	2	3.3	0.4	11.3	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
Swelling (mm)	All	27	4	14.8	4.2	33.7	61	17	27.9	17.1	40.8	49	5	10.2	3.4	22.2
	>20	27	0	0.0	0.0	12.8	61	2	3.3	0.4	11.3	49	2	4.1	0.5	14.0
	≥50mm	27	0	0.0	0.0	12.8	61	2	3.3	0.4	11.3	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3

		Control														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	All	81	40	49.4	38.1	60.7	134	54	40.3	31.9	49.1	143	38	26.6	19.5	34.6
	Grade 2 or 3	81	14	17.3	9.8	27.3	134	9	6.7	3.1	12.4	143	8	5.6	2.4	10.7
	Grade 3	81	1	1.2	0.0	6.7	134	1	0.7	0.0	4.1	143	2	1.4	0.2	5.0
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
Redness (mm)	All	81	16	19.8	11.7	30.1	134	24	17.9	11.8	25.5	143	13	9.1	4.9	15.0
	>20	81	1	1.2	0.0	6.7	134	2	1.5	0.2	5.3	143	1	0.7	0.0	3.8
	≥50mm	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
Swelling (mm)	All	81	12	14.8	7.9	24.4	134	19	14.2	8.8	21.3	143	10	7.0	3.4	12.5
	>20	81	2	2.5	0.3	8.6	134	5	3.7	1.2	8.5	143	3	2.1	0.4	6.0
	≥50mm	81	0	0.0	0.0	4.5	134	1	0.7	0.0	4.1	143	1	0.7	0.0	3.8
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 8.14 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period by age stratum (Total Vaccinated Cohort at Year 9)

		Boostrix														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	All	67	19	28.4	18.0	40.7	104	25	24.0	16.2	33.4	135	27	20.0	13.6	27.7
	Grade 2 or 3	67	8	11.9	5.3	22.2	104	7	6.7	2.7	13.4	135	8	5.9	2.6	11.3
	Grade 3	67	1	1.5	0.0	8.0	104	2	1.9	0.2	6.8	135	0	0.0	0.0	2.7
	Related	67	16	23.9	14.3	35.9	104	25	24.0	16.2	33.4	135	16	11.9	6.9	18.5
	Grade 3 Related	67	1	1.5	0.0	8.0	104	2	1.9	0.2	6.8	135	0	0.0	0.0	2.7
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
Gastrointestinal symptoms	All	67	9	13.4	6.3	24.0	104	8	7.7	3.4	14.6	135	10	7.4	3.6	13.2
	Grade 2 or 3	67	1	1.5	0.0	8.0	104	2	1.9	0.2	6.8	135	3	2.2	0.5	6.4
	Grade 3	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Related	67	7	10.4	4.3	20.3	104	5	4.8	1.6	10.9	135	6	4.4	1.6	9.4
	Grade 3 Related	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
Headache	All	67	13	19.4	10.8	30.9	104	23	22.1	14.6	31.3	135	16	11.9	6.9	18.5
	Grade 2 or 3	67	3	4.5	0.9	12.5	104	4	3.8	1.1	9.6	135	5	3.7	1.2	8.4
	Grade 3	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Related	67	9	13.4	6.3	24.0	104	17	16.3	9.8	24.9	135	11	8.1	4.1	14.1
	Grade 3 Related	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	1	0.7	0.0	4.1
Temperature (°C)	All	67	2	3.0	0.4	10.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	>38.5	67	1	1.5	0.0	8.0	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	>39.0	67	1	1.5	0.0	8.0	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	>39.5	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	>40.0	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Related	67	2	3.0	0.4	10.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	>40.0 Related	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7
	Medical advice	67	0	0.0	0.0	5.4	104	0	0.0	0.0	3.5	135	0	0.0	0.0	2.7

		Adacel														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	27	4	14.8	4.2	33.7	61	12	19.7	10.6	31.8	49	7	14.3	5.9	27.2
	Grade 2 or 3	27	2	7.4	0.9	24.3	61	4	6.6	1.8	15.9	49	4	8.2	2.3	19.6
	Grade 3	27	0	0.0	0.0	12.8	61	1	1.6	0.0	8.8	49	0	0.0	0.0	7.3
	Related	27	4	14.8	4.2	33.7	61	11	18.0	9.4	30.0	49	6	12.2	4.6	24.8
	Grade 3 Related	27	0	0.0	0.0	12.8	61	1	1.6	0.0	8.8	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
Gastrointestinal symptoms	All	27	0	0.0	0.0	12.8	61	3	4.9	1.0	13.7	49	1	2.0	0.1	10.9
	Grade 2 or 3	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Grade 3	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Related	27	0	0.0	0.0	12.8	61	3	4.9	1.0	13.7	49	1	2.0	0.1	10.9
	Grade 3 Related	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
Headache	All	27	3	11.1	2.4	29.2	61	14	23.0	13.2	35.5	49	8	16.3	7.3	29.7
	Grade 2 or 3	27	2	7.4	0.9	24.3	61	3	4.9	1.0	13.7	49	1	2.0	0.1	10.9
	Grade 3	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	1	2.0	0.1	10.9
	Related	27	2	7.4	0.9	24.3	61	11	18.0	9.4	30.0	49	6	12.2	4.6	24.8
	Grade 3 Related	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
Temperature (°C)	All	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	>38.5	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	>39.0	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	>39.5	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	>40.0	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Related	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	>40.0 Related	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3
	Medical advice	27	0	0.0	0.0	12.8	61	0	0.0	0.0	5.9	49	0	0.0	0.0	7.3

		Control														
		28-38					39-58					59-73				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	All	81	15	18.5	10.8	28.7	134	13	9.7	5.3	16.0	143	23	16.1	10.5	23.1
	Grade 2 or 3	81	0	0.0	0.0	4.5	134	4	3.0	0.8	7.5	143	5	3.5	1.1	8.0
	Grade 3	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Related	81	11	13.6	7.0	23.0	134	9	6.7	3.1	12.4	143	14	9.8	5.5	15.9
	Grade 3 Related	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
Gastrointestinal symptoms	All	81	9	11.1	5.2	20.0	134	8	6.0	2.6	11.4	143	12	8.4	4.4	14.2
	Grade 2 or 3	81	3	3.7	0.8	10.4	134	4	3.0	0.8	7.5	143	2	1.4	0.2	5.0
	Grade 3	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Related	81	5	6.2	2.0	13.8	134	7	5.2	2.1	10.5	143	5	3.5	1.1	8.0
	Grade 3 Related	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
Headache	All	81	13	16.0	8.8	25.9	134	22	16.4	10.6	23.8	143	18	12.6	7.6	19.2
	Grade 2 or 3	81	1	1.2	0.0	6.7	134	6	4.5	1.7	9.5	143	1	0.7	0.0	3.8
	Grade 3	81	0	0.0	0.0	4.5	134	1	0.7	0.0	4.1	143	0	0.0	0.0	2.5
	Related	81	8	9.9	4.4	18.5	134	10	7.5	3.6	13.3	143	10	7.0	3.4	12.5
	Grade 3 Related	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
Temperature (°C)	All	81	0	0.0	0.0	4.5	134	1	0.7	0.0	4.1	143	1	0.7	0.0	3.8
	>38.5	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	>39.0	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	>39.5	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	>40.0	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Related	81	0	0.0	0.0	4.5	134	1	0.7	0.0	4.1	143	1	0.7	0.0	3.8
	>40.0 Related	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5
	Medical advice	81	0	0.0	0.0	4.5	134	0	0.0	0.0	2.7	143	0	0.0	0.0	2.5

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
28-38 = 28-38Years
39-58 = 39-58Years
59-73 = 59-73Years

N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 8.15 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period by gender (Total Vaccinated Cohort at Year 9)

		Boostrix										Adacel										Control									
		Male					Female					Male					Female					Male					Female				
					95 % CI					95 % CI					95 % CI				95 % CI					95 % CI					95 % CI		
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	104	54	51.9	41.9	61.8	202	126	62.4	55.3	69.1	43	18	41.9	27.0	57.9	94	66	70.2	59.9	79.2	164	48	29.3	22.4	36.9	194	84	43.3	36.2	50.6
	Grade 2 or 3	104	12	11.5	6.1	19.3	202	39	19.3	14.1	25.4	43	2	4.7	0.6	15.8	94	19	20.2	12.6	29.8	164	11	6.7	3.4	11.7	194	20	10.3	6.4	15.5
	Grade 3	104	0	0.0	0.0	3.5	202	3	1.5	0.3	4.3	43	0	0.0	0.0	8.2	94	1	1.1	0.0	5.8	164	4	2.4	0.7	6.1	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
Redness (mm)	All	104	20	19.2	12.2	28.1	202	54	26.7	20.8	33.4	43	9	20.9	10.0	36.0	94	23	24.5	16.2	34.4	164	23	14.0	9.1	20.3	194	30	15.5	10.7	21.3
	>20	104	0	0.0	0.0	3.5	202	17	8.4	5.0	13.1	43	2	4.7	0.6	15.8	94	3	3.2	0.7	9.0	164	0	0.0	0.0	2.2	194	4	2.1	0.6	5.2
	≥50mm	104	0	0.0	0.0	3.5	202	5	2.5	0.8	5.7	43	0	0.0	0.0	8.2	94	2	2.1	0.3	7.5	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
Swelling (mm)	All	104	14	13.5	7.6	21.6	202	43	21.3	15.9	27.6	43	7	16.3	6.8	30.7	94	19	20.2	12.6	29.8	164	15	9.1	5.2	14.6	194	26	13.4	8.9	19.0
	>20	104	0	0.0	0.0	3.5	202	8	4.0	1.7	7.7	43	1	2.3	0.1	12.3	94	3	3.2	0.7	9.0	164	3	1.8	0.4	5.3	194	7	3.6	1.5	7.3
	≥50mm	104	0	0.0	0.0	3.5	202	4	2.0	0.5	5.0	43	0	0.0	0.0	8.2	94	2	2.1	0.3	7.5	164	1	0.6	0.0	3.4	194	1	0.5	0.0	2.8
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 8.16 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period by gender (Total Vaccinated Cohort at Year 9)

		Boostrix										Adacel										Control									
		Male					Female					Male					Female					Male					Female				
					95 % CI					95 % CI					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	All	104	11	10.6	5.4	18.1	202	60	29.7	23.5	36.5	43	5	11.6	3.9	25.1	94	18	19.1	11.8	28.6	164	23	14.0	9.1	20.3	194	28	14.4	9.8	20.2
	Grade 2 or 3	104	4	3.8	1.1	9.6	202	19	9.4	5.8	14.3	43	1	2.3	0.1	12.3	94	9	9.6	4.5	17.4	164	5	3.0	1.0	7.0	194	4	2.1	0.6	5.2
	Grade 3	104	1	1.0	0.0	5.2	202	2	1.0	0.1	3.5	43	0	0.0	0.0	8.2	94	1	1.1	0.0	5.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Related	104	11	10.6	5.4	18.1	202	46	22.8	17.2	29.2	43	5	11.6	3.9	25.1	94	16	17.0	10.1	26.2	164	16	9.8	5.7	15.4	194	18	9.3	5.6	14.3
	Grade 3 Related	104	1	1.0	0.0	5.2	202	2	1.0	0.1	3.5	43	0	0.0	0.0	8.2	94	1	1.1	0.0	5.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
Gastrointestinal symptoms	All	104	9	8.7	4.0	15.8	202	18	8.9	5.4	13.7	43	1	2.3	0.1	12.3	94	3	3.2	0.7	9.0	164	11	6.7	3.4	11.7	194	18	9.3	5.6	14.3
	Grade 2 or 3	104	1	1.0	0.0	5.2	202	5	2.5	0.8	5.7	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	4	2.4	0.7	6.1	194	5	2.6	0.8	5.9
	Grade 3	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Related	104	6	5.8	2.1	12.1	202	12	5.9	3.1	10.1	43	1	2.3	0.1	12.3	94	3	3.2	0.7	9.0	164	7	4.3	1.7	8.6	194	10	5.2	2.5	9.3
	Grade 3 Related	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
Headache	All	104	9	8.7	4.0	15.8	202	43	21.3	15.9	27.6	43	7	16.3	6.8	30.7	94	18	19.1	11.8	28.6	164	16	9.8	5.7	15.4	194	37	19.1	13.8	25.3
	Grade 2 or 3	104	1	1.0	0.0	5.2	202	11	5.4	2.7	9.5	43	1	2.3	0.1	12.3	94	5	5.3	1.7	12.0	164	1	0.6	0.0	3.4	194	7	3.6	1.5	7.3
	Grade 3	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	1	1.1	0.0	5.8	164	0	0.0	0.0	2.2	194	1	0.5	0.0	2.8
	Related	104	8	7.7	3.4	14.6	202	29	14.4	9.8	20.0	43	5	11.6	3.9	25.1	94	14	14.9	8.4	23.7	164	9	5.5	2.5	10.2	194	19	9.8	6.0	14.9
	Grade 3 Related	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	1	0.5	0.0	2.7	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
Temperature (°C)	All	104	0	0.0	0.0	3.5	202	2	1.0	0.1	3.5	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	2	1.0	0.1	3.7
	>38.5	104	0	0.0	0.0	3.5	202	1	0.5	0.0	2.7	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	>39.0	104	0	0.0	0.0	3.5	202	1	0.5	0.0	2.7	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	>39.5	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	>40.0	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Related	104	0	0.0	0.0	3.5	202	2	1.0	0.1	3.5	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	2	1.0	0.1	3.7
	>40.0 Related	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9
	Medical advice	104	0	0.0	0.0	3.5	202	0	0.0	0.0	1.8	43	0	0.0	0.0	8.2	94	0	0.0	0.0	3.8	164	0	0.0	0.0	2.2	194	0	0.0	0.0	1.9

Boostrix = Subjects who had received GSK Biologicals Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Adacel = Subjects who had received Sanofi Pasteurs Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
Control = Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
N = number of subjects with the documented dose

n/% = number/percentage of subjects reporting the symptom at least once
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering.

Modular appendices	ICH numbering
Protocol and protocol amendments.	16.1.1
Sample Case Report form	16.1.2
List of IECs or IRBs & List of Investigators and other important participants in the study	16.1.3 & 16.1.4
Representative written information for patient and sample consent forms.	16.1.3
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used	16.1.6
Randomization list	16.1.7
Audit certificates	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Protocol and Protocol Amendments

Sponsor
GlaxoSmithKline Biologicals
2301 Renaissance Blvd.
King of Prussia, PA 19406-2772

Study vaccines	• GlaxoSmithKline (GSK) Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, containing 0.3 mg aluminum [776423/Tdap, (Boostrix®)] • Sanofi Pasteur's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap) vaccine (Adacel®)
eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
Investigational New Drug (IND) number	BB-IND-8461
Date of approval	Final: 17 April 2007
Date of amendments/ administrative change approval	Administrative Change 1 Final: 14 April 2009 Amendment 1 Final: 09 November 2010 Amendment 2 Final: 18 February 2014 Amendment 3 Final: 10 December 2014 Administrative Change 2 Final: 03 February 2015
Title	Persistence study of GSK Biologicals' Tdap vaccine (776423), 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Co-ordinating authors	PPD Scientific writer
Contributing authors	• PPD Senior Manager, Clinical Development, Combination Vaccines, Global Vaccine Development • PPD Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
Investigational New Drug (IND) number	BB-IND-8461
Title	Persistence study of GSK Biologicals' Tdap vaccine (776423), 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Contributing authors	• PPD Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development • PPD Project Level Clinical Research and Development Lead, Combination Vaccines, Global Vaccine Development • PPD Study Delivery Lead • PPD Director, Clinical Development, Lead, DTP Combination Vaccines, Global Vaccine Development PPD Director, Project Level Clinical Research and Development Lead, DTP Combination Vaccines and Rotavirus Vaccines • PPD Biostatistician, *Boostrix* • PPD Project statistician, *Boostrix* • PPD Director, Biometrics • PPD Global Study Manager, Harrison Clinical Research Benelux for GSK Biologicals • PPD Study Manager • PPD Clinical Data Coordinator • PPD Study Data Manager • PPD Study Data Manager • PPD Senior Manager, Biologicals Clinical Safety & Pharmacovigilance • PPD Safety Physician, Vaccines Clinical Safety & Pharmacovigilance

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
Investigational New Drug (IND) number	BB-IND-8461
Title	Persistence study of GSK Biologicals' Tdap vaccine (776423), 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Contributing authors	• PPD Safety Physician • PPD Safety Physician • PPD GVCL Project Manager • PPD GVCL Study Manager • PPD Global Patents Representative • PPD Global Clinical Regulatory Affairs Representative • PPD Vaccine Supply Coordinator • PPD Vaccine Supply Coordinator • PPD Director, Global Regulatory Affairs • PPD US Vaccines Medical Affairs Lead • PPD Local Delivery Lead • PPD Specialist, Science Writing

GSK Biologicals' Protocol DS V 12.4

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Protocol Administrative Change 2 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Sponsor signatory	Narcisa Elena Mesaros, Project Level Clinical and Research Development Lead, Combination Vaccines, Global Vaccine Development
Signature	_____
Date	_____

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Protocol Administrative Change 2 Rationale

Amendment number:	Administrative Change 2

Rationale/background for changes:

For the persistence only group, serious adverse events occurring due to study related procedures will be collected. This is noted in section 8.4 “Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies”, but due to a typographical error, it has not been noted in section 5.5 “Outline of study procedures”. This administrative change has been prepared to correct this typographical error in Table 3 “List of study procedures” as seen under section 5.5 “Outline of study procedures”.

Protocol Administrative Change 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut, 89
1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.9.2.

Synopsis

Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Indication/Study population	Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.
Rationale	This study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, up to 9 years following vaccination with GlaxoSmithKline's tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (*Boostrix*). In addition, this study will provide the immunogenicity and safety data of *Boostrix* as a second dose of Tdap vaccine ***9*** years following vaccination with either *Boostrix* or *Adacel* in the study 106316. The data from this study is planned to support the indication of *Boostrix* as a second dose of Tdap vaccine. As per advice from Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the control group will receive *Boostrix* as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.
Objectives	**Co-Primary** • To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years. • To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

The criterion for meeting the above objective is defined as:

- One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).
- One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  - One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.
  - One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

The criterion for meeting the above objective is defined as:

- One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

[$]Booster response to D and T antigens is defined as:

- for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and
- for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.

[$]Booster response to PT, FHA and PRN antigens is defined as:

- for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;
- for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
- for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.

Secondary

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA,

and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.

- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

*Refer to co-primary objectives for the definition of booster response.

*Alternative Booster response to D and T antigens is defined as:

- for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
- for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
- Subjects with pre-vaccination concentration

≥ 6.0 IU/mL are not evaluable for vaccine response.

*Alternative Booster response to PT, FHA and PRN antigens is defined as:

- for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
- for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
- for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase in antibody concentration from the pre-vaccination concentration, one month after vaccination.

Study design

- Experimental design: A phase III, parallel, open-label, interventional, multicenter study with the same two parallel groups as in the 106316 study and one Control group receiving the first dose of Tdap vaccine (*Boostrix*).
- Study groups:
  - Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (*Boostrix*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (*Adacel*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

Synopsis Table 1 Study groups foreseen in the study

Study Groups	Number of subjects	Age (Min - Max) (age unit)
Boostrix Group	Approximately 733	28 years-73 years
Adacel Group	Approximately 367	28 years-73 years
Control Group	Approximately 367	28 years-73 years

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups		
		Boostrix Group	Adacel Group	Control Group
Boostrix	Tdap	x	x	x

- Blinding: This study will be an open study since this is an extension of study 106316 (Tdap 0.3-007) which was un-blinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups.
- Treatment allocation: Non-randomized, all the study groups will receive a single dose of *Boostrix*.
- Control: Active control.
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects at Visit 6 i.e. at Year 9 (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The stud y procedures will be similar across all groups at Visit 6 and Visit 7).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 and who participated in all phases of the study including Year 9 time point and approximately one month for the Control group.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.
For example, if the subject did not want to participate in the

Year 1 evaluation, he/she can participate at Years 3, 5 and 9.

In addition, approximately 367 subjects will be newly enrolled at Year ***9*** time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups.

Total enrolment in the 106316 study was 2284 subjects, 1522 of whom were vaccinated with *Boostrix*. There were 1587 subjects (1064 *Boostrix* recipients) who returned for the Year 1 time point, 1441 subjects (976 *Boostrix* recipients) returned for the Year 3 time point and 1257 subjects (856 *Boostrix* recipients) returned for the Year 5 time point. Assuming an attrition rate of 15% from Year 5, it is estimated that 1100 subjects (733 *Boostrix* recipients) might return for the Year 9 time point. Also, approximately 367 subjects are planned to be enrolled in the Control group.

Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination (Refer to the co-primary objectives for the definition of booster response).

Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study

vaccine at Year ***9*** time point.

- Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
- Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to secondary objectives for the definition of booster response).

* Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.

- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited AEs during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF APPENDICES

PAGE

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
D	Diphtheria
DTaP	Diphtheria, Tetanus, Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EDD	Estimated Date of Delivery
eTDF	Electronic Temperature excursion Decision Form
EGA	Estimated Gestational Age
EL.U.	ELISA Units
ELISA	Enzyme-Linked Immunosorbant Assay
FHA	Filamentous Hemagglutinin from Bordetella pertussis
GCP	Good Clinical Practice
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medical Products
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
LMP	Last Menstrual Period
MedDRA	Medical Dictionary For Regulatory Activities
mL	Milliliter

PRN	Pertactin from Bordetella pertussis
PT	Pertussis Toxoid from Bordetella pertussis
RCC	Reverse Cumulative distribution Curve
RDE	Remote Data Entry
SAE	Serious Adverse Event
SBIR	Randomization System on Internet
SPM	Study Procedures Manual
SOP	Standard Operating Procedure
T	Tetanus
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed

Glossary of Terms

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,
- The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or

misuse.

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 10.4 for details on criteria for evaluability).
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, the larche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively

	solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Boostrix®	Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine
Infanrix®	Combined diphtheria, tetanus and acellular pertussis vaccine

1. INTRODUCTION

1.1. Background

Diphtheria, tetanus (toxoids) and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades. Since the 1980s, there has been an increase in the number of reported cases of pertussis in the United States (US), especially among 10-19 year olds and infants younger than six months of age. By December 2012, 48,227 cases of pertussis were reported to Centers for Disease Control and Prevention (CDC), more than twice the number reported during the same time period in 2011 [CDC, 2012a]. The incidence of confirmed and probable pertussis among persons aged ≤ 19 years, by age and vaccine received in the US shows that high rates of pertussis is observed among adolescents and older children 7 through 10 years of age suggesting early waning of immunity [CDC, 2012b]. According to the recent General Recommendations on Immunization, adolescents and adults 11-18 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults 19 years of age and older who have not received a dose of Tdap [ACIP, 2012]. All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should receive a Tdap vaccine at 27-36 weeks gestation during each pregnancy [CDC, 2012c; CDC, 2012d].

Boostrix is based on GSK Biologicals' DTaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti, 2002; Greco, 1996; Schmitt , 1996a; Schmitt , 1996b]. The tetanus and diphtheria toxoid content is in the range of that of licensed adult combined tetanus-diphtheria (Td) vaccines and is reduced as compared with *Infanrix*. The quantities of the pertussis antigens in *Boostrix* are approximately one-third of those in *Infanrix*. Outside of the US, *Boostrix* vaccine contains 0.5 mg Al (as aluminum phosphate and aluminum hydroxide) per 0.5 milliliter (mL) dose, while the US formulation of *Boostrix* contains 0.3 mg Al (as aluminum hydroxide) per 0.5 mL dose. In 2005, *Boostrix* (0.3 mg) was approved in the US for use in 10-18 year olds. In December 2008, it was approved for use in adults 19-64 years of age and in 2011, it was approved in the US for use in adults 65 years of age and older.

Please refer to the Prescribing Information for information regarding the potential risks and benefits of *Boostrix*.

1.2. Rationale for the study

A study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. This study compared the immunogenicity and reactogenicity of *Boostrix* to that elicited by Sanofi Pasteur's *Adacel* vaccine. All primary objectives were met with the exception of pertactin booster response which was observed to be below the 80% margin. Despite this failure, *Boostrix* recommendation in adults 19 years of age or older has been obtained.

Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005] and recent data shows that protection starts to wane within three years [Koepke, 2014]. Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first ***five*** years after vaccination [Weston, 2011; GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5)]. The current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to ***9*** years following vaccination with *Boostrix*.

Providing pertussis booster vaccination aims to boost immunity and disrupt the disease cycle. Currently in the US, no data is available on the immunogenicity and safety of *Boostrix* given as a second dose of Tdap vaccine. This study is intended to assess subjects who were vaccinated in the 106316 study and they will be invited to participate in this long-term follow-up and re-vaccination study at Year 9 time point. The purpose of vaccination with *Boostrix* at Year 9 time point instead of the previously intended Year 10 time point is to evaluate the immunogenicity and safety of a second dose of *Boostrix* at a time point earlier than the ten year interval. This study will also evaluate the immune response to the booster dose with *Boostrix* in subjects whose previous Tdap vaccination was a non-GSK vaccine.

As per advice from the Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive *Boostrix* as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.

2. OBJECTIVES

2.1. *Co*-Primary objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

  – One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of Infanrix vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

  – One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

Refer to Section 10.1 for definition of the co-primary endpoints and Section 10.3.1 for the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.

[$]Refer to Section 10.5 for the definition of booster response.

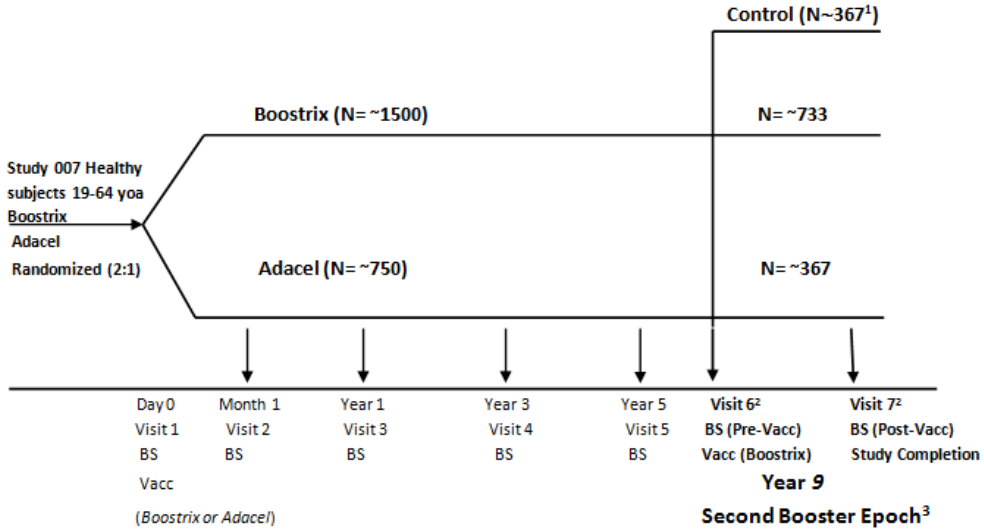
2.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.
- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination**.**
- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of alternate booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 10.2 for definitions of secondary endpoints.

*Refer to Section 10.5 for the definitions of booster response and alternate booster response.

3. STUDY DESIGN OVERVIEW



Yoa= Year of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch is a non-randomized study, for practical purposes group ratio of 1:2 :1 is assigned for the Control, Boostrix and Adacel groups respectively for the Year ***9*** time point.
[1]Subjects who were not part of the 106316 study will be recruited as the Control group.
[2]For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch has been added for practical purposes and it has no relation to the number of epochs in this study.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: A phase III, parallel, open-label, interventional, multicenter study with the same two parallel groups as in the 106316 study and one new Control group receiving the first dose of Tdap vaccine (*Boostrix*).
- Study groups:
  - Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (*Boostrix*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (*Adacel*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

– Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

Table 1 Study groups foreseen in the study

Study Groups	Number of subjects	Age (Min - Max) (age unit)
Boostrix Group	Approximately 733	28 years-73 years
Adacel Group	Approximately 367	28 years-73 years
Control Group	Approximately 367	28 years-73 years

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups		
		Boostrix Group	Adacel Group	Control Group
Boostrix	Tdap	x	x	x

- Blinding: This study will be an open study since this is an extension of study 106316 (Tdap 0.3-007) which was unblinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups. Subjects in the Control group will also be analyzed as a separate group.
- Treatment allocation: Non-randomized, all the study groups will receive a single dose of *Boostrix* at Year 9 (Visit 6).
- Control: Active control.
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9 (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 and who participated in all phases of the study including Year 9 time point and approximately one month for the Control group.
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects / centers

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

For example, if the subject did not want to participate in the Year 1 evaluation, he/she can participate at Years 3, 5 and 9.

In addition, approximately 367 subjects will be newly enrolled at Year 9 time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- 28-38 years:~25.4%
- 39-58 years: ~35.5%
- 59-73 years: ~39.1%

Total enrolment in the 106316 study was 2284 subjects, 1522 of whom were vaccinated with *Boostrix*. There were 1587 subjects (1064 *Boostrix* recipients) who returned for the Year 1 time point, 1441 subjects (976 *Boostrix* recipients) returned for the Year 3 time point and 1257 subjects (856 *Boostrix* recipients) returned for the Year 5 time point. Assuming an attrition rate of 15% from Year 5, it is estimated that 1100 subjects (733 *Boostrix* recipients) might return for the Year 9 time point. Also, approximately 367 subjects are planned to be enrolled in the Control group.

4.2. Inclusion criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

Vaccination phase at Year 9 applicable for subjects in the Boostrix and Adacel groups only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix and Adacel groups only:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.

Vaccination phase at Year 9 applicable for subjects in the Control group only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Control group only:

- Subjects within the age range of 28-73 years will be considered eligible to participate in this study in the Control group.

Vaccination phase at Year 9 applicable for ALL subjects (Control, Boostrix and Adacel groups):

The following criteria are applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix, Adacel and Control groups:

All subjects must satisfy the following criteria at study entry at Year 9 time point:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject for vaccination at Year 9 time point.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the Glossary of Terms for the definition of menarche and menopause.

- Female subjects of child bearing potential may be enrolled in the study, if the subject
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination, and
  - has agreed to continue adequate contraception for 1 month after completion of the vaccine dose.

Please refer to the Glossary of Terms for the definition of adequate contraception.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of Year 9 vaccination time point. If any criteria are applicable, the subject must not be vaccinated in the study:

For subjects in the Boostrix and Adacel groups:

- Administration of Tdap vaccine since the last dose received in the study 106316.

For subjects in the Control group:

- Administration of Tdap *(Boostrix or Adacel)* vaccine at any time prior to the administration of *Boostrix* vaccine in this study.

For ALL subjects (Control, Boostrix and Adacel groups):

- Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of *Boostrix* vaccine in this study.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to Visit 6 (pre-vacc). For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with the exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Hypersensitivity to latex.
- History of diphtheria, tetanus or pertussis diseases.
- Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of *Boostrix*.
- History of any neurological disorders or seizures.

- Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 100.4°F by any route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.

4.4. Elimination criteria during the study

The following criteria should be checked at Visit 6 and are applicable to all subjects. If any become applicable during the study, from Visit 6, it will not require withdrawal of the subject from the study but may determine a subject's eligibility in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a vaccine against diphtheria, tetanus or pertussis during the study period (Visit 6 through Visit 7).
- Administration of any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier during the study period (Visit 6 through Visit 7).
- Diphtheria and/or tetanus and/or pertussis disease diagnosed during the study period (Visit 6 through Visit 7).
- Administration of immunoglobulins and/or any blood products within three months of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids are allowed).

- Any confirmed or suspected immunosuppressive or immuno-deficient condition based on medical history and physical examination (no laboratory testing is required) diagnosed during the study period (Visit 6 through Visit 7).

4.5. Contraindications to vaccination

Since this is a single dose booster study, contraindications to vaccination for vaccination at Year 9 time point are included in the exclusion criteria. Refer to Section 4.3.

- The following adverse events (AEs) constitute contraindications to administration of *Boostrix* at that point in time; if any one of these AEs occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).
- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 100.4 °F by any route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the vaccine dose, at the discretion of the investigator.

4.6. Warnings and Precautions

Refer to the approved product label/package insert of *Boostrix*.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 Declaration of Helsinki (Protocol Appendix A), US 21 CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favorable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator.

A list of the professions of the IRB/IEC members should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfill its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favorable opinion from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favorable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favorable opinion of the IRB/IEC will be transmitted by investigator to CRA prior to shipment of vaccine supplies and eCRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favorable opinion of an appropriate amendment or administrative change, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].)

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,

- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the October 1996 Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects face to face. The Informed Consent Form may be read to the subjects but, in any event, the investigator or designate shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subjects and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the

presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The subjects should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects for participating in the trial.

l. The anticipated expenses, if any, to subjects for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject is authorizing such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly

available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects will be informed in a timely manner if information becomes available that may be relevant to the subjects' willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgment, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. Subject identification and randomization of treatment

5.2.1. Subject identification

For the subjects in Boostrix and Adacel groups:

Subjects will retain their subject numbers as in the 106316 study.

For the subjects in the Control group:

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.2.2. Allocation of treatment

5.2.2.1. Numbering of supplies

The numbering of supplies will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

5.2.2.2. Treatment allocation to the subject

5.2.2.2.1. Study group and treatment number allocation

There will be no randomization of subjects into groups in this study. The subjects in this study will be allocated to the same groups as in the vaccination study 106316. Subjects will be allocated a new treatment number, but will retain the same subject number as in the 106316 study (Boostrix and Adacel groups), or subject numbers will be assigned sequentially (for the subjects in the Control group).

The central randomisation system on internet (SBIR) will be used at the investigator site to track enrolment at Year 9 i.e. to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- 28-38 years: ~25.4%
- 39-58 years: ~35.5%
- 59-73 years: ~39.1%

The number of the administered treatment must be recorded in the eCRF on the Vaccine Administration form.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.3. Method of blinding

This study will be conducted in an open manner.

Investigators will be provided with the identification of subjects with low immunogenicity results (see Section 5.7.2).

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site

personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

(Administrative change: 03 February 2015)

The summary of study procedures is summarized in Table 3.

Table 3 List of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix*/ *Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix*/ *Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix*/ *Adacel* vaccination	VISITS 6 AND 7[1] Year *9* *9* years following *Boostrix*/ *Adacel* vaccination Administration of *Boostrix* vaccine	
				Visit 6	Visit 7
Informed consent for persistence follow-up	●	●	●	●[3]	
Informed consent for vaccination				●	
Check inclusion criteria	●	●	●	●[3]	
Check exclusion criteria				●	
Check elimination criteria	●	●	●	●[3]	●
Collect demographic data[2]				●	
Medical history				●	
Vaccination history				●[3]	
Pre-vaccination body temperature				●	
Recording of administered treatment number				●	
Urine Pregnancy test[4]				●	
Check contraindications to vaccination				O	
Check warnings and precautions				O	
Blood sampling (~5 mL) for antibody determination	●	●	●	●[3]	●
Vaccination				●	
Distribution of diary card				O	
Daily recording of solicited adverse events during the 4-day Day (0-3) follow-up period post-vaccination, by subjects				●	
Recording of non-serious adverse events during the 31 day Day (0-30) follow-up period post-vaccination, by subjects				●	●
Return of diary cards					O

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following *Boostrix/ Adacel* vaccination**	**VISIT 4** **Year 3** **3 years following *Boostrix/ Adacel* vaccination**	**VISIT 5** **Year 5** **5 years following *Boostrix/ Adacel* vaccination**	**VISITS 6 AND 7[1]** **Year *9*** ***9* years following *Boostrix/ Adacel* vaccination** **Administration of *Boostrix* vaccine**	
				Visit 6	**Visit 7**
Diary card transcription by investigator					●
Record concomitant medication/vaccination	●	●	●	●[3]	●
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●[3]	●
Recording of any large injection site reactions in the eCRF by the investigator[5]				●	
Reporting of SAEs				●[3]	●
Recording of pregnancies				●	●
Record any intercurrent medical conditions					●
Study Continuation	●	●	●	O (NA for Control group)	●
Study conclusion for persistence follow-up				●[3]	
Study Conclusion for vaccinated groups					●
Investigator sign-off on data for persistence follow-up				●[3]	
Investigator sign-off on data					●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
[1]Applicable to Control, Boostrix and Adacel groups.
[2] Year of birth, gender, ethnicity and race for subjects in the Control group.
[3]These are the only study procedures applicable for subjects who refuse vaccination at Year 9 time point.
[4]Applicable to female subjects of childbearing potential only.
[5]Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed.

Table 4 Intervals between study visits

Intervals between study visits for subjects in Boostrix and Adacel groups:

Visit	Optimum length of interval [1]	Maximum interval allowed [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	9 years – 3 months	9 years +6 months
Visit 7 (Visit 6→ Visit 7)	30-48 days (at least 30 days[3])	21-48[3] days

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year ***9*** cohort for analysis if they make the study visit outside this interval.
[3]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Intervals between study visits for subjects in Control group:

Visit	Optimum length of interval [1]	Maximum interval allowed[2]
Visit 6→Visit 7[3]	30-48 days (at least 30 days[4])	21-48 days

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year 9 cohort for analysis if they make the study visit outside this interval.
[3]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[4]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

5.6. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

Procedures at Visits 3, 4, 5 and 6:

Persistence follow-up phase up to Year 9 time point:

The following study procedures are applicable to subjects who refuse vaccination at Year 9 time point:

- Obtain written informed consent from all subjects at all long-term time points.
- Check inclusion criteria at all study visits.
- Check elimination criteria at all study visits.
- Record concomitant medication/vaccination as described in Section 6.9.
- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Study continuation at Years 3 and 5.
- Study conclusion at Year 9 (Visit 6).

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- Obtain written informed consent from all subjects consenting for vaccination.
- Check inclusion and exclusion criteria.
- Check elimination criteria.
- Check medical and vaccination history:
  - Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.
  - Obtain the subject's vaccination history by interview and/or review of the subject's medical records and record any vaccine administration within 30 days prior to the study vaccination in the eCRF.
- Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.
- Treatment number allocation will be performed as described in Section 5.2.2.2. The number of each administered treatment must be recorded in the eCRF.
- Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 4.5 and 4.6 for more details.
- Record pre-vaccination body temperature.

- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D.
- Administration of a single dose of *Boostrix* vaccine to all study participants as described in Section 6.2. The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.
- Management of diary cards:

  After vaccination, diary cards will be provided to the subject. The subjects will be instructed to record the following information in appropriate sections of the diary card:

  – Record body (oral) temperature and any solicited local/general AEs on the day of vaccination and during the next 4 days, i.e. (Day 0-3).

  – Any unsolicited AEs on the day of vaccination and during the 31 day, i.e. Day (0-30) follow-up period post vaccination.

  – Record any large injection site reactions (Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions).

  – Any concomitant medication/vaccination given after the administration of the study vaccine.

  – The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious and also to contact the investigator in case of large injection site reactions.
- Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.
- Refer to Section 8.4 for procedures for the investigator to record AEs, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.

Procedures at Visit 7:

- The completed diary card will be collected and reviewed during discussion with the subject at this visit. Any unreturned diary cards will be sought from the holder through telephone call(s) or any other convenient procedure such as courier, home pick-up etc.
- Collect approximately 5 mL of whole venous blood to provide approximately 1.5 mL of serum for antibody testing, according to instructions in Appendix D.
- Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.

- Refer to Section 8.4 for procedures for the investigator to record AEs, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.
- Record any pregnancies up to Visit 7 (post-vacc).
- Study conclusion.

5.6.1. Activities at study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness.
- complete the Study Conclusion section in the eCRF.

At/after study completion, no post-trial commercial vaccines will be provided in this study.

5.7. Sample handling and analysis

5.7.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

5.7.2. Laboratory assays

Please refer to Appendix G for the address of the clinical laboratories used for sample analysis.

Table 5 presents the details of laboratory assays.

A sample of approximately 5 mL of whole venous blood, to provide approximately 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and nine years [at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups following study vaccination in 106316 study, and only at (pre-vacc) and Visit 7 (post-vacc) for the Control group. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C (alternatively at approximately -70°/80°C is also acceptable) until sent to the sponsor. Sera will be sent to Quest Diagnostics Laboratories (Valencia, CA) and subsequently to GSK Biologicals, for the laboratory assays.

All serological assays will be performed at GSK Biologicals' central laboratory or in a laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus (anti-T and anti-D) will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off for seroprotection of both assays is 0.1 IU/mL [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL (The Vero cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL and will be used for pre /post vaccination assays at Year 9. The study will consider anti-D concentrations greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection). The ELISA test will define the seroprotection status for the primary endpoint).

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA technique. The cut-off of the three assays is 5 EL.U/mL [Sato, 1982].

Table 5 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off †
Serological	anti-D	ELISA	In-house assay	IU/mL	0.1
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016/0.004*
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA	In-house assay	EL.U./mL	5

ELISA = enzyme-linked immunosorbent assay
IU/mL = International Units per millilitre
EL.U/mL = ELISA units per milliliter
**VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.
*VERO cut off is ≥ 0.004 IU/mL for Year 5 and Year ***9*** time points
† The cut-off of the diphtheria (ELISA and VERO-cell), tetanus and pertussis assays may be subject to change.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

The investigator is encouraged to share the immunological assay results for low immunological assay results with the study subjects.

Low result is defined as:

- Antibody concentrations < 0.01 IU/mL for diphtheria antigen and,
- Antibody concentrations < 0.1 IU/mL for tetanus antigen.

For the study subjects identified as low-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

5.7.3. Immunological read-outs

Table 6 Immunological read-outs for all subjects

Blood sampling time point		Marker
Timing	Visit no.	
Year 1	3	D
		T
		PT
		FHA
		PRN
Year 3	4	D
		T
		PT
		FHA
		PRN
Year 5	5	D
		T
		PT
		FHA
		PRN
Year 9	6 and 7†	D*
		T
		PT
		FHA
		PRN

†Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7, respectively to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
*VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.

Samples will not be labeled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.

- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Study vaccines in study 106316 were *Boostrix* and *Adacel*.

6.1. Study vaccine

The study vaccine to be used at the Year 9 time point has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine

Treatment name	Vaccine/product name	Formulation	Presentation	Volume	Number of doses
Boostrix	Tdap	Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf , Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as $Al(OH)_3$:≤ 0.39 mg, Sodium chloride	Pre-filled syringes, Homogeneous turbid white suspension	0.5 mL	1

6.2. Dosage and administration

In order to monitor enrolment and to control age distribution in the Control group, allocation of treatment number will be performed using SBIR. The application will ensure enrolment in the Control group is performed as per target age distribution (see Section 4.1).

The vaccines will be administered as detailed in Table 8.

The vaccine is to be administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. *Boostrix* should in no circumstances be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1 - 1 1/2 inch length, 25 gauge will be used [ACIP, 2011; Zuckerman, 2000].

* Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.

Table 8 Dosage and Administration

Visit	Dose	Vaccine	Route	Site	Side
Visit 6[e]	1	Tdap[a]	IM[b]	D[c]	Non-Dominant[d]

a. Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
b. Intramuscular (IM)
c. Deltoid (D)
d. Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.
e. Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

6.3. Storage

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Temperature excursions must be reported in degree Celsius.

Vaccines will be stored at the defined temperature range (i.e. 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature monitoring device will be used as a backup device and it will be opened in case of any temperature deviation (temperature outside the defined range, i.e. 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature monitoring device), if:

- proper functioning was demonstrated during the monitor's site evaluation,
- if the system continues to work in case of a power failure, and
- if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working after the alarm is activated.

It is also required to place a validated freezing point indicator close to the vaccines as a back-up device.

Any temperature excursion outside the range of 0.0 to +8.0°C impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix F.

6.4. Treatment allocation and randomization

Subjects in the treatment groups- Boostrix, Adacel and Control will be analyzed as separate groups and will receive a dose of Tdap vaccine (*Boostrix*) at Year 9 time point.

It is anticipated that approximately 1100 subjects (733 subjects from Boostrix group and 367 from Adacel group in the primary study) would return for the Year 9 vaccination visit. Approximately 367 subjects who were not part of the 106316 study will be enrolled in the Control group to receive the first dose of Tdap vaccine (*Boostrix*). All subjects participating in the vaccination phase will receive a single dose of *Boostrix*.

6.5. Method of blinding and breaking the study blind

The study is an open study, since this is an extension of study 106316 which was un-blinded at the time of primary analysis. At Year 9 time point all the subjects in all the groups will receive a single dose of *Boostrix*.

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix F for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF, in SBIR and on the vaccine accountability form.

6.7. Packaging

Vaccination phase at Year 9 time point, refer to Appendix F.

6.8. Vaccine accountability

Vaccination phase at Year 9 time point, refer to Appendix F.

6.9. Concomitant medication/treatment

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

At each study visit, the investigator should question the subject about any medication /product taken and vaccination received by the subject.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to any study blood sampling) are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment.

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration.

Vaccination phase at Year 9 time point:

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of the dose of study vaccine and ending up to next study visit after the dose of study vaccine are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to study vaccination or at any time during the study period are to be recorded with the generic name for the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Sections 4.3 and 4.4

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding the dose of study vaccine and ending 31 days (Day 0-30) after the dose of study vaccine is to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [Temperature by any route < 100.4 °F. The preferred route for recording temperature in this study will be oral] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for

combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

During the period starting with administration of the dose of study vaccine and ending 31 (Day 0-30) days after the dose of study vaccine, concomitant medication administered for the treatment of an AE must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form/ SAE screens in the eCRF, as applicable. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study (i.e. from Visit 6 through Visit 7) must be recorded in the eCRF.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action.
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Aes to be recorded as endpoints (solicited Aes) are described in Section 8.6. All other Aes will be recorded as UNSOLICITED Aes.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Aes may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. Aes to be recorded as endpoints (solicited events) are described in Section 8.5. All other Aes will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

8.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation

and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are Aes. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.3. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE, (Refer to Sections 8.1 and 8.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as Aes or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.4. Time period, frequency, and method of detecting *adverse* events, serious adverse events and pregnancies

Persistence follow-up phase up to Year 9 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 9 time point:

Because subjects are not being vaccinated as part of the time points Year 1, 3 and 5, investigators are not required to specifically solicit SAEs. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, he/she should do so within 24 hours of learning of the event. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g. blood draws) will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

When an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after removal of write access of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.9.2 for details of the back-up reporting system.

Vaccination phase at Year 9 time point:

For subjects who receive vaccination at the Year 9 time point: All AEs occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to riter international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting pregnancies.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 9.

Table 9 Reporting periods for adverse events, serious adverse events and pregnancies

Event	Pre-vacc (consent obtained)	Vaccination	4 days (Day 0-3) post-vacc	31 days (Day 0-30) post-vacc
				Study conclusion
Solicited local and general Aes including large injection site reactions				
Unsolicited Aes				
Aes/SAEs leading to withdrawal from the study				
SAEs				
SAEs related to study participation or concurrent GSK medication/vaccination				
Pregnancies				

Pre-vacc.: pre-vaccination; Post-vacc.: post-vaccination.

The investigator will inquire about the occurrence of Aes/SAEs at every visit during the study and throughout the follow-up phase as appropriate.

All Aes either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. Aes not previously documented in the study will be recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. Refer to Section 6.9.

8.5. Solicited adverse events

The following local (injection-site) Aes will be solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they will be asked to contact study personnel and to visit the investigator's office and/or home visit for evaluation as soon as possible. The investigator will record detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

Table 11 Solicited general adverse events

The following general Aes will be solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

8.6. Evaluating adverse events and serious adverse events

8.6.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting Aes, the subject should be asked a non-leading question such as:

"Have you felt different in any way since receiving the vaccine or since the previous visit?"

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6.2. Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 12.

Table 12 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity

*Fever is defined as temperature ≥ 100.4 °F by any route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0	:	Absent
1	:	≤ 20 mm
2	:	> 20 mm and < 50 mm
3	:	≥ 50 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

0	:	<100.4°F
1	:	≥100.4°F to ≤102.2°F
2	:	>102.2°F to ≤104.0°F
3	:	> 104.0°F

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited Aes (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity of each AE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. (In adults, such an AE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.2.

8.6.3. Assessment of causality

The definitions for "NO" and "YES" have been written in such a way that all events that have been attributed a "NO" can be pooled with events which in the primary vaccination study were determined to be "not related" or "unlikely to be related" to vaccination. Those events that are attributed a "YES" can be pooled with those events that in the past were determined to have a "suspected" or "probable" relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general Aes to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other Aes should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.
YES	:	There is a reasonable possibility that the vaccine contributed to the AE.

Non-serious and serious Aes will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.7. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if they received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.8. Follow-up of adverse events, serious adverse events, pregnancies and assessment of outcome

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until the end of the study.

All Aes documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

Investigators will follow-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE; until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE screens in the eCRF. The updated SAE screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.9.1.

In case the electronic SAE reporting system does not work or after removal of write ***access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.9.2. for details of the back-up reporting system.

Outcome of any non-serious AE occurring during the 31 day (Day 0-30) follow-up period post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

Follow-up of pregnancies

Pregnant subjects will be followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.9. Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after removal of write access of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

8.9.1. Time frames for submitting serious adverse event reports and pregnancies to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. Because subjects are not being vaccinated as part of the study protocol at the Year 1, 3 and 5 time points investigators are not required to specifically solicit SAEs in the persistence follow-up phase. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 or in case of vaccination phase at Year ***9***, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information (Refer Table 13).

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after removal of write access of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional information.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Table 13 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information.

8.9.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours as outlined in Section 8.9.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received WITHIN 24 HOURS as outlined in Section 8.9.1.

8.9.2.1. Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.9.2.2. Updating of SAE or pregnancy information after removal of write access of the subject's eCRF

When additional SAE or pregnancy information is received after removal of write access of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 13.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.3.

Please see Sponsor Information Sheet for contact details

US Safety Contact for Faxing/Reporting SAE Information
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD **US Study Contacts for Concerns Relating to an SAE** GSK Biologicals Medical Monitor: PPD Office: PPD Cell: PPD Fax: PPD GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD or PPD

8.9.3. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.10. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.9. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.11. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 9. Investigators are not obligated to actively seek Aes or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.12. Pregnancy

Persistence follow-up phase up to Year 9 time point:

The following criterion is applicable to subjects who refuse vaccination at Year 9 time point:

Because subjects are not being vaccinated as part of the time points at Year 1, 3 and 5, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit during the time points at Year 1, 3 and 5 should not be excluded from the visit on the basis of their pregnancy.

Vaccination phase at Year 9 time point:

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on a electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.9 and 8.9.1:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of fetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.9.2. While the investigator is not obligated

to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.13. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for a study visit as specified in the protocol is considered to have completed the study phase (time point) pertaining to that study visit.

9.2. Subject withdrawal

Subjects who are withdrawn because of Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE/ AE until resolution of the event (see Section 8.1).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5 and 9 year persistence analyses.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter.

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the

decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event*
- Moved from the study area
- Lost to follow-up
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.8).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.

Refer to Section 10.5 for the definition of booster response.

10.2. Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and ***9*** years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at the Year ***9*** time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the definitions of booster response and alternate booster response).

  * Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited Aes during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.

10.3. Estimated sample size

No sample size is calculated for the time points at Year 1, 3 and 5. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study.

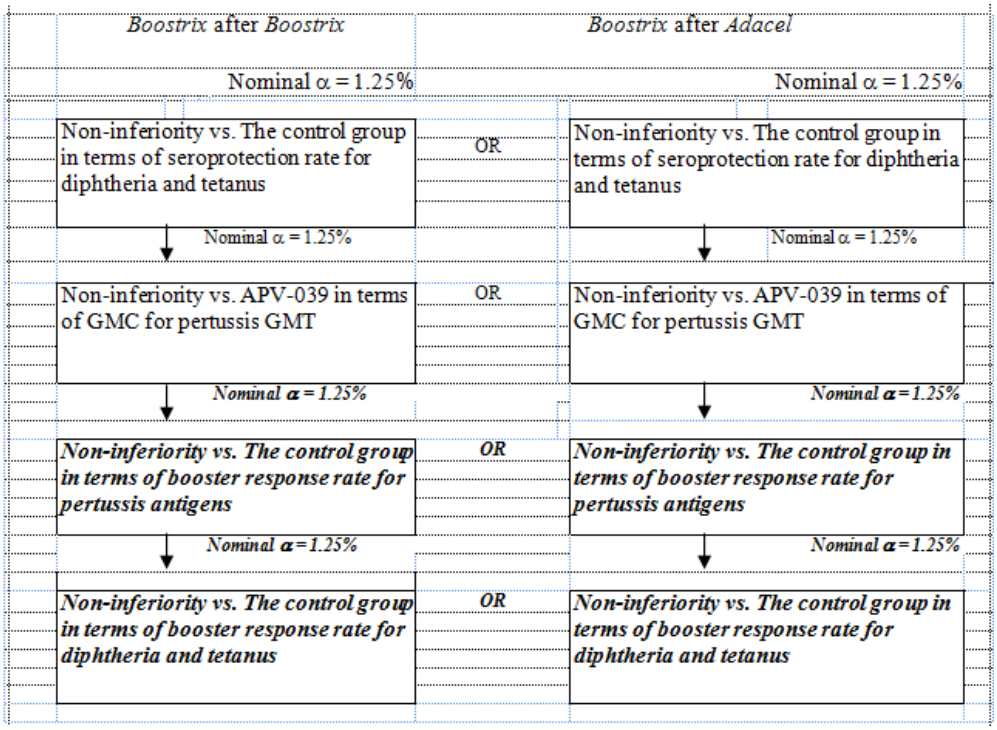
It is estimated that around 1100 subjects (733 subjects from Boostrix group and 367 subjects from Adacel group in the primary study) would return for Year 9 study. Around 367 subjects are to be recruited for the Control group to receive the first dose of Tdap vaccine (*Boostrix*). Assuming 80% of enrolled subjects will be evaluable, this gives 586 evaluable subjects in Boostrix group, 293 evaluable subjects in Adacel group and 293 evaluable subjects in the Control group.

10.3.1. Control on type I error

This study is designed to assess independently non-inferiority of Boostrix group to the Control group, and non-inferiority of Adacel group to the Control group. To control the overall type I error below 2.5%, a Bonferroni adjustment is used, i.e., type I error allowed for each non-inferiority assessment is 1.25% (one-sided). In addition to further control misinterpretation related to multiple primary objectives, a hierarchy procedure will be used as described in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%

An objective will be reached if the associated criteria are met and the previous objectives were reached



10.3.2. Power computation

With 293 evaluable subjects in the Adacel group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Adacel group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Adacel group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 88.91% (See Table 14 and Table 15 respectively).

As shown in Table 16, the power to demonstrate non-inferiority of Adacel group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be very low (4%). In

other words, there is a big chance that non-inferiority would not be demonstrated for one or more of the antibodies.

With 586 evaluable subjects in the Boostrix group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Boostrix group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Boostrix group to *Infanrix* in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 97.87 % (See Table 17 and Table 18 respectively).

As shown in Table 19, the power to demonstrate non-inferiority of Boostrix group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be 48%. It is likely that non-inferiority might not be demonstrated for one or more of the antibodies.

Table 14 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	**DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)**	**Non-inferiority criterion Difference(2nd dose-1st dose)**	**293 (*Boostrix* following *Adacel*) 293 (First *Boostrix*)**
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 15 Power to demonstrate non-inferiority of *Boostrix* following *Adacel* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 (BOOSTRIX)-007 (*Boostrix*)**	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =293 in Adacel+Boostrix**
Anti-PT	0.480	0.306	2884	99.99%
Anti-FHA	0.422	0.370	685	99.99%
Anti-PRN	0.710	0.413	631	88.93%
Overall power**				88.91%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 16 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
	DTPA 0.3 (BOOSTRIX)-007 (Boostrix Group)	Non-inferiority criterion Difference(2nd dose- 1st dose)	293 (Boostrix following Adacel) 293 (First Boostrix)
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	74.19%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	57.51%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	73.64%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	98.81%
		Overall power**	4.14%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

Table 17 Power to demonstrate non-inferiority of a second dose of *Boostrix* following the first dose of *Boostrix* with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <-10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)	Non-inferiority criterion Difference(2nd dose- 1st dose)	586 (*Boostrix* following *Boostrix*) 293 (First *Boostrix*)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 18 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to *Infanrix* vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (*Boostrix/Infanrix*) < 0.67	
Endpoint (GMCs)	**DTPA 0.3 (BOOSTRIX)-007 (*Boostrix)***	**APV-039 *Infanrix***	**N in APV-039 (TVC)**	**N =586 in Boostrix+Boostrix**
Anti-PT	0.480	0.306	2884	>99.99%
Anti-FHA	0.422	0.370	685	>99.99%
Anti-PRN	0.710	0.413	631	97.87%
Overall power**				97.87%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Table 19 Power to demonstrate non-inferiority of *Boostrix* following *Boostrix* to the first dose of *Boostrix* with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

Endpoint (booster response rate)	**Reference values**	**Non-inferiority criterion Difference(2nd dose- 1st dose)**	**Power* to reject H0: LL of 97.5%CI of difference <-10%**
	DTPA 0.3 (BOOSTRIX)-007 (Boostrix Group)		**586 (Boostrix following Boostrix) 293 (First Boostrix)**
Anti-D	77.6%	LL of 97.5% CI ≥ -10%	88.89%
Anti-T	48.8%	LL of 97.5% CI ≥ -10%	71.39%
Anti-PT	77.2%	LL of 97.5% CI ≥ -10%	88.45%
Anti-FHA	96.9%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-PRN	93.2%	LL of 97.5% CI ≥ -10%	99.96%
		Overall power**	48.69%

*Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.

10.4. Study cohorts to be evaluated

10.4.1. Year X (1, 3, 5, 9) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

10.4.2. According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5) cohort

The ATP Year X (1, 3, 5) cohort will include all subjects from Year X (1, 3, 5) cohort who were in the ATP cohort for analysis of immunogenicity in 106316 study and who did not meet the following elimination criteria:

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

This cohort is the primary cohort for the analysis.

10.4.3. Additional cohorts defined for Year 9 analysis

10.4.3.1. Total Vaccinated Cohort (TVC) at Year 9

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.
- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

10.4.3.2. ATP cohort for analysis of safety at Year 9

The ATP cohort for analysis of safety at Year 9 time point will include all eligible and vaccinated subjects.

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis as listed in Section 6.9.

10.4.3.3. ATP cohort for analysis of immunogenicity at Year 9 (ATP Year 9)

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who comply with the procedures and intervals defined in the protocol (refer to Section 5.5 and Table 4).
- Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 4.4) during the study.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after Year 9 vaccination.

10.5. Derived and transformed data

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.2.
- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 10.6.2 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years, 5 years, and 9 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the Boostrix and Adacel groups, 1 year, 3 years, 5 years and 9 years following vaccination will be derived to evaluate the first secondary objective.
- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 9 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

Booster responses to be considered for Year 9 time point:

- Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and
  - for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
- Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL, one month after vaccination;
  - for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and
  - for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL: antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.
- Alternative Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and
  - for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.
  - for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.
  - Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.
- Alternative Booster response to PT, FHA and PRN antigens is defined as:
  - for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;
  - for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and

- for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.
- for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase of antibody concentration from the pre-vaccination concentration, one month after vaccination.

Handling of missing data:

Immunogenicity:

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Reactogenicity and Safety:

- For a given subject and the analysis of solicited symptom during the 4 day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.

10.6. Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 9) on cleaned data obtained through each Year X. A clinical study report (CSR) will also be written following each analysis.

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, time since last DT vaccination, gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year 9) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 9) cohort and in the ATP Year X (1, 3, 5 or 9) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 9) (in years) will be summarized using descriptive statistics.

10.6.2. Analysis of persistence

The primary analysis will be based on the ATP cohort for analysis of immunogenicity Year X (1, 3, 5, 9).

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X (1, 3, 5, 9) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves (RCC) by group.

Comparability between Groups - Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO), Year X (1, 3, 5, 9) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 9) after vaccination will be calculated.
- For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 5 EL.U/mL by ELISA, Year X (1, 3, 5, 9) after vaccination will also be calculated.

10.6.3. Analysis of immunogenicity at booster dose

The following analyses will be carried out after Year 9 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 9 cohort. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC at Year 9 will be performed to complement the ATP analysis.

Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% Cis.
- GMCs or GMTs at pre-vaccination, one month post-vaccination will be tabulated with 95% Cis.
- Booster response rate one month post-vaccination will be calculated with exact 95% Cis.
- Antibody concentrations/titres distribution at pre-vaccination and one month post-vaccination will be displayed using RCC.

Comparability between Groups – confirmatory analyses:

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm_{10} transformation of the concentrations.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.

Comparability between Groups – exploratory analyses:

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.
- For anti-D, anti-T antibody response, the two-sided 95% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Boostrix group and Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) will be calculated.

Sensitivity analysis

A complementary analysis will be carried out in order to evaluate the robustness of GMT/GMC results with respect to drop-out from the parent study (106316). More specifically multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC/GMT that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

In addition, within group assessment for the ATP analysis of immunogenicity at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***-3***8*** years old, 3***9***-5***8*** years old and 5***9***-7***3*** years old).

10.6.4. Analysis of safety

Persistence follow-up phase up to Year ***9*** time point:

The following is applicable to subjects who refuse vaccination at Year ***9*** time point:

No safety analysis will be performed for this study. If GSK is informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

Vaccination phase at Year 9 time point:

The primary analysis will be based on the TVC at Year 9. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 9 is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the treatment groups by solicited local and general symptom terms, and, for unsolicited Aes, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 0.9°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

The percentage of subjects who reports at least one unsolicited adverse event classified by MedDRA during the 31 day (Day 0-30) follow-up period after vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, Aes resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

In addition, safety analysis for TVC at Year 9 will be performed separately for each level of the age stratum (Subjects age at Year 9 vaccination will be classified into three categories, 28-38 years old, 39-58 years old and 59-73 years old).

10.6.5. Statistical methods

- The exact Cis for a proportion within a group will be computed using SAS, [Clopper, 1934].
- The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].
- The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown

variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

10.7. Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5 and Year 9) as available and reported separately. At Year 9 time point immunogenicity and safety of vaccine administration will be reported.

10.8. Planned interim analysis

No interim analysis is planned for this persistence study.

11. ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

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Appendix A World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the

study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B Administrative Matters

I. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities and equipment which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments/administrative changes is required prior to implementation.
- Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local

regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favourable opinion on the amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

V. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

VI. Record retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location (except for those required by local regulations to be maintained elsewhere). The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that there is an acceptable quality control procedure in place.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/

institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability

- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of CRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.
- GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

IX. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

X. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before criterion of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

XI. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Appendix C Overview of the Recruitment Plan

- All subjects who received vaccination in the study 106316 will be invited to participate in this long-term study.
- As part of the visit activities at the study conclusion visit in the 106316 study, subjects were asked to state their interest in participating in an extension study. Subjects who responded positively to this question will be contacted by the site as the sampling time point approaches in order to schedule the study visit.
- Subjects who do not provide samples at earlier long-term time points may still be considered eligible to provide samples at later long-term time points.
- The study will take place at multiple centres in the US.
- The Site Monitor will perform monitoring of actual enrolment against target enrolment on a continuous basis.
- Enrolment will be monitored through RDE.
- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date the subject received vaccination in study 106316. A window of ± 8 weeks around the actual time point for each subject will be permitted.

For the Control group:

- Approximately 367 subjects will be recruited to receive the first dose of Tdap vaccine (*Boostrix*) in this study.
- The study will take place at multiple centers in the US.
- The study duration per subject will be approximately one month.
- The recruitment of subjects into the study will be performed using RDE.
- Recruitment will be monitored by the site monitor.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used to minimize the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".
- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- The tube should not be overfilled (max. ¾ of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate label provided by GSK Biologicals (see point 3).

3. Labeling

- The standard labels provided by Quest should be used to label each serum sample.
- If necessary, any hand-written additions to the labels should be made using indelible ink.

4. Sorting and storage

- The tubes of serum should be stored in a vertical position at approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to Quest Diagnostics. Wherever possible, a backup facility for storage of serum samples should be available.
- Detailed instructions concerning the collection, Quest labelling and storage of all serum specimens are provided in the Quest Diagnostics Clinical Trials Investigator Manual for Protocol Number 110080, 110082, 110084, and 110086.

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, Valencia, California.

Refer to the separate Quest Diagnostics Clinical Trials Investigator Manual for Protocol Numbers 110080, 110082, 110084, 110086 for shipping details.

Appendix F Vaccine supplies, packaging and accountability

1. Vaccine and/or other supplies

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- *Boostrix* in pre-filled syringes

At least an additional 10% of the study vaccine will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject).

All pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:

The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each time point. Each label will contain the following information: study number, identification number for the subject (e.g. **Subject number)**, sampling time point (e.g., post ri 3), timing (e.g., study Month 7).

- Other supplies provided by GSK Biologicals:
  In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:
  - tubes with screw caps for serum samples,
  - racks and cardboard boxes for the tubes of serum.

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in criterio boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site from local country medical department to investigational site

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : PPD
E-mail: PPD

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

4. Vaccine accountability

At all times the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP WWD-1102, used and unused vaccine syringes should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine syringes are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP WWD-1102.

If no processes for destruction of unused clinical trial supplies are in place in the local GSK Biologicals site in the US, the unused supplies must be returned to GSK according to the instructions given by the GSK Biologicals responsible staff (in accordance with SOP-NPD-7200).

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Appendix G Clinical laboratories

Table 20 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, North America-Laval	Biospecimen Reception – Clinical Serology 525 Cartier blvd West – Laval – Quebec – Canada – H7V 3S8
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 – B-1300 Wavre – Belgium

Appendix H Amendments and Administrative changes to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to:	
US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE *(Amended 14 April 2009)*	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office:~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Amendment number:	Amendment 1
Amendment date:	09 November 2010
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

- The list of coordinating and contributing authors for this amendment was updated.
- The maximum window period allowed for the return of subjects for the Year 5 and Year 10 follow-up visits (Visit 5 and Visit 6) has been extended from ± 5 weeks to ± 8 weeks.
- The contact details for reporting of SAEs have been clarified. As of now, two fax numbers will be used as back-up for the safety contact for reporting SAEs.
- Text pertaining to the reporting of spontaneous abortion has been removed from the protocol. Since this follow-up study involves no vaccine exposure, investigators are not obligated to report such an event.
- The number of attempts to contact subjects who do not return for scheduled persistence visits has been clarified.

Amended text has been included in *bold italics* in the following section:

Title page:

Co-ordinating author *(Amended 09 November 2010)*	PPD Scientific writer
Contributing authors *(Amended 09 November 2010)*	• PPD ***Senior Manager, Clinical Development, Boostrix/Hepatitis Vaccines, Global Vaccine Development*** • PPD ***Director, Lead Clinical Development, DTP Combination Vaccines, Global Vaccine Development*** • PPD ***Biostatistician, Boostrix (US)*** • PPD Project statistician, Boostrix (US) • PPD ***Global Study Manager*** • PPD ***Clinical Data Coordinator*** • PPD ***Senior Manager, Biologicals Clinical Safety & Pharmacovigilance*** • ~~PPD Director, Vaccines (US)~~ • ~~PPD Biostatistician (US)~~ • PPD Clinical Development Manager, Vaccine (US) • PPD Study Manager (US) • ~~PPD , Director, Clinical R&D, World-Wide Clinical Development, Life-cycle Vaccines~~ • PPD ~~Central Study Coordinator~~

Section 5.3 Outline of study procedures

Table 2 Intervals between study visits *(Amended 09 November 2010)*

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	***1 year ± 5 weeks***
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	***3 years ± 5 weeks***
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	***5 years ± 8 weeks***
Visit 6 (Tdap vaccination in parent study →Visit 6)	10 years ± 5 weeks	***10 years ± 8 weeks***

1. Whenever possible the investigator should arrange study visits within this interval
2. Subjects will not be eligible for inclusion in the ATP Year X cohort for analysis if they make the study visit outside this interval.

Section 8.6.2 Completion and transmission of serious adverse event reports to GSK Biologicals
US Safety Contact for Faxing/Reporting SAE Information
Fax to:
US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD
US Study Contacts for Concerns Relating to an SAE
GSK Biologicals Medical Monitor: PPD MD Office: PPD Cell: PPD Fax: PPD
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD
After Hours (8:00 pm to 8:00 am EST) and Weekends in the US: Call the GSK Customer Response Center (CRC) at PPD and follow the Interactive Voice Response System (IVRS) menu, i.e. • Say "Provider", "Emergency" when prompted and you will be transferred to the CRC Answering Service. • The CRC Answering Service will collect basic information from you and will page a Medical Information Scientist who will return your call. • The Medical Information Scientist will relay the information to the Clinical Development Manager on call who will then contact you regarding the SAE.
Back-up Study Contact for Reporting SAEs (Amended 09 November 2010)
24/24 hour and 7/7 day availability ***GSK Biologicals Clinical Safety & Pharmacovigilance***
Fax: PPD ***or*** PPD

Section 8.9 Pregnancy ***(Amended 09 November 2010)***

Because subjects are not being vaccinated as part of the study protocol, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit should not be excluded from the visit on the basis of their pregnancy.

~~A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.6. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to GSK Biologicals as described in Section 8.8. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.~~

Section 9.2.1 Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5, *7* and 10 year persistence analyses.

A subject qualifies as a withdrawal from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for the subject since the last contact.

Investigators will make at least 4 attempts to contact subjects who do not return for scheduled persistence visits. The first three attempts will be by phone contact. The fourth attempt will be done through a certified letter. Subjects lost to follow-up will be confirmed by a returned certified letter. (Amended 09 November 2010)

Information relative to the withdrawal of a subject will be documented on the study continuation/conclusion pages of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject or by the investigator, as well as the reason for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (includes receipt of prohibited vaccine or medication; specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (specify).

Appendix C Overview of the Recruitment Plan

- Enrolment in study 106316 began on 13 July 2006 and was completed on 14 August 2006. Scheduling of visits in the extension studies will follow from the date ***the*** subject received vaccination in study 106316. A window of ~~± 5~~ ***± 8*** weeks around the actual time point for each subject will be permitted. ~~Visits for the year 1, 3, 5, and 10 samplings are therefore expected to take place between 8 June – 17 August 2007, 2009, 2011, and 2016.~~ ***(Amended 09 November 2010)***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 2

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***8***)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***8*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) ***and evaluation of immunogenicity and safety of an additional dose of Boostrix, when administered at Year 8.***
Amendment number:	Amendment 2
Amendment date:	Amendment 2 Final: 18 February 2014
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

The main purpose of this amendment is to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap vaccine when administered 8 years after an initial dose of Tdap. To evaluate *Boostrix* as a second dose of Tdap vaccine at Year 8, administration of *Boostrix* at Year 8 to the returning subjects from initial cohort has been added. This study will also evaluate the persistence of antibodies against diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens, 8 years instead of 10 years after an initial dose of Tdap vaccine [*Boostrix* or *Adacel* (Sanofi-Pasteur)] administered in 106316 (Tdap 0.3-007) study. The Year 10 time point for evaluation of persistence has been cancelled because it is no longer feasible to conduct after a second dose of Tdap vaccine has been administered at Year 8.

For evaluation of *Boostrix* as a second dose of Tdap vaccine and as per advice from Centre for Biological Research and Evaluation (CBER):

- An additional treatment group acting as control is also added and the subjects enrolled in the control group will receive *Boostrix* as a first dose of Tdap vaccine.

Alternative booster response definitions are given for diphtheria, tetanus and pertussis antigens since the traditional booster response definitions applied for evaluation of initial dose of *Boostrix* are based on the level of antibodies observed in subjects prior to the first dose of *Boostrix*. The definition of booster responses to D, T and pertussis antigens currently used may not accurately depict a true immunologic booster response of the vaccine in the context where subjects have high pre-vaccination concentrations (≥ 6.0 IU/mL for diphtheria and tetanus and ≥ 60 EL.U/mL for pertussis). Therefore, applying the traditional booster response definitions in such a context would lead to lower booster response rate despite a higher observed geometric mean antibody concentration (GMC) after the second booster dose.

The data from this study are planned to support the indication of *Boostrix* as a second dose of Tdap vaccine.

Amended text has been included in *bold italics* in the following section:

Title page:
The names of the contributing authors have been updated in the title page.

Protocol Amendment 2 Sponsor Signatory Approval page:
The name of the sponsor signatory has also been updated on the protocol amendment 2 sponsor signatory approval page.

eTrack study numbers and abbreviated titles
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, ***Y8*** ~~Y10~~)

The title and detailed title was updated in all applicable sections of the protocol

Title
Persistence study of GSK Biologicals Tdap vaccine 776423, 1, 3, 5 and ***8*** ~~10~~ years following the administration as a single dose in ~~the~~ 106316 study ***and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 8.***

Detailed Title
A phase III~~b~~, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5, and ***8*** ~~10~~ years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) ***and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 8***.

Indication/Study population

Booster vaccination against diphtheria, tetanus and pertussis diseases in adults.
~~Healthy adults, 19 years of age and older, who received a single dose study vaccination in study 106316~~.

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***8*** ~~10~~)
Sponsor Information	
1. Sponsor	
GlaxoSmithKline Biologicals ***Rue de l'Institut, 89*** ***1330 Rixensart, Belgium***	
2. Sponsor Medical Expert for the Study	
Refer to the local study contact information document.	
3. Sponsor Study Monitor	
Refer to the local study contact information document.	
4. Sponsor Study Contact for Reporting of a Serious Adverse Event	
GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.9.2.	
List of Abbreviations:	
~~**DTPw**~~	~~Diphtheria, Tetanus Whole Cell Pertussis Vaccine~~
~~**FDA**~~	~~Food And Drug Administration, United States~~
~~**IB**~~	~~Investigator Brochure~~
D	***Diphtheria***
EDD	***Estimated Date of Delivery***
eTDF	***Electronic Temperature excursion Decision Form***
EGA	***Estimated Gestational Age***
FHA	Filamentous Hemagglutinin **from** ***Bordetella pertussis***
IMP	***Investigational Medical Products***
LMP	***Last Menstrual Period***
PRN	Pertactin **from** ***Bordetella pertussis***
PT	Pertussis Toxoid **from** ***Bordetella pertussis***
RCC	***Reverse Cumulative distribution Curve***
SPM	***Study Procedures Manual***
T	***Tetanus***

Glossary of Terms	
Adequate contraception:	***Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:*** • ***abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,*** • ***oral contraceptives, either combined or progestogen alone,*** • ***injectable progestogen,*** • ***implants of etenogestrel or levonorgestrel,*** • ***estrogenic vaginal ring,*** • ***percutaneous contraceptive patches,*** • ***intrauterine device or intrauterine system,*** • ***male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,*** • ***The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.*** • ***male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),*** • ***male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).*** ***Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.***
Adverse event:	***Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*** ***An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.***

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. ~~In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g. double-blinded consistency lots which are open with respect to the control group.~~ The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. ***In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned. In a single-blind study, the investigator and/or his staff are aware of the treatment assignment but the subject is not.***
~~**Central Study Co-ordinator:**~~	~~An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.~~
Epoch:	***An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.***
Primary completion date:	***The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.***

Menarche:	***Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, the larche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).***
Menopause:	***Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.***
Primary completion date:	***The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.***
Randomization:	***Process of random attribution of treatment to subjects in order to reduce bias of selection.***
Solicited adverse event:	***Aes to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.***
Unsolicited adverse event:	***Any AE reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.***

Trademarks
The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ® and in italics.

Trademarks of the GlaxoSmithKline group of companies	***Generic description***
Boostrix®	***Reduced antigen content Diphtheria and Tetanus toxoids and acellular Pertussis (Tdap) vaccine***
Infanrix®	***Combined diphtheria, tetanus and acellular pertussis vaccine***

Section 1.1 Background

~~Reported pertussis incidence in the United States increased from 1010 cases in 1976 to 25,827 cases in 2004 [CDC, 2004; CDC 2002]. On October 26, 2005, ACIP issued a provisional recommendation for a single dose of Tdap for adults 19-64 years of age to replace the next booster dose of tetanus and diphtheria toxoids vaccine (Td) as the vaccine-induced immune response to pertussis declines over time.~~ ***Since the 1980s, there has been an increase in the number of reported cases of pertussis in the United States (US), especially among 10-19 year olds and infants younger than six months of age. By December 2012, 48,227 cases of pertussis were reported to Centers for Disease Control and Prevention (CDC), more than twice the number reported during the same time period in 2011 [CDC, 2012a]. The incidence of confirmed and probable pertussis among persons aged ≤ 19 years, by age and vaccine received in the US shows that high rates of pertussis is observed among adolescents and older children 7 through 10 years of age suggesting early waning of immunity [CDC, 2012b]. According to the recent General Recommendations on Immunization, adolescents and adults 11-18 years of age are recommended to receive a single Tdap dose by the Advisory Committee on Immunization Practices (ACIP). It is also recommended for all adults 19 years of age and older who have not received a dose of Tdap [ACIP, 2012]. All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should take a Tdap vaccine [CDC, 2012c; CDC, 2012d].***

~~This vaccine~~ ***Boostrix*** is based on GSK Biologicals' DtaP vaccine (*Infanrix*), a US-licensed pediatric vaccine with proven efficacy [Campins-Marti , 2002; Greco , 1996; Schmitt , 1996a; Schmitt , 1996b].~~Recently, GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed, (*Boostrix*) vaccine was licensed in the US as a single-dose booster for adolescent 10-18 years of age.~~ ***In 2005, Boostrix (0.3 mg) was approved in the US for use in 10-18 year olds. In December 2008, it was approved for use in adults 19-64 years of age and in 2011, it was approved in the US for use in elderly adults 65 years of age and older.***

~~A total of 6,173,696 doses have been distributed since launch until 02 August 2006.~~

~~Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of *Boostrix*.~~ ***Please refer to the Prescribing Information for information regarding the potential risks and benefits of Boostrix.***

Section 1.2 Rationale for the study

~~Recently~~ ***A*** study (106316) was conducted to provide pivotal data in support of extending the age range for *Boostrix* vaccine to include adults 19-64 years of age. ***All primary objectives were met with the exception of pertactin booster response which was observed to be below the 80% margin. Despite this failure Boostrix recommendation in adults 19 years of age or older has been obtained.***

~~Data on persistence of antibodies and longer-term protection against diphtheria, tetanus and pertussis after vaccination with *Boostrix* is limited and thus the current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 10 ***8*** years following vaccination with GlaxoSmithKline Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (*Boostrix*).~~

Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005]. Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first three years after vaccination [Weston, 2011]. The current study will provide information regarding the persistence of antibodies to diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens up to 8 years following vaccination with Boostrix.

Providing pertussis booster vaccination aims to boost immunity and disrupt the disease cycle. Currently in the US, no data is available on the immunogenicity and safety of Boostrix given as a second dose of Tdap vaccine. This study is intended to assess subjects who were vaccinated in the 106316 study and they will be invited to participate in this long-term follow-up and re-vaccination study at Year 8 time point. The purpose of vaccination with Boostrix at Year 8 time point instead of the previously intended Year 10 time point is to evaluate the immunogenicity and safety of a second dose of Boostrix at a time point earlier than the ten year interval. This study will also evaluate the immune response to the booster dose with Boostrix in subjects whose previous Tdap vaccination was a non-GSK vaccine. The data from this study is planned to support the indication of Boostrix as a second dose of Tdap vaccine.

As per advice from Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive Boostrix as a first dose of Tdap vaccine. Enrolment of subjects to the Control group will be stratified by age to ensure similar age distribution between Boostrix and Adacel groups.

Section 2.1 *Co*-Primary Objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of ***Tdap vaccine*** (*Boostrix* ***and Adacel)***, ~~with respect to the percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.016 IU/mL (VERO, for subjects with an ELISA result of < 0.1 IU/mL), and anti-T antibody concentrations ≥ 0.1 IU/mL,~~ ***at*** 1 year, 3 years, 5 years***,*** and ***8*** years ~~10 following Tdap vaccination~~.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  – ***One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).***

  – ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).***
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of Infanrix vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  – ***One month after vaccination, the lower limit of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.***

  – ***One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.***

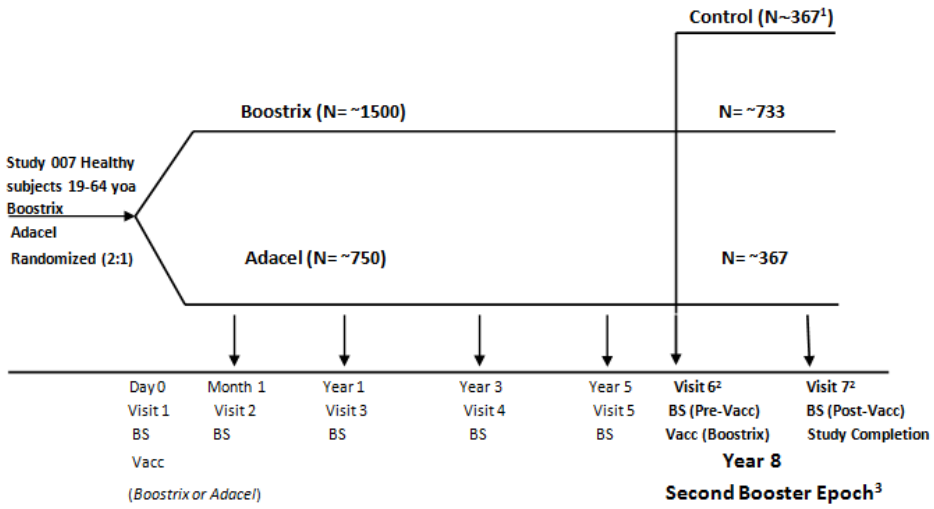
Refer to Section 10.1 for definition of the ***co-***primary endpoint***s and Section 10.3.1 for the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.***

Section 2.2 Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti-~~pertussis toxoid (~~PT~~)~~, anti-~~filamentous hemagglutinin (~~FHA~~)~~, and anti-~~pertactin (~~PRN~~)~~ antibody concentrations ≥5 EL.U/mL, 1 year, 3 years, 5 years~~,~~ and ***8*** years ~~10~~ following a single dose of *Boostrix* ***and Adacel***.
- To evaluate ~~geometric mean antibody concentrations (~~GMCs~~)~~ of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and ~~10~~ ***8*** years after vaccination with *Boostrix* ***and Adacel***.
- ***To assess the immunogenicity of Boostrix in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.***
- ***To assess the immunogenicity of Boostrix in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination***
- ***To explore the potential difference in terms of booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.***
- ***To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).***
- ***To evaluate and compare the safety of an second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).***

****Refer to Section 10.5 for definition of booster response.***

Section 3 Study design overview



Yoa=Years of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch is a non-randomized study, for practical purposes group ratio of 1:2 :1 is assigned for the Control, Boostrix and Adacel groups respectively for the Year 8 time point.
[1]Subjects who were not part of the 106316 study will be recruited as the Control group
[2]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch has been added for practical purposes and it has no relation to the number of epochs in this study.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: ***A phase III,*** ~~Non-~~ ***parallel, open-label***, interventional**,** ~~observational~~ multicenter ***study*** with the same two parallel groups as in the 106316 study ***and one new Control group receiving the first dose of Tdap vaccine (Boostrix)***.
- ***Study groups:***
  - ***Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (Boostrix) in study 106316 will receive a second dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***

- ***Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (Adacel) in study 106316 will receive a second dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***
- ***Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (Boostrix) in this study at Year 8 (Visit 6).***

Table 1 Study groups foreseen in the study

Study Groups	*Number of subjects*	*Age (Min – Max) (age unit)*
Boostrix Group	*Approximately 733*	*27 years-72 years*
Adacel Group	*Approximately 367*	*27 years-72 years*
Control Group	*Approximately 367*	*27 years-72 years*

Table 2 Study groups and treatment foreseen in the study

Treatment name	*Vaccine/Product name*	*Study Groups*		
		Boostrix Group	*Adacel Group*	*Control Group*
Boostrix	*Tdap*	*x*	*x*	*x*

- Blinding: This study will be an open study since ***this is an extension of study 106316 (Tdap 0.3-007) which was un-blinded at the time of primary analysis.*** ~~There is no vaccination this study. Blinding will be maintained for subjects enrolled from the 106316 study and will be maintained until analysis of the 106316 study is complete. Once results of the 106316 study are available, the blind will no longer need to be maintained.~~
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups. ***Subjects in the Control group will also be analyzed as a separate group.***
- Treatment allocation: ***Non-randomized, all the study groups will receive a single dose of Boostrix at Year 8 (Visit 6).*** ~~No treatment is planned to be given in this study.Subjects in the 106316 study were randomized into treatment groups, *Boostrix* or *Adacel* (2:1 ratio, with stratified age group of 19-29, 30-49, and 50-64 years old).~~
- ***Control: Active control.***
- ***Vaccination schedule: A single dose of Boostrix vaccine will be administered to all subjects at Visit 6 i.e.at Year 8 time point (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The stud y procedures will be similar across all groups at Visit 6 and Visit 7).***
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and ~~10 years after the dose of vaccination~~ ***8 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.***

- Duration of the study: Approximately ~~10~~ ***8*** years for subjects who ***were enrolled in study 106316 and who*** ~~participate~~ ***participated*** in all phases ~~of the extension~~ ***of the study including Year 8 time point and approximately one month for the Control group.***
- Data collection: ~~Remote Data Entry (RDE)~~ ***Electronic Case Report Form (eCRF).***

Section 4.1 Number of subjects/centers

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. At the time of initiation of the study, the investigator will ***attempt to*** contact ALL subjects who received vaccination in study 106316 ***and indicated approval of further contact for study related activities at their last attended study visit.*** If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented ~~as instructed on the "subject tracking document" provided by GSK Biologicals.~~ ***In the study continuation screen in eCRF***.

For example, if the subject did not want to participate in the Year 1 evaluation, he***/she*** can participate at Years 3, 5 and ***8***.

In addition, approximately 367 subjects will be newly enrolled at Year 8 time point as Control group to receive the first dose of Tdap vaccine (Boostrix). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- ***27-37 years: ~25.4%***
- ***38-57 years: ~35.5%***
- ***58-72 years: ~39.1%***

Total enrolment in the 106316 study was 2284 subjects, ~~approximately~~ 1522 of whom were vaccinated with *Boostrix*. ***There were 1587 subjects (1064 Boostrix recipients) who returned for the Year 1 time point, 1441 subjects (976 Boostrix recipients) returned for the Year 3 time point and 1257 subjects (856 Boostrix recipients) returned for the Year 5 time point. Assuming an attrition of 15% from Year 5, it is estimated that 1100 subjects (733 Boostrix recipients) might return for the Year 8 time point. Also, approximately 367 sujects are planned to be enrolled in the Control group.*** ~~Assuming a 15% attrition rate per year, approximately 1941 subjects (1294 *Boostrix* recipients) are expected to participate at the 1 year time point, 1402 subjects (935 *Boostrix* recipients) for the 3 year time point, 1013 subjects (675 *Boostrix* recipients) for the 5 year time point, *and 1100 subjects (733 Boostrix recipients) for the 7 year time point.* And 449 subjects (300 *Boostrix* recipients) for the 10 year time point.~~

Section 4.2 Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point:

- All subjects who received study vaccination (*Boostrix* or *Adacel*) in study 106316 will be considered eligible to participate in this study.
- Written informed consent must be obtained from the subject prior to each study time point.

Vaccination phase at Year 8 applicable for subjects in Boostrix and Adacel groups only:

- ***All subjects who received study vaccination (Boostrix or Adacel) in study 106316 will be considered eligible to participate in this study.***

Vaccination phase at Year 8 applicable for subjects in the Control group only:

- ***Subjects within the age range of 27-72 years will be considered eligible to participate in this study in the Control group.***

Vaccination phase at Year 8 applicable for ALL subjects (Control, Boostrix and Adacel groups):

All subjects must satisfy the following criteria at study entry at Year 8 time point:

- ***Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).***
- ***Written informed consent obtained from the subject for vaccination at Year 8 time point.***
- ***Healthy subjects as established by medical history and clinical examination before entering into the study.***
- ***Female subjects of non-childbearing potential may be enrolled in the study.***
  - ***Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.***

Please refer to the Glossary of Terms for the definition of menarche and menopause.

- ***Female subjects of child bearing potential may be enrolled in the study, if the subject***
  - ***has practiced adequate contraception for 30 days prior to vaccination, and***
  - ***has a negative pregnancy test on the day of vaccination, and***
  - ***has agreed to continue adequate contraception for 1 month after completion of the vaccine dose.***

Please refer to the Glossary of Terms for the definition of adequate contraception.

Section 4.3 Exclusion Criteria for enrolment

Section 8.4 ***Exclusion criteria for enrolment***

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of Year 8 vaccination time point. If any criteria is applicable, the subject must not be vaccinated in the study:

For subjects in Boostrix and Adacel groups:

- ***Previous booster vaccination against diphtheria, tetanus or pertussis since the last dose received in the study 106316.***

For subjects in the Control group:

- ***Administration of Tdap vaccine at any time prior to study entry.***

For ALL subjects (Control, Boostrix and Adacel groups):

- ***Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).***
- ***Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to Visit 6 (pre-vacc). For corticosteroids, this will mean prednisone ≥ 20 mg/day , or equivalent. Inhaled and topical steroids are allowed.***
- ***Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with the exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).***
- ***Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).***

- ***Hypersensitivity to latex.***
- ***History of diphtheria, tetanus or pertussis diseases.***
- ***Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.***
- ***History of any neurological disorders or seizures.***
- ***Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.***
- ***Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).***
- ***Acute disease and/or fever at the time of enrolment.***
  - ***Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***
  - ***Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.***
- ***Administration of immunoglobulins and/or any blood products within three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).***
- ***Pregnant or lactating female.***
- ***Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.***

Section 4.4 Elimination Criteria during the study

The following criteria should be checked at ***Visit 6*** ~~each long-term visit~~ ***and are applicable to all subjects***. If any become applicable during the study, ***from Visit 6,*** it will not require withdrawal of the subject from the study but may determine a subject's ~~evaluability~~ ***eligibility*** in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier ~~after the vaccination in 106316 study.~~***during the study period.***
- Diphtheria and/or tetanus and/or pertussis disease diagnosed ~~after the vaccination in 106316 study.~~***during the study period.***

- Administration of immunoglobulins and/or any blood products within ~~-~~***three months*** ~~90 days~~ of each study visit. Investigators may defer the blood draw for these subjects until such time as the criterion no longer applies.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ ***20*** ~~0.5~~ mg/~~kg~~/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required) ***diagnosed during the study period***.

Section 4.5 Contraindications to vaccination

Section 8.4 Contraindications to ~~subsequent~~ vaccination

~~Not applicable~~ ***Since this is a single dose booster study, contraindications to vaccination for vaccination at Year 8 time point are included in the exclusion criteria. Refer to Section 4.3.***

- ***The following adverse events (Aes) constitute contraindications to administration of Boostrix at that point in time; if any one of these Aes occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).***
- ***Acute disease and/or fever at the time of vaccination.***
  - ***Fever is defined as temperature ≥ 99.5 F for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***
  - ***Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered the vaccine dose, at the discretion of the investigator.***

Section 4.6 Warnings and Precautions

~~Not Applicable~~***. Refer to the approved product label/package insert of Boostrix.***

Section 5.1 Ethics and regulatory considerations

The study will be conducted in accordance with all applicable regulatory requirements.

Section 5.2 Subject identification and randomization of treatment

5.2 Subject identification ***and randomization of treatment***

5.2.1 Subject identification

For the subjects in Boostrix and Adacel groups:

Subjects will retain their subject numbers as in the 106316 study.

For the subjects in the Control group:

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

Section 5.2.2 Allocationof treatment

Numberingof supplies

The numbering of supplies within blocks will be performed at GSK Biologicals, using MATerial Excellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

5.2.2.2 Trearment allocation to the subject

5.2.2.2.1 Study group and treatment number allocation

There will be no randomization of subjects into groups in this study. The subjects in this study will be allocated to the same groups as in the vaccination study 106316. Subjects will be allocated a new treatment number, but will retain the same subject number as in the 106316 study (Boostrix and Adacel groups),or subject numbers will be assigned sequentially (for the subjects in the Control group).

The central randomisation system on internet (SBIR) will be used at the investigator site to track enrolment at Year 8 i.e. to confirm or to cancel the vaccination and to give the treatment number associated with the vaccination.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

After obtaining the signed and dated informed consent form from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon identifying the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the dose.

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- ***27-37 years: ~25.4%***
- ***38-57 years: ~35.5%***
- ***58-72 years: ~39.1%***

The number of the administered treatment must be recorded in the eCRF on the Vaccine Administration form.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

Section 5.3 Method of blinding

This study will be conducted in an open manner.

Investigators will be provided with the identification of subjects with low immunogenicity results (see Section 5.7.2).

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

Section 5.4 General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

Section 5.5 Outline of study procedures

Table 3 List of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 *AND 7*[1] ~~Year 10~~ *Year 8* ~~10 years~~ *8 years* following *Boostrix/ Adacel* vaccination *Administration of Boostrix vaccine*	
				Visit 6	*Visit 7*
Informed consent ***for persistence follow-up***	●	●	●	●[3]	
Informed consent for vaccination				●	
Check inclusion criteria	●	●	●	●[3]	
Check exclusion criteria				●	
Check elimination criteria	●	●	●	●[3]	●
Collect demographic data[2]				●	
Medical history				●	
Vaccination history				●[3]	
Pre-vaccination body temperature				●	
Recording of administered treatment number				●	
Urine Pregnancy test[4]				●	
Check contraindications to vaccination				O	
Check warnings and precautions				O	
Blood sampling (~5 mL) for antibody determination	●	●	●	●[3]	●
Vaccination				●	
Distribution of diary card				O	
Daily recording of solicited adverse events during the 4-day Day (0-3) follow-up period post-vaccination, by subjects				●	
Recording of non-serious adverse events during the 31 day Day (0-30) follow-up period post-vaccination, by subjects				●	●
Return of diary cards					O
Diary card transcription by investigator					●
Record concomitant medication/vaccination	●	●	●	●[3]	●

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following *Boostrix/ Adacel* vaccination**	**VISIT 4** **Year 3** **3 years following *Boostrix/ Adacel* vaccination**	**VISIT 5** **Year 5** **5 years following *Boostrix/ Adacel* vaccination**	**VISITS 6 *AND 7*[1]** ~~**Year 10**~~ ***Year 8*** ~~**10 years**~~ ***8 years* following *Boostrix/ Adacel* vaccination** ***Administration of Boostrix vaccine***	
				Visit 6	***Visit 7***
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●	●
Recording of any large injection site reactions in the eCRF by the investigator[5]				●	
Reporting of SAEs				●	●
Recording of pregnancies				●	●
Record any intercurrent medical conditions					●
Study Continuation	●	●	●	● (NA for Control group)	
Study conclusion for persistence follow-up				●[3]	
Study Conclusion					●
Investigator sign-off on data for persistence follow-up				●[3]	
Investigator sign-off on data					●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ ***is used to indicate a study procedure that does not require documentation in the individual eCRF.***
[1]Applicable to Control, Boostrix and Adacel groups.
[2] DOB, gender, ethnicity and race for subjects in the Control group.
[3]These are the only study procedures applicable for subjects who refuse vaccination at Year 8 time point.
[4]Applicable to female subjects of childbearing potential only.
[5] Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions.

Section 5.3

Table 4 Intervals between study visits

Intervals between study visits for subjects in Boostrix and Adacel groups:

Visit	*Optimum* length of interval [1]	*Maximum interval allowed* [2]
Visit 6 (Tdap vaccination in parent study →Visit 6)	*8 years ± 3 months*	*8 years – 3 months to 8 years +6 months*
Visit 7 (Visit 6→ Visit 7)	*30-48 days (at least 30 days[3])*	*21-48[3] days*

[2] Subjects will not be eligible for inclusion in the ATP Year ~~X~~ *8* cohort for analysis if they make the study visit outside this interval.

[3]If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Intervals between study visits for subjects in Control group:

Visit	*Optimum* length of interval [1]	*Maximum interval allowed*[2]
Visit 6→Visit 7[3]	*30-48 days (at least 30 days[4])*	*21-48 days*

[1] Whenever possible the investigator should arrange study visits within this interval
[2] Subjects will not be eligible for inclusion in the ATP Year 8 cohort for analysis if they make the study visit outside this interval.
[3]For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[4] If subjects return for the visits prior to 30 days, they should take home the diary card and continue to record unsolicited safety information during the 31 day (Day 0-30) follow-up period post-vaccination and mail/send it upon completion. Investigators will make an attempt to retrieve diary cards from subjects who have not mailed/sent them in.

Section 5.6 Detailed description of study stages/visits

Procedures at Visits 3,4,5 and 6:

Persistence follow-up phase up to Year 8 time point:

The following study procedures are applicable to subjects who refuse vaccination at Year 8 time point :

- Study continuation at Years 3, 5~~,~~ and ***8*** ~~10~~.
- Study conclusion at Year ***8*** ~~10~~ ~~visit~~ (Visit 6-).

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- ***Obtain written informed consent from all subjects consenting for vaccination.***
- ***Check inclusion and exclusion criteria.***
- ***Check elimination criteria.***

- ***Check medical and vaccination history:***
  - ***Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination in the eCRF.***
  - ***Obtain the subject's vaccination history by interview and/or review of the subject's medical records and record any vaccine administration within 30 days prior to the study vaccination in the eCRF.***
- ***Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.***
- ***Treatment number allocation will be performed as described in Section 5.2.2.2. The number of each administered treatment must be recorded in the eCRF.***
- ***Contraindications, warnings and precautions to vaccination must be checked at the beginning of the vaccination visit. Refer to Sections 4.5 and 4.6 for more details.***
- ***Record pre-vaccination body temperature.***
- ***Collect approximately 5 mL of whole venous blood to provide at least 1.5 mL of serum for antibody testing, according to instructions in Appendix D.***
- ***Administration of a single dose of Boostrix vaccine for all study participants as described in Section 6.2. The criterio will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.***

Management of diary cards:

After vaccination, diary cards will be provided to the subject. The subjects will be instructed to record the following information in appropriate sections of the diary card:

- ***Record body (oral) temperature and any solicited local/general Aes on the day of vaccination and during the next 4 days, i.e. Day (0-3).***
- ***Any unsolicited Aes on the day of vaccination and during the 31 day, i.e. Day (0-30) follow-up period post vaccination.***
- ***Record any large injection site reactions (Refer to Section 8.5 for detailed explanation on the reporting of large injection site reactions).***
- ***Any concomitant medication/vaccination given after the administration of the study vaccine.***
- ***The subject will be instructed to return the completed diary card to the investigator at the next study visit.***

• ***The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious and also to contact the investigator in case of large injection site reactions.*** • ***Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9***. • ***Refer to Section 8.4 for procedures for the investigator to record Aes, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.*** ***Procedures at Visit 7:*** • ***The completed diary card will be collected and reviewed during discussion with the subject at this visit. Any unreturned diary cards will be sought from the holder through telephone call(s) or any other convenient procedure such as courier, home pick-up etc.***
• ***Collect approximately 5 mL of whole venous blood to provide at least 1.5 mL of serum for antibody testing, according to instructions in Appendix D.*** • ***Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.9.*** • ***Refer to Section 8.4 for procedures for the investigator to record Aes, SAEs, and pregnancies. Refer to Section 8.9 for guidelines on how to submit SAE and pregnancy reports to GSK Biologicals.*** • ***Record any pregnancies up to Visit 7 (post-vacc).*** • ***Study conclusion.***
Section 5.6.1 Activities at study conclusion ~~All subjects will be offered a booster dose of Td vaccine following the blood draw at the 10 year visit. A booster dose of Tdap may be offered instead if a second dose of Tdap is recommended at that time.~~ ***The investigator will:*** • ***review data collected to ensure accuracy and completeness.*** • ***complete the Study Conclusion section in the eCRF.*** ***At/after study completion, no post-trial commercial vaccines will be provided in this study.***

Section 5.7.2 Laboratory assays

Please refer to APPENDIX G for the address of the clinical laboratories used for sample analysis.

A sample of approximately 5 mL of whole venous blood, to provide ~~a minimum of~~ ***at least*** 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years~~,~~ and ***eight*** ~~ten~~ years [***at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups*** following study vaccination in 106316 study, ***and only at Visit 6 (pre-vacc) and Visit 7 (post-vacc) for the Control Group***. After blood centrifugation and serum separation, serum samples will be stored at approximately –20°C ***(alternatively at approximately -70°/80°C is also acceptable)*** until sent to the sponsor. Sera will be sent to Quest ***Diagnostics*** ~~Laboratories (~~***Valencia*** ~~Van Nuys~~, CA) and subsequently to GSK Biologicals, Belgium for the laboratory assays.

Antibodies against Diphtheria and Tetanus

Antibody concentrations against diphtheria and tetanus ***(anti-T and anti-D)*** will be measured by enzyme-linked immunosorbent assay (ELISA). The cut-off ***for seroprotection*** of both assays is 0.1 IU/mL [Camargo, 1984; Melville-Smith, 1983].

All samples with anti-D antibody concentrations < 0.1 IU/mL will be re-tested using the neutralization assay on VERO cells, which is more sensitive for low antibody concentrations and has a cut-off of 0.016 IU/mL mL ***(The Vero cell assay was re-validated in order to lower the cut-off and to evaluate the precision around the cut-off. The cut-off for the VERO test used for Year 5 was calculated at 0.004 IU/mL instead of 0.016 IU/mL and will be used for pre /post vaccination assays at Year 8. The study will consider anti-D concentrations greater than or equal to 0.01 IU/mL as the minimum level correlating with some degree of protection). The ELISA test will define the seroprotection status for the primary endpoint.***

Antibodies against PT, FHA and PRN

Antibody concentrations against the vaccine's pertussis components PT, FHA and PRN will be measured by ELISA ~~or multiplex (Luminex)~~ techniques~~.~~

Table 5 Laboratory assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off
Serological	anti-D	Neutralisation test on VERO cell**	In-house assay	IU/mL	0.016/***0.004****
Serological	anti-T	ELISA	In-house assay	IU/mL	0.1
Serological	anti-PT	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-FHA	ELISA or Luminex	In-house assay	EL.U./mL	5
Serological	anti-PRN	ELISA or Luminex	In-house assay	EL.U./mL	5

VERO cut off is ≥ 0.004 IU/mL for Year 5 and Year 8 time points

The investigator is encouraged to share the immunological assay results for low immunological assay results with the study subjects.

Low-result is defined as:

- ***Antibody concentrations < 0.01 IU/mL for diphtheria antigen and,***
- ***Antibody concentrations < 0.1 IU/mL for tetanus antigen.***

For the study subjects identified as low-responders, it remains the responsibility of the study investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

Section 5.5.3 Immunological read-outs

Table 6 Immunological read-outs for all subjects

Blood sampling time point		Marker
Timing	**Visit no.**	
Year 8	***6 and 7†***	***D****
		T
		PT
		FHA
		PRN
~~Year 10~~	~~6~~	~~D~~
		~~T~~
		~~PT~~
		~~FHA~~

~~All: All subjects enrolled at the long-term time point~~
†Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7, respectively to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
****VERO cell testing will be performed in subjects with an ELISA result of < 0.1 IU/mL.***

Samples will not be criterio with information that directly identifies the subjects but will be coded with the identification number for the subject ***(subject number).***

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- ***Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.***
- ***Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.***

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored ***for*** ~~up to~~ ~~15~~ ***a maximum of 20*** years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent.

Section 6 Investigational Product and Administration

Study vaccines in study 106316 were *Boostrix* and *Adacel*. ~~No additional vaccination will be given as part of this study.~~

Section 6.1 Study Vaccine

The study vaccine to be used at the Year 8 time point has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine

Treatment name	*Vaccine/product name*	*Formulation*	*Presentation*	*Volume*	*Number of doses*
Boostrix	*Tdap*	*Diphtheria toxoid: 2.5 Lf, Tetanus toxoid: 5 Lf , Pertussis toxoid: 8 µg, Filamentous hemagglutinin: 8 µg, Pertactin: 2.5 µg, Aluminum as $Al(OH)_3$:≤ 0.39 mg, Sodium chloride*	*Pre-filled syringes, Homogeneous turbid white suspension*	*0.5 mL*	*1*

Section 6.2 Dosage and Administration

In order to monitor enrolment and to control age distribution in the Control group, allocation of treatment number will be performed using SBIR. The application will ensure enrolment in the Control group is performed as per target age distribution (see section 4.1).

The vaccines will be administered as detailed in Table 8.

The vaccine is to be administered as a deep intramuscular injection into the deltoid muscle of the non-dominant arm*, i.e. in the left arm if the subject is right-handed or in the right arm if the subject is left-handed. Boostrix should in no circumstances be administered intravascularly.

In order to ensure proper intramuscular injection of the vaccine, a needle of 1 – 1 ½ inch length, 25 gauge will be used [ACIP, 2011b; Zuckerman, 2000].

*** Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.***

Table 8 Dosage and administration

Visit	*Dose*	*Vaccine*	*Route*	*Site*	*Side*
Visit 6[e]	*1*	*Tdap[a]*	*IM[b]*	*D[c]*	*Non-Dominant[d]*

a. Tdap= Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
b. Intramuscular (IM)
c. Deltoid (D)
d. Vaccination can be performed in dominant arm in case of medical indication preventing vaccination in the non-dominant arm, as judged by the investigator.
e. Applicable to the Control, Boostrix and Adacel groups. For the Control group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups.

The criterio will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Section 6.3 Storage

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Temperature excursions must be reported in degree Celsius.

Vaccines will be stored at the defined temperature range (i.e. 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature monitoring device will be used as a backup device and it will be opened in case of any temperature deviation (temperature outside the defined range, i.e. 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature monitoring device), if:

- ***proper functioning was demonstrated during the monitor's site evaluation,***
- ***if the system continues to work in case of a power failure, and***
- ***if the system is maintained regularly (e.g. once/year) as documented in the site files.***

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working after the alarm is activated.

It is also required to place a validated freezing point indicator close to the vaccines as a back-up device.

Any temperature excursion outside the range of 0.0 to +8.0°C impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix F.

Section 6.4 Treatment allocation and randomization

~~Not applicable~~ ***Subjects in the treatment groups- Boostrix, Adacel and Control will be analyzed as separate groups and will receive a dose of Tdap vaccine (Boostrix) at Year 8 time point.***

It is anticipated that approximately 1100 subjects (733 subjects from Boostrix group and 367 from Adacel group in the primary study) would return for the Year 8 vaccination visit. Approximately 367 subjects who were not part of the 106316 study will be enrolled in the Control group to receive the first dose of Tdap vaccine (Boostrix). All subjects will receive a single dose of Boostrix.

Section 6.5 Method of blinding and breaking the study blind

The study is an open study, since ***this is an extension of study 106316 which was un-blinded at the time of primary analysis. At Year 8 time point all the subjects in all the groups will receive a single dose of Boostrix.*** ~~There is no administration of vaccination in this study.~~

Section 6.6 Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix F for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF, in SBIR and on the vaccine accountability form.

Section 6.7 Packaging

Vaccination phase at Year 8 time point, refer to Appendix F.

Section 6.8 Vaccine accountability

Vaccination phase at Year 8 time point, refer to Appendix F

Section 6.9 Concomitant medication/treatment

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point :

At each study visit, the investigator should question the subject about any medications ~~taken.~~ ***/product taken and vaccination received by the subject***.

Any treatments and/or medications specifically contraindicated (e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within ***three months*** prior to any study blood sampling) are to be recorded with the generic name for the medication, medical indication, total daily dose, route of administration, and start and end dates of treatment. ~~Refer to Section 4.4.~~

Any Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier administered at any time after vaccination in the 106316 study, is to be recorded with the trade name, route of administration, and date of administration. ~~Refer to Section 4.4.~~

Vaccination phase at Year 8 time point:

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of the dose of study vaccine and ending up to next study visit after the dose of study vaccine are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered within three months prior to study vaccination or at any time during the study period are to be recorded with the generic name for the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, and start and end dates of treatment. Refer to Sections 4.3 and 4.4.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine and ending 31 days (Day 0-30) after the dose of study vaccine is to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [Oral temperature < 99.5°F] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

During the period starting with administration of each dose of study vaccine and ending 31 days (Day 0-30) after each dose of study vaccine, concomitant medication administered for the treatment of an AE must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form/ SAE screens in the eCRF, as applicable. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study (i.e. from Visit 6 through Visit 7) must be recorded in the eCRF.

Section 8 Adverse events and Serious adverse events

Section 8 Adverse events and Serious adverse events

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

~~The investigator is responsible for the detection and documentation of events meeting the criteria and definition of serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting SAEs, as detailed in this section of the protocol.~~

Section 8.1 Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- ***Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.***
- ***New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.***
- ***Signs, symptoms, or the clinical sequelae of a suspected interaction.***
- ***Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).***
- ***Significant failure of expected pharmacological or biological action.***
- ***Signs, symptoms temporally associated with vaccine administration.***
- ***Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).***

Aes to be recorded as endpoints (solicited Aes) are described in Section 8.6. All other Aes will be recorded as UNSOLICITED Aes.

Examples of an AE DO NOT include:

- ***Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.***
- ***Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).***
- ***Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.***

Aes may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. Aes to be recorded as endpoints (solicited events) are described in Section 8.5. All other Aes will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- ***Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).***

Section 8.2 Definition of a serious adverse event

A ~~serious adverse event (~~SAE~~)~~ is any untoward medical occurrence that

Hospitalization for elective treatment of a pre-existing condition ***(known or diagnosed prior to informed consent signature)*** *that did not worsen from baseline is not considered an AE.*

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza ***like illness****, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

Section 8.3 Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Section 8.3 Clinical laboratory parameters and other abnormal assessments qualifying as *adverse events or* serious adverse events

In absence of diagnosis, ~~***A***~~***a***bnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as ***AE or*** SAE~~s~~ if they meet the definition of ***an AE or*** SAE, ~~as defined in~~ ***(Refer*** to Section***s 8.1 and*** 8.2***)***. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as ***Aes or*** SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Section 8.4 Time period, frequency and method of detecting adverse events, serious adverse events and pregnancies

Section 8.4 Time period, frequency and method of detecting *adverse events*, serious adverse events *and pregnancies*

Persistence follow-up phase up to Year 8 time point:

The following criteria are applicable to subjects who refuse vaccination at Year 8 time point :

Because subjects are not being vaccinated as part of the ***time points Year 1, 3 and 5*** ~~study protocol~~, investigators are not required to specifically solicit SAEs.

In case this electronic system for reporting SAEs does not work or after ***removal of write access*** ~~freezing~~ of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Vaccination phase at Year 8 time point:

All Aes occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to riter international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the receipt of study vaccine and will end 31 days (Day 0-30) following administration of the dose of study vaccine for each subject. See Section 8.9 for instructions for reporting pregnancies.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 9.

Table 9 Reporting periods for adverse events, serious adverse events and pregnancies

Event	*Pre-vacc (consent obtained)*	*Vaccination*	*4 days (Day 0-3) post-vacc*	*31 days (Day 0-30) post-vacc*
				Study conclusion
Solicited local and general Aes including large injection site reactions				
Unsolicited Aes				
Aes/SAEs leading to withdrawal from the study				
SAEs				
SAEs related to study participation or concurrent GSK medication/vaccination				
Pregnancies				

Pre-vacc.: pre-vaccination; Post-vacc.: post-vaccination.

The investigator will inquire about the occurrence of Aes/SAEs at every visit during the study and throughout the follow-up phase as appropriate.

All Aes either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. Aes not previously documented in the study will be recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. Refer to Section 6.9.

Section 8.5 Solicited adverse events

The following local (injection-site) Aes will be solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

N.B. If subjects observe any large injection site reaction (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), they will be asked to contact study personnel and to visit the investigator's office and/or home visit for evaluation as soon as possible. The investigator will record detailed information describing the adverse event on a specific large injection site reaction in the eCRF.

Table 11 Solicited general adverse events

The following general Aes will be solicited:

Fatigue
Fever
Gastrointestinal symptoms †
Headache

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

Section 8.6 Evaluating adverse events and serious adverse events

Section 8.6 Evaluating *adverse events and* serious adverse events

~~This section is only applicable if an investigator becomes aware of an SAE that warrants notification of the sponsor.~~

Section 8.6.1 ***Active questioning to detect adverse events and serious adverse events***

As a consistent method of soliciting Aes, the subject should be asked a non-leading question such as:

"Have you felt different in any way since receiving the vaccine or since the previous visit?"

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Section 8.6.2 Assessment of intensity

The intensity scale for assessment of intensity for solicited symptoms in adults is presented in Table 12.

Table 12 Intensity scales for solicited symptoms in adults

Adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	~~Absent~~ ***None***
	1	~~Painful on touch~~ ***Mild: Any pain neither interfering with nor preventing normal every day activities.***
	2	~~Painful when limb is moved~~ ***Moderate: Painful when limb is moved and interferes with every day activities.***
	3	~~Pain that prevents normal activity~~ ***Severe: Significant pain at rest. Prevents normal every day activities.***
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in ~~°C /~~ °F
Headache	0	Normal
	1	***Mild:*** Headache that is easily tolerated
	2	***Moderate:*** Headache that interferes with normal activity
	3	***Severe:*** Headache that prevents normal activity
Fatigue	0	Normal
	1	***Mild:*** Fatigue that is easily tolerated
	2	***Moderate:*** Fatigue that interferes with normal activity
	3	***Severe:*** Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	***Mild:*** Gastrointestinal symptoms that are easily tolerated
	2	***Moderate:*** Gastrointestinal symptoms that interfere with normal activity
	3	***Severe:*** Gastrointestinal symptoms that prevent normal activity

~~*Fever is defined as: rectal temperature ≥38°C (100.4°F) / axillary temperature ≥37.5°C (99.5°F) / oral temperature ≥37.5°C (99.5°F) / tympanic temperature on oral setting ≥37.5°C (99.5°F) / tympanic temperature on rectal setting ≥38°C (100.4°F).~~ ****Fever is defined as temperature ≥ 99.5°F for oral, axillary or tympanic route, or ≥100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.***

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

0	***:***	***Absent***
1	***:***	***≤ 20 mm***
2	***:***	***> 20 mm and < 50 mm***
3	***:***	***≥ 50 mm***

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		Oral
0	***:***	***< 99.5°F***
1	***:***	***≥ 99.5°F and ≤ 100.4°F***
2	***:***	***> 100.4°F and ≤ 102.2°F***
3	***:***	***> 102.2°F***

~~The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for SAEs reported during the study.~~ ***The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited Aes (including SAEs) recorded during the study.***

The intensity of each ***AE*** recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An ***AE*** ~~SAE~~ which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An ***AE*** ~~SAE~~ which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An ~~S~~AE which prevents normal, everyday activities. (In adults, such an ***AE*** ~~SAE~~ would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as Grade 3. ~~Grade 3 is a category utilized for rating the intensity of an event; ***Aes*** and SAEs can be assessed as Grade 3~~

Section 8.6.3 Assessment of causality

The definitions for "NO" and "YES" have been written in such a way that all events that have been attributed a "NO" can be pooled with events which in the primary vaccination study were determined to be "not related" or "unlikely to be related" to vaccination. Those events that are attributed a "YES" can be pooled with those events that in the past were determined to have a "suspected" or "probable" relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each ***AE/***SAE.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general Aes to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other Aes should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product ?

NO	***:***	***There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.***
YES	***:***	***There is a reasonable possibility that the vaccine contributed to the AE.***

Non-serious and serious Aes will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 for definition of serious adverse event), ***additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.***~~it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.~~

~~Other possible contributors include:~~ ***Possible contributing factors include***:

Section 8.7 Medically attended visits

Section 8.7 Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if they received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

Section 8.8 Follow-up of adverse events, serious adverse events, pregnancies and assessment of outcome

Section 8.8 Follow-up of *adverse events,* serious adverse events, *pregnancies* and assessment of outcome

After the initial ***AE/***SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

In case the electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until the end of the study.

All Aes documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visit/contact until 30 days after the last vaccination.

~~All SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits.~~

Investigators will follow-up subjects:

- with SAEs ***or subjects withdrawn from the study as a result of an AE*****;** until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the ***AE or*** SAE.

Outcome of any ***non-serious AE occurring during the 31 days (Day 0-30) follow-up period post-vaccination (i.e. unsolicited AE)*** **or any** SAE reported during the entire study will be assessed as:

Follow-up of pregnancies

Pregnant subjects will be followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the SAE report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

Section 8.9 Prompt reporting of serious adverse events and pregnancies to GSK Biologicals

Section 8.9 Prompt reporting of serious adverse events *and pregnancies* to GSK Biologicals

In case the electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Section 8.9.1 Time frames for submitting serious adverse event reports *and pregnancies* to GSK Biologicals

Because subjects are not being vaccinated as part of the study protocol ***at the Year 1, 3 and 5 time points***, investigators are not required to specifically solicit SAEs ***in the persistence follow-up phase***. However, if an investigator becomes aware of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316 ***or in case of vaccination phase at Year 8***, the investigator will complete and submit relevant information on the SAEs in the SAE screens in eCRF **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS.** Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information ***(Refer Table 13).***

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after ~~freezing~~ ***removal of write access*** of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting.

Pregnancies that occur in the time period defined in Section 8.4 will be reported promptly to GSK within the timeframes described in Table 13, once the investigator becomes aware of the pregnancy.

Table 13 Timeframes for submitting serious adverse event, pregnancy and other event reports to GSK Biologicals

Type of Event	*Initial Reports*		*Follow-up of Relevant Information on a Previous Report*	
	Timeframe	*Documents*	*Timeframe*	*Documents*
SAEs	*24 hours**	*electronic SAE report*	*24 hours**	*electronic SAE report*
Pregnancies	*2 weeks**	*electronic pregnancy report*	*2 weeks**	*electronic pregnancy report*
** Timeframe allowed after receipt or awareness of the information.*				

Section 8.9.2 Completion and transmission of serious adverse event reports to GSK Biologicals

~~When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 24 hours as outlined in Section 8.9.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator, and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.~~

~~When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.9.1.~~

~~In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.9.1.~~

~~In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.~~

Section 8.9.2.1 Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

Section 8.9.2.2 Updating of SAE or pregnancy information after removal of write access of the subject's eCRF

When additional SAE or pregnancy information is received after removal of write access of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 13.

GSK Biologicals Medical Monitor: PPD ~~MD~~ PPD
Office: PPD
Cell: PPD
Fax: PPD

~~GSK Biologicals Clinical Safety Physician: PPD MD~~
~~Office: PPD~~
~~Cell: PPD~~

GSK Biologicals Clinical Safety Physician:
PPD ***MD***
Office: PPD
Cell: PPD

Section 8.9.3 Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

Section 8.10 Regulatory reporting requirements for serious adverse events

~~The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.~~

~~An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.~~

Section 8.11 Post-study adverse events and serious adverse events

~~A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.4. Investigators are not obligated to actively seek SAEs in former study participants.~~

~~However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.~~

~~After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.~~

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 9. Investigators are not obligated to actively seek Aes or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

Section 8.12 Pregnancy

Persistence follow-up phase up to Year 8 time point:

The following criteria is applicable to subjects who refuse vaccination at Year 8 time point :

Because subjects are not being vaccinated as part of ~~this study protocol~~ ***the time points at Year 1, 3 and 5***, investigators are not required to specifically solicit information regarding pregnancy or outcomes of pregnancy in female subjects. Subjects who are pregnant at the time of a study visit ***during the time points at Year 1, 3 and 5*** should not be excluded from the visit on the basis of their pregnancy.

Vaccination phase at Year 8 time point:

Female subjects who become pregnant after the vaccination may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on a electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.9 and 8.9.1:

- ***Spontaneous pregnancy loss, including:***
  - ***spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)***
  - ***ectopic and molar pregnancy***
  - ***stillbirth (intrauterine death of fetus after 22 weeks of gestation).***

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- ***Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).***
- ***Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.***

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.9.2. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Section 8.13 Treatment of adverse events

Section 8.13 Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

Section 9.2 Subject withdrawal

Subjects who are withdrawn because of ~~S~~SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as a result of an SAE***/ AE*** until resolution of the event (see Section 8.1).

Section 9.2.1 Subject withdrawal from the study

From an analysis perspective, a withdrawal from the study is any subject who was not available for the contact foreseen in the protocol at a given persistence time point. Subjects may participate in each persistence time point independent of other persistence time points. For example, a subject who does not participate in the Year 1 antibody persistence analysis may be approached for participation in the 3, 5~~,~~ and ***8***~~10~~ year persistence analyses.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

- Consent withdrawal, not due to an adverse event*****

****In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.***

Subjects who are withdrawn from the study because of SAEs/Aes must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.8).

Section 10.1 Primary endpoint

Section 10.1 *Co*-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ~~≥ 0.016 IU/mL~~ ***≥ 0.01 IU/mL (VERO)*** and anti-T antibody concentrations ≥ 0.1 IU/mL ***(ELISA)*** in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and ***8***~~10~~ years following ***first Tdap*** vaccination.
- ***Immunogenicity with respect to components of the study vaccine at Year 8 time point.***
  - ***Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.***
  - ***Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.***
  - ***Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.***

Section 10.2 Secondary endpoints

- Subjects with anti-~~pertussis toxoid (~~PT~~)~~, anti-~~filamentous hemagglutinin (~~FHA~~)~~, and anti-~~pertactin (~~PRN~~)~~ antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years~~,~~ and ***8~~10~~*** years following ***first Tdap*** vaccination.

- ~~Anti-D concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~

- ~~Anti-T concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~

- ~~Anti-PT concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~

- ~~Anti-FHA concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~

- ~~Anti-PRN concentration for each subject at the time of analysis in the *Boostrix* and *Adacel* groups.~~

- ***Immunogenicity with respect to components of the study vaccine at the Year 8 time point.***
  - ***Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.***
  - ***Booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the definition of booster response).***

  **** Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.***

- ***Solicited local and general symptoms.***
  - ***Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.***
  - ***Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.***

- ***Unsolicited adverse events.***
  - ***Occurrence of unsolicited Aes during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.***
- ***Serious adverse events.***
  - ***Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.***

Section 10.3 Estimated sample size

No sample size is calculated for ***the time points Year 1, 3 and 5*** ~~this study~~. All subjects who received vaccination in study 106316 will be eligible for enrolment in this study

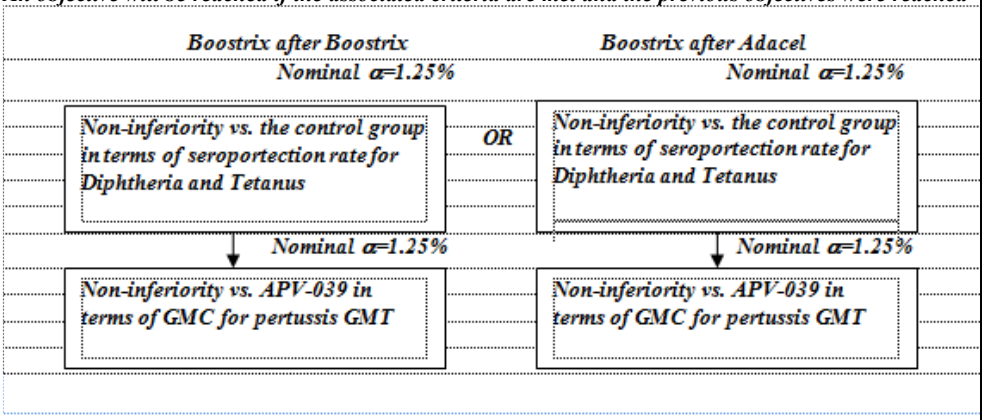
~~With a total of 2284 enrolled subjects in primary study 106316, it is expected approximately 1941 subjects will be present for the 1 year time point, 1402 subjects for the 3 year time point, 1013 subjects for the 5 year time point, and 449 subjects for the 10 year time point, assuming a 15% attrition rate per year.~~

It is estimated that around 1100 subjects (733 subjects from Boostrix group and 367 subjects from Adacel group in the primary study) would return for Year 8 study. Around 367 subjects are to be recruited for the Control group to receive the first dose of Tdap vaccine (Boostrix). Assuming 80% of enrolled subjects will be evaluable, this gives 586 evaluable subjects in Boostrix group, 293 evaluable subjects in Adacel group, and 293 evaluable subjects in Control group.

Section 10.3.1 Control on type 1 error

This study is designed to assess independently non-inferiority of Boostrix group to the Control group, and non-inferiority of Adacel group to the Control group. To control the overall type I error below 2.5%, a Bonferroni adjustment is used, i.e., type I error allowed for each non-inferiority assessment is 1.25% (one-sided). In addition to further control misinterpretation related to multiple primary objectives, a hierarchy procedure will be used as described in Figure 1.

Figure 1 Sequence for evaluating the study objectives in order to control the overall type I error below 2.5%



Section 10.3.2 Power computation

With 293 evaluable subjects in the Adacel group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Adacel group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Adacel group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 88.91%. (See Table 14 and Table 15 respectively).

With 586 evaluable subjects in the Boostrix group and 293 evaluable subjects in the Control group, the power to conclude non-inferiority of Boostrix group to the Control group in terms of anti-D, anti-T seroprotection rates and non-inferiority of Boostrix group to Infanrix group in study APV-039 in terms of anti-PT, anti-FHA and anti-PRN GMC simultaneously would be 97.87 %. (See Table 16 and Table 17 respectively).

Table 14 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to anti-D and anti-T seroprotection rate

	Reference values		*Power* to reject H0: LL of 97.5%CI of difference <- 10%*
Endpoint (antibody concentration >0.1 IU/mL)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)*	*Non-inferiority criterion Difference(2nd dose- first dose)*	*293 (Boostrix following Adacel) 293 (First Boostrix)*
Anti-D	*98.2%*	*LL of 97.5% CI ≥ -10%*	*>99.99%*
Anti-T	*99.6%*	*LL of 97.5% CI ≥ -10%*	*>99.99%*
*Overall power***			*>99.99%*

**Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.*
***Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.*

Table 15 Power to demonstrate non-inferiority of Boostrix following Adacel to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		*Power* to reject H0: LL of 97.5%CI of GMC ratio (Boostrix/Infanrix) < 0.67*	
Endpoint (GMCs)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix)*	*APV-039 Infanrix*	*N in APV-039 (TVC)*	*N =293 in Adacel+Boostrix*
Anti-PT	*0.480*	*0.306*	*2884*	*99.99%*
Anti-FHA	*0.422*	*0.370*	*685*	*99.99%*
Anti-PRN	*0.710*	*0.413*	*631*	*88.93%*
*Overall power***				*88.91%*

**Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$ (0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.*
***Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.*

Table 16 Power to demonstrate non-inferiority of a second dose of Boostrix following the first dose of Boostrix with respect to anti-D and anti-T seroprotection rate

	Reference values		Power* to reject H0: LL of 97.5%CI of difference <- 10%
Endpoint (antibody concentration >0.1 IU/mL)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)	Non-inferiority criterion Difference(2nd dose- first dose)	586 (Boostrix following Boostrix) 293 (First Boostrix)
Anti-D	98.2%	LL of 97.5% CI ≥ -10%	>99.99%
Anti-T	99.6%	LL of 97.5% CI ≥ -10%	>99.99%
Overall power**			>99.99%

*Pass 2005, one-sided non-inferiority test for the difference of two independent proportions (Likelihood Score [Miettienen and Nurminen approach]), alpha=1.25%; non-inferiority margin=-10% power under alternative of equal proportions in both groups; LL= lower limit.
**Overall power is the probability to reject all two null hypotheses simultaneously, computed by subtracting the two type-II errors (beta) from 1.

Table 17 Power to demonstrate non-inferiority of Boostrix following Boostrix to Infanrix vaccine in APV-039 with respect to anti-PT, anti-FHA and anti-PRN GMCs

	Reference values (Standard Deviation of log10 transformed concentration)		Power* to reject H0: LL of 97.5%CI of GMC ratio (Boostrix/Infanrix) < 0.67	
Endpoint (GMCs)	DTPA 0.3 (BOOSTRIX)-007 (Boostrix)	APV-039 Infanrix	N in APV-039 (TVC)	N =586 in Boostrix+Boostrix
Anti-PT	0.480	0.306	2884	>99.99%
Anti-FHA	0.422	0.370	685	>99.99%
Anti-PRN	0.710	0.413	631	97.87%
Overall power**				97.87%

*Pass 2005, non-inferiority test on two independent means, alpha=1.25%; equivalence margin=$\log_{10}$(0.67), variance from DTPA 0.3 (BOOSTRIX)-007 was considered as common variance for both groups, power under alternative of equal means in both groups; LL= lower limit.
**Overall power is the probability to reject the primary objective and all three null hypotheses simultaneously, computed by subtracting the three type-II errors (beta) from 1.

Section 10.4 Study cohorts to be evaluated

Section 10.4.1 **Year X (1, 3, 5, *8,* ~~10~~) cohort**

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination.

Section 10.4.2 **According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5,~~10~~) cohort**

The ATP Year X (1, 3, 5,~~10~~) cohort will include all subjects from Year X (1, 3, 5,~~10~~) cohort who ***were*** is in the ATP cohort for analysis of immunogenicity in 106316 study and who ***did*** ~~have~~ not ***meet*** the following elimination criteria.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ ~~0.5~~ ***20*** mg/~~kg~~/day. Inhaled and topical steroids are allowed).

~~**ATP Complete Year X (1, 3, 5, 10) cohort**~~

~~The ATP Complete Year X (1, 3, 5, 10) cohort will include all subjects who belong to the According-To-Protocol (ATP) Year X and all previously defined yearly ATP cohorts.~~

Section 10.4.3 Additional cohorts defined for Year 8 analysis

Section 10.4.3.1 Total Vaccinated Cohort (TVC) at Year 8

The TVC will include all subjects with a study vaccine administration dose documented:

- ***A safety analysis based on the TVC will include all vaccinated subjects.***
- ***An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.***

Section 10.4.3.2 ATP cohort for analysis of safety at Year 8

The ATP cohort for analysis of safety at Year 8 time point will include all eligible and vaccinated subjects.

- ***Who have received the dose of study vaccine.***
- ***For whom administration site of study vaccine is known.***
- ***Who did not receive a vaccine leading to elimination from an ATP analysis as listed in Section 6.9.***

Section 10.4.3.3 ATP cohort for analysis of immunogenicity at Year 8 (ATP Year 8)

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- ***Who comply with the procedures and intervals defined in the protocol (refer to Section 5.5 and Table 4).***
- ***Who do not meet any of the criteria for elimination from an ATP analysis (refer to Section 4.4) during the study.***
- ***For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after Year 8 vaccination.***

Section 10.5 Derived and transformed data

- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA) ~~or ≥ 0.016 IU/mL~~ and anti-T antibody concentrations ≥ 0.1 IU/mL in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and ***8 years*** ~~10~~ following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ 5 EL.U/mL in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and ***8***~~10~~ years following vaccination will be derived to evaluate the first secondary objective.
- The ~~geometric mean antibody concentrations (~~GMCs~~)~~ of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and ***8*** years ~~10~~ after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

Booster responses to be considered for Year 8 time point:

- ***Traditional Booster response to D and T antigens is defined as:***
  - ***for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and***
  - ***for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL): an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***
- ***Traditional Booster response to PT, FHA and PRN antigens is defined as:***
  - ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL, one month after vaccination;***
  - ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
  - ***for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.***
- ***Alternative Booster response to D and T antigens is defined as:***
  - ***for initially seronegative subjects (pre-vaccination concentration below cut-off: < 0.1 IU/mL): antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL) one month after vaccination, and***
  - ***for subjects with pre-vaccination concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***
  - ***for subjects with pre-vaccination concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-vaccination concentration, one month after vaccination.***
  - ***Subjects with pre-vaccination concentration ≥ 6.0 IU/mL are not evaluable for vaccine response.***

- ***Alternative Booster response to PT, FHA and PRN antigens defined as:***
  - ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL: antibody concentration ≥ 20 EL.U/mL one month after vaccination;***
  - ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 10 EL.U/mL: antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
  - ***for subjects with pre-vaccination antibody concentration ≥ 10 EL.U/mL and < 60 EL.U/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-vaccination concentration, one month after vaccination.***
  - ***for subjects with pre-vaccination antibody concentration ≥ 60 EL.U/mL : at least 1.5 fold increase in antibody concentration from the pre-vaccination concentration, one month after vaccination.***

Handling of missing data:

Immunogenicity:

- ***For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.***

Reactogenicity and Safety:

- ***For a given subject and the analysis of solicited symptom during the 4 day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).***
- ***For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.***
- ***For summaries reporting both solicited and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.***

Section 10.6 Final analyses

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5~~,~~and Year ***8*** ~~10~~) on cleaned data obtained through ***each*** Year X. A clinical study report (CSR) will also be written following each analysis.

Section 10.6.1 Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination, ***time since last DT vaccination,*** gender, ethnicity and race) of each study cohort (Year 1, Year 3, Year 5 and Year ***8*** ~~10~~) will be tabulated.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5~~,~~ or ~~***8***10~~) cohort ***and*** in the ATP Year X (1, 3, 5~~,~~ or ***8***~~10~~) cohort ~~and in the ATP complete Year X (1, 3, 5, and 10) cohort~~ will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, ***8***~~10~~) (in years) will be summarized using descriptive statistics.

Section 10.6.2 Analysis of *persistence* ~~immunogenicity~~

The primary analysis will be based on the ATP ***cohort for analysis of immunogenicity*** Year X ~~cohort~~ ***(1, 3, 5, 8)***.

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥ 0.01~~6~~ IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with exact 95% CI, will be calculated by group.

In addition, at Year X (1, 3, 5, ***8~~,~~*** ~~10~~) visit:

- the distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves ***(RCC)*** by group.

Comparability between Groups:

Exploratory analyses

- For anti-D antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group – *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA ~~or ≥ 0.016 IU/mL by VERO cell assay when~~ ***or*** anti-D concentrations ***≥0.01 IU/mL by VERO*** ~~< 0.1 IU/mL by ELISA~~), Year X (1, 3, 5, ***8~~,~~*** ~~10~~) after vaccination will be calculated.

- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (*Boostrix* group – *Adacel* group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, ***8,*** ~~10~~) after vaccination will be calculated.
- ***For anti-PT, anti-FHA and anti-PRN antibody responses, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 5 EL.U/mL by ELISA, Year X (1, 3, 5, 8) after vaccination will also be calculated.***

Section 10.6.3 Analysis of immunogenicity at booster dose

The following analyses will be carried out after Year 8 vaccination primarily on the ATP cohort for analysis of immunogenicity at Year 8. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC at Year 8 will be performed to complement the ATP analysis

Within groups assessment

For each group and each antigen:

- ***Seropositivity/seroprotection rate at pre-vaccination, one month post-vaccination will be calculated with exact 95% Cis.***
- ***GMCs or GMTs at pre-vaccination, one month post-vaccination will be tabulated with 95% Cis.***
- ***Booster response rate one month post-vaccination will be calculated with exact 95% Cis.***
- ***Antibody concentrations/titres distribution at pre-vaccination and one month post-vaccination will be displayed using RCC.***

Between groups assessment

- ***For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.***
- ***For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm$_{10}$ transformation of the concentrations.***

Exploratory between group assessment

- ***For anti-D, anti-T antibody response, the two-sided 95% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm$_{10}$ transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.***
- ***For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Boostrix group and Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm$_{10}$ transformation of the concentrations. The pre-vaccination status in study 106316 will be used as co-variable.***
- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) will be calculated.***

Sensitivity analysis

A complementary analysis will be carried out in order to evaluate the robustness of GMT/GMC results with respect to drop-out from the parent study (106316). More specifically multiple imputation techniques will be used to estimate the seropositivity and seroprotection rates and GMC/GMT that would have been observed if all subjects had been enrolled in this study. The imputation of missing data will account for the correlation between results from previous study and this study.

In addition, within group assessment for the ATP analysis of immunogenicity at Year 8 will be performed separately for each level of the age stratum (Subjects age at Year 8 vaccination will be classified into three categories, 27-37 years old, 38-57 years old and 58-72 years old).

Section 10.6.4 Analysis of Safety

Persistence follow-up phase up to Year 8 time point:

No safety analysis will be performed for this study. If GSK is informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

Vaccination phase at Year 8 time point:

The primary analysis will be based on the TVC at Year 8. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 8 is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the treatment groups by solicited local and general symptom terms, and, for unsolicited Aes, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per 32.9°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

The percentage of subjects who reports at least one report of an unsolicited adverse event classified by MedDRA during the 31 day (Day 0-30) follow-up period after vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, Aes resulting in a medically attended visit and for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

In addition, safety analysis for TVC at Year 8 will be performed separately for each level of the age stratum (Subjects age at Year 8 vaccination will be classified into three categories, 27-37 years old, 38-57 years old and 58-72 years old).

Section 10.6.5 Statistical methods

- ***The exact Cis for a proportion within a group will be computed using SAS, [Clopper, 1934].***
- ***The standardized asymptotic 95% CI or 97.5% CI for the group difference in proportion will be based on Method 6 as published by Newcombe [Newcombe, 1998].***
- ***The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.***

Section 10.7 Reporting of final analysis

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5~~,~~ and Year 8 ~~10~~) as available and reported separately. ***At Year 8 time point immunogenicity and safety of vaccine administration will be reported.***

Section 12 References

~~CDC. Bacterial Vaccine Preventable Diseases Branch. National Immunization Program. *Pertussis Surveillance Report (provisional).* 2004:2/23/05.~~

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Appendix B Administrative matters

IV Remote Data Entry Instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

~~Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.~~

~~Specific instructions for use of RDE will be included in the training material provided to the investigational site.~~

V *Study* Monitoring by GSK Biologicals

~~To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.~~

~~These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF/ RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.~~

GSK will monitor the study to verify that, amongst others, the:

- ***Data are authentic, accurate, and complete.***
- ***Safety and rights of subjects are being protected.***
- ***Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.***

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

VI ~~Archiving of Data~~ ***Record retention***

Following closure of the study, the investigator must maintain all site study records in a safe and secure location ***(except for those required by local regulations to be maintained elsewhere)***. ~~The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff.~~ ***The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff***. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must ~~assure~~ ***ensure*** that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that ~~an acceptable quality control process exists for making these reproductions~~ ***there is an acceptable quality control procedure in place***.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to ~~that~~ ***a particular*** site for the study, as dictated by ICH GCP ~~E6 Section 4.9~~, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

IX Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

X Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

XI Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Appendix C Overview of recruitment plan

For the Control group:

- ***Approximately 367 subjects will be recruited to receive the first dose of Tdap vaccine (Boostrix) in this study.***
- ***The study will take place at multiple centers in the US.***
- ***The study duration per subject will be approximately one month.***
- ***The recruitment of subjects into the study will be performed using RDE.***
- ***Recruitment will be monitored by the site monitor.***

Appendix E Shipment of Biological Samples

Shipment of biological samples will be done directly from study sites to Quest Diagnostics, ~~Van Nuys~~ ***Valencia***, California.

Appendix F Vaccine supplies, packaging and accountability

1. Vaccine and/or other supplies

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- ***Boostrix in pre-filled syringes***

At least an additional 10% of the study vaccine will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject).

All pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:
The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each time point. Each label will contain the following information: study number, identification number for the subject (e.g. Subject number), sampling time point (e.g., post ri 3), timing (e.g., study Month 7).

Other supplies provided by GSK Biologicals:
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:

- ***tubes with screw caps for serum samples,***
- ***racks and cardboard boxes for the tubes of serum.***

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site from local country medical department to investigational site

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : PPD
E-mail: PPD

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

4. Vaccine accountability

At all times the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP WWD-1102, used and unused vaccine syringes should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine syringes are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP WWD-1102.

If no processes for destruction of unused clinical trial supplies are in place in the local GSK Biologicals site in the US, the unused supplies must be returned to GSK according to the instructions given by the GSK Biologicals responsible staff (in accordance with SOP-NPD-7200).

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to GSK for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Appendix G Clinical laboratories

Table 18 GSK Biologicals laboratories

Laboratory	***Address***
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	***Biospecimen Reception – B7/44 Rue de l'Institut, 89 – B-1330 Rixensart – Belgium***
GSK Biologicals Global Vaccine Clinical Laboratory, North America-Laval	***Biospecimen Reception – Clinical Serology 525 Cartier blvd West – Laval – Quebec – Canada – H7V 3S8***
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	***Avenue Fleming, 20 – B-1300 Wavre – Belgium***

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 3

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and evaluation of immunogenicity and safety of an additional dose of *Boostrix*, when administered at Year ***9***.
Amendment number:	Amendment 3
Amendment date:	Amendment 3 Final: 10 December 2014
Coordinating author:	PPD Scientific Writer

Rationale/background for changes:

- Following feedback from the Centre for Biological Research and Evaluation (CBER), the following changes have been made to this protocol:
  - A co-primary objective has been added to demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.
  - The interval between study visits for Year 8 time-point has been updated to include the maximum number of subjects from the previous time-points.
  - The statistical section has been updated to include the power computation for the new objective.
  - Exclusion criteria for subjects in the Boostrix and Adacel groups as well as Control group has been updated.
  - The text regarding documentation of non-participation of subjects who decline to participate in this long-term study has been removed.
  - Measurement of temperature for fever has been amended.
- The list of contributing authors for this amendment was updated.
- Typographical errors have been corrected. These changes have not been reflected as amended text.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Throughout the protocol, the year 8 time point has been amended to year 9 time point to reflect the change in study start. This change can be seen in bold italics within the protocol.

Synopsis

Co-primary objectives

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, ***Boostrix*** (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  - ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).***

[$] Booster response to D and T antigens is defined as:

- ***for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and***
- ***for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.***

[$] ***Booster response to PT, FHA and PRN antigens is defined as:***

- ***for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;***
- ***for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and***
- ***for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination***.

Secondary objectives

- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.

****Refer to co-primary objective for the definition of booster response*** ~~Booster response to D and T antigens is defined as:~~

- ~~for initially seronegative subjects (pre-vaccination concentration below cut-off < 0.1 IU/mL) antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 0.4 IU/mL), one month after vaccination, and~~
- ~~for initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/mL) an increase in antibody concentrations of at least four times the pre-vaccination concentration, one month after vaccination.~~

~~*Booster response to PT, FHA and PRN antigens is defined as:~~

- ~~for subjects with pre-vaccination antibody concentration < 5 EL.U/mL antibody concentration ≥ 20 EL.U/mL, one month after vaccination;~~
- ~~for subjects with pre-vaccination antibody concentration ≥ 5 EL.U/mL and < 20 EL.U/mL antibody concentration at least four times the pre-vaccination concentration, one month after vaccination; and~~
- ~~for subjects with pre-vaccination antibody concentration ≥ 20 EL.U/mL antibody concentration at least two times the pre-vaccination concentration, one month after vaccination.~~

Synopsis Table 1: Study groups foreseen in the study

Study Groups	***Number of subjects***	***Age (Min – Max) (age unit)***
Boostrix Group	Approximately 733	2~~*8*7~~ years-7~~*3*2~~ years
Adacel Group	Approximately 367	2~~*8*7~~ years-7~~*3*2~~ years
Control Group	Approximately 367	2~~*8*7~~ years-7~~*3*2~~ years

Number of subjects

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

Co-primary endpoints

- ***Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination (Refer to the co-primary objectives for the definition of booster response).***

Section 1 Introduction

All pregnant women and postpartum mothers irrespective of previous Tdap vaccination history should ~~take~~ ***receive*** a Tdap vaccine ***at 27-36 weeks gestation during each pregnancy*** [CDC, 2012c; CDC, 2012d].

Section 1.2 Rationale for the study

~~The data from this study is planned to support the indication of *Boostrix* as a second dose of Tdap vaccine.~~

Research suggests that immunity to pertussis wanes approximately 5-10 years after vaccination [Olin, 2003; Tan, 2005; Wendelboe, 2005] ***and recent data shows that protection starts to wane within three years*** [***Koepke, 2014].*** Subjects in study 106316 were followed up for three years after vaccination. The persistence data demonstrates antibodies against vaccine antigens through the first ~~three~~ ***five*** years after vaccination [Weston, 2011; ***GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5)***].

As per advice from ***the*** Centre for Biologics and Research Evaluation (CBER), an additional treatment group acting as control is also added at this time point and the subjects enrolled in the Control group will receive Boostrix as a first dose of Tdap vaccine.

Section 2.1: Co-Primary Objectives

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, ***Boostrix*** (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of *Infanrix* vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.
- ***To demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.***

  The criterion for meeting the above objective is defined as:

  – ***One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).***

[$]Refer to Section 10.5 for the definition of booster response.

Section 2.2: Secondary Objectives

- To explore the potential difference in terms of ***alternate*** booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.

****Refer to Section 10.5 for the definitions of booster response and alternate booster response.***

Section 3 Study design overview

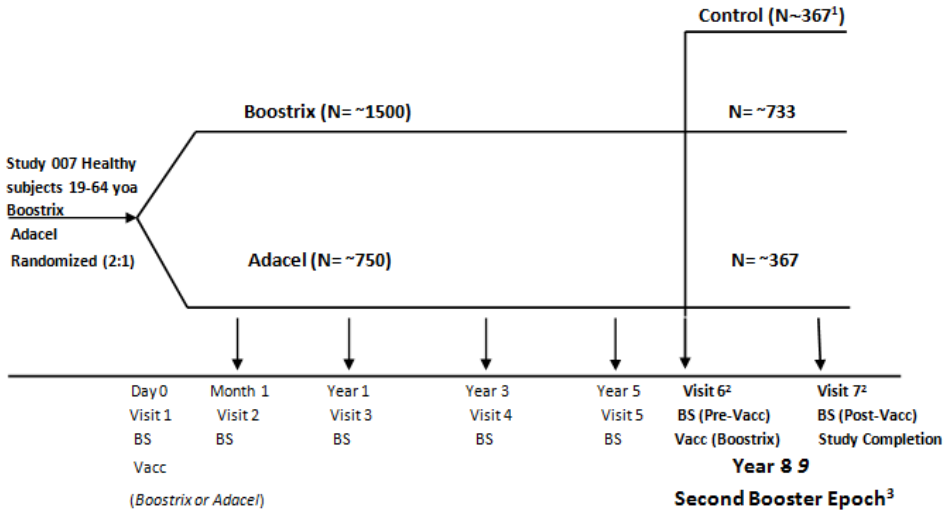


Table 1 Study groups foreseen in the study

Study Groups	*Number of subjects*	*Age (Min – Max) (age unit)*
Boostrix Group	Approximately 733	2~~8~~7 years-7~~3~~2 years
Adacel Group	Approximately 367	2~~8~~7 years-7~~3~~2 years
Control Group	Approximately 367	2~~8~~7 years-7~~3~~2 years

- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects ***participating in the vaccination phase*** at Visit 6 i.e. at Year ***9*** (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7).

Section 4: Study cohort

All subjects who received vaccination in study 106316 will be eligible for enrolment in this study. ~~At the time of initiation of the study, the investigator will~~ ***~~attempt to~~*** ~~contact ALL subjects who received vaccination in study 106316~~ ***~~and indicated approval of further contact for study related activities at their last attended study visit.~~*** ~~If at the time of initiation of the long-term study, any subject declines participation, refusal will be documented~~ ***~~in the study continuation screen in eCRF.~~*** ~~The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.~~Subjects who did not participate at a particular persistence time point are still eligible to be included at later time points.

In addition, approximately 367 subjects will be newly enrolled at Year ***9*** time point as Control group to receive the first dose of Tdap vaccine (*Boostrix*). Enrolment of subjects in the Control group will be stratified by age to ensure similar age distribution to that of Boostrix and Adacel groups:

- 2***~~8~~7***-3***~~8~~7*** years: ~25.4%
- 3***~~9~~8***-5***~~8~~7*** years: ~35.5%
- 5***~~9~~8***-7***~~3~~2*** years: ~39.1%

Section 4.2 Inclusion criteria

Vaccination phase at Year ***9*** applicable for subjects in the Boostrix and Adacel groups only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix and Adacel groups:

Vaccination phase at Year ***9*** applicable for subjects in the Control group only:

The following criterion is applicable to subjects willing to consent to vaccination at Year 9 time point in the Control group only:

Vaccination phase at Year ***9*** applicable for ALL subjects (Control, Boostrix and Adacel groups):

The following criteria are applicable to subjects willing to consent to vaccination at Year 9 time point in the Boostrix, Adacel and Control groups:

- Subjects within the age range of 2***~~8~~7***-7***~~3~~2*** years will be considered eligible to participate in this study in the Control group.

Section 4.3: Exclusion criteria for enrolment

The following criteria should be checked at the time of Year 8 vaccination time point. If any ***criteria are*** applicable, the subject must not be vaccinated in the study:

For subjects in the Boostrix and Adacel groups:

- ***Administration of Tdap vaccine since the last dose received in the study 106316.***
- ~~***Previous booster vaccination against diphtheria, tetanus or pertussis since the last dose received in the study 106316.***~~

For subjects in the Control group:

- Administration of Tdap ***(Boostrix or Adacel)*** vaccine at any time prior to ***the administration of Boostrix vaccine in this*** study ~~entry~~.

For ALL subjects (Control, Boostrix and Adacel groups):

- ***Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of Boostrix vaccine in this study.***
- ***Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.***
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

Section 4.4: Elimination criteria during the study

- Administration of a ~~Td or Tdap~~ vaccine ~~or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier~~ ***during the study period against diphtheria, tetanus or pertussis during the study period (Visit 6 through Visit 7).***
- ***Administration of*** any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier ***during the study period (Visit 6 through Visit 7).***
- Diphtheria and/or tetanus and/or pertussis disease diagnosed during the study period ***(Visit 6 through Visit 7)***.
- Any confirmed or suspected immunosuppressive or immuno-deficient condition based on medical history and physical examination (no laboratory testing is required) diagnosed during the study period ***(Visit 6 through Visit 7)***.

Section 4.5 Contraindications to vaccination

- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

Section 5.2.2.2.1 Study group and treatment number allocation

Enrolment of subjects in the Control group will be stratified by age to ensure age distribution will be similar to that of Boostrix and Adacel groups:

- 2***8***~~7~~-3***8***~~7~~ years: ~25.4%
- 3***9***~~8~~-5***8***~~7~~ years: ~35.5%
- 5***9***~~8~~-7***3***~~2~~ years: ~39.1%

Section 5.5 Outline of study procedures

Table 3 List of study procedures

Timing **Sampling time point**	**VISIT 3** **Year 1** **1 year following Boostrix/ Adacel vaccination**	**VISIT 4** **Year 3** **3 years following Boostrix/ Adacel vaccination**	**VISIT 5** **Year 5** **5 years following Boostrix/ Adacel vaccination**	**VISITS 6 AND 7[1]** **Year *9*** ***9* years following Boostrix/ Adacel vaccination** **Administration of Boostrix vaccine**	
				Visit 6	**Visit 7**
Study Continuation	•	•	•	***O*** (NA for Control group)	•
Study Conclusion ***for vaccinated groups***					•

[2] ~~DOB~~ ***Year of birth***, gender, ethnicity and race for subjects in the Control group.

Table 4 Intervals between study visits

Visit	***Optimum* length of interval** [1]	***Maximum interval allowed*** [2]
Visit 3 (Tdap vaccination in parent study→Visit 3)	1 year ± 5 weeks	1 year ± 5 weeks
Visit 4 (Tdap vaccination in parent study →Visit 4)	3 years ± 5 weeks	3 years ± 5 weeks
Visit 5 (Tdap vaccination in parent study →Visit 5)	5 years ± 5 weeks	5 years ± 8 weeks
Visit 6 (Tdap vaccination in parent study →Visit 6)	~~8 years ± 3 months~~ ***9 years – 3 months***	~~8 years – 3 months to 8 years +6 months~~ ***9 years +6 months***
Visit 7 (Visit 6→ Visit 7)	30-48 days (at least 30 days[3])	21-48[3] days

Section 5.6 Detailed description of study stages/visits

Procedures at Visits 3, 4, 5 and 6:

Persistence follow-up phase up to Year ***9*** time point:

- Study continuation at Years 3~~,~~ ***and*** 5~~, and ***9***~~.
- Collect approximately 5 mL of whole venous blood to provide ~~a minimum~~ ***approximately*** ~~of~~ 1.5 mL of serum for antibody testing, according to instructions in Appendix D at all study visits.

The following study procedures are applicable to subjects who receive vaccination including the Control group (vaccination phase):

- Collect approximately 5 mL of whole venous blood to provide ~~at least~~ ***approximately*** 1.5 mL of serum for antibody testing, according to instructions in Appendix D.

Procedures at Visit 7:

- Collect approximately 5 mL of whole venous blood to provide ~~at least~~ ***approximately*** 1.5 mL of serum for antibody testing, according to instructions in Appendix D.

Section 5.7.2 Laboratory assays

A sample of approximately 5 mL of whole venous blood, to provide ~~at least~~ ***approximately*** 1.5 mL of serum will be obtained at each of the following long-term time points: one year, three years, five years and ~~eight~~ ***nine*** years [at Visit 6 (pre-vacc) and Visit 7 (post-vacc)] for the Boostrix and Adacel groups following study vaccination in 106316 study, and only at (pre-vacc) and Visit 7 (post-vacc) for the Control group.

Section 6.4 Treatment allocation and randomization

All subjects ***participating in the vaccination phase*** will receive a single dose of *Boostrix*.

Section 6.9 Concomitant medication/treatment

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [~~Oral~~ Temperature ***by any route*** < ***100.4*** ~~99.5~~ °F. ***The preferred route for recording temperature in this study will be oral***] and any other symptom, to prevent fever from occurring).

Section 8.4 Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies

For subjects who receive vaccination at the Year 9 time point: All AEs occurring within 31 days (Day 0-30) following administration of the dose of vaccine must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Section 8.6.2 Assessment of intensity

Table 12 Intensity scales for solicited symptoms in adults

*Fever is defined as temperature ≥ ~~99.5~~ ***100.4***°F ***by any route*** ~~for oral, axillary or tympanic route, or ≥ 100.4°F for rectal route~~. The preferred route for recording temperature in this study will be oral.

The maximum intensity of fever will be scored at GSK Biologicals as follows:

		~~Oral~~
0	:	~~< 99.5°F~~ ***<100.4°F***
1	:	~~≥ 99.5°F and ≤ 100.4°F~~ ***≥100.4°F to ≤102.2°F***
2	:	~~> 100.4°F and ≤ 102.2°F~~ ***>102.2°F to ≤104.0°F***
3	:	~~> 102.2°F~~ ***> 104.0°F***

Section 10.1: Co-primary endpoints

- ***Immunogenicity with respect to components of the study vaccine at Year 9 time point.***
  - ***Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.***

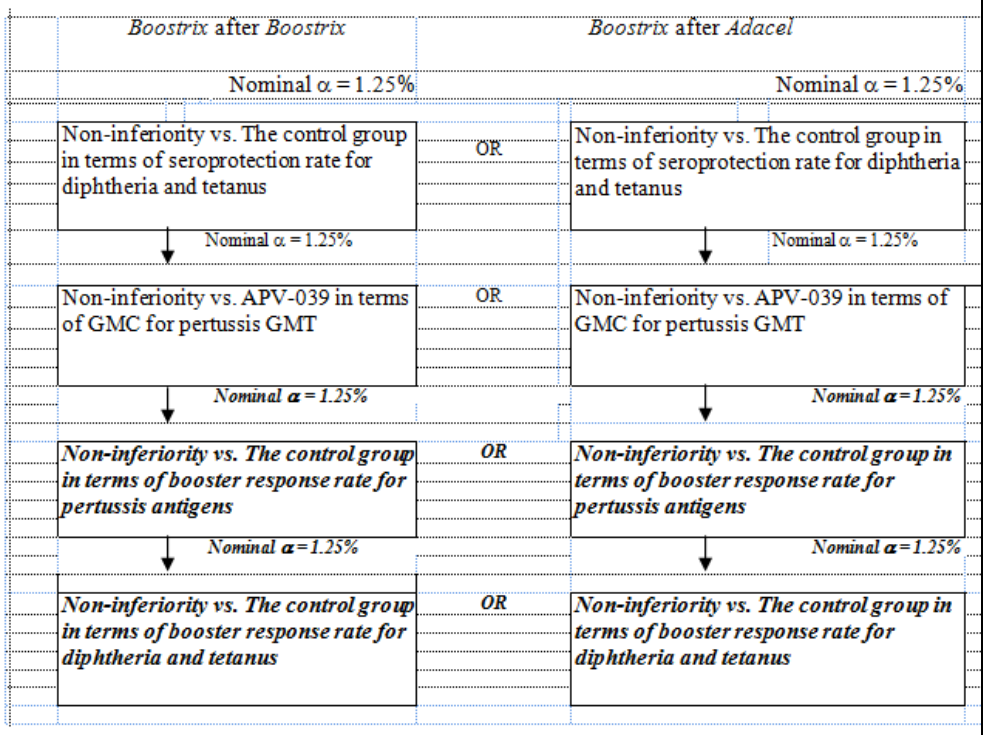
Refer to Section 10.5 for the definition of booster response.

Section 10.2: Secondary endpoints

- Immunogenicity with respect to components of the study vaccine at the Year 8 time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - ***Alternate*** ~~***B***~~***b***ooster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 10.5 for the ***definitions of booster response and alternate booster response***).

Section 10.3.1 Control on type I error

The figure 1 showing Sequence for evaluating the study objectives in order to control the overall type I error below 2.5% was updated to include the new co-primary objective.



Section 10.3: Power computation

As shown in Table 16, the power to demonstrate non-inferiority of Adacel group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be very low (4%). In other words, there is a big chance that non-inferiority would not be demonstrated for one or more of the antibodies.

Table 16 Power to demonstrate non-inferiority of Boostrix following Adacel to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

	Reference values		*Power* to reject H0: LL of 97.5%CI of difference <- 10%*
Endpoint (booster response rate)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)*	*Non-inferiority criterion Difference(2nd dose- 1st dose)*	*293 (Boostrix following Adacel) 293 (First Boostrix)*
Anti-D	*77.6%*	*LL of 97.5% CI ≥ -10%*	*74.19%*
Anti-T	*48.8%*	*LL of 97.5% CI ≥ -10%*	*57.51%*
Anti-PT	*77.2%*	*LL of 97.5% CI ≥ -10%*	*73.64%*
Anti-FHA	*96.9%*	*LL of 97.5% CI ≥ -10%*	*99.99%*
Anti-PRN	*93.2%*	*LL of 97.5% CI ≥ -10%*	*98.81%*
*Overall power***			*4.14%*

**Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.*
***Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.*

As shown in Table 19, the power to demonstrate non-inferiority of Boostrix group to the Control group in terms of booster response rate in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies simultaneously was estimated to be 48%. It is likely that non-inferiority might not be demonstrated for one or more of the antibodies.

Table 19 Power to demonstrate non-inferiority of Boostrix following Boostrix to the first dose of Boostrix with respect to Anti-D, Anti-T, Anti-PT, Anti-FHA and Anti-PRN booster response rate

	Reference values		*Power* to reject H0: LL of 97.5%CI of difference <- 10%*
Endpoint (booster response rate)	*DTPA 0.3 (BOOSTRIX)-007 (Boostrix group)*	*Non-inferiority criterion Difference(2nd dose- 1st dose)*	*586 (Boostrix following Boostrix) 293 (First Boostrix)*
Anti-D	*77.6%*	*LL of 97.5% CI ≥ -10%*	*88.89%*
Anti-T	*48.8%*	*LL of 97.5% CI ≥ -10%*	*71.39%*
Anti-PT	*77.2%*	*LL of 97.5% CI ≥ -10%*	*88.45%*
Anti-FHA	*96.9%*	*LL of 97.5% CI ≥ -10%*	*>99.99%*
Anti-PRN	*93.2%*	*LL of 97.5% CI ≥ -10%*	*99.96%*
*Overall power***			*48.69%*

**** Pass 2012, non-inferiority test on proportions, alpha=1.25%; non-inferiority margin=10% power under alternative of equal proportions in both groups; LL= lower limit.***
*****Overall power is the probability to reject all five null hypotheses simultaneously, computed by subtracting the five type-II errors (beta) from 1.***

Section 10.5 Derived and transformed data

- ~~Traditional~~ Booster response to D and T antigens is defined as:
- ~~Traditional~~ Booster response to PT, FHA and PRN antigens is defined as:

Section 10.6.3: Analysis of immunogenicity at booster dose

~~Between groups assessment~~ ***Comparability between Groups - confirmatory analyses:***

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using an analysis of variance (ANOVA) model on the logarithm_{10} transformation of the concentrations.
- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.***

~~Exploratory between group assessment~~ ***Comparability between Groups - exploratory analyses:***

- ***For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.***

In addition, within group assessment for the ATP analysis of immunogenicity at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***~~7~~-3***8***~~7~~ years old, 3***9***~~8~~-5***8***~~7~~ years old and 5***9***~~8~~-7***3***~~2~~ years old).

Section 10.6.4 Analysis of safety

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity of grade 3 (occurrence of fever will be reported per ~~3~~2***0.9***°F cumulative increments), as well as for solicited general events with relationship to vaccination. All solicited local adverse events are considered to be causally related.

In addition, safety analysis for TVC at Year ***9*** will be performed separately for each level of the age stratum (Subjects age at Year ***9*** vaccination will be classified into three categories, 2***8***~~7~~-3***8***~~7~~ years old, 3***9***~~8~~-5***8***~~7~~ years old and 5***9***~~8~~-7***3***~~2~~ years old).

Section 12 References

GlaxoSmithKline Biologicals Clinical Study Report 110084 (Tdap-0.3-009 Ext: 007 Year 5). A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).

Koepke R, et al, Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis 2014; 210:942–53].

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change 2

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Protocol title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and evaluation of immunogenicity and safety of an additional dose of *Boostrix*, when administered at Year 9.
Administrative change number:	Administrative change 2
Administrative change date:	Administrative change 2 Final: 03 February 2015
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:
For the persistence only group, serious adverse events occurring due to study related procedures will be collected. This is noted in section 8.4 "Time period, frequency, and method of detecting adverse events, serious adverse events and pregnancies", but due to a typographical error, it has not been noted in section 5.5 "Outline of study procedures". This administrative change has been prepared to correct this typographical error in Table 3 "List of study procedures" as seen under section 5.5 "Outline of study procedures".

Amended text has been indicated in *bold italics* in the following sections:
Section 5.5 Outline of study procedures
Table 3 List of study procedures

Timing Sampling time point	VISIT 3 Year 1 1 year following *Boostrix/ Adacel* vaccination	VISIT 4 Year 3 3 years following *Boostrix/ Adacel* vaccination	VISIT 5 Year 5 5 years following *Boostrix/ Adacel* vaccination	VISITS 6 AND 7[1] Year *9* *9* years following *Boostrix/ Adacel* vaccination Administration of *Boostrix* vaccine	
				Visit 6	Visit 7
Recording of SAEs related to study participation or to a concurrent GSK medication/vaccine				●[3]	●
Reporting of SAEs				●[3]	●

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of approval	17 April 2007 (Final)
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatory approval	
Sponsor signatory:	Leonard Friedland, MD, Director, Clinical Research and Development and Medical Affairs, Vaccines.
Signature:	PPD
Date:	5/10/07

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Appendix F Administrative change to the protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer
Rationale/background for changes: This administrative change is being done to reflect a change of study personnel. **Amended text has been included in *bold italics* in the following section:**	
US Safety Contact for Faxing/Reporting SAE Information	
Fax to: US Safety Contact, GSK Biologicals Fax: PPD Tel: PPD	
US Study Contacts for Concerns Relating to an SAE	
~~GSK Biologicals Medical Monitor:~~ PPD ~~MD~~ ~~Office:~~ PPD ~~Cell:~~ PPD ***GSK Biologicals Medical Monitor:*** PPD ***MD*** ***Office:*** PPD ***Cell:*** PPD ***Fax:*** PPD	
GSK Biologicals Clinical Safety Physician: PPD MD Office: PPD Cell: PPD	

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Tdap-0.3-009 Ext:007
Administrative Change 1

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

eTrack Study Number and Abbreviated Title	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Protocol title:	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Administrative Change number:	Administrative Change 1
Administrative Change date:	14 April 2009
Coordinating author:	PPD Scientific Writer

Approved by:

Senior Manager, Global Clinical R&D, Paediatric and Hepatitis Vaccines, GlaxoSmithKline Biologicals

PPD

PPD

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 10)
IND number	BB-IND-8461
Date of amendment approval	Amendment 1 Final: 09 November 2010
Detailed Title	A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007).
Sponsor signatories	
	Karin Hardt, Director, Clinical Development, Lead, DTP Combination Vaccines, Global Vaccine Development, GSK Biologicals
Signature	PPD
Date	22/11/2010
	Francesca Ceddia, Vice President and Vaccine Development Leader (DTP Portfolio, Neisseria), Global Vaccine Development, GSK Biologicals
Signature	PPD
Date	22/11/2010

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Protocol Amendment 2 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles **(Amended: 18 February 2014)**	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***8)***
IND number	BB-IND-8461
Date of protocol amendment	Amendment 2 Final: 18 February 2014
Detailed Title **(Amended: 18 February 2014)**	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***8*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) ***and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 8.***
Sponsor signatory **(Amended: 18 February 2014)**	***Htay Htay Han, Director, Project Level Clinical and Research Development Lead, DTP Combination Vaccines and Rotavirus Vaccines***
Signature	PPD
Date	Mar 11, 2014

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Protocol Amendment 3 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Sponsor signatory	Narcisa Elena Mesaros, Project Level Clinical and Research Development Lead, Combination Vaccines, Global Vaccine Development
Signature	PPD PP (on behalf of Narcisa Mesaros)
Date	19 Dec. 2014

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Ronald L. Asher
Signature	PPD
Date	Jan 16. 2015

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Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Ronald L. Asher
Signature	PPD
Date	Jan 16. 2015

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	DONALD M. BRANDON, M.D.
Signature	PPD
Date	1-14-15

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Daniel H. Bruwer
Signature	PPD
Date	1-15-15

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Shane Glade Christensen, MD, FAAFP, CCRP
Signature	PPD
Date	1/12/2015

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Donna M. DeSantis, MD
Signature	PPD
Date	1/13/15

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Hugh D. Durrance
Signature	PPD
Date	3/31/15

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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	John Keith Earl, MD
Signature	PPD
Date	01/14/2015

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	John E. Ervin MD F.A.C.P, F.A.C.R.
Signature	PPD
Date	1-13-2015

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Darren Farnesi, MD
Signature	PPD
Date	3/31/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Thomas C. Fiel, DO
Signature	PPD
Date	1-15-15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
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Investigator name	Phillip M. Green, MD
Signature	PPD
Date	1/20/15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Stephen R Graham MD
Signature	PPD
Date	3/11/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	James A. Hedrick, MD
Signature	PPD
Date	3/3/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	LAURA L. HELMANN
Signature	PPD
Date	3-25-15

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Protocol Amendment 3 Final

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Dan C. Henry, MD, CCRP
Signature	PPD
Date	1/12/15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Katie Ann Julien, MD, CCRP
Signature	PPD
Date	1/12/15

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eTrack study numbers and *abbreviated titles (Amended:* 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	MURRAY A. KIMMEL, DO
Signature	PPD
Date	13 APR 2015

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Randle M. Bolick
Signature	PPD
Date	13 Mar 15

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eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year *9*)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and *9* years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year *9*.
Investigator name	Stephanie Johnson Powell, MD
Signature	PPD
Date	10 Mar 2015

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

eTrack study numbers and abbreviated titles (Amended: 10 December 2014)	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year ***9***)
IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Ernie Riffer, MD
Signature	PPD
Date	PPD 1-12-15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	John Rubino MD
Signature	PPD
Date	11/12/2015

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Amendment 3 Final

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Donald R. Sislen, MD
Signature	PPD
Date	1/15/15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Gerald R. Shockey, MD
Signature	PPD
Date	1-13-15

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IND number	BB-IND-8461
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Investigator name	Mark A. Turner, MD
Signature	PPD
Date	3 MAR 15

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Jonathan Paul Wilson, DO
Signature	PPD
Date	22 JAN 2015

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IND number	BB-IND-8461
Date of protocol amendment	Amendment 3 Final: 10 December 2014
Detailed Title (Amended: 10 December 2014)	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year ***9***.
Investigator name	Duane G. Womboldt, MD, FACP, CPI
Signature	PPD
Date	06 Apr 2015

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Protocol Administrative Change 2 Sponsor Signatory Approval

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and ***9*** years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Sponsor signatory	Narcisa Elena Mesaros, Project Level Clinical and Research Development Lead, Combination Vaccines, Global Vaccine Development
Signature	PPD
Date	26 FEB 2015

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Protocol Administrative Change 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Ronald L. Asher
Signature	PPD
Date	march 10 2015

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IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	DONALD M. BRANDON, M.D.
Signature	PPD
Date	3-18-15

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IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Daniel W. Brune MD.
Signature	PPD
Date	3-9-15

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IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
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Investigator name	Shane Glade Christensen, MD, FAAFP, CCRP
Signature	PPD
Date	3/16/15

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IND number	BB-IND-8461
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Investigator name	Donna M. DeSantis, MD
Signature	PPD
Date	3/23/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
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Investigator name	Hugh D. Dorrance
Signature	PPD
Date	3/31/15

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IND number	BB-IND-8461
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Investigator name	John Keith Earl, MD
Signature	PPD
Date	3-11-2015

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

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IND number	BB-IND-8461
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Investigator name	John E. Ervin, M.D, F.A.C.P, F.A.C.R.
Signature	PPD
Date	3-10-15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

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IND number	BB-IND-8461
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Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Darren Farnesi, MD
Signature	PPD
Date	31-Mar-2015

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IND number	BB-IND-8461
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Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Thomas C. Fiel, DO
Signature	PPD
Date	3-10-15

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Investigator name	Phillip M. Green, MD.
Signature	PPD
Date	3/9/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
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Investigator name	Stephen D. Grubb, M.D
Signature	PPD
Date	3/11/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

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Investigator name	James A. Hedrick, MD
Signature	PPD PPD
Date	3/12/15

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Investigator name	LAURA L. HELMAN
Signature	PPD
Date	4-15-15

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eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
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Investigator name	Dan C. Henry, MD, CCRP
Signature	PPD
Date	3/02/15

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110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
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IND number	BB-IND-8461
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Investigator name	Katie Ann Julien, MD, CCRP
Signature	PPD
Date	3/9/15

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Investigator name	MURRAY A. KIMMEL, DO
Signature	PPD
Date	13 APR 2015

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Investigator name	Randle Middleton
Signature	PPD
Date	3-31-15

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Investigator name	Stephanie Johnson Powell, MD
Signature	PPD
Date	03/10/2015

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Investigator name	Ernie Riffer, MD
Signature	PPD
Date	PP 3-7-15

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Investigator name	John Rubino
Signature	PPD
Date	3/11/2015

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Investigator name	Gerald R. Shockey, MD
Signature	PPD
Date	3-9-15

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Investigator name	Donald R. Sislen, MD
Signature	PPD
Date	3/12/15

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IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Leslie M. Tharenos, MD, MPH
Signature	PPD
Date	9-19-16

- ----------Checksum----------!Ver.!Created On - -
e7a2d235af9753649d52130796dd424806819423 2.0 2/25/2015 10:11:52 AM - -
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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Mark A. Turner, MD
Signature	PPD
Date	10 MAR 15

For internal use only

----------Checksum----------!Ver.!Created On - -
e7a2d235af9753649d52130796dd424806819423 2.0 2/25/2015 10:11:52 AM - -
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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Jonathan Paul Wilson, DO
Signature	PPD
Date	09 MAR 2015

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- ----------Checksum----------!Ver.!Created On - -
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CONFIDENTIAL
110080, 110082, 110084, 110086 (Tdap-0.3-009 Ext:007 Y1, Y3, Y5, Y9)
Protocol Administrative Change 2 Final

eTrack study numbers and abbreviated titles	110080 (Tdap-0.3-009 Ext:007 Year 1) 110082 (Tdap-0.3-009 Ext:007 Year 3) 110084 (Tdap-0.3-009 Ext:007 Year 5) 110086 (Tdap-0.3-009 Ext:007 Year 9)
IND number	BB-IND-8461
Date of protocol administrative change	Administrative Change 2 Final: 03 February 2015
Detailed Title	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
Investigator name	Duane G. Wombolt, MD, FACP, CPI
Signature	PPD
Date	06 Apr 2015

For internal use only

- ----------Checksum----------!Ver.!Created On - -
e7a2d235af9753649d52130796dd424806819423 2.0 2/25/2015 10:11:52 AM - -
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Sample Case Report Form

Annotated Study Book for Study Design: TDAP-0.3-009 EXT:007 YEAR 9 (110086)

Study Design Version: 1.0

Sponsor: GlaxoSmithKline

Protocol: TDAP-0.3-009 EXT007 YR9(110086)

Generic Drug Name: Tdap vaccine

Trade Drug Name: Boostrix®

A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9.

Generated by Central Designer TM

October 28, 2015 8:05

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SCREENING (Screening)		
SCREENING		
1.* ✔	Please tick box to confirm CRF creation:	**[CRF_FLG]** *[A:Y]* ☐

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

TDAP-0.3-009 EXT:007 YEAR 9 (110086): ENROLLMENT (Enrollment)		
ENROLLMENT		
Primary study: 106316 (Tdap 0.3-007) Previous Study: 110084 (Tdap-0.3-009 Ext:007 Year 5) **Subject number will be same as in the primary study for BOOSTRIX AND ADACEL GROUPS ONLY.**		
1.* ✔	Subject Number: [Sub] Nr]	**[PID]** N9

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SUBJECT IDENTIFICATION (Subj ident)		
SUBJECT IDENTIFICATION		
1.* ✔	Please choose the subject group: [subject group]	**[VALUE]** *[A:1]* ◯ **[VACC]** Subjects who received study vaccination (Boostrix or Adacel) in study 106316 Did the subject agree to be vaccinated in this study? *[A:Y]* ◯ Yes *[A:N]* ◯ No *[A:2]* ◯ Control group to receive the first dose of Tdap vaccine
2.* ✔	Subject Number: [Subj Nr]	**[PID]** N9

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): DEMOGRAPHY (FOR NEW SUBJECTS) (Demog - new subj)

1.* ✔	Date of birth: [DOB]	**[DOB_RAW]** Req/Unk / Req (1940-2015)
2.* ✔	Gender: [Gender]	**[SEX]** *[A:M]* Male *[A:F]* Female
3.* ✔	Ethnicity: [Ethnicity]	**[ETHNIC]** *[A:1]* American Hispanic or Latino *[A:2]* Not American Hispanic or Latino
4.* ✔	Geographic Ancestry: [Geographic Ancestry]	**[RACE]** *[A:1]* African Heritage / African American *[A:2]* American Indian or Alaskan Native *[A:3]* Asian - Central/South Asian Heritage *[A:4]* Asian - East Asian Heritage *[A:5]* Asian - Japanese Heritage *[A:6]* Asian - South East Asian Heritage *[A:7]* Native Hawaiian or Other Pacific Islander *[A:8]* White - Arabic / North African Heritage *[A:9]* White - Caucasian / European Heritage *[A:99]* **[RACE_OTH]** Other, Specify: A40

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): DEMOGRAPHY (FOR SUBJECTS FROM PREVIOUS STUDY) (Demog - prev study subj)		
DEMOGRAPHY		
Primary study: 106316 (Tdap 0.3-007) **Subject number will be same as in the primary study for BOOSTRIX AND ADACEL GROUPS ONLY.**		
1.* ✔	Date of birth: [DOB]	**[DOB_RAW]** Req/Unk / Req (1940-2003)
2.* ✔	Gender: [Gender]	**[SEX]** *[A:M]* Male *[A:F]* Female

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): INFORMED CONSENT (IC)		
DATE OF VISIT		
1.* ✔	Date of visit: [DOV]	**[ACTRDATE]** Req / Req / Req (2015-2017)
INFORMED CONSENT		
I certify that Informed Consent has been obtained prior to any study procedure.		
2.* ✔	Informed Consent Date: [IC date]	**[CONS_DAT]** Req / Req / Req (2015-2017)
3.* ✔	Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for future research? (Type 4 tests) [Did the subject agree that her/his biological sample(s) may be used by GSK Biologicals for future research? (Type 4 tests)]	**[CONS_LAB_Q4]** *[A:Y]* Yes *[A:N]* No *[A:NA]* Not applicable

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
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PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): GENERAL MEDICAL HISTORY / EXAMINATION (Gen Med Hist)

GENERAL MEDICAL HISTORY / EXAMINATION

1.* ✔	Are you aware of any pre-existing conditions, signs or symptoms? [Are you aware of any pre-existing conditions, signs or symptoms having started before first study vaccination?]	**[MED_COND]** *[A:N]* ◯ No *[A:Y]* ◯ Yes -> Please give diagnosis and tick appropriate Past/Current box in the table below

	MedDRA SYSTEM ORGAN CLASS	Diagnosis	Past / Current?
2. ✔			

DIAGNOSIS Entry

Please report medication(s) as specified in the protocol and fill in the medication section.

2.1* ✔	MedDRA SYSTEM ORGAN CLASS: [MedDRA SYSTEM ORGAN CLASS]	**[DIAGTERM]** **[MEDHIST]**
2.2* ✔	Diagnosis: [Diagnosis]	**[DIAGNOSI]** A80
2.3* ✔	Past / Current? [Past / Current?]	**[DIAGSTAT]** *[A:P]* ◯ Past *[A:C]* ◯ Current

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: GENERAL MEDICAL HISTORY / EXAMINATION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
MEDHIST	String	Skin and subcutaneous tissue	1	SKINANDSUBCUTANEOUSTISSUE	DIAGTERM
		Musculoskeletal and connective tissue	2	MUSCULOSKELETALANDCONNECTIVETISSUE	
		Cardiac	3	CARDIAC	
		Vascular	4	VASCULAR	
		Respiratory, thoracic and mediastinal	5	RESPIRATORYTHORACICANDMEDIASTINAL	
		Gastrointestinal	6	GASTROINTESTINAL	
		Hepatobiliary	7	HEPATOBILIARY	
		Renal and urinary	8	RENALANDURINARY	
		Nervous system	9	NERVOUSSYSTEM	
		Eye	10	EYE	
		Ear and labyrinth	11	EARANDLABYRINTH	
		Endocrine	12	ENDOCRINE	
		Metabolism and nutrition	13	METABOLISMANDNUTRITION	
		Blood and lymphatic system	14	BLOODLYMPHATICSYSTEM	
		Immune system	15	IMMUNESYSTEM	
		Infections and infestations	16	INFECTIONSINFESTATIONS	
		Neoplasm benign, malignant and unspecified	17	NEOPLASMBENIGNMALIGNANTANDUNSPECIFIED	
		Surgical and medical procedures	18	SURGICALANDMEDICALPROCEDURES	
		Reproductive system and breast	19	REPRODUCTIVESYSTEMANDBREAST	
		Psychiatric	20	PSYCHIATRIC	
		Other	99	OTHER_99	

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): VACCINATION HISTORY (Vacc Hist)

BOOSTRIX AND ADACEL GROUP: Administration of Tdap vaccine since the last dose received in the study 106316. (In this case, subject will be ineligible for the study and exclusion criteria 7A must be ticked)
CONTROL GROUP: Administration of Tdap (Boostrix or Adacel) vaccine at any time prior to the administration of Boostrix vaccine in this study entry. (In this case, subject will be ineligible for the study and exclusion criteria 7b must be ticked)
BOTH: Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of Boostrix vaccine in this study entry. (In this case, subject will be ineligible for the study and exclusion criteria 8 must be ticked)

1.* ✔	Has the subject received any vaccination? [Has the subject received Td or Tdap vaccination?]	**[VACC_HIST_FLG]** *[A:Y]* ◯ Yes -> Please complete the following table *[A:N]* ◯ No *[A:U]* ◯ Unknown

	Vaccine name	Route	Date of administration
2. ✔			

2.1* ✔	Vaccine name: (Trade name is preferred) [Vaccine name]	**[CVACC_TRADNAME]** A60
2.2* ✔	Route: [Route]	**[CVACC_ROUTE]** **[MEDROUT_CVACC]**
2.3* ✔	Date of administration: [Date of administration]	**[CVACC_RDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018)

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: VACCINATION HISTORY

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
MEDROUT_CVACC	String	Inhalation	IH	Inhalation	CVACC_ROUTE
		Intradermal	ID	Intradermal	
		Intramuscular	IM	Intramuscular	
		Intranasal	IN	Intranasal	
		Intravenous	IV	Intravenous	
		Oral	PO	Oral	
		Parenteral	PE	Parenteral	
		Subcutaneous	SC	Subcutaneous	
		Sublingual	SL	Sublingual	
		Transdermal	TD	Transdermal	
		Other	OTH	OTHER_OTH	
		Unknown	UNK	Unknown	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): ELIGIBILITY CHECK (BOOSTRIX AND ADACEL GROUP) (Elig-vacc grp)

ELIGIBILITY CHECK

1.* ✔ Did the subject meet all the entry criteria? [Eligible]

[ELIGIBIL]

[A:Y] ○ Yes

[A:N] ○ **[INCL_EXCL_CRITERIA]**

No -> Tick all boxes corresponding to violations of any inclusion/exclusion criteria.

Do not enter the subject into the study if he/she failed any of the inclusion or exclusion criteria below.

[INCL_CRITERIA]
INCLUSION CRITERIA
Tick the boxes corresponding to any of the inclusion criteria the subject failed.

[A:1A]	☐	1a. All subjects who received study vaccination (Boostrix or Adacel) in study 106316 will be considered eligible to participate in this study.
[A:2]	☐	2. Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
[A:3]	☐	3. Written informed consent obtained from the subject for vaccination at Year 9 time point.
[A:4]	☐	4. Healthy subjects as established by medical history and clinical examination before entering into the study.
[A:5]	☐	5. Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy or ovariectomy or post menopause.
[A:6]	☐	6. Female subj of childbearing potential can be enrolled, if has practiced adequate contraception 30 days prior to vacc, has negative pregnancy test on day of vacc and has agreed to continue adequate contraception for 1 month after completion of vac dose.

[EXCL_CRITERIA]
EXCLUSION CRITERIA
Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[A:7A]	☐	7A. Administration of Tdap vaccine since the last dose received in the study 106316.
[A:8]	☐	8. Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of Boostrix vaccine in this study.
[A:9]	☐	9. Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).
[A:10]	☐	10. Chronic adm. (more than 14 days in total) of immunosupp or other immune-modifying drugs within 6 mons prior to V6 (pre-vacc). For corticosteroids: prednisone >= 20 mg/day or equiv.Inhaled and topical steroids are allowed
[A:11]	☐	11. Planned adm/adm of vacc not foreseen by study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).
[A:12]	☐	12. Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
[A:13]	☐	13. Hypersensitivity to latex.
[A:14]	☐	14. History of diphtheria, tetanus or pertussis diseases.
[A:15]	☐	15. Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.
[A:16]	☐	16. History of any neurological disorders or seizures.
[A:17]	☐	17. Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.
[A:18]	☐	18. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
[A:19]	☐	19. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
[A:20]	☐	20. Acute disease and/or fever at time of enrol, Fever: temp > =100.4 °F any route Pref. rout:oral, Subj with minor illness (refer to protocol)without fever may, be enrolled at the discretion of the investigator.
[A:21]	☐	21. Administration of immunoglobulins and/or any blood products within the three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).
[A:22]	☐	22. Pregnant or lactating female.
[A:23]	☐	23. Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.

RANDOMISATION/TREATMENT ALLOCATION

Treatment number of the subject should be provided here and replacement number should be provided on vaccine administration form

2.* ✔ Administered treatment number: [Treatment number]

[V_TRT]
N10

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
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PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): ELIGIBILITY CHECK (CONTROL GROUP) (Elig-Ctrl grp)

1.* ✔ Did the subject meet all the entry criteria? [Eligible]

[ELIGIBIL]

[A:Y] ◯ Yes

[A:N] ◯ **[INCL_EXCL_CRITERIA]**

No -> Tick all boxes corresponding to violations of any inclusion/exclusion criteria.

[INCL_CRITERIA]

INCLUSION CRITERIA

Tick the boxes corresponding to any of the inclusion criteria the subject failed.

[A:1B]	☐	1b.Subjects within the age range of 28-73 years will be considered eligible to participate in the control group in this study.
[A:2]	☐	2. Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
[A:3]	☐	3. Written informed consent obtained from the subject for vaccination at Year 9 time point.
[A:4]	☐	4. Healthy subjects as established by medical history and clinical examination before entering into the study.
[A:5]	☐	5. Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy or ovariectomy or post menopause.
[A:6]	☐	6. Female subj of childbearing potential can be enrolled, if has practiced adequate contraception 30 days prior to vacc, has negative pregnancy test on day of vacc and has agreed to continue adequate contraception for 1 month after completion of vac dose.

[EXCL_CRITERIA]

EXCLUSION CRITERIA

Tick the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[A:7B]	☐	7b. Administration of Tdap (Boostrix or Adacel) vaccine at any time prior to the administration of Boostrix vaccine in this study.
[A:8]	☐	8. Administration of any tetanus or diphtheria containing vaccine or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of Boostrix vaccine in this study.
[A:9]	☐	9. Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of study vaccine, or planned use during the study period, 31 days (Day 0-30).
[A:10]	☐	10. Chronic adm. (more than 14 days in total) of immunosupp or other immune-modifying drugs within 6 mons prior to V6 (pre-vacc). For corticosteroids: prednisone >= 20 mg/day or equiv.Inhaled and topical steroids are allowed
[A:11]	☐	11. Planned adm/adm of vacc not foreseen by study protocol in the period starting 30 days before and ending 30 days after the dose of vaccine, with exception of inactivated Influenza vaccine which is allowed throughout the study period, 31 days (Day 0-30).
[A:12]	☐	12. Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
[A:13]	☐	13. Hypersensitivity to latex.
[A:14]	☐	14. History of diphtheria, tetanus or pertussis diseases.
[A:15]	☐	15. Severe allergic reaction (e.g. anaphylaxis) after previous administration of any tetanus toxoid, diphtheria toxoid, or pertussis-antigen containing vaccines, or any component of Boostrix.
[A:16]	☐	16. History of any neurological disorders or seizures.
[A:17]	☐	17. Encephalopathy (e.g. coma, decreased level of consciousness, prolonged seizures) of unknown etiology occurring within seven days following previous vaccination with pertussis-containing vaccine.
[A:18]	☐	18. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
[A:19]	☐	19. Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
[A:20]	☐	20. Acute disease and/or fever at time of enrol, Fever: temp > =100.4 °F any route Pref. rout:oral, Subj with minor illness (refer to protocol)without fever may, be enrolled at the discretion of the investigator.
[A:21]	☐	21. Administration of immunoglobulins and/or any blood products within the three months preceding the dose of study vaccine or planned administration during the study period, 31 days (Day 0-30).
[A:22]	☐	22. Pregnant or lactating female.
[A:23]	☐	23. Female planning to become pregnant or planning to discontinue contraceptive precautions during the 31 day (Day 0-30) follow-up period post-vaccination.

RANDOMISATION/TREATMENT ALLOCATION

Treatment number of the subject should be provided here and replacement number should be provided on vaccine administration form

2.* ✔ Administered treatment number: [Treatment number]

[V_TRT]

N10

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): ELIGIBILITY CHECK (PERSISTENCE) (Elig-Persistence)

ELIGIBILITY CHECK (For subjects in Boostrix and Adacel Groups who refuse vaccination in this study)

1.* ✔	Did the subject meet all the entry criteria? [Eligible]	**[ELIGIBIL]** *[A:Y]* ◯ Yes *[A:N]* ◯ **[INCL_EXCL_CRITERIA]** No ->Tick all boxes corresponding to violations of any inclusion/exclusion criteria. **[INCL_CRITERIA]** **INCLUSION CRITERIA** Tick the boxes corresponding to any of the inclusion criteria the subject failed. *[A:1A]* ☐ 1a. All subjects who received study vaccination (Boostrix or Adacel) in study 106316 will be considered eligible to participate in this study. *[A:3]* ☐ 3. Written informed consent must be obtained from the subject prior to each study time point.

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

TDAP-0.3-009 EXT:007 YEAR 9 (110086): BLOOD SAMPLING FOR ANTIBODY DETERMINATION (Blood Samp)

BLOOD SAMPLE

1.* ✔	Has a blood sample been taken? [SER sample taken]	**[SAMPTAKE_SER]** *[A:Y]* ○ **[SAMPLE_DET_SER]** Yes -> **[SAMPRDAT_D]** Date of collection: Req / Req / Req (2015-2017) **[SAME_DATE]** Or tick box if date is the same as visit date *[A:Y]* ☐ **[REQ_NUM]** Requisition number: A9 *[A:N]* ○ No

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): URINE PREGNANCY TEST (preg test)

HCG URINE PREGNANCY TEST

1.* ✔	Has a urine sample been taken? [PRG sample taken]	**[SAMPTAKE_PRG]** *[A:Y]* ◯ **[SAMPLE_DET_PRG]** Yes -> **[SAMPRDAT_D]** Date of collection: Req / Req / Req (2015-2017) **[SAME_DATE]** Or tick box if date is the same as visit date *[A:Y]* ☐ **[RAWRES_PRG]** Pregnancy test result: *[A:NEG]* ◯ Negative *[A:POS]* ◯ Positive *[A:N]* ◯ No *[A:NA]* ◯ Not applicable

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: URINE PREGNANCY TEST

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
COMPONEN	String	Alanine Aminotransferase	ALAT01	ALAT01	COMPONEN_HID
		Albumin	ALB01	ALB01	
		Alkaline Phosphatase	ALKP01	ALKP01	
		Aspartate Aminotransferase	ASPT01	ASPT01	
		Total Bilirubin	BILI01	BILI01	
		Bilirubin Conjugated / Direct	BILI03	BILI03	
		Calcium	CA01	CA01	
		Chloride	CL01	CL01	
		Creatinine	CREA01	CREA01	
		Gamma Glutamyl Transferase	GGT01	GGT01	
		Glucose	GLUC01	GLUC01	
		Lactate Dehydrogenase	LDH01	LDH01	
		Magnesium	MG01	MG01	
		Potassium	K01	K01	
		Protein	PROT01	PROT01	
		Sodium	NA01	NA01	
		Urea Nitrogen	URNI01	URNI01	
		Activated Partial Thromboplastin Time	APTT01	APTT01	
		Basophils	BASO01	BASO01	
		Basophils/100 Leukocytes	BASO02	BASO02	
		Cells.CD4+	CD401	CD401	
		Eosinophils	EOSI01	EOSI01	
		Hematocrit	HEM01	HEM01	
		Hemoglobin	HGB01	HGB01	
		Lymphocytes	LYMP01	LYMP01	
		Monocytes	MONO01	MONO01	
		Neutrophils	NEU01	NEU01	
		Neutrophils.Band Form	NEU03	NEU03	
		Platelets	PLA01	PLA01	

PPD

		Prothrombin Time	PT01	PT01	
		Prothrombin Time.International Normalised Ratio	PT02	PT02	
		Red Blood Cells	RBC01	RBC01	
		White Blood Cells	WBC01	WBC01	
		Choriogonadotropin	HCG01	HCG01	
		C Reactive Protein	CRP01	CRP01	
METHOD	String	NA	NA	NA	METHOD_HID
SCALE	String	MULTI-RESULTS	MULTRE	MULTRE	SCALE_HID
		NARRATIVE	NAR	NAR	
		NOMINAL	NOM	NOM	
		ORDINAL	ORD	ORD	
		QUANTITATIVE	QN	QN	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): VACCINE ADMINISTRATION (Vacc adm)

PRE-VACC TEMPERATURE

1.* ✔ Pre-vaccination temperature:
[Pre-vacc temp]

[PRE_TEMP]
[PRE_TEMP]
Temperature (°F): xxx.x

[TEMP_ROUTE]
Route: *[A:A]* Axillary *[A:O]* Oral (preferred) *[A:R]* Rectal *[A:T]* Tympanic

VACCINE ADMINISTRATION

Boostrix Vaccine

2.* ✔ Has Study Vaccine been administered?
[Vaccinated]

[V_ADM]
[A:Y] **[VACC_DET_1VACC]**
[VIAL_TYP]
Yes -> *[A:S]* Study Vaccine
[A:R] **[V_TRT]**
Replacement vial -> Administered vial number: N10

[VACCRDAT]
Date of administration: Req / Req / Req (2015-2018)

[SAME_DATE]
Or tick box if date is the same as visit date *[A:Y]*

[P_AP]
Injection Site/Side/Route:
(Deltoid - Non-Dominant - IM)
[A:Y] According to protocol
[A:N] **[P_AP_DET]**
Not according to protocol -> **[P_APSIDE]**
Side: *[A:D]* Dominant *[A:ND]* Non Dominant

[P_APROUTE]
Route: *[A:IM]* Intramuscular *[A:SC]* Subcutaneous

[P_APSITE]
Site: *[A:1]* Deltoid *[A:3]* Thigh *[A:6]* Buttock

[VADM_COM]
If relevant, comment on administration:
A200

[A:N] **[VACC_REAS]**
No -> **[VACC_REAS]**
Please select the major reason for non administration:
[A:SAE] **[SAE_CASE]**
Serious Adverse Event -> Please complete a SAE Report and specify SAE Report No. N2

[A:AEX] **[AE_NB]**
Non-Serious Adverse Event -> Please complete Non-Serious Adverse Event section and specify AE No. N2

[A:OTH] **[V_OTH]**
Other, please specify (e.g.: consent withdrawal, Protocol violation, ...)
A100

[DECISION]
Please select who made the decision: *[A:I]* Investigator
[A:S] Subject

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: VACCINE ADMINISTRATION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable

VSORRESU	String	beats per minute	BPM	BPM	TEMP_UNIT_HID
		breaths per minute	BRTH	BRTH	
		Celsius	CE	CE	
		Fahrenheit	FA	FAR	
		feet	FT	FT	
		inches	IN	INCH	
		kg	KG	KG	
		ounces	OZ	OZ	
		pounds	LB	LB	
		cm	CM	CM	
		mmHg	MMHG	MMHG	
		grams	G	GRAM	
VSTEST	String	Diastolic Blood Pressure	DIASTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	VSTEST
		Heart Rate	HEART RATE	HEART RATE	
		Height	HEIGHT	HEIGHT	
		Mid Upper Arm Circumference	MUAC	MUAC	
		Respiratory Rate	RESPIRATORY RATE	RESPIRATORY RATE	
		Systolic Blood Pressure	SYSTOLIC BLOOD PRESSURE	SYSTOLIC BLOOD PRESSURE	
		Temperature	TEMPERATURE	TEMPERATURE	
		Weight	WEIGHT	WEIGHT	
		Cranial Perimeter	CRANIAL PERIMETER	CRANIAL PERIMETER	
		Apgar Score	APGAR SCORE	APGAR SCORE	
VSTESTCD	String	DIABP	DBP	DBP	VSTESTCD
		HEART RATE	HR	HR	
		HEIGHT	HE	HEI	
		MUAC	MUAC	MAUC2	
		RESP RATE	RR	RESPR	
		SYSBP	SBP	SBP	
		TEMP	TE	TEMP	
		WEIGHT	WE	WEIGHT2	
		CRANIAL PERIMETER	CRP	CRP	
		APGAR SCORE	APGAR	APGAR	
VACCSITE	String	Deltoid	1	Deltoid	P_SITE
		Thigh	3	Thigh	
		Buttock	6	Buttock	
VACCSIDE	String	Dominant	D	DOMINANT	P_SIDE
		Non Dominant	ND	NON DOMINANT	
MEDROUT_VACC	String	Intramuscular	IM	Intramuscular	P_ROUTE
		Subcutaneous	SC	Subcutaneous	
PRODNAMES	String	Boostrix Vaccine	125	125	P_CODE

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SOLICITED SYMPTOMS (Sol symp flag)

SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS

1.* ✔	Has the subject experienced any of the Local Solicited signs/symptoms between Day 0 and Day 3?	**[LOCSOL_YN]** *[A:Y]* ◯ Yes -> Please tick No/Yes for each symptom and complete further as necessary *[A:N]* ◯ No *[A:U]* ◯ Unknown, no information available

SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

2.* ✔	Has the subject experienced any of the General Solicited signs/symptoms between Day 0 and Day 3?	**[GENSOL_YN]** *[A:Y]* ◯ Yes -> Please tick No/Yes for each symptom and complete further as necessary *[A:N]* ◯ No *[A:U]* ◯ Unknown, no information available

LARGE SWELLING REACTION

Definition of a Large swelling reaction:
- any local swelling with diameter >100 mm
- and/or any noticeable diffuse injection site swelling (diameter not measurable)
- and/or any noticeable increased circumference of the injected limb

The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious and also to contact the investigator in case of large injection site reactions.

3.* ✔	Is a swelling as defined above present? [Large swelling reaction]	**[LARGESWELLING_FLAG]** *[A:Y]* ◯ Yes -> Please complete Large Injection Site Reaction form *[A:N]* ◯ No

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: SOLICITED SYMPTOMS

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
LOCALISATION	String	Generalised	G	GENERALISED	SOL_TYP_HID,
		Localised	L	LOCALISED	SOL_TYP_HID

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS (Local symp)

If any of these adverse events meets the definition of serious, complete a Serious Adverse Event Report.

REDNESS

1.* ✔ Occurred?

[RE_YN]
[A:N] ◯ No
[A:Y] ◯ **[SYMP_VAL_MM]**
Yes -> **[SYMP_VAL_MM_D0]** **[SYMP_VAL_MM_D1]** **[SYMP_VAL_MM_D2]** **[SYM_VAL_MM_D3]**
Size (mm): Day 0: N5 Day 1: N5 Day 2: N5 Day 3: N5
[RE_ONG]
After Day 3: Ongoing? [A:N] ◯ No
[A:Y] ◯ **[SYMP_ONG_MM]**
Yes -> **[ERDAT]**
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018)
[MED_TYPE]
Medically attended visit: [A:ER] ◯ Emergency Room
[A:HO] ◯ Hospitalisation
[A:MD] ◯ Medical Personnel
[A:NO] ◯ None

SWELLING

In case of large swelling reaction at the injection limb, please fill in ALSO the large Swelling Reaction form

2.* ✔ Occurred?

[SW_YN]
[A:N] ◯ No
[A:Y] ◯ **[SYMP_VAL_MM]**
Yes -> **[SYMP_VAL_MM_D0]** **[SYMP_VAL_MM_D1]** **[SYMP_VAL_MM_D2]** **[SYM_VAL_MM_D3]**
Size (mm): Day 0: N5 Day 1: N5 Day 2: N5 Day 3: N5
[SW_ONG]
After Day 3: Ongoing? [A:N] ◯ No
[A:Y] ◯ **[SYMP_ONG_MM]**
Yes -> **[ERDAT]**
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018)
[MED_TYPE]
Medically attended visit: [A:ER] ◯ Emergency Room
[A:HO] ◯ Hospitalisation
[A:MD] ◯ Medical Personnel
[A:NO] ◯ None

PAIN

3.* ✔ Occurred?

[PA_YN]
[A:N] ◯ No
[A:Y] ◯ **[SYMP_VAL_INTEN]**
Yes -> **[SYMP_VAL_INTEN_D0]** **[SYMP_VAL_D1]** **[SYMP_VAL_INTEN_D2]** **[SYMP_VAL_INTEN_D3]**
Intensity: Day 0: **[INTENSITYSOL]** Day 1: **[INTENSITYSOL]** Day 2: **[INTENSITYSOL]** Day 3: **[INTENSITYSOL]**
[PA_ONG]
After Day 3: Ongoing? [A:N] ◯ No
[A:Y] ◯ **[SYMP_ONG_INTEN]**
Yes -> **[ERDAT]**
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018)
[MED_TYPE]
Medically attended visit: [A:ER] ◯ Emergency Room
[A:HO] ◯ Hospitalisation
[A:MD] ◯ Medical Personnel
[A:NO] ◯ None

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

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Codelist Values Tables: SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
SYMPCODE	String	Fatigue	FA	FA	SYMP_COD_HID, SYMP_COD_HID, SYMP_COD_HID
		Fever	FE	FE	
		Gastrointestinal symptoms	GI	GI	
		Headache	HE	HE	
		Pain	PA	PA	
		Redness	RE	RE	
		Swelling	SW	SW	
SYMPUNITS	String	Celsius	CE	CE	SYMP_UNI, SYMP_UNI
		Coded	CO	CODED	
		Fahrenheit	FA	FAR	
		inches	IN	INCH	
		Millimeters	MM	MM	
		Occurence	OC	OC	
		Score	SC	SCORE	
INTENSITYSOL	String	0	0	0	SYMP_VAL_INTEN_D0, SYMP_VAL_D1, SYMP_VAL_INTEN_D2, SYMP_VAL_INTEN_D3
		1	1	1	
		2	2	2	
		3	3	3	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (Gen symp)

If any of these adverse events meets the definition of serious, complete a Serious Adverse Event Report.

TEMPERATURE (°F)

Fever is defined as temperature >= 100.4 °F by any route. The preferred route for recording temperature in this study will be oral.

1.* ✔ Occurred?

[FE_YN]
[A:N] ○ No
[A:NT] ○ Not taken
[A:Y] ○ **[SYMP_VAL_TEMP]**
Yes -> **[FE_VAL_D0]** Day 0: **[FE_VAL]** | **[FE_VAL_D1]** Day 1: **[FE_VAL]** | **[FE_VAL_D2]** Day 2: **[FE_VAL]** | **[FE_VAL_D3]** Day 3: **[FE_VAL]**
Not taken xxx.x | xxx.x | xxx.x | xxx.x
[FE_NT] *[A:Y]* ☐ | **[FE_NT]** *[A:Y]* ☐ | **[FE_NT]** *[A:Y]* ☐ | **[FE_NT]** *[A:Y]* ☐
[TEMP_ROUTE]
Route: *[A:A]* ○ Axillary *[A:O]* ○ Oral (preferred) *[A:R]* ○ Rectal *[A:T]* ○ Tympanic
[FE_ONG]
After Day 3: Ongoing? *[A:N]* ○ No
[A:Y] ○ **[SYMP_ONG_TEMP]**
Yes -> **[ERDAT]**
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018)
[CAUSAL]
Is there a reasonable possibility that the AE may have been caused by the investigational product? *[A:Y]* ○ Yes
[A:N] ○ No
[MED_TYPE]
Medically attended visit: *[A:ER]* ○ Emergency Room
[A:HO] ○ Hospitalisation
[A:MD] ○ Medical Personnel
[A:NO] ○ None

HEADACHE

2.* ✔ Occurred?

[HE_YN]
[A:N] ○ No
[A:Y] ○ **[SYMP_VAL_INTEN]**
Yes -> **[SYMP_VAL_INTEN_D0]** Intensity: Day 0: **[INTENSITYSOL]** | **[SYMP_VAL_D1]** Day 1: **[INTENSITYSOL]** | **[SYMP_VAL_INTEN_D2]** Day 2: **[INTENSITYSOL]** | **[SYMP_VAL_INTEN_D3]** Day 3: **[INTENSITYSOL]**
[HE_ONG]
After Day 3: Ongoing? *[A:N]* ○ No
[A:Y] ○ **[SYMP_ONG_INTEN]**
Yes -> **[ERDAT]**
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018)
[CAUSAL]
Is there a reasonable possibility that the AE may have been caused by the investigational product? *[A:Y]* ○ Yes
[A:N] ○ No
[MED_TYPE]
Medically attended visit: *[A:ER]* ○ Emergency Room
[A:HO] ○ Hospitalisation
[A:MD] ○ Medical Personnel
[A:NO] ○ None

FATIGUE

3.* ✔ Occurred?

[FA_YN]
[A:N] ○ No
[A:Y] ○ **[SYMP_VAL_INTEN]**
Yes -> **[SYMP_VAL_INTEN_D0]** Intensity: Day 0: **[INTENSITYSOL]** | **[SYMP_VAL_D1]** Day 1: **[INTENSITYSOL]** | **[SYMP_VAL_INTEN_D2]** Day 2: **[INTENSITYSOL]** | **[SYMP_VAL_INTEN_D3]** Day 3: **[INTENSITYSOL]**
[FA_ONG]
After Day 3: Ongoing? *[A:N]* ○ No

PPD

		[A:Y] [SYMP_ONG_INTEN] Yes -> [ERDAT] Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018) [CAUSAL] Is there a reasonable possibility that the AE may have been caused by the investigational product? [A:Y] Yes [A:N] No [MED_TYPE] Medically attended visit: [A:ER] Emergency Room [A:HO] Hospitalisation [A:MD] Medical Personnel [A:NO] None
GASTROINTESTINAL SYMPTOMS		
Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain		
4.* ✔	Occurred?	[GI_YN] [A:N] No [A:Y] [SYMP_VAL_INTEN] Yes -> [SYMP_VAL_INTEN_D0] [SYMP_VAL_D1] [SYMP_VAL_INTEN_D2] [SYMP_VAL_INTEN_D3] Intensity: Day 0: [INTENSITYSOL] Day 1: [INTENSITYSOL] Day 2: [INTENSITYSOL] Day 3: [INTENSITYSOL] [GI_ONG] **After Day 3**: Ongoing? [A:N] No [A:Y] [SYMP_ONG_INTEN] Yes -> [ERDAT] Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (1940-2018) [CAUSAL] Is there a reasonable possibility that the AE may have been caused by the investigational product? [A:Y] Yes [A:N] No [MED_TYPE] Medically attended visit: [A:ER] Emergency Room [A:HO] Hospitalisation [A:MD] Medical Personnel [A:NO] None

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
SYMPCODE	String	Fatigue	FA	FA	SYMP_COD_HID, SYMP_COD_HID, SYMP_COD_HID, SYMP_COD_HID
		Fever	FE	FE	
		Gastrointestinal symptoms	GI	GI	
		Headache	HE	HE	
		Pain	PA	PA	
		Redness	RE	RE	
		Swelling	SW	SW	
SYMPUNITS	String	Celsius	CE	CE	SYMP_UNI
		Coded	CO	CODED	
		Fahrenheit	FA	FAR	
		inches	IN	INCH	
		Millimeters	MM	MM	
		Occurence	OC	OC	
		Score	SC	SCORE	
INTENSITYSOL	String	0	0	0	SYMP_VAL_INTEN_D0, SYMP_VAL_D1,

PPD

		1	1	1	SYMP_VAL_INTEN_D2, SYMP_VAL_INTEN_D3, SYMP_VAL_INTEN_D0,
		2	2	2	SYMP_VAL_D1, SYMP_VAL_INTEN_D2, SYMP_VAL_INTEN_D3,
		3	3	3	SYMP_VAL_INTEN_D0, SYMP_VAL_D1, SYMP_VAL_INTEN_D2, SYMP_VAL_INTEN_D3

TDAP-0.3-009 EXT:007 YEAR 9 (110086): LARGE INJECTION SITE REACTION (Large inj site reaction) - Repeating Form

#	Date of physical examination	Start date of swelling	Size of swelling	Type of swelling	Circumference	Temperature	Redness	Induration	Pain	Functional impairment	Case description	Last date when the swelling was still considered to be a large swelling reaction:	Outcome of the large swelling reaction	Is there an alternative explanation for the swelling?
1														

If hospitalisation is required, please also complete a Serious Adverse Event Report.

REPORT OF PHYSICAL EXAMINATION

1.* ✔	Date of physical examination: [Date of physical examination]	**[PHYSICAL EXAMDATE]** **[PHYSDAT]** NReq / NReq / NReq (2015-2018) **[Examination performed]** Was the examination performed by a member of study personnel during the large injection site reaction period? *[A:N]* ◯ No *[A:Y]* ◯ Yes
2.* ✔	Date when the swelling was first considered to be a large injection site reaction: [Start date of swelling]	**[FIRST SWELLING DATE]** **[SWFDAT]** NReq / NReq / NReq (2015-2018) **[SWFHH]** If occurring within 24 hours after vaccination, please specify how long after vaccination: NReq *24-hour clock*
3.* ✔	Size of swelling: [Size of swelling]	**[SIZE OF SWELLING]** Measurement of the greatest diameter: mm N10
4.* ✔	Type of swelling: *Please specify in the case description section* [Type of swelling]	**[TYPE OF SWELLING]** *[A:1]* ◯ Local swelling around injection site, not involving adjacent joint *[A:2]* ◯ Diffuse swelling, not involving adjacent joint *[A:3]* ◯ Swelling, involving adjacent joint
5.* ✔	Circumference: [Circumference]	**[CIRCUMFERENCE]** **[CIRCUMFERENCE SWOLLEN LIMB]** Circumference of swollen limb (at the site of maximum swelling): mm N10 **[CIRCUMFERENCE OPPOSITE LIMB]** Circumference of the opposite limb (at the same level): mm N10

ASSOCIATED SIGNS

For Redness, Induration, Pain and Functional impairment, please select the Yes/No box for each symptom occurring during the large injection site reaction period. If other symptoms are associated with the large swelling, please specify in the case description section.

6.* ✔	Temperature: *Please record the temperature. If temperature has been taken more than once a day please report the highest value.* *[Temperature]*	**[TEMP]** **[Temperature Value]** Temperature (°F): xxx.x **[TEMP_ROUTE]** Route: *[A:A]* ◯ Axillary *[A:O]* ◯ Oral (preferred) *[A:R]* ◯ Rectal *[A:T]* ◯ Tympanic
7.* ✔	Redness [Redness]	**[REDNESS]** *[A:N]* ◯ No *[A:Y]* ◯ **[DIAMETER for REDNESS]** Yes -> Largest diameter: mm N10
8.* ✔	Induration [Induration]	**[INDURATION]** *[A:N]* ◯ No *[A:Y]* ◯ **[DIAMETER for INDURATION]** Yes -> Largest diameter: mm N10
9.* ✔	Pain (at administration site): [Pain]	**[PAIN AT ADMINISTRATION SITE]** *[A:N]* ◯ No *[A:Y]* ◯ **[INSTENSITY FOR PAIN]** Yes -> Intensity *[A:1]* ◯ Grade 1 *[A:2]* ◯ Grade 2 *[A:3]* ◯ Grade 3
10.* ✔	Functional impairment: [Functional impairment]	**[FUNCTIONAL IMPAIRMENT]** *[A:N]* ◯ No *[A:Y]* ◯ **[INSTENSITY FOR FUNCTIONAL IMPAIRMENT]**

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		Yes -> Intensity [A:1] Grade 1 [A:2] Grade 2 [A:3] Grade 3
CLINICAL CASE DESCRIPTION		
11.* ✔	Case description [Case description]	**[CASE DESCRIPTION]** Please give a clinical description of the observed swelling, including a description of the joint involved and specific associated symptoms. Please mention also eventual diagnostic(s) procedures and therapeutic interventions. A500
12. ✔	Last date when the swelling was still considered to be a large injection site reaction: [Last date when the swelling was still considered to be a large swelling reaction:]	**[LAST SWELLING DATE]** **[SWLDAT]** NReq / NReq / NReq (2015-2018) **[SWLHH]** If lasting for less than 24 hours, please specify duration: NReq *24-hour clock*
13.* ✔	Outcome of the large injection site reaction: [Outcome of the large swelling reaction]	**[OUTCOME_SW]** [A:1] Recovered / Resolved [A:2] Recovering / Resolving [A:3] Not recovered / Not resolved [A:4] Recovered / Resolved with sequelae
14.* ✔	Is there an alternative explanation for the swelling? (e.g.: allergy, infection, trauma, underlying conditions) [Is there an alternative explanation for the swelling?]	**[SWELLING ALTERNATIVE]** [A:N] No [A:Y] **[SWELLING EXPLANATION]** Yes -> Please specify: A500

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: LARGE INJECTION SITE REACTION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
SYMPUNITS	String	Celsius	CE	CE	SIZE OF SWELLING_UNI, CIRCUMFERENCE SWOLLEN LIMB_UNI_HD, CIRCUMFERENCE OPPOSITE LIMB_UNI
		Coded	CO	CODED	
		Fahrenheit	FA	FAR	
		inches	IN	INCH	
		Millimeters	MM	MM	
		Occurence	OC	OC	
		Score	SC	SCORE	

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): CHECK FOR STUDY CONTINUATION (Study Cont)

CHECK FOR STUDY CONTINUATION

1.* ✔	Did the subject return for this visit?	**[VIS_FLG]** *[A:Y]* **[ACTRDATE]** Yes -> Date of visit: Req / Req / Req (2015-2017) *[A:N]* **[VIS_REAS]** No **[VIS_REAS]** **-> Please select the major reason:** *[A:SAE]* **[SAE_CASE]** Serious Adverse Event **[SAE_CASE]** -> Please complete a **SAE** Report and specify SAE Report No. N2 *[A:AEX]* **[AE_NB]** Non-Serious Adverse Event **[AE_NB]** -> Please complete **Non-Serious Adverse Event** section and specify AE No. N2 **[SYMP_COD]** or Solicited AE code: **[SYMPCODE]** *[A:OTH]* **[V_OTH]** Other, please specify A100 **[DECISION]** **-> For serious (except death), non-serious adverse events and Other reasons only:** **Please select who made the decision:** *[A:I]* Investigator *[A:S]* Subject

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: CHECK FOR STUDY CONTINUATION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
SYMPCODE	String	Fatigue	FA	FA	SYMP_COD
		Fever	FE	FE	
		Gastrointestinal symptoms	GI	GI	
		Headache	HE	HE	
		Pain	PA	PA	
		Redness	RE	RE	
		Swelling	SW	SW	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): LOG STATUS (Log status-VACC)		
CONCOMITANT VACCINATION		
1.* ✔	Have any vaccines required to be reported as per protocol other than the study vaccine(s) been administered?	**[CV_FLAG]** *[A:Y]* ◯ Yes -> Please complete the corresponding page *[A:N]* ◯ No
MEDICATION		
2.* ✔	Have any medications that are required to be reported per protocol been administered?	**[MD_FLAG]** *[A:Y]* ◯ Yes -> Please complete the corresponding page *[A:N]* ◯ No
NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS		
Please report serious adverse events only in the Serious Adverse Events Report, not here.		
3.* ✔	Have any non-serious adverse events that are required to be reported per protocol occurred?	**[AE_FLAG]** *[A:Y]* ◯ Yes -> Please complete the corresponding page *[A:N]* ◯ No
PREGNANCY		
4.* ✔	Did the subject experience a pregnancy that is required to be reported as per protocol?	**[PREG_FLG]** *[A:Y]* ◯ Yes -> Please remember to complete a Pregnancy Report *[A:N]* ◯ No *[A:NA]* ◯ NA >-> The subject is not of childbearing potential or is a male

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): LOG STATUS (PERSISTENCE SUBJECTS) (Log status - PER)		
CONCOMITANT VACCINATION		
1.* ✔	Have any vaccines required to be reported as per protocol other than the study vaccine(s) been administered?	**[CV_FLAG]** *[A:Y]* ◯ Yes -> Please complete the corresponding page *[A:N]* ◯ No
MEDICATION		
2.* ✔	Have any medications that are required to be reported per protocol been administered?	**[MD_FLAG]** *[A:Y]* ◯ Yes -> Please complete the corresponding page *[A:N]* ◯ No

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): CONCOMITANT VACCINATION (Conc vacc) - Repeating Form

#	Drug Name	Route	Date of administration
1			

CONCOMITANT VACCINATION

1.* ✔	Drug/Vaccine name: [Drug Name]	**[CMTERM]** A100
2.* ✔	Route: [Route]	**[CVACC_ROUTE]** **[MEDROUT_CVACC]**
3.* ✔	Date of administration: [Date of administration]	**[CVACC_RDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018)

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: CONCOMITANT VACCINATION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
MEDROUT_CVACC	String	Inhalation	IH	Inhalation	CVACC_ROUTE
		Intradermal	ID	Intradermal	
		Intramuscular	IM	Intramuscular	
		Intranasal	IN	Intranasal	
		Intravenous	IV	Intravenous	
		Oral	PO	Oral	
		Parenteral	PE	Parenteral	
		Subcutaneous	SC	Subcutaneous	
		Sublingual	SL	Sublingual	
		Transdermal	TD	Transdermal	
		Other	OTH	OTHER_OTH	
		Unknown	UNK	Unknown	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): MEDICATION (Medic) - Repeating Form

#	Drug Name	Medical indication:	Total daily dose	Route	Start date	End date
1						

MEDICATION

1.* ✔	Drug/Vaccine name: [Drug Name]	**[CMTERM]** A100
2.* ✔	Medical indication:	**[MEDINDIC]** **[MEDINDIC]** A80 **[PROPH_CK]** In anticipation of study vaccine reaction *[A:Y]* ☐ (Not applicable for Persistence group) **[CHRON_CK]** Chronic use *[A:1]* ☐
3.* ✔	Total daily dose: [Total daily dose]	**[TOTDDOSE]** **[MED_DOSE]** Dose: A20 **[MED_UNIT]** Unit: A20
4.* ✔	Route: [Route]	**[MED_ROUT]** **[MEDROUT_MED]**
5.* ✔	Start date: [Start date]	**[SRDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018)
6.* ✔	End date: or tick box if continuing at the end of the study [End date]	**[MEDERDAT]** **[ERDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018) **[CONT_END]** Continuing at the end of the study *[A:Y]* ☐

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: MEDICATION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
MEDROUT_MED	String	Inhalation	IH	Inhalation	MED_ROUT
		Intraarticular	IR	Intraarticular	
		Intradermal	ID	Intradermal	
		Intramuscular	IM	Intramuscular	
		Intranasal	IN	Intranasal	
		Intravenous	IV	Intravenous	
		Oral	PO	Oral	
		Parenteral	PE	Parenteral	
		Rectal	PR	Rectal	
		Subcutaneous	SC	Subcutaneous	
		Sublingual	SL	Sublingual	
		Topical	TO	Topical	
		Transdermal	TD	Transdermal	
		Vaginal	VA	Vaginal	
		Other	OTH	OTHER_OTH	

PPD

		Unknown	UNK	Unknown	

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS (Non-Ser AE) - Repeating Form

#	AE No.	Event	Site:	Start date:	Outcome	End date	Maximum intensity	Is there a reasonable possibility that the AE may have been caused by the investigational product?	Medically attended visit
1									

NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

1.	AE No. *[read-only]*	**[AE_NO]** N3
2.* ✔	Event: Diagnosis only (if known), otherwise sign/symptom [Event]	**[AETERM]** A100
3.* ✔	Site:	**[AE_LG]** *[A:L]* ◯ Administration site *[A:G]* ◯ Non-administration site
4.* ✔	Start date:	**[AE_SRDAT]** **[SRDAT]** Req/Unk / Req/Unk / Req/Unk (2015-2018) **[AEPOSTVC]** 30 minutes immediate post-vaccination *[A:Y]* ☐
5.* ✔	Outcome: [Outcome]	**[OUTCOME_NSAE]** *[A:1]* ◯ Recovered/resolved *[A:2]* ◯ Recovering/resolving *[A:3]* ◯ Not recovered/not resolved *[A:4]* ◯ Recovered/resolved with sequelae
6. ✔	End date: [End date]	**[ERDAT]** Req/Unk / Req/Unk / Req/Unk (2015-2018)
7.* ✔	Maximum intensity: [Maximum intensity]	**[AE_INTEN]** *[A:1]* ◯ Mild *[A:2]* ◯ Moderate *[A:3]* ◯ Severe
8.* ✔	Is there a reasonable possibility that the AE may have been caused by the investigational product?	**[CAUSAL]** *[A:Y]* ◯ Yes *[A:N]* ◯ No
9.* ✔	Medically attended visit: [Medically attended visit]	**[MED_TYPE]** *[A:ER]* ◯ Emergency Room *[A:HO]* ◯ Hospitalisation *[A:MD]* ◯ Medical Personnel *[A:NO]* ◯ None

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
AFTER / BEFORE	String	After vaccination	A	After	AE_VACC
		Before vaccination	B	Before	

PPD

TDAP-0.3-009 EXT:007 YEAR 9 (110086): PREGNANCY REPORT (Pregnancy) - Repeating Form

#	Pregnancy report number:	Mother's date of birth:	Date of last menstrual period:	Estimated date of delivery:	Was the mother using a method of contraception?	Type of conception:	Relevant laboratory tests and procedures	Previous pregnancies?	Medical condition	Any additional factors in mother, father or family that may have an impact on the outcome of the pregnancy?	Was the subject withdrawn from the study as a result of this pregnancy?	Drug exposure - Non-investigational product(s)	Drug exposure - Non-investigational vaccine(s)	Pregnancy outcome:	Date of outcome	Method used for delivery:	Number of neonates:	Gestational weeks at birth / miscarriage / termination:	Infant information	Additional details:
1																				

1. NOTIFICATION REPORT

This report should be completed according to the protocol reporting requirements.

1.	Pregnancy report number: *[read-only]*	**[PREG_NB]** N2
2.* ✔	Mother's date of birth:	**[MDOBDTC]** Req/Unk / Req (1942-2017)
3.* ✔	Date of last menstrual period:	**[LMPDTC]** Req/Unk / Req/Unk / Req/Unk (2015-2018)
4.* ✔	Estimated date of delivery:	**[ESTDLDTC]** Req/Unk / Req/Unk / Req (2015-2018)
5.* ✔	Was the mother using a method of contraception?	**[CONT_YN]** *[A:N]* No *[A:Y]* **[CONTMET]** Yes, specify: A50
6.* ✔	Type of conception:	**[CONC_TYP]** *[A:01]* Normal (includes use of fertility drugs) *[A:02]* IVF (in vitro fertilisation)
7.* ✔	Relevant laboratory tests and procedures (e.g. ultrasound, amniocentesis and chorionic villi sampling including dates of tests and procedures): [Relevant laboratory tests and procedures]	**[LAB_YN]** *[A:N]* No *[A:Y]* **[LAB_DET]** Yes, Specify: A200
8.* ✔	Previous pregnancies?	**[PRPRG_YN]** *[A:N]* No *[A:Y]* **[PRG_CNT]** Yes, record the number in the appropriate categories: **[NBRTH_CNT]** Normal birth: N2 **[STBRTH_CNT]** Stillbirth: N2 **[SPABO_CNT]** Spontaneous abortion: N2 **[ELABO_CNT]** Elective abortion: N2 **[CONGANO_CNT]** Congenital anomaly in offspring: N2 **[ECTPRG_CNT]** Ectopic pregnancy: N2 **[MOLPRG_CNT]** Molar pregnancy: N2

	Medical condition:	Start date	Ongoing at time of pregnancy?
9. ✔			

Medical condition Entry

Use the 'Add Entry' button to enter any mother's medical condition that may have an impact on the outcome of the pregnancy

9.1* ✔	Medical condition:	**[RMC_DESC]** A50
9.2* ✔	Start date: [Start date]	**[SRDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018)
9.3* ✔	Ongoing at time of pregnancy?	**[RMC_ONG]** *[A:Y]* Yes

		[A:N] ○ **[ERDAT]** End date: Req/Unk / Req/Unk / Req/Unk (1940-2018)
10.* ✔	Any additional factors in mother, father or family that may have an impact on the outcome of the pregnancy (including habitual exposure such as alcohol / substance abuse, chronic illnesses, familial birth defect / genetic / chromosomal disorders and medication use)? For family history, specify who is concerned (uncle, grand-father,...) [Any additional factors in mother, father or family that may have an impact on the outcome of the pregnancy?]	**[AD_FACT]** *[A:N]* ○ No *[A:Y]* ○ **[PRGCOMMENTS]** Yes-> Specify: A150
11.* ✔	Was the subject withdrawn from the study as a result of this pregnancy?	**[PRGWITHDRAWN]** *[A:N]* ○ No *[A:Y]* ○ Yes

	Drug name	Total daily dose	Route	Start date	End date	Medical indication
12. ✔						

Drug exposure - Non-investigational product(s) Entry

Use the 'Add Entry' button to enter ALL medications (e.g. prescription, OTC, etc.) taken by the mother 60 days before or during pregnancy.

12.1* ✔	Drug name (Trade name is preferred): [Drug name]	**[MD_TRADNAME]** A60
12.2* ✔	Total daily dose: [Total daily dose]	**[TOTDDOSE]** **[MED_DOSE]** Dose: A20 **[MED_UNIT]** Unit: A20
12.3* ✔	Route: [Route]	**[MED_ROUT]** **[MEDROUT_MED]**
12.4* ✔	Start date: [Start date]	**[SRDAT]** Req/Unk / Req/Unk / Req/Unk (1940-2018)
12.5* ✔	End date: or tick box if continuing at the end of the study [End date]	**[MEDERDAT]** **[ERDAT]** End date: Req/Unk / Req/Unk / Req/Unk (1940-2018) **[CONT_END]** Continuing at the end of the study *[A:Y]* ☐
12.6* ✔	Medical indication: [Medical indication]	**[MEDINDIC]** A80

	Vaccine name	Manufacturer	Route	Date of administration
13. ✔				

Drug exposure - Non-investigational vaccine(s) Entry

Use the 'Add Entry' button to enter ALL non-investigational vaccines taken by the mother 60 days before or during pregnancy.

13.1* ✔	Vaccine name: (Trade name is preferred) [Vaccine name]	**[CVACC_TRADNAME]** A60
13.2* ✔	Manufacturer: [Manufacturer]	**[MANUFACT]** A20
13.3* ✔	Route: [Route]	**[CVACC_ROUTE]** **[MEDROUT_CVACC]**
13.4*	Date of administration:	**[CVACC_RDAT]**

PPD

✔	[Date of administration]	Req/Unk / Req/Unk / Req/Unk (1940-2018)
2. FOLLOW-UP REPORT - PREGNANCY STATUS		
If any of the outcomes / associated events fulfil the criteria of an SAE, complete an SAE Report.		
14.* ✔	Pregnancy outcome: (Outcome with a * must be recorded as an SAE.) [Pregnancy outcome:]	**[PROUTCOM]** **[PREGOUTCOM]**
15. ✔	Date of outcome: (Date of birth, miscarriage, ...) [Date of outcome]	**[OUTDTC]** Req/Unk / Req/Unk / Req/Unk (2015-2018)
16. ✔	Method used for delivery:	**[DELIVMET]** *[A:01]* Normal vaginal *[A:02]* Caesarean section *[A:03]* Forceps delivery *[A:04]* Vacuum delivery
Foetal/neonatal information		
17. ✔	Number of neonates:	**[NNCNT]** N3
18. ✔	Gestational weeks at birth / miscarriage / termination:	**[WKCNT]** N10 weeks

	Infant's gender	Length	Weight	Apgar score
19. ✔				

Infant information Entry		
Use the 'Add Entry' button to enter Infant(s) information. Add as many rows as number of neonates		
19.1* ✔	Infant's gender: [Infant's gender]	**[SEX INF]** *[A:M]* Male *[A:F]* Female *[A:U]* Unknown
19.2* ✔	Length: [Length]	**[LENGTH_US]** N3 inches
19.3* ✔	Weight: [Weight]	**[WEIGHT]** **[POUNDS]** **[OUNCES]** N3 pounds N2 ounces
19.4* ✔	Apgar score: [Apgar score]	**[APGAR]** **[APGAR1]** **[APGAR2]** **[APGAR3]** N2 N2 N2
Other information		
Provide additional details on current labor / delivery / discharge notes, neonate condition, prematurity, other disorders,..		
20. ✔	Additional details:	**[DETAILS]** A200

Key: [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: PREGNANCY REPORT

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
MEDROUT_MED	String	Inhalation	IH	Inhalation	MED_ROUT
		Intraarticular	IR	Intraarticular	
		Intradermal	ID	Intradermal	
		Intramuscular	IM	Intramuscular	
		Intranasal	IN	Intranasal	
		Intravenous	IV	Intravenous	

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		Oral	PO	Oral	
		Parenteral	PE	Parenteral	
		Rectal	PR	Rectal	
		Subcutaneous	SC	Subcutaneous	
		Sublingual	SL	Sublingual	
		Topical	TO	Topical	
		Transdermal	TD	Transdermal	
		Vaginal	VA	Vaginal	
		Other	OTH	OTHER_OTH	
		Unknown	UNK	Unknown	
MEDROUT_CVACC	String	Inhalation	IH	Inhalation	CVACC_ROUTE
		Intradermal	ID	Intradermal	
		Intramuscular	IM	Intramuscular	
		Intranasal	IN	Intranasal	
		Intravenous	IV	Intravenous	
		Oral	PO	Oral	
		Parenteral	PE	Parenteral	
		Subcutaneous	SC	Subcutaneous	
		Sublingual	SL	Sublingual	
		Transdermal	TD	Transdermal	
		Other	OTH	OTHER_OTH	
		Unknown	UNK	Unknown	
PREGOUTCOM	String	Live infant NO apparent congenital anomaly	01	Live infant	PROUTCOM
		Live infant congenital anomaly*	02	Live infant ANO	
		Elective termination NO apparent congenital anomaly	03	Elective	
		Elective termination congenital anomaly*	04	Elective ANO	
		Spontaneous abortion NO apparent congenital anomaly*	05	Spontaneous abo	
		Spontaneous abortion congenital anomaly*	06	Spontaneous abo ANO	
		Stillbirth NO apparent congenital anomaly*	07	Stillbirth	
		Stillbirth congenital anomaly*	08	Stillbirth ANO	
		Ectopic pregnancy*	09	Ectopic	
		Molar pregnancy*	10	Molar	
		Lost to follow-up	11	lfu_11	
		Pregnancy ongoing	12	Preg ongoing	
VSORRESU	String	beats per minute	BPM	BPM	INCHES_UNI, POUNDS_UNI, OUNCES_UNI
		breaths per minute	BRTH	BRTH	
		Celsius	CE	CE	
		Fahrenheit	FA	FAR	
		feet	FT	FT	
		inches	IN	INCH	
		kg	KG	KG	
		ounces	OZ	OZ	
		pounds	LB	LB	
		cm	CM	CM	
		mmHg	MMHG	MMHG	

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		grams	G	GRAM	

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TDAP-0.3-009 EXT:007 YEAR 9 (110086): OCCURRENCE OF SERIOUS ADVERSE EVENTS (SAE Flag)		
OCCURRENCE OF SERIOUS ADVERSE EVENTS		
1.* ✔	Did the subject experience any Serious Adverse Events that are required to be reported per protocol?	**[SAE_FLG]** *[A:Y]* ◯ Yes -> Please remember to complete a SAE Report *[A:N]* ◯ No *[A:NA]* ◯ Not applicable

Key: [*] = Item is required [✔] = Source verification required
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

TDAP-0.3-009 EXT:007 YEAR 9 (110086): SERIOUS ADVERSE EVENTS (SAE) - Repeating Form

#	SAE Report No.	Did SAE occur after initiation of study medication?	SERIOUS ADVERSE EVENT	Seriousness	RELEVANT CONCOMITANT/TREATMENT MEDICATIONS/VACCINATIONS	RELEVANT MEDICAL CONDITIONS/RISK FACTORS	RELEVANT DIAGNOSTIC RESULTS	Relevant diagnostic results not noted on the left columns	General narrative comments
1									

If you wish to record a new SAE please determine if the new SAE is clinically or temporally related to an SAE previously entered on this form.
If yes, record the details below using the 'Add Entry' button in this form.
If not clinically or temporally related, create a new SAE form for this subject by clicking on the 'New' button at the top of the page.
Do not record pre and post randomization events on the same form.

SAE REPORT NO.

1. ✔ SAE Report No. *[read-only]*
[SAE Report No.]
[SAE_NB] N2

TYPE OF REPORT

RANDOMIZATION

2.* Did the event occur after initiation of investigational product (s)?
[Did SAE occur after initiation of study medication?]
[rdcSAERAND]
[A:N] ○ No
[A:Y] ○ Yes

	No.	Event	Start date and time	Outcome / End date and time	Maximum Intensity	Action taken with investigational product(s) as a result of the event	Did the subject withdraw from study due to this event?	Is there a reasonable possibility that the event may have been caused by the investigational product(s)?	Was the AE caused by activities related to study participation other than investigational product?	Medically attended visit
3. ✔										

SERIOUS ADVERSE EVENT Entry

Use the 'Add Entry' button to enter details of the SAE. For additional SAEs that are clinically or temporally related (e.g., SAEs that occur during the same hospitalization) use the 'Add Entry' button to create a new row for entry of the additional SAE. Enter ONE event per row.

3.1 No. *[read-only]*
[No.]
[AESEQ] N5

3.2* ✔ Event:
Diagnosis only (if known), otherwise sign/symptom
[Event]
[AETERM] A100

3.3* Start date and time
Hr:Min (00:00-23:59)
[Start date and time]
[AESTDTTM]
Req/Unk / Req/Unk / Req (2015-2018)
NReq : NReq *24-hour clock*

3.4* Outcome / End date and time
Hr:Min (00:23-59)
[Outcome / End date and time]
[AEOUTCD1]
[A:1] ○ **[AEENDTTM1]**
Recovered/resolved, provide End date and time
Req/Unk / Req/Unk / Req (2015-2018)
NReq : NReq *24-hour clock*
[A:2] ○ Recovering/resolving
[A:3] ○ Not recovered/not resolved
[A:4] ○ **[AEENDTTM2]**
Recovered/resolved with sequelae, provide End date and time
Req/Unk / Req/Unk / Req (2015-2018)
NReq : NReq *24-hour clock*
[A:5] ○ **[AEENDTTM3]**
Fatal, record Date and time of Death
Req/Unk / Req/Unk / Req (2015-2018)
NReq : NReq *24-hour clock*

3.5* Maximum Intensity
Record maximum intensity throughout duration of event
[Maximum Intensity]
[AESEVCD]
[A:1] ○ Mild
[A:2] ○ Moderate
[A:3] ○ Severe
[A:X] ○ Not applicable

3.6* Action taken with investigational product(s) as a result of the
[AEACTRCD]

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	event: [Action taken with investigational product(s) as a result of the event]	*[A:1]* Investigational product(s) withdrawn *[A:4]* Dose not changed *[A:5]* Dose delayed *[A:X]* Not applicable
3.7*	Did the subject withdraw from study due to this event? [Did the subject withdraw from study due to this event?]	**[AEWD]** *[A:Y]* Yes *[A:N]* No
3.8*	Is there a reasonable possibility that the event may have been caused by the investigational product(s)? ***Use best judgment at initial entry. May be amended when additional information becomes available.*** [Is there a reasonable possibility that the event may have been caused by the investigational product(s)?]	**[AEREL]** *[A:N]* No *[A:Y]* Yes
3.9*	Was the AE caused by activities related to study participation other than investigational product? [Was the AE caused by activities related to study participation other than investigational product?]	**[rdcAESREL]** *[A:Y]* Yes *[A:N]* No
3.10* ✔	Medically attended visit: [Medically attended visit]	**[MED_TYPE]** *[A:ER]* Emergency Room *[A:HO]* Hospitalisation *[A:MD]* Medical Personnel *[A:NO]* None

SERIOUSNESS

4. ✔	Specify the reason for considering this event as SAE. (Tick all that apply) [Seriousness]	**[chkAESER]** *[A:A]* Results in death *[A:B]* Is life-threatening (subject was at risk of death at time of event) *[A:C]* Requires hospitalisation or prolongation of hospitalisation (Provide admission and discharge date(s) in narrative) *[A:D]* Results in disability/incapacity (substantial / permanent) *[A:E]* Congenital anomaly/birth defect (in offspring of subject) *[A:F]* Other, specify within general narrative comment

	Drug Name	Total daily dose	Route	Start Date	End date	Medical Indication	Drug type
5. ✔							

RELEVANT CONCOMITANT/TREATMENT MEDICATIONS/VACCINATIONS Entry

Use the 'Add Entry' button to enter details of any medication/vaccine that may help to explain the SAE, may have caused the SAE or was used to treat the SAE. Ensure each concomitant vaccination or medication recorded in this section is also recorded in the corresponding form located in the LOGS section of the eCRF.

5.1* ✔	Drug/Vaccine name: [Drug Name]	**[CMTERM]** (Trade name is preferred) A100
5.2 ✔	Total daily dose: [Total daily dose]	**[SAECMDOS]** **[txtSAECMDOS]** Dose: xxxxxxxxx. **[pdcCMUNIT]** Unit: **[clCMUNITSAE]**
5.3*	Route [Route]	**[pdcCMROUTCD]** **[MEDROUT_MEDSAE]**
5.4*	Start Date [Start Date]	**[dtmSAECMSTD]** NReq/Unk / NReq/Unk / NReq/Unk (1940-2018)
5.5 ✔	End date: or tick box if continuing at the end of the study [End date]	**[SAECMEND]** **[dtmSAECMEND]** NReq/Unk / NReq/Unk / NReq/Unk (1940-2018) **[rdcSAECMONG]** Continuing at the end of the study *[A:Y]*

PPD

5.6	Medical indication *Enter a medical diagnosis not description* [Medical Indication]	**[txtCMIND]** A50
5.7*	Drug type: [Drug type]	**[pdcCMDRGTYP]** **[clDRUGTYP]**

	Condition	Start date	Continuing at time of SAE?
6. ✔			

RELEVANT MEDICAL CONDITIONS/RISK FACTORS Entry

Use the 'Add Entry' button to enter each past or current medical disorder, allergy or surgery that may be RELEVANT to the SAE. Enter a diagnosis, not description. Relevant family or social history shoud be described in the 'General Narrative Comments' at the bottom of this form. Ensure each medical condition/risk factor recorded in this section is also recorded in the General Medical History form located at the beginning of the eCRF.

6.1*	Condition ***Enter a medical diagnosis not description.*** [Condition]	**[txtSAEMHTRM]** A100
6.2*	Start date: [Start date]	**[dtmMHSTDTM]** Req/Unk / Req/Unk / Req (1940-2018)
6.3*	Continuing at time of SAE? [Continuing at time of SAE?]	**[rdcMHCONT]** *[A:Y]* Yes *[A:N]* **[dtmMHLSTOC]** No, specify end date or date of last occurrence Req/Unk / Req/Unk / Req (1940-2018) *[A:U]* Unknown, no information available

	Test name	Test date	Test result	Test units	Normal low range	Normal high range
7. ✔						

RELEVANT DIAGNOSTIC RESULTS Entry

Use the 'Add Entry' button to enter details of relevant tests or procedures carried out to diagnose or confirm the SAE or rule out other diagnoses

7.1*	Test name [Test name]	**[pdcLBTST]** **[clSAELBTST]**
7.2*	Test date [Test date]	**[dtmLABDTM]** Req/Unk / Req/Unk / Req (2015-2018)
7.3*	Test result [Test result]	**[txtLABRES]** A12
7.4*	Test units [Test units]	**[txtLABUNIT]** A12
7.5*	Normal low range [Normal low range]	**[txtLABNLR]** xxxxxxxxx.xx
7.6*	Normal high range [Normal high range]	**[txtLABNHR]** xxxxxxxxx.xx
8.	Enter here only the diagnostic results that could not be entered in the above grid, including procedure such as ECG, X rays, etc and tests on stool, CSF etc. Also provide dates. [Relevant diagnostic results not noted on the left columns]	**[cmpLABTEXT]** **[txtLABTEXT]** A1000 **[txtLABTEXT1]** A1000

GENERAL NARRATIVE COMMENTS

PPD

Provide a clear (this narrative will be provided to regulatory authorities) and brief chronological description (with dates) of the clinical course of the event including:
- Associated signs and symptoms
- Clinical evolution (hospitalisation, outcome, description of sequelae if any, autopsy results, etc.)
- Non-drug treatment such as surgery
- Other information useful for the medical assessment of the case (e.g. reason for diagnosis if not obvious or if diagnosis changed)
- Relevant additional risk factors including family or social history (negative sentence can also be helpful)
- Possible cause(s) of the event
- Rationale for relationship when SAE is possibly related to study product, concomitant product or study procedure, etc.

Complete a new box only when the previous one is full.

9.*	General narrative comments	**[cmpNARRATIVE]** **[txtSAECOMM]** A1000 **[txtSAECOMM1]** A1000 **[txtSAECOMM2]** A1000 **[txtSAECOMM3]** A1000

PPD

NON CLINICAL

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: SERIOUS ADVERSE EVENTS

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
clCMUNITSAE	String	ACTU	ACTU	clCMUNIT_ACTU	pdcCMUNIT
		AMP	AMP	clCMUNIT_AMP	
		application(s)	AP	clCMUNIT_AP	
		BT	BT	clCMUNIT_BT	
		capsule	CAP	clCMUNIT_CAP	
		Cubic centimeter	CC	clCMUNIT_CC	
		MBecquerel	16	citmCMUNIT_MBQ	
		Variable dose	VA	citmCMUNIT_VA	
		blister	BLS	citmCMUNIT_BLS	
		caplet(s)	CAPL	citmCMUNIT_CAPL	
		cg	CG	citmCMUNIT_CG	
		drop(s)	31	citmCMUNIT_DROP	
		elisa unit	EU	citmCMUNIT_EU	
		g/L	GML	citmCMUNIT_GM/L	
		g/M2	GM/M2	citmCMUNIT_GM/M2	
		g/kg	GM/KG	citmCMUNIT_GM/KG	
		grain	GR	citmCMUNIT_GR	
		gram(s)	2	citmCMUNIT_G	
		inch	INCH	citmCMUNIT_INCH	
		injection	INJ	citmCMUNIT_INJ	
		iu	25	citmCMUNIT_IU	
		iu x 10**3	26	citmCMUNIT_IU3	
		iu x 10**6	27	citmCMUNIT_IU6	
		liter	11	citmCMUNIT_L	
		lozenge	LOZ	citmCMUNIT_LOZ	
		mCi	19	citmCMUNIT_MCI	
		mEq	29	citmCMUNIT_MEQ	
		mcg	4	citmCMUNIT_MCG	
		mcg/mg	MCG/MG	citmCMUNIT_MCG/MG	
		Megaunits (million units)	MEGU	citmCMUNIT_MEGU	
		mg	3	citmCMUNIT_MG	
		mg/kg	7	citmCMUNIT_MGK	
		mg/m2	9	citmCMUNIT_MGM2	
		mg/min	MGM	citmCMUNIT_MGM	
		mg/ml	MGML	citmCMUNIT_MGML	
		micro unit	MCRU	citmCMUNIT_MCU	
		ml	12	citmCMUNIT_ML	
		ml/hr	MLH	citmCMUNIT_MLH	
		mm	MM	citmCMUNIT_MM	

PPD

		mmol	23	citmCMUNIT_MMOL	
		nebule(s)	NEB	citmCMUNIT_NEB	
		ng	5	citmCMUNIT_NG	
		ng/kg	NGK	citmCMUNIT_NGK	
		ounce	OZ	citmCMUNIT_OZ	
		patch	PAT	citmCMUNIT_PAT	
		percent	30	citmCMUNIT_PCT	
		puff(s)	PUFF	citmCMUNIT_PUFF	
		sachet	SAC	citmCMUNIT_SAC	
		spray	SPR	citmCMUNIT_SPR	
		suppository	SUP	citmCMUNIT_SUP	
		tablespoon	TBS	citmCMUNIT_TBS	
		tablet	TAB	citmCMUNIT_TAB	
		teaspoon	TSP	citmCMUNIT_TSP	
		uBecquerel	14	citmCMUNIT_UBQ	
		ugk	8	citmCMUNIT_UGK	
		umol	24	citmCMUNIT_UMOL	
		unit	UNT	citmCMUNIT_UNT	
		unknown	U	citmCMUNIT_U	
		vial(s)	VIA	citmCMUNIT_VIA	
clSAECMFRQ	String	2 times per week	2W	clSAECMFRQ_2W	pdcSAECMFRQ
		3 times per week	3W	clSAECMFRQ_3W	
		4 times per week	4W	clSAECMFRQ_4W	
		5 times per day	5D	clSAECMFRQ_5D	
		5 times per week	5W	clSAECMFRQ_5W	
		AC	AC	clSAECMFRQ_AC	
		BID	2D	clSAECMFRQ_2D	
		Continuous infusion	CO	clSAECMFRQ_CO	
		Every 2 weeks	FO	clSAECMFRQ_FO	
		Every 3 weeks	Q3W	clSAECMFRQ_Q3W	
		Every 3 months	Q3M	clSAECMFRQ_Q3M	
		Every other day	AD	clSAECMFRQ_AD	
		Once a month	MO	clSAECMFRQ_MO	
		Once a week	WE	clSAECMFRQ_WE	
		Once daily	1D	clSAECMFRQ_1D	
		Once only	1S	clSAECMFRQ_1S	
		PC	PC	clSAECMFRQ_PC	
		PRN	PRN	clSAECMFRQ_PRN	
		Q2H	12D	clSAECMFRQ_Q2H	
		Q3D	Q3D	clSAECMFRQ_Q3D	
		Q4D	Q4D	clSAECMFRQ_Q4D	
		Q4H	6D	clSAECMFRQ_Q4H	
		QAM	1M	clSAECMFRQ_QAM	
		QH	24D	clSAECMFRQ_QH	
		QID	4D	clSAECMFRQ_QID	

PPD

		QPM	1N	clSAECMFRQ_QPM	
		TID	3D	clSAECMFRQ_TID	
MEDROUT_MEDSAE	String	Inhalation	055	Inhalation	pdcCMROUTCD
		Intraarticular	014	Intraarticular	
		Intradermal	023	Intradermal	
		Intramuscular	030	Intramuscular	
		Intranasal	045	Intranasal	
		Intravenous	042	Intravenous	
		Oral	048	Oral	
		Parenteral	051	Parenteral	
		Rectal	054	Rectal	
		Subcutaneous	058	Subcutaneous	
		Sublingual	060	Sublingual	
		Topical	061	Topical	
		Transdermal	062	Transdermal	
		Vaginal	067	Vaginal	
		Other	050	Other	
		Unknown	065	Unknown	
clDRUGTYP	String	Concomitant	2	clDRUGTYP_01	pdcCMDRGTYP
		Treatment	T	clDRUGTYP_02	
		Cause of AE	1	clDRUGTYP_03	
clSAELBTST	String	Activated partial thromboplastin time	Activated partial thromboplastin time	SAELBTST01	pdcLBTST
		Alanine aminotransferase	Alanine Amino Transferase	SAELBTST79	
		Albumin	Albumin	SAELBTST02	
		Alkaline phosphatase	Alkaline phosphatase	SAELBTST03	
		Amylase	Amylase	SAELBTST04	
		Aspartate Amino Transferase	Aspartate Amino Transferase	SAELBTST80	
		Band Neutrophil count	Band Neutrophil count	SAELBTST81	
		Base Excess	Base Excess	SAELBTST82	
		Basophils	Basophils	SAELBTST05	
		Bicarbonate	Bicarbonate	SAELBTST06	
		Bilirubin	Bilirubin	SAELBTST07	
		Bilirubin direct	Bilirubin direct	SAELBTST08	
		Bilirubin total	Bilirubin total	SAELBTST09	
		Blood glucose	Blood glucose	SAELBTST83	
		Blood myoglobin	Blood myoglobin	SAELBTST10	
		Blood pH	Blood pH	SAELBTST11	
		Blood pressure	Blood pressure	SAELBTST12	
		Blood urea nitrogen	Blood urea nitrogen	SAELBTST13	
		Body temperature	Body temperature	SAELBTST14	
		Calcium	Calcium	SAELBTST15	
		Carbone dioxide	Carbone dioxide	SAELBTST84	
		CD4 lymphocytes	CD4 lymphocytes	SAELBTST16	
		CD8 lymphocytes	CD8 lymphocytes	SAELBTST17	
		Chloride	Chloride	SAELBTST18	

PPD

Cholesterol total	Cholesterol total	SAELBTST19
C-reactive protein	C-reactive protein	SAELBTST20
Creatine	Creatine	SAELBTST21
Creatine phosphokinase	Creatine phosphokinase	SAELBTST22
Creatine phosphokinase MB	Creatine phosphokinase MB	SAELBTST23
Creatinine	Creatinine	SAELBTST24
Creatinine clearance	Creatinine clearance	SAELBTST25
Diastolic blood pressure	Diastolic blood pressure	SAELBTST26
Eosinophils	Eosinophils	SAELBTST27
Erythrocyte sedimentation rate	Erythrocyte sedimentation rate	SAELBTST28
Fasting blood glucose	Fasting blood glucose	SAELBTST29
FEV 1	FEV 1	SAELBTST30
Gamma-glutamyltransferase	Gamma-glutamyltransferase	SAELBTST31
Granulocyte count	Granulocyte count	SAELBTST85
HbA1c	HbA1c	SAELBTST34
HBV-DNA decreased	HBV-DNA decreased	SAELBTST35
HBV-DNA increased	HBV-DNA increased	SAELBTST36
Heart rate	Heart rate	SAELBTST37
Hematocrit	Hematocrit	SAELBTST38
Hemoglobin	Hemoglobin	SAELBTST39
High density lipoprotein	High density lipoprotein	SAELBTST40
HIV viral load	HIV viral load	SAELBTST41
INR	INR	SAELBTST42
International normalized ratio	International normalized ratio	SAELBTST88
Lactate dehydrogenase	Lactate dehydrogenase	SAELBTST43
Lipase	Lipase	SAELBTST44
Low density lipoprotein	Low density lipoprotein	SAELBTST45
Lymphocytes	Lymphocytes	SAELBTST46
Magnesium	Magnesium	SAELBTST47
Mean cell hemoglobin concentration	Mean cell hemoglobin concentration	SAELBTST48
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin	SAELBTST49
Mean corpuscular volume	Mean corpuscular volume	SAELBTST50
Mean Platelet Volume	Mean Platelet Volume	SAELBTST89
Monocytes	Monocytes	SAELBTST51
Myoglobin urine	Myoglobin urine	SAELBTST90
Neutrophils	Neutrophils	SAELBTST52
Oxygen saturation	Oxygen saturation	SAELBTST53
pCO2	pCO2	SAELBTST54
pH	pH	SAELBTST55
pH urine	pH urine	SAELBTST91
Phosphate	Phosphate	SAELBTST56
Platelet count	Platelet count	SAELBTST57
pO2	pO2	SAELBTST58
Polymerase Chain Reaction	Polymerase Chain Reaction	SAELBTST92
Polymorphonuclear Count	Polymorphonuclear Count	SAELBTST93
Potassium		

PPD

			Potassium	SAELBTST59	
		Protein total	Protein total	SAELBTST60	
		Prothrombin time	Prothrombin time	SAELBTST61	
		Red blood cell count	Red blood cell count	SAELBTST62	
		Red Cell Distribution Width	Red Cell Distribution Width	SAELBTST94	
		Respiratory rate	Respiratory rate	SAELBTST63	
		Reticulocyte count	Reticulocyte count	SAELBTST64	
		Segmented Neutrophil Count	Segmented Neutrophil Count	SAELBTST95	
		Serum glucose	Serum glucose	SAELBTST65	
		Serum uric acid	Serum uric acid	SAELBTST66	
		Sodium	Sodium	SAELBTST67	
		Systolic blood pressure	Systolic blood pressure	SAELBTST68	
		Thrombin time	Thrombin time	SAELBTST69	
		Total lung capacity	Total lung capacity	SAELBTST70	
		Triglycerides	Triglycerides	SAELBTST71	
		Troponin	Troponin	SAELBTST72	
		Troponin I	Troponin I	SAELBTST73	
		Troponin T	Troponin T	SAELBTST74	
		Urine myoglobin	Urine myoglobin	SAELBTST75	
		Urine pH	Urine pH	SAELBTST76	
		Vital capacity	Vital capacity	SAELBTST77	
		White blood cell count	White blood cell count	SAELBTST78	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): STUDY CONCLUSION (Study Conc)

STUDY CONCLUSION

1.* ✔ Was the subject withdrawn from the study?

[DROP_OUT]
[A:Y] ◯ **[WD_REAS]**
[NOPROTCA]
Yes -> Please choose reason for withdrawal:
[A:PTV] ◯ Protocol violation
[A:SAE3] ◯ **[SAE_CASE]**
Serious Adverse Event -> Please complete a **SAE** Report and specify SAE Report No. N2
[A:CWS2] ◯ Consent withdrawal, not due to a Serious Adverse Event
[A:MIG] ◯ Migrated / moved from the study area
[A:LFU] ◯ Lost to follow-up
[A:OTH] ◯ **[V_OTH]**
Other, please specify A100
[A:AEX] ◯ **[AE_NB]**
Non-Serious Adverse Event **[AE_NB]**
-> Please complete **Non-Serious Adverse Event** section and specify AE No. N2
[SYMP_COD]
Solicited AE code: **[SYMPCODE]**
[DECISION]
Please select who made the decision:
[A:I] ◯ Investigator
[A:S] ◯ Subject
[A:N] ◯ No

2.* ✔ Date of last contact :

[LC_RDAT]
Req / Req / Req (2015-2018)

3.* ✔ Was the subject in good condition at this date?

[LC_GC]
[A:N] ◯ No
[A:Y] ◯ Yes

OCCURENCE OF SERIOUS ADVERSE EVENT

4.* ✔ Did the subject experience any Serious Adverse Events that are required to be reported per protocol?

[SAE_FLG]
[A:Y] ◯ **[SAE_CNT]**
If Yes, please specify the total number of SAEs N2
[A:N] ◯ No
[A:NA] ◯ Not applicable

PREGNANCY OCCURENCE

5.* ✔ Did the subject experience a pregnancy that is required to be reported as per protocol?

[PREG_FLG]
[A:Y] ◯ Yes
[A:N] ◯ No
[A:NA] ◯ Not applicable

ELIMINATION CRITERIA

6.* ✔ Did any elimination criteria become applicable during the study ?
[Elim Crit]

[ELIM_CRIT]
[A:Y] ◯ **[CRITSPEC]**
Yes -> Specify : A50
[A:N] ◯ No
[A:NA] ◯ Not applicable

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

Codelist Values Tables: STUDY CONCLUSION

Codelist	Codelist Data Type	Label	Code	Codelist Item	Data Variable
SYMPCODE	String	Fatigue	FA	FA	SYMP_COD

PPD

		Fever	FE	FE	
		Gastrointestinal symptoms	GI	GI	
		Headache	HE	HE	
		Pain	PA	PA	
		Redness	RE	RE	
		Swelling	SW	SW	

TDAP-0.3-009 EXT:007 YEAR 9 (110086): INVESTIGATOR SIGNATURE (Inv sign)		
INVESTIGATOR SIGNATURE		
1. * ✔	Is this casebook ready to sign? If not, click on the **RETURN** button below	**[INVSIGN]** *[A:Y]* ☐ Ready to sign

Key: [*] = Item is required [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

TDAP-0.3-009 EXT:007 YEAR 9 (110086): USE OF HUMAN SAMPLES (UHS) - Repeating Form

#	Text 3A	Text 4	Please check GSK Biologicals sample storage period specified in the ICF in use at your centre.	If new version of UHS: Date at which the new ICF version was first signed by a Subject :
1				

In addition to the tests described in the study protocol, please check what may also be done with the subject samples as per the Informed Consent Form (ICF) in use at your center.

TYPE 3A TESTS

1.* ✔	Use of samples to improve tests and develop new tests linked to study vaccine(s)/product(s) or the disease under study. These tests will never include tests related to genes' hereditary characteristics. [Text 3A]	**[CONS_YN_3A]** *[A:Y]* ◯ Yes *[A:N]* ◯ No

TYPE 4 TESTS

2.* ✔	With the prior permission of the Subject : GSK may perform future research on collected samples. Any research undertaken with samples collected will be performed after obtaining approval for the research by an IRB/IEC. [Text 4]	**[CONS_YN_4]** *[A:Y]* ◯ Yes *[A:N]* ◯ No

SAMPLE STORAGE PERIOD

3.* ✔	Please tick below box if a 20 years GSK storage period is covered by the subject's Informed Consent form of your center. [Please check GSK Biologicals sample storage period specified in the ICF in use at your centre.]	**[PERIOD]** *[A:20]* ◯ For a maximum of 20 years *[A:9]* ◯ **[PERIODSP]** Other, please specify: A200

Complete and submit a new Use of Human Samples by GSK form for each change in the ICF that affects the use of samples.

4. ✔	ICF Effective date: [If new version of UHS: Date at which the new ICF version was first signed by a Subject :]	**[UHS_DATE]** NReq / NReq / NReq (2015-2018)

Key: [✔] = Source verification required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

PPD

CONFIDENTIAL

Panel 100

GlaxoSmithKline

Diary Cards

Subject number

|__|__|__|__|__|__|__|__|

To be completed by the Investigator or delegate

***Protocol* 110086**

(Tdap-0.3-009 Ext:007 Year 9)

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD AT THE NEXT VISIT

CONFIDENTIAL

General Instructions

Thank you for your participation in this clinical trial.

During your last study visit, you received a “Diary Card” to fill in every day for a defined period, so that your study doctor or the study staff will know your general health status after the vaccination.

Here below you will find general instructions on how to complete the “Diary Card”. There are also other specific instructions relative to each part of the “Diary Card” that you will need to fill in.

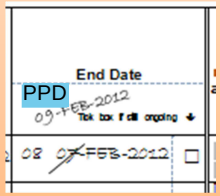
INSTRUCTIONS TO COMPLETE THE “DIARY CARD”

- Write in clearly, use a pen (never pencil).
- The grey areas are dedicated to the investigator or delegate only. Do not write in these areas.

Illness/Sign/Symptom ☑ if at vaccine injection site ↓	Worst Intensity 1/2/3	Start Date	End Date Tick box if still ongoing ↓	Did you receive medical attention?	Type of medical attention To be completed by the investigator or delegate	Relationship to inv. Product To be completed by the investigator or delegate
Tendinitis ☐	2	04-FEB-2012	08-FEB-2012 ☐	☐ No ☒ Yes	HOER/MD ☐☐	☐ No ☐ Yes

➢ *HOW TO CORRECT MISTAKES?*

- Cross out the mistake with a single line.
- Don't hide the mistake. Don't use correction fluid or don't make inkblots.
- Write the correct response close to the mistaken one.
- If the correct response is written outside of the box, circle it and point to it with an arrow towards the box.
- **Put your initials near the correction.**
- **Date the correction**



➢ *WHO TO CONTACT IN CASE OF QUESTIONS?*

If you have any questions, please contact your study doctor or the study staff on the following phone number:

[insert phone n° of the study doctor or study staff]

Please contact your study doctor or the study staff immediately if you have any symptoms you think are serious.

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Instructions to complete:
Local and general symptoms

- If you experience any other symptoms than those listed in the local symptoms or general symptoms pages, please write these symptoms down in the Adverse Event section.
- If a symptom <u>appears only after</u> day 3, please write this symptom down in the Adverse Event section.

➢ *<u>HOW TO COMPLETE "AFTER DAY 3"?</u>*

- In the columns "After day 3", if the symptom is still ongoing* after day 3, tick "Yes". Otherwise, tick "No".

  * The symptom is ongoing if after day 3:
  - The intensity of the symptom is 1 or higher.
  - The oral (in the mouth), axillary (under the armpit), tympanic (in the ear) or rectal (in the anus) temperature is higher or equal to 100.4°F.

- If Yes,
  - Please write the worst intensity, the highest temperature or the greatest measurement recorded during this follow-up period, after day 3.
  - Note the date when the symptom has disappeared or tick the box "still ongoing".
- If No, then leave empty the columns "Worst intensity/ greatest size/ highest temperature" and "End Date".

➢ *<u>BOX "STILL ONGOING" IN COLUMN "END DATE" – WHEN TO TICK IT?</u>*

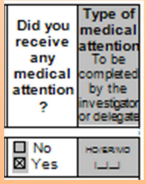
- Tick the box "Still ongoing" if the illness /sign /symptom is still present at the time you return the diary card to the site.

	Day 0	Day 1	Day 2	Day 3	After Day 3			Did you receive any medical attention ?	Type of medical attention To be completed by the investigator or delegate
					Ongoing	Worst Intensity/ Greatest size	End Date Tick box if still ongoing ↓		
Injection site **Redness** → size (mm)	mm 10	mm 8	mm 5	mm 3	☐ No ☒ Yes →	mm 2	☒	☐ No ☒ Yes	HO/ERMD LL

➢ *DID YOU RECEIVE ANY MEDICAL ATTENTION? HOW TO COMPLETE THIS QUESTION?*

- Medical attention means hospitalisation, an emergency room visit or a visit to or from medical personnel.
- Tick the box "No" if you did not visit medical personnel or were not visited by medical personnel or did not go to the hospital or an emergency room for the symptom.
- Tick the box "Yes" if you went to the hospital, an emergency room, if you visited medical personnel or were visited by medical personnel for the symptom.

  Keep the type of medical attention (grey column) empty. It will be completed by the study doctor or study staff.



CONFIDENTIAL

Instructions to complete:

Local symptoms

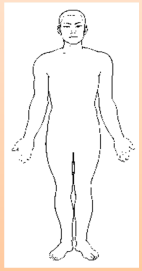
- If you receive more than one vaccine, you will have to fill in one section for each administered vaccine.

➢ *HOW TO COMPLETE THE DAILY VALUE?*

- Write down a value for each symptom and each day (measure or intensity). **Don't leave any field empty.**
- If there is no symptom, please write "0".

Injection site **Swelling** → size (mm)	mm 2	mm 0	mm 0	mm 0	☒ No ☐ Yes →	mm		☐	☒ No ☐ Yes	HOERMD LLL

- Redness, swelling and pain may appear around the area where you received the vaccine (administration site(s)). These are called LOCAL symptoms.
- If similar symptoms appear on another part of your body than this/those corresponding to the administration site(s), please report them in the Adverse Event section.



.

- Write down the size of the redness and swelling in millimetres (mm) only. Use the ruler given to you by the site staff.

. ➢ *LARGE SWELLING REACTION*

In case of large injection site reactions (defined as swelling with a diameter greater than 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference), please contact the study doctor or study staff and go as soon as possible to the study doctor or study staff's office for evaluation.

➢ *INTENSITY DEFINITIONS*

- Redness and swelling:

  Measure and record the greatest surface diameter in millimetres (mm).

- Pain: 0: **None,**

  1: **Mild**: Any pain neither interfering with nor preventing normal every day activities.

  2: **Moderate**: Painful when limb is moved and interferes with every day activities.

  3: **Severe:** Significant pain at rest. Prevents normal every day activities.

(Tdap-0.3-009 Ext:007 Year 9) 110086	**DIARY CARDS** *Boostrix*	**Subject Number** |___|___|___|___|___|___| To be completed by the investigator or delegate

LOCAL SYMPTOMS

To be completed by the investigator or delegate:
Date of vaccination = Day 0: _____ **Injection Site**: _____ **Side**: _____

	Day 0	Day 1	Day 2	Day 3	After Day 3: Ongoing	After Day 3: Worst Intensity/ Greatest size	After Day 3: End Date (Tick box if still ongoing ↓)	Did you receive any medical attention ?	Type of medical attention (To be completed by the investigator or delegate)
Injection site **Redness** → size (mm)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD ⌊_⌋⌊_⌋
Injection site **Swelling** → size (mm)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD ⌊_⌋⌊_⌋
Injection site **Pain** → intensity (0/1/2/3)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD ⌊_⌋⌊_⌋

Clarification(s) for Investigator or delegate only:

(Tdap-0.3-009 Ext:007 Year 9) 110086	**DIARY CARDS** *Boostrix*	**Subject Number** |___|___|___|___|___|___| To be completed by the investigator or delegate

LOCAL SYMPTOMS

To be completed by the investigator or delegate:
Date of vaccination = Day 0: _____ **Injection Site**: _____ **Side**: _____

	Day 0	Day 1	Day 2	Day 3	After Day 3: Ongoing	After Day 3: Worst Intensity/ Greatest size	After Day 3: End Date (Tick box if still ongoing ↓)	Did you receive any medical attention ?	Type of medical attention (To be completed by the investigator or delegate)
Injection site **Redness** → size (mm)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD |_|_|
Injection site **Swelling** → size (mm)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD |_|_|
Injection site **Pain** → intensity (0/1/2/3)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD |_|_|

Clarification(s) for Investigator or delegate only:

CONFIDENTIAL

Instructions to complete:
General symptoms

➢ *HOW TO COMPLETE THE DAILY VALUE?*

- Write down a value for each symptom and each day (measure or intensity). **Don't leave any field empty.**
- Write "0" if there is no increase in intensity compared to normal

	Day 0	Day 1	Day 2	Day 3	After Day 3: Ongoing	After Day 3: Worst Intensity	After Day 3: End Date (Tick box if still ongoing)	Did you receive medical attention?*	Type of medical attention (To be completed by the investigator or delegate)	Relationship to inv. Product (To be completed by the investigator or delegate)
Drowsiness → Intensity (0/1/2/3)	0/1/2/3	0/1/2/3	0/1/2/3	0/1/2/3	☐No ☐Yes →	1/2/3	☐	☐No ☐Yes	HOSPMD L_L_I	☐No ☐Yes

➢ *GENERAL SYMPTOMS: TEMPERATURE*

- Please use the provided thermometer.
- Take your temperature each day from day of vaccination (day 0) until day 3, and write down the values.
- If you took your temperature more than once a day, then write down the highest one.
- The preferred route for recording temperature in this study will be oral.

Example: if on Day 0
- At 8 am: 98.8°F
- At 1 pm: 99.3°F
- At 7 pm: 99.7°F

→ 99.7°F is to be recorded in for Day 0

- Please write down NT (Not Taken) if you did not take the temperature.

	Day 0	Day 1	Day 2	Day 3	After Day 3: Ongoing 100.4 °F any route	After Day 3: Highest Temperature	After Day 3: End Date (Tick box if still ongoing)	Did you receive any medical attention?	Type of medical attention (To be completed by the investigator or delegate)	Relationship To Inv. Product (To be completed by the investigator or delegate)
Temperature →	99.4	99.6	99.5	99.5	☐No ✖ Yes →	100	✖	☐No ✖ Yes	HOSPMD L_L_I	☐No ✖ Yes

(Tdap-0.3-009 Ext:007 Year 9) 110086	**DIARY CARDS** *Boostrix*	**Subject Number** |___|___|___|___|___|___| To be completed by the investigator or delegate

GENERAL SYMPTOMS

To be completed by the investigator or delegate: **Date of vaccination = Day 0**: _____

	Day 0	Day 1	Day 2	Day 3	After Day 3: Ongoing 100.4 °F any route	After Day 3: Highest Temperature	After Day 3: End Date (Tick box if still ongoing ↓)	Did you receive any medical attention?	Type of medical attention (To be completed by the investigator or delegate)	Relationship To inv. Product (To be completed by the investigator or delegate)
Temperature →					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes

Temperature: ☐ Fahrenheit

Route of measurement:
(The same route must be used for all your measurements.)

- ☐ Axillary (under the armpit)
- ☐ Oral (in the mouth) **(Preferred)**
- ☐ Rectal (in the anus)
- ☐ Tympanic (in the ear)

Clarification(s) for Investigator or delegate only:

CONFIDENTIAL

➢ *INTENSITY DEFINITIONS*

- Headache:

0: Normal
1: Mild: Headache that is easily tolerated
2: Moderate: Headache that interferes with normal activity
3: Severe: Headache that prevents normal activity

- Fatigue:

0: Normal
1: Mild: Fatigue that is easily tolerated
2: Moderate: Fatigue that interferes with normal activity
3: Severe: Fatigue that prevents normal activity

- Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain):

0: Gastrointestinal symptoms normal
1: Mild: Gastrointestinal symptoms that are easily tolerated
2: Moderate: Gastrointestinal symptoms that interfere with normal activity
3: Severe: Gastrointestinal symptoms that prevent normal activity

GENERAL SYMPTOMS

To be completed by the investigator or delegate: **Date of vaccination = Day 0**: _____

	Day 0	Day 1	Day 2	Day 3	After Day 3			Did you receive medical attention?*	Type of medical attention To be completed by the investigator or delegate	Relationship to Inv. Product To be completed by the investigator or delegate
					Ongoing	Worst Intensity	End Date Tick box if still ongoing ↓			
Headache → Intensity (0/1/2/3)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD └┴┘	☐ No ☐ Yes
Fatigue → intensity (0/1/2/3)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD └┴┘	☐ No ☐ Yes
Gastrointestinal symptoms → intensity (0/1/2/3)					☐ No ☐ Yes →		☐	☐ No ☐ Yes	HO/ER/MD └┴┘	☐ No ☐ Yes

Clarification(s) for Investigator or delegate only:

Instructions to complete:

Adverse Events

- If you experience any other symptoms than those listed in the local symptoms or general symptoms pages, please write these symptoms down in this section.
- If a symptom appears only after day 3, please write this symptom down in this section.
- If redness, swelling or pain appears on another area than area where your received the vaccine, please report these symptoms in this section.

➢ *INTENSITY DEFINITIONS*

- **1**: **Mild.** An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **2**: **Moderate.** An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
- **3**: **Severe.** An adverse event which prevents normal, everyday activities. (In adults, such an AE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

➢ *BOX "STILL ONGOING" IN THE COLUMN "END DATE" – WHEN TO TICK IT?*

- Tick the box "Still ongoing" if the illness / sign / symptom is still present at the time you return the diary card to the site.

DID YOUR RECEIVE ANY MEDICAL ATTENTION? HOW TO COMPLETE THIS QUESTION?

- Medical attention means hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor).
- Tick the box "No" if you did not visit a doctor or go to the hospital or an emergency room for the symptom
- Tick the box "Yes" if you went to the hospital, an emergency room or if you visited a doctor for the symptom. Keep the type of medical attention (grey column) empty. It will be completed by the study doctor or study staff.

GlaxoSmithKline **(Tdap-0.3-009 Ext:007 Year 9)** **110086**	**DIARY CARDS** *Boostrix*	**Subject Number** |__|__|__|__|__|__| To be completed by the investigator or delegate

ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms listed on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

Illness/Sign/Symptom ☑ if at vaccine injection site ↓	**Worst Intensity** 1/2/3	**Start Date**	**End Date** Tick box if still ongoing ↓	**Did you receive medical attention?**	**Type of medical attention** To be completed by the investigator or delegate	**Relationship to inv. Product** To be completed by the investigator or delegate
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes
☐			☐	☐ No ☐ Yes	HO/ER/MD |_|_|	☐ No ☐ Yes

Clarification(s) for Investigator or delegate only:

(Tdap-0.3-009 Ext:007 Year 9) GlaxoSmithKline 110086	DIARY CARDS	Subject Number |__|__|__|__|__|__|__| To be completed by the investigator or delegate

VACCINATION

Record any vaccination received since the last study vaccination

Vaccination	Date of administration	Route* To be completed by the investigator or delegate

* **Route codes** = inhalation [IH], intradermal [ID], intramuscular [IM], intranasal [IN], intravenous [IV], oral [PO], parenteral [PE], subcutaneous [SC], sublingual [SL],transdermal [TD], other [OTH], unknown [UNK]

Clarification(s) for Investigator or delegate only:

Instructions to complete:
Medication

➢ *DOSE, UNIT AND FREQUENCY*

- Write the amount of the medication your took.

Dose, unit and frequency
200mg pill 3 times a day
2 coffee spoon 100mg once per day
3 suppositories per day
Nasal drops 4 times per day

- Most of this information can be found on the label of the medication. You may want to bring the medication to your next visit with the study doctor or study staff. Then they can help you to fill in the required information.

➢ *BOX "STILL ONGOING" IN THE COLUMN "END DATE" – WHEN TO TICK IT?*

- Tick the box "Still ongoing" if the medication is still taken at the time you return the diary card to the site.

(Tdap-0.3-009 Ext:007 Year 9) GlaxoSmithKline 110086	**DIARY CARDS** *Boostrix*	**Subject Number** |___|___|___|___|___|___| To be completed by the investigator or delegate

MEDICATION

Record any medication taken since the last study vaccination.

Medication	Reason	Dose, unit and frequency	Start Date	End Date Tick box if still ongoing↓	**Route*** To be completed by the investigator or delegate
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* **Route codes** = inhalation [IH], intraarticular [IR], intradermal [ID], intramuscular [IM], intranasal [IN], intravenous [IV], oral [PO], parenteral [PE], rectal [PR], subcutaneous [SC], sublingual [SL], topical [TO], transdermal [TD], vaginal [VA], other [OTH], unknown [UNK]

Clarification(s) for Investigator or delegate only:

(Tdap-0.3-009 Ext:007 Year 9) 110086	DIARY CARDS *Boostrix*	Subject Number |__|__|__|__|__|__|__| To be completed by the investigator or delegate

NOTES

INVESTIGATOR'S OR DELEGATE'S SIGNATURE

Investigator's or delegate's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|

Printed Investigator's or delegate's name: _____

List of investigators, IEC/IRB and distribution of subjects

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
United States						
PPD		PPD	PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	35	3.26
	PPD		PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	52	4.85
			PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	60	5.60
			PPD PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	75	7.0

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD			PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	65	6.06
			PPD PPD United States,PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	8	0.74
			PPD PPD , United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	33	3.08
			PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	52	4.85

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD			PPD United States PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	25	2.33
			PPD PPD United States PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	3	0.28
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	16	1.49
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	41	3.82
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	68	6.34

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD			PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	10	0.93
			PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	60	5.60
			PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	76	7.09

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD			PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	7	0.65
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	33	3.08
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	88	8.21
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	79	7.37
			PPD PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	22	2.05

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD	PPD		PPD PPD United States,	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	31	2.89
PPD PPD FPI)			PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101	21	1.96
PPD			PPD PPD United States PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	32	2.98

Investigator	Sub-Investigator	Center no.	Description of Research Facility, Hospital/ Institution, and Address	Name of IEC/IRB Committee, Address	Number of Subjects	% of Subjects
PPD			PPD PPD United States PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	50	4.66
			PPD United States, PPD	Quorum Review IRB, 1501Fourth Avenue, Suite 800, Seattle, WA, United States, 98101.	29	2.70

Representative written information for patient and sample consent forms

CONFIDENTIAL

Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK Biologicals' **mandatory** wording and should be retained; any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red hidden text must not be retained.

Refer to SOP_54823, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).

INFORMED CONSENT FORM for Boostrix and Adacel groups

Study Identification: 110086 (Tdap-0.3-009 Ext: 007 Year 9)

Study Title: Persistence study of GSK Biologicals' Tdap vaccine 776423, 1, 3, 5 and 9 years following administration as a single dose in the 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.

Model ICF Version Number: 02 **(replace with Version of Local ICF)**

Date: Final: 02/January/2015 **(replace with Date of Local ICF)**

Company Name: GlaxoSmithKline (GSK) Biologicals S.A.

Subject Identification: _____

Insert subject ID here

What is consent?

Consent means agreeing to take part in this research study. You can decide if you want to take part in this study or not. Please take time to read the following information and ask the study doctor or study staff if you have any questions. They will explain the study fully to you. You can talk in confidence with family, friends and your doctor to help you make a decision. You must sign the consent pages at the end of this form if you decide to join this study. You will receive a copy of this form.

Why is this study being done?

You were vaccinated with a Tdap (tetanus toxoid, diphtheria toxoid and acellular pertussis) vaccine in study 106316 (Tdap-0.3-007). Vaccines work by stimulating antibodies (substances that protect against diseases).

GlaxoSmithKline (GSK) Biologicals' Tdap vaccine is approved in the United States of America (USA) under the trade name *Boostrix. Boostrix* is approved as a booster vaccination against diphtheria, tetanus and pertussis. The study staff can provide you with more details of the diseases. This study is being done to test how long the antibodies remain in the body approximately nine years after receiving Tdap vaccine and how people who have already gotten the first dose of *Boostrix* respond to receiving a second dose of the vaccine approximately nine years later.

This study involves three groups. Depending on whether you participated in the study 106316 (Tdap-0.3-007) nine years ago, or if you are new to the study, you will be placed in one of the following three study groups:

- Control group: This is a new group being introduced in the study and participants enrolled in this group will receive *Boostrix* for the first time in this study.
- Boostrix group: The participants in this group had received *Boostrix* approximately nine years ago and will receive another dose of *Boostrix* vaccine in this study.

- Adacel group: The participants in this group had received Sanofi Pasteur's Tdap vaccine (*Adacel*) approximately nine years ago and will receive a dose of *Boostrix* vaccine in this study.

How is GSK involved?

GSK is a company that studies and makes vaccines, medicines and other health products. GSK planned and organized this study. GSK pays the study doctor and the institution to run this study.

GSK will be the owner of the study results. GSK plans to use these to get patents, sell the vaccine in the future or make profits in other ways. You will not be paid for any part of this.

The information and materials we give you about this study are confidential and belong to GSK. We ask that you keep it private. You can share this information with your doctor, family or friends when discussing about your participation in this study and your healthcare.

Who can join this study?

You can participate in this study if:

- You have signed this informed consent form.
- You had taken part in the previous study 106316 (Tdap-0.3-007) conducted by GSK Biologicals, nine years ago.
- You have not had any Tdap or pertussis containing vaccine since the last dose received in the study 106316 (Tdap-0.3-007).
- You have not received any tetanus or diphtheria containing vaccine or any registered or investigational vaccine using a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of *Boostrix* vaccine in this study.
- You do not have a history of diphtheria, tetanus or pertussis diseases since the previous vaccination in the study 106316 (Tdap-0.3-007).
- You have not had any serious side effects after previous administration of diphtheria, tetanus or pertussis vaccines.
- You are not pregnant or breast-feeding your baby (if applicable).
- You are healthy.

If you do not wish to receive vaccine, you can participate in the persistence only part of this study in which you will not receive any vaccinations or other treatment as a part of the study. Instead, you will be asked to provide a blood sample of about 5 mL (about 1 teaspoon).

The study doctor will also explain and check some other aspects before you can join this study. You can ask your study doctor for more details.

What does this study involve?

This study will be done across different centers in the USA. All those people who participated in the study 106316 (Tdap-0.3-007) will be invited to participate in this follow-up study. Additionally, others who did not participate in study 106316 (Tdap-0.3-007) but who meet the eligibility criteria will be invited to participate as a part of the Control group. All the participants in all the groups will receive a single dose of *Boostrix* vaccine. Approximately 367 participants will be enrolled in the Control group and we expect that approximately 733 participants in the Boostrix group and 367 participants in the Adacel group will be enrolled.

The study will last for approximately 30 days. You will need to visit the study site twice. You will receive one vaccine injection in your arm on the first visit. The study staff will ask you questions about your health since previous vaccination. You will also be asked to provide a blood sample of about 5 mL (about 1 teaspoon) before and one month after vaccination. The study doctor will ask you whether you have received any medication or vaccination since the last visit.

The study staff will give you a card (called a diary card) to write down information about how you feel on the day of vaccination and during the 30 days after you receive the vaccine:

- The doctor will explain to you how to record information on any pain, redness or swelling at the injection site, body temperature, headache, tiredness or stomach disorder that you may experience on the day of vaccination and the following 3 days.
- You will also be asked to record any other symptoms that you may experience between the two study visits.

If you take part in this study then it is important that you follow all study activities as described here below:

Visit	What will happen at this visit
First Visit [Visit 6 (Day 0)]	You will be explained the study procedures and you will be asked to sign the present "informed consent" document. The doctor will ask you about your medical history, medication and vaccination you have taken. You will undergo: • Physical examination including measurement of body temperature • Urine pregnancy test (if applicable) • Blood sampling • Administration of *Boostrix* vaccine You will receive a diary card and will be asked to use it to record any symptom you may experience during the follow-up until the next visit.

Visit	What will happen at this visit
Second Visit [Visit 7 (Day 30)]	You will return the diary card. The doctor will ask you if you have received any medication or vaccination since the previous visit. You will undergo: • Blood sampling End of study

In addition, you should call the doctor if at any time during the study:

- you are hospitalized
- you have symptoms that made it difficult for you to carry out your normal daily activities.

You will receive a card with study contact information. Keep this card with you at all times during the study. Show this card to the medical staff if you need emergency care during the study. The medical staff can then contact your study doctor if needed to ask about the vaccine or product you received.

What about pregnancy and breastfeeding?

It is not known whether the vaccine used in this study may have an effect on the unborn baby. You should not join this study if you are pregnant. Mothers should not breastfeed their baby while in this study.

If you are a woman who can get pregnant, you will need to use birth control while in this study. You will have a pregnancy test before receiving the dose of the vaccine. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods may not be allowed to use during this study.

Tell the study doctor if you are pregnant. If you get pregnant during the study, you can remain in the study for follow-up. We will follow-up until the delivery of the baby.

What will happen to samples taken in this study?

The content of this section needs to be aligned with the Use of Human Samples form. Any request to changes in this section must be discussed with the central study team and the GSK Biologicals' ICF taskforce prior to finalization of the ICF.

As part of the study, you will be asked to give samples of your blood. Your blood samples may be sent to GSK or other laboratories working with GSK including those outside [insert name of country] to:

- measure how your body reacts to the study vaccine.
- **ensure the quality of the tests we use for the study vaccine and/ or diseases.**

- **improve tests and develop new tests linked to the study vaccine and/or diseases. These tests will never include testing related to your genes' hereditary characteristics.**

Your samples will be given a code so that it does not directly identify you.

Your samples will be kept for a maximum of 20 **years from the end of the study**. **Any sample remaining at that time will be destroyed**.

Optional tests on your samples:

If you agree, your sample(s) may also be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board.

You can choose not to allow these optional tests and still be in the study.

What side effects or risks can you expect in this study?

The following side effects related to the study procedures may occur:

When you give blood, you may feel like fainting, or experience mild pain, bruising, irritation or redness at the site where blood was taken or where you received vaccination.

The tip caps of the syringes used may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals.

The potential side effects associated with *Boostrix* is similar to those seen with routine vaccination. They can be mild or more severe. We will follow-up everyone in the study for any side effects.

There may be other side effects that are not known now.

The following side effects may be observed within 4 days of vaccine administration:

- Injection site reactions: Pain, redness and swelling.
- General side effects: Tiredness, fever, headache, nausea, vomiting, diarrhea and abdominal pain.

Expected risks for adults are detailed below according to the following frequency of occurrence:

- Very common: Injection-site pain, injection-site reactions (such as redness and/or swelling), tiredness headache and generally feeling unwell.
- Common: Fever (temperature greater than or equal to 99.5° F), hard lump and pus at injection site, nausea and dizziness.
- Uncommon: Fever (temperature greater than 102.2°F), pain, vomiting, sore throat, and discomfort while swallowing, cough, fainting, skin rash, flu like symptoms like fever, sore throat, runny nose, cough and chills, muscle stress, muscle pain, joint

stiffness, excessive sweating, itching all over the body, swelling of glands in neck, groin and arm pits, diarrhea and infection of the upper respiratory tract.

- Rare: Water retention with swelling of the injected limb, allergic reaction, (characterized by swelling of lips, tongue, or other parts of the body, shortness of breath, rashes across body and difficulty swallowing), unusual weakness and fits.
- Very rare: As with all injectable vaccines, severe allergic reactions (anaphylactic and anaphylactoid reactions) may very rarely occur. They are characterized by, itchy rash of the hands and feet, swelling of the eyes and face, difficulty in breathing or swallowing, sudden drop in blood pressure and fainting.

In addition to the side effects mentioned above, the following side effects were reported voluntarily throughout the world in persons aged 10 years and older since the introduction of *Boostrix* vaccine to the market. These reported side effects have not been established as caused due to vaccination:

Myocarditis (swelling up of heart muscle), extensive swelling of the injected limb, itching of the injection site, injection site mass, warmth at injection site, joint pain, back pain, encephalitis (swelling up of brain), facial palsy (loss of facial movement), paresthesia (refers to a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body), angioedema (rapid swelling under the skin), exanthema (eruptive skin rash), Henoch-Schonlein purpura (involves the development of purple spots on the skin, joint pain, problems with stomach, intestine and kidneys) and urticaria (also known as hives which is an outbreak of swollen, pale red bumps, patches on the skin that appear suddenly).

The vaccines in this study may not protect all people who get them. Your response to the vaccine in this study will be tested. In some cases, the test results may show your response to the vaccination was not optimal. If the study doctor believes you would benefit from another vaccination, he or she will contact you.

What benefits can you expect in this study?

This study may be beneficial to you in the following ways:

- You will receive information about the vaccine or diseases.
- The vaccine and study tests will be free for you. However, there is no guarantee that you will be protected against these diseases following vaccination.

Are there other products or treatment?

This section should be completed locally using the most current information regarding the treatments/ vaccines/ products that are available in the country and their important potential benefits and risks. State if there are no alternate treatments.

In the USA, there is no recommendation currently for receiving more than one dose of any Tdap vaccine. You do not have to participate in the study to receive Tdap vaccine and there are other commercially available Tdap vaccines in the US.

Talk with your doctor about your options, before you decide to take part in this study. The study doctor can advise you if you need more information.

Do you have to stay in the study?

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

We will share with you as soon as possible any new information that may change your choice to stay in the study.

Tell the study doctor if you no longer want to take part in the study.

GSK may choose to stop your participation in the study or the study doctor may choose to stop your participation in the study at any time. We will then tell you why. We may ask you to leave the study if:

- You do not follow study instructions
- The study doctor thinks it is in your best interest to stop, e.g. if you have specific health problems

What happens if you leave the study?

Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in the Local ICF compared to the Model ICF, in response to a request from any source, these should be discussed with the central study team and GSK Vaccines ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection can be taken into account.

No more information about you will be collected after you leave the study. All the information and samples collected before you left the study will still be used.

If the doctor becomes aware of any relevant safety information about you after you left the study, this will be collected.

We may also contact you later for information. This is to help us better understand the safety profile of the vaccine.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations.

Informed Consent Form

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Boostrix and Adacel groups

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information can be used as described here.

- Your personal and medical information may be checked by GSK and others (like agencies that approve and monitor studies for example, Food and Drug administration (FDA)). This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labeled with a code number (for example, PPD It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - keep it electronically, and analyze it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - share it with regulatory agencies that approve new vaccines and medicines,
  - share it with people who check that the study is done properly (like the independent ethics committee or review boards),
  - combine it with results from other studies to learn more about the vaccine and other vaccines and these diseases and related diseases. This may help us to assess the risks and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,
  - publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.
  - share coded information with other companies, organizations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the trial may be moved to, stored and used in the country where you live or another country where GSK or those working with

GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical trial will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the clinical study is conducted.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

What happens if you get hurt while taking part in this study?

GSK will help pay for your care if you are hurt by the study vaccine or a procedure done to you as part of the study. GSK will pay for reasonable and necessary care for the injury that is not covered by the National Vaccine Injury Compensation Fund. GSK will not pay for any other expenses. To pay these medical expenses, GSK will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because GSK has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare. GSK will not use this information for any other purpose.

Signing this consent form does not change any legal rights you may have.

Will you be paid for being in the study?

This section should be completed locally.

You will not be paid for taking part of this study. **OR**

We will reimburse you for the cost of travelling to your study visits. You may receive up to **[amount]** for travel / per visit.

Do you have to pay anything to be in the study?

Authors note that this section is optional. This section should be completed locally.

You will get all the study tests and procedures for free **[or indicate if there is a cost]**.

Who should you contact if you have questions?

Identify who the subject should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: **name, address, telephone number.**

Person to contact about your rights: **name, address, telephone number.**

Person to contact in case of injury: **name, address, telephone number.**

Informed Consent Form Subject ID_____

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Boostrix and Adacel groups

Consent statement

I,

_____

Printed name of Subject

- confirm that I have read the written information (or have had the information read to me) for study 110086 (Tdap-0.3-009 Ext: 007 Year 9), Version 02, 02/January/2015, 12 pages **(to be updated locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the chance to ask questions about this study and I am satisfied with the answers and explanations that have been given.
- understand that I give access to data about me to authorized persons described in this information sheet.
- I know what will happen to my blood samples.
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider taking part to take part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my family doctor will be told about my participation in the study.

☐ **Yes** ☐ **No**

Tick as appropriate

I agree that my biological sample(s) may be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board. I understand that if I select "No", I can still take part in the study.

☐ **Yes** ☐ **No**

I agree to take part in this study.

Signature of subject _____ Date: _____ day/ month/ year

Indicate version: i.e. Local **(specify country and subset if applicable)** ICF Version Number **NN**, Dated: **DD/MMM/YYYY**, based on Model ICF (Boostrix and Adacel groups) Version Number 02, Dated: 02/JAN/2015

Informed Consent Form Subject ID_____

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Boostrix and Adacel groups

I confirm that I have conducted the consent process according to applicable regulations.

Printed name of person conducting consent _____

Signature of person conducting consent _____ Date: _____ day/ month/ year

Delete the following Appendix in the Final local ICF.

Appendix A GlaxoSmithKline Biologicals Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Biologicals internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator's study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject's confidentiality would be maintained for the retained samples, must be reported in the ICF.

The content of this section must be fully aligned with the Use of Human Samples form. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and

local regulations. To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account

Type of changes

Changes to the local ICF can be classified into 3 categories:

'Not permitted' changes

BOLD BLACK mandatory text in the model ICF should not be changed.

'Required' changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as **BOLD RED** text in the model ICF e.g. investigator details).

'Justified' changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Study Identification		
Check if study identification is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Study Title		
Check if study title is identical to Model ICF.	Not permitted	The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
ICF Version Number and Date		
Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
Company Name		
Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required by local regulations.	Justified	A change to this section is permitted if it is justified by local regulations. For some countries, the local GSK affiliate should be indicated as Company Name.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Subject/Patient Identification		
Check whether there is space foreseen to insert the subject ID.	Required	The subject/patient ID should be mentioned on the ICF to be able to link the subject/patient ID with the corresponding source documents and RDE entries.
Header		
Check if study identification in header is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Footer		
Indicate version of Local ICF and check if reference to the Model ICF version is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject/patient may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
What is consent?		
Explain the consent process and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	Freely given and written informed consent must be obtained from each subject/patient/LAR prior to study participation. Informed consent involves an education and information exchange that takes place between the researcher and the potential subject/patient. How the process of consenting looks like, needs to be explained in the

ICF section	Type of changes	Rationale/Impact
		ICF. The text can be simplified, if necessary.
Why is this study being done?		
Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
How is GSK involved?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The role of the sponsor should be explained in this section. The text can be simplified if necessary.
Who can join this study?		
Summarize the main inclusion and exclusion criteria. Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What does this study involve?		
Explain the approximate number of subjects/patients involved in the study, the study design and groups, the study procedures and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary
If subject cards are used, check if the text is identical to the Model ICF.	Not permitted	Subject cards provide information about the study which can be used in the event of a medical emergency. Provision of this information in the ICF ensures that the subject/patient is aware of the use of the subject card. This

ICF section	Type of changes	Rationale/Impact
		information will also indicate to the ethics committee that it is provided to the subject/patient.
What about pregnancy and breastfeeding?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What will happen to samples taken in this study?		
Check if all mandatory wording from the Model ICF is present in the Local ICF.	Not permitted	If this text is changed, there is a risk to use human samples outside the subject‘s/patient’s consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data etc… .
Check if the content of this section is aligned with the Use of Human samples form (UHSF).	Not permitted	The text in the ICF should match 100% with the information documented in the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject‘s/ patient’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

ICF section	Type of changes	Rationale/Impact
Check if the QA (Quality Assurance) on tests related to the study vaccine/ disease (type 2 testing) is reported in the Local ICF.	Not permitted	QA testing will be done at <u>all times</u>, assuming it is allowed as per individual subject's/patient's consent. If QA testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted.
Check local regulations regarding tests related to the product/disease under study (type 3a and 3b testing). [If there are concerns regarding this text then this should be discussed with the central team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since type 3a or 3b should be chosen according to local regulations. However, <u>the wording of the text itself, should not be changed</u>! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording. So if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject's consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Check Local regulations regarding storage duration. Check if the wording "for a maximum of 20 years" is not changed into "for 20 years". [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for "for a maximum of"20 years. Attention should be paid to the used wording "**for a maximum of**" 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the UHSF. This will allow the laboratory to take the appropriate measures for sample storage, "for a maximum of 20" years or as defined in the ICF and documented in the UHSF section called "other".
Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, <u>the wording of the text itself, should not be changed and nothing should be added</u>! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's/patient's consent and local regulations. If this text is changed, there is a risk to use human samples outside the

ICF section	Type of changes	Rationale/Impact
		subject‘s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….
What side effects or risks can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary. Refer to the GSK Position Paper on ‘Communication of Individual Immunological Assay Results to Study Sites’ for additional information.
Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.	Not permitted	The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The AID wording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.
Check if the text on Rotarix, if applicable, is identical to the Model ICF.	Not permitted	This text has been approved by GSK upper management following feedback from Authorities.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
What benefits can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary
Are there other products or treatment?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
Add currently available local alternatives, if applicable.	Required	This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.
Do you have to stay in the study?		
Explain voluntary participation and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
What happens if you leave the study?		
Check if the text on the use of data after subject/patient withdrawal is identical to the	Justified	The bold text in this section has been approved by Medical Governance. Changes to this

ICF section	Type of changes	Rationale/Impact
Model ICF. [Check local regulations and seek local legal advice] [If the text needs to be changed it should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF].		section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to GSK's Clarification Paper on 'Handling Data after Subject withdrawal' for additional information.
What about your personal and medical information?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]	Justified	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary.
What happens if you get hurt while taking part in this study?		
- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]	Justified	The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury
- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.	Justified	The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Will you be paid for being in the study?		
Information related to this section is added at a regional or country level.	Required	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject/patient is well informed before consenting to participation. The anticipated prorated payment or other financial benefit, if any, to the subject for participating in the study should be mentioned in the ICF. Explain if expenses incurred by subjects for clinical visits made because of their participation in the study will be reimbursed or not.
Do you have to pay anything to be in the study?		
This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.	Justified	If appropriate for a study, include here information on cost/expenses that subject/patient will have to bear for taking part in the study i.e., whether the subject/patient or the subject's/patient's insurance will be charged for any study item or procedure. According to ICH-GCP, the anticipated expenses, if any, to the subject/patient for participating in the study should be mentioned.
Who should you contact if you have questions?		
Add local contact details.	Required	The content of this section is required by ICH-GCP. The subject/patient must have a contact person for further information regarding the study, his rights and who to contact in the event of trial-related injury.
Consent statement		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The consent statement should be aligned with ICH-GCP requirements. Omitting any of the information can have legal

ICF section	Type of changes	Rationale/Impact
		implications
Check local regulations regarding future research (type 4 testing). Check if the wording is identical to the wording in the body of the ICF. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. This type of testing is optional for the subject/patient, meaning that if this testing is mentioned in the body of the ICF, a tick box should be available in the consent statement. The wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by using the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF.

References

SOP_54823, Development and implementation of Informed Consent for clinical studies.

GUI_51905, Guidance for Informed Consent documents.

GUI-BIO-CLIN-0014, Guidance for the development of Informed Consent-related documents.

GSK's Position Paper on Communication of Individual Immunological Assay Results To Study Sites.

GSK's Clarification Paper on Handling Data after Subject withdrawal.

GSK's Clarification Paper on Future Use of Biospecimens

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Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK Biologicals' **mandatory** wording and should be retained; any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red hidden text must not be retained.

Refer to SOP_54823, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).

INFORMED CONSENT FORM for Control group

Study Identification: 110086 (Tdap-0.3-009 Ext: 007 Year 9)

Study Title: Persistence study of GSK Biologicals' Tdap vaccine 776423, 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.

Model ICF Version Number: 02 **(replace with Version of Local ICF)**

Date: Final: 02/January/2015 **(replace with Date of Local ICF)**

Company Name: GlaxoSmithKline (GSK) Biologicals S.A.

Subject Identification: _____

Insert subject ID here

What is consent?

Consent means agreeing to take part in this research study. You can decide if you want to take part in this study or not. Please take time to read the following information and ask the study doctor or study staff if you have any questions. They will explain the study fully to you. You can talk in confidence with family, friends and your doctor to help you make a decision. You must sign the consent pages at the end of this form if you decide to join this study. You will receive a copy of this form.

Why is this study being done?

GlaxoSmithKline (GSK) Biologicals' Tdap vaccine is approved in the United States of America (USA) under the trade name *Boostrix. Boostrix* is approved as a booster vaccination against diphtheria, tetanus and pertussis. The study staff can provide you with more details of the diseases.

Vaccines work by stimulating antibodies (substances that protect against diseases). This study is being done to test how long the antibodies remain in the body approximately nine years after receiving Tdap vaccine and how people who have already gotten the first dose of *Boostrix* respond to receiving a second dose of the vaccine approximately nine years later.

This study involves three groups:

- Control group: This is a new group being introduced in the study and participants enrolled in this group will receive *Boostrix* for the first time in this study.
- Boostrix group: The participants in this group had received *Boostrix* approximately nine years ago and will receive another dose of *Boostrix* vaccine in this study.

- Adacel group: The participants in this group had received Sanofi Pasteur's Tdap vaccine (*Adacel*) approximately nine years ago and will receive a dose of *Boostrix* vaccine in this study.

Since you are a new participant in this study you will be placed in the Control group.

How is GSK involved?

GSK is a company that studies and makes vaccines, medicines and other health products. GSK planned and organized this study. GSK pays the study doctor and the institution to run this study.

GSK will be the owner of the study results. GSK plans to use these to get patents, sell the vaccine in the future or make profits in other ways. You will not be paid for any part of this.

The information and materials we give you about this study are confidential and belong to GSK. We ask that you keep it private. You can share this information with your doctor, family or friends when discussing about your participation in this study and your healthcare.

Who can join this study?

You can participate in this study if:

- You are between the age of 28-73 years old and you have signed this informed consent form.
- You have not previously gotten a Tdap vaccine (either *Boostrix* or *Adacel*) at any time prior to study entry.
- You do not have a history of diphtheria, tetanus or pertussis diseases.
- You have not received any tetanus or diphtheria containing vaccine or any registered or investigational vaccine using a diphtheria toxoid or tetanus toxoid carrier within 5 years prior to the administration of *Boostrix* vaccine in this study.
- You have not had any serious side effects after previous administration of diphtheria and/or tetanus vaccines.
- You are not pregnant or breast-feeding your baby (if applicable).
- You are healthy.

The study doctor will also explain and check some other aspects before you can join this study. You can ask your study doctor for more details.

What does this study involve?

This study will be done across different centers in the USA. You will be placed in the Control group. For the other two groups, those subjects who participated in the previous

study 106316 (Tdap-0.3-007) will be invited to participate in this follow-up study and will be placed in either Boostrix group or Adacel group.

When we have enough people enrolled in the Control group, we will not include or invite any more people. All the participants in all the three groups mentioned above will receive a single dose of *Boostrix* vaccine. Approximately 367 participants will be enrolled in the Control group, and we expect that approximately 733 participants in the Boostrix group and 367 participants in the Adacel group will be enrolled.

The study will last for approximately 30 days. You will need to visit the study site twice. You will get one injection in your arm on the first visit. You will also be asked to provide a blood sample of about 5 mL (about 1 teaspoon) before and one month after vaccination. The study doctor will ask you whether you have received any medication or vaccination since the last visit.

The study staff will give you a card (called a diary card) to write down information about how you feel on the day of vaccination and during the 30 days after you receive the vaccine:

- You will be instructed to record information on any pain, redness or swelling at the injection site, body temperature, headache, tiredness or stomach disorder that you may experience on the day of vaccination and the following three days.
- You will also be asked to record any other symptoms that you may experience between the two study visits.

If you decide to take part in this study then it is important that you follow all study activities as described below:

Visit	What will happen at this visit
First Visit [Visit 6 (Day 0)]	You will be explained the study procedures and you will be asked to sign the present "informed consent" document. The doctor will ask you about your medical history, medication and vaccination you may have taken. You will undergo: • Physical examination including measurement of body temperature • Urine pregnancy test (if applicable) • Blood sampling • Administration of *Boostrix* vaccine You will receive a diary card and will be asked to use it to record any symptom you may experience during the follow-up until the next visit.
Second Visit [Visit 7 (Day 30)]	You will return the diary card. The doctor will ask you whether you have received any medication or vaccination since the previous visit. You will undergo: • Blood sampling End of study

In addition, you should call the study doctor if at any time during the study:

- you are hospitalized
- you have symptoms that make it difficult for you to carry out your normal daily activities

You will receive a card with study contact information. Keep this card with you at all times during the study. Show this card to the medical staff if you need emergency care during the study. The medical staff can then contact your study doctor if needed to ask about the vaccine or product you received.

What about pregnancy and breastfeeding?

It is not known whether the vaccine used in this study may have an effect on the unborn baby. You should not join this study if you are pregnant. Mothers should not breastfeed their baby while in this study.

If you are a woman who can get pregnant, you will need to use birth control while in this study. You will have a pregnancy test before receiving the dose of the vaccine. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods may not be allowed to use during this study.

Tell the study doctor if you are pregnant. If you get pregnant during the study, you can remain in the study for follow-up. We will follow-up until the delivery of the baby.

What will happen to samples taken in this study?

The content of this section needs to be aligned with the Use of Human Samples form. Any request to changes in this section must be discussed with the central study team and the GSK Biologicals' ICF taskforce prior to finalization of the ICF.

As part of the study, you will be asked to give samples of your blood. Your blood samples may be sent to GSK or other laboratories working with GSK including those outside [insert name of country] to:

- measure how your body reacts to the study vaccine.
- **ensure the quality of the tests we use for the study vaccine and/ or diseases.**
- **improve tests and develop new tests linked to the study vaccine and/or diseases. These tests will never include testing related to your genes' hereditary characteristics.**

Your samples will be given a code so that it does not directly identify you.

Your samples will be kept for a maximum of 20 **years from the end of the study. Any sample remaining at that time will be destroyed**.

Optional tests on your samples:

If you agree, your sample(s) may also be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board.

You can choose not to allow these optional tests and still be in the study.

What side effects or risks can you expect in this study?

The following side effects related to the study procedures may occur:

When you give blood, you may feel like fainting, or experience mild pain, bruising, irritation or redness at the site where blood was taken or where you received vaccination.

The tip caps of the syringes used may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals.

The potential side effects associated with *Boostrix* is similar to those seen with routine vaccination. They can be mild or more severe. We will follow-up everyone in the study for any side effects.

There may be other side effects that are not known now.

The following side effects may be observed within four days of vaccine administration:

- Injection site reactions: Pain, redness and swelling.
- General side effects: Tiredness, fever, headache, nausea, vomiting, diarrhea and abdominal pain.

Expected risks for adults are detailed below according to the following frequency of occurrence:

- Very common: Injection-site pain, injection-site reactions (such as redness and/or swelling), tiredness headache and generally feeling unwell.
- Common: Fever (temperature greater than or equal to 99.5° F), hard lump and pus at injection site, nausea and dizziness.
- Uncommon: Fever (temperature greater than 102.2°F), pain, vomiting, sore throat, and discomfort while swallowing, cough, fainting, skin rash, flu like symptoms like fever, sore throat, runny nose, cough and chills, muscle stress, muscle pain, joint stiffness, excessive sweating, itching all over the body, swelling of glands in neck, groin and arm pits, diarrhea and infection of the upper respiratory tract.
- Rare: Water retention with swelling of the injected limb, allergic reaction, (characterized by swelling of lips, tongue, or other parts of the body, shortness of breath, rashes across body and difficulty swallowing), unusual weakness and fits.
- Very rare: As with all injectable vaccines, severe allergic reactions (anaphylactic and anaphylactoid reactions) may very rarely occur. They are characterized by, itchy rash

of the hands and feet, swelling of the eyes and face, difficulty in breathing or swallowing, sudden drop in blood pressure and fainting.

In addition to the side effects mentioned above, the following side effects were reported voluntarily throughout the world in persons aged 10 years and older since the introduction of *Boostrix* vaccine to the market. These reported side effects have not been established as caused due to vaccination:

Myocarditis (swelling up of heart muscle), extensive swelling of the injected limb, itching of the injection site, injection site mass, warmth at injection site, joint pain, back pain, encephalitis (swelling up of brain), facial palsy (loss of facial movement), paresthesia (refers to a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body), angioedema (rapid swelling under the skin), exanthema (eruptive skin rash), Henoch-Schonlein purpura (involves the development of purple spots on the skin, joint pain, problems with stomach, intestine and kidneys) and urticaria (also known as hives which is an outbreak of swollen, pale red bumps, patches on the skin that appear suddenly).

The vaccine in this study may not protect all people who get them. Your response to the vaccine in this study will be tested. In some cases, the test results may show your response to the vaccination was not optimal. If the study doctor believes you would benefit from another vaccination, he or she will contact you.

What benefits can you expect in this study?

This study may be beneficial to you in the following ways:

- You will receive information about the vaccine or diseases.
- The vaccine and study tests will be free for you. However, there is no guarantee that you will be protected against these diseases following vaccination.

Are there other products or treatment?

This section should be completed locally using the most current information regarding the treatments/ vaccines/ products that are available in the country and their important potential benefits and risks. State if there are no alternate treatments.

In the USA, there is no recommendation currently for receiving more than one dose of any Tdap vaccine. You do not have to participate in the study to receive Tdap vaccine and there are other commercially available Tdap vaccines in the US.

Talk with your doctor about your options, before you decide to take part in this study. The study doctor can advise you if you need more information.

Do you have to stay in the study?

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

We will share with you as soon as possible any new information that may change your choice to stay in the study.

Tell the study doctor if you no longer want to take part in the study.

GSK may choose to stop your participation in the study or the study doctor may choose to stop your participation in the study at any time. We will then tell you why. We may ask you to leave the study if:

- You do not follow study instructions
- The study doctor thinks it is in your best interest to stop, e.g. if you have specific health problems.

What happens if you leave the study?

Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in the Local ICF compared to the Model ICF, in response to a request from any source, these should be discussed with the central study team and GSK Biologicals ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection can be taken into account.

No more information about you will be collected after you leave the study. All the information and samples collected before you left the study will still be used.

If the doctor becomes aware of any relevant safety information about you after you left the study, this will be collected.

We may also contact you later for information. This is to help us better understand the safety profile of the vaccine.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations.

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information

can be used as described here.

- Your personal and medical information may be checked by GSK and others [like agencies that approve and monitor studies for example, Food and Drug administration (FDA)]. This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labeled with a code number (for example, PPD It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - keep it electronically, and analyze it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - share it with regulatory agencies that approve new vaccines and medicines,
  - share it with people who check that the study is done properly (like the independent ethics committee or review boards),
  - combine it with results from other studies to learn more about the vaccine and other vaccines and these diseases and related diseases. This may help us to assess the risks and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,
  - publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.
  - share coded information with other companies, organizations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the trial may be moved to, stored and used in the country where you live or another country where GSK or those working with GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical trial will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the clinical study is conducted.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

What happens if you get hurt while taking part in this study?

GSK will help pay for your care if you are hurt by the study vaccine or a procedure done to you as part of the study. GSK will pay for reasonable and necessary care for the injury that is not covered by the National Vaccine Injury Compensation Fund. GSK will not pay for any other expenses. To pay these medical expenses, GSK will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because GSK has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare. GSK will not use this information for any other purpose.

Signing this consent form does not change any legal rights you may have.

Will you be paid for being in the study?

This section should be completed locally.

You will not be paid for taking part of this study. **OR**

We will reimburse you for the cost of travelling to your study visits. You may receive up to **[amount]** for travel / per visit.

Do you have to pay anything to be in the study?

Authors note that this section is optional. This section should be completed locally.

You will get all the study tests and procedures for free **[or indicate if there is a cost]**.

Who should you contact if you have questions?

Identify who the subject should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: **name, address, telephone number.**

Person to contact about your rights: **name, address, telephone number.**

Person to contact in case of injury: **name, address, telephone number.**

Informed Consent Form Subject ID_____

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Control group

Consent statement

I,

_____

Printed name of Subject

- confirm that I have read the written information (or have had the information read to me) for study 110086 (Tdap-0.3-009 Ext: 007 Year 9), Version 02, 02/January/2015, 12 pages **(to be updated locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the chance to ask questions about this study and I am satisfied with the answers and explanations that have been given.
- understand that I give access to data about me to authorized persons described in this information sheet.
- I know what will happen to my blood samples.
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider taking part to take part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my family doctor will be told about my participation in the study.

☐ **Yes** ☐ **No**

Tick as appropriate

I agree that my biological sample(s) may be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board. I understand that if I select "No", I can still take part in the study.

☐ **Yes** ☐ **No**

I agree to take part in this study.

Signature of subject _____ Date: _____ day/ month/ year

Indicate version: i.e. Local **(specify country and subset if applicable)** ICF Version Number **NN**, Dated: **DD/MMM/YYYY**, based on Model ICF (Control group) Version Number 02, Dated: 02/JAN/2015

Informed Consent Form Subject ID_____

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Control group

I confirm that I have conducted the consent process according to applicable regulations.

Printed name of person conducting consent _____

Signature of person conducting consent _____ Date: _____ day/ month/ year

Delete the following Appendix in the Final local ICF.

Appendix A GlaxoSmithKline Biologicals Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Biologicals internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator's study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject's confidentiality would be maintained for the retained samples, must be reported in the ICF.

The content of this section must be fully aligned with the Use of Human Samples form. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and

local regulations. To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account

Type of changes

Changes to the local ICF can be classified into 3 categories:

'Not permitted' changes

BOLD BLACK mandatory text in the model ICF should not be changed.

'Required' changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as **BOLD RED** text in the model ICF e.g. investigator details).

'Justified' changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Study Identification		
Check if study identification is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Study Title		
Check if study title is identical to Model ICF.	Not permitted	The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
ICF Version Number and Date		
Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
Company Name		
Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required by local regulations.	Justified	A change to this section is permitted if it is justified by local regulations. For some countries, the local GSK affiliate should be indicated as Company Name.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Subject/Patient Identification		
Check whether there is space foreseen to insert the subject ID.	Required	The subject/patient ID should be mentioned on the ICF to be able to link the subject/patient ID with the corresponding source documents and RDE entries.
Header		
Check if study identification in header is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Footer		
Indicate version of Local ICF and check if reference to the Model ICF version is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject/patient may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
What is consent?		
Explain the consent process and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	Freely given and written informed consent must be obtained from each subject/patient/LAR prior to study participation. Informed consent involves an education and information exchange that takes place between the researcher and the potential subject/patient. How the process of consenting looks like, needs to be explained in the

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
		ICF. The text can be simplified, if necessary.
Why is this study being done?		
Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
How is GSK involved?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The role of the sponsor should be explained in this section. The text can be simplified if necessary.
Who can join this study?		
Summarize the main inclusion and exclusion criteria. Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What does this study involve?		
Explain the approximate number of subjects/patients involved in the study, the study design and groups, the study procedures and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary
If subject cards are used, check if the text is identical to the Model ICF.	Not permitted	Subject cards provide information about the study which can be used in the event of a medical emergency. Provision of this information in the ICF ensures that the subject/patient is aware of the use of the subject card. This

ICF section	Type of changes	Rationale/Impact
		information will also indicate to the ethics committee that it is provided to the subject/patient.
What about pregnancy and breastfeeding?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What will happen to samples taken in this study?		
Check if all mandatory wording from the Model ICF is present in the Local ICF.	Not permitted	If this text is changed, there is a risk to use human samples outside the subject‘s/patient’s consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data etc… .
Check if the content of this section is aligned with the Use of Human samples form (UHSF).	Not permitted	The text in the ICF should match 100% with the information documented in the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject‘s/ patient’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

ICF section	Type of changes	Rationale/Impact
Check if the QA (Quality Assurance) on tests related to the study vaccine/ disease (type 2 testing) is reported in the Local ICF.	Not permitted	QA testing will be done at <u>all times</u>, assuming it is allowed as per individual subject's/patient's consent. If QA testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted.
Check local regulations regarding tests related to the product/disease under study (type 3a and 3b testing). [If there are concerns regarding this text then this should be discussed with the central team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since type 3a or 3b should be chosen according to local regulations. However, <u>the wording of the text itself, should not be changed</u>! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording. So if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject's consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Check Local regulations regarding storage duration. Check if the wording "for a maximum of 20 years" is not changed into "for 20 years". [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for "for a maximum of"20 years. Attention should be paid to the used wording "**for a maximum of**" 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the UHSF. This will allow the laboratory to take the appropriate measures for sample storage, "for a maximum of 20" years or as defined in the ICF and documented in the UHSF section called "other".
Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, the wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's/patient's consent and local regulations. If this text is changed, there is a risk to use human samples outside the

ICF section	Type of changes	Rationale/Impact
		subject‘s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….
What side effects or risks can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary. Refer to the GSK Position Paper on ‘Communication of Individual Immunological Assay Results to Study Sites’ for additional information.
Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.	Not permitted	The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The AID wording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.
Check if the text on Rotarix, if applicable, is identical to the Model ICF.	Not permitted	This text has been approved by GSK upper management following feedback from Authorities.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
What benefits can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary
Are there other products or treatment?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
Add currently available local alternatives, if applicable.	Required	This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.
Do you have to stay in the study?		
Explain voluntary participation and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
What happens if you leave the study?		
Check if the text on the use of data after subject/patient withdrawal is identical to the	Justified	The bold text in this section has been approved by Medical Governance. Changes to this

ICF section	Type of changes	Rationale/Impact
Model ICF. [Check local regulations and seek local legal advice] [If the text needs to be changed it should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF].		section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to GSK's Clarification Paper on 'Handling Data after Subject withdrawal' for additional information.
What about your personal and medical information?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]	Justified	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary.
What happens if you get hurt while taking part in this study?		
- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]	Justified	The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury
- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.	Justified	The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Will you be paid for being in the study?		
Information related to this section is added at a regional or country level.	Required	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject/patient is well informed before consenting to participation. The anticipated prorated payment or other financial benefit, if any, to the subject for participating in the study should be mentioned in the ICF. Explain if expenses incurred by subjects for clinical visits made because of their participation in the study will be reimbursed or not.
Do you have to pay anything to be in the study?		
This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.	Justified	If appropriate for a study, include here information on cost/expenses that subject/patient will have to bear for taking part in the study i.e., whether the subject/patient or the subject's/patient's insurance will be charged for any study item or procedure. According to ICH-GCP, the anticipated expenses, if any, to the subject/patient for participating in the study should be mentioned.
Who should you contact if you have questions?		
Add local contact details.	Required	The content of this section is required by ICH-GCP. The subject/patient must have a contact person for further information regarding the study, his rights and who to contact in the event of trial-related injury.
Consent statement		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The consent statement should be aligned with ICH-GCP requirements. Omitting any of the information can have legal

ICF section	Type of changes	Rationale/Impact
		implications
Check local regulations regarding future research (type 4 testing). Check if the wording is identical to the wording in the body of the ICF. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. This type of testing is optional for the subject/patient, meaning that if this testing is mentioned in the body of the ICF, a tick box should be available in the consent statement. The wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by using the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF.

References

SOP_54823, Development and implementation of Informed Consent for clinical studies.

GUI_51905, Guidance for Informed Consent documents.

GUI-BIO-CLIN-0014, Guidance for the development of Informed Consent-related documents.

GSK's Position Paper on Communication of Individual Immunological Assay Results To Study Sites.

GSK's Clarification Paper on Handling Data after Subject withdrawal.

GSK's Clarification Paper on Future Use of Biospecimens

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Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK Biologicals' **mandatory** wording and should be retained, any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red hidden text must not be retained.

Refer to SOP_54823, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).

INFORMED CONSENT FORM for Persistence only

Study Identification: 110086 (Tdap-0.3-009 Ext: 007 Year 9)

Study Title: Persistence study of GSK Biologicals' Tdap vaccine 776423, 1, 3, 5 and 9 years following administration as a single dose in 106316 study and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.

Model ICF Version Number: 02 **(replace with Version of Local ICF)**

Date: Final**:** 02/January/2015 **(replace with Date of Local ICF)**

Company Name: GlaxoSmithKline (GSK) Biologicals S.A.

Subject Identification: _____

Insert subject ID here

What is consent?

Consent means agreeing to take part in this research study. You can decide if you want to take part in this study or not. Please take time to read the following information and ask the study doctor or study staff if you have any questions. They will explain the study fully to you. You can talk in confidence with family, friends and your doctor to help you make a decision. You must sign the consent pages at the end of this form if you decide to join this study. You will receive a copy of this form.

Why is this study being done?

You were vaccinated with a Tdap (tetanus toxoid, diphtheria toxoid and acellular pertussis) vaccine in study 106316 (Tdap-0.3-007). Vaccines work by stimulating antibodies (substances that protect against diseases).

GlaxoSmithKline (GSK) Biologicals' Tdap vaccine is approved in the United States of America (USA) under the trade name *Boostrix. Boostrix* is approved as a booster vaccination against diphtheria, tetanus and pertussis. The study staff can provide you with more details of the diseases. This study is being done to test how long the antibodies remain in the body approximately nine years after receiving Tdap vaccine and how people who have already gotten the first dose of *Boostrix* respond to receiving a second dose of the vaccine approximately nine years later.

Because you do not meet the eligibility criteria for receiving a second dose of Tdap vaccine as a part of this study, or because you do not want to receive a second dose of Tdap vaccine, you are being asked to provide a blood sample to help test how long the antibodies remain in the body approximately nine years after receiving Tdap vaccine. Apart from the blood draw you will not receive any vaccinations or other treatment as a part of this study.

How is GSK involved?

GSK is a company that studies and makes vaccines, medicines and other health products. GSK planned and organized this study. GSK pays the study doctor and the institution to run this study.

GSK will be the owner of the study results. GSK plans to use these to get patents, sell the vaccine in the future or make profits in other ways. You will not be paid for any part of this.

The information and materials we give you about this study are confidential and belong to GSK. We ask that you keep it private. You can share this information with your doctor, family or friends when discussing about your participation in this study and your healthcare.

Who can join this study?

In order to be included in this study, the following requirements must be met:

- You have signed this informed consent form.
- You had taken part in the previous study 106316 (Tdap-0.3-007) conducted by GSK Biologicals, approximately nine years ago in which you received a dose of Tdap vaccine (either *Boostrix* or *Adacel*).

You can ask your study doctor for more details.

What does this study involve?

The study will be done across different centres in the USA.

You will need to visit the study site once. The study staff will ask you questions about your health since previous vaccination. You will also be asked to provide a blood sample of about 5 mL (about 1 teaspoon). You will not get any vaccinations or other treatments as a part of this study.

If you take part in this study then it is important that you follow all study activities as described here below:

Day	What will happen at this visit
First Visit [Visit 6 (Day 0)]	You will be explained the study procedures and you will be asked to sign the present "informed consent" document. The doctor will ask you about your medical history, medication and vaccination you may have taken. You will undergo: • Blood sampling End of study

What will happen to samples taken in this study?

The content of this section needs to be aligned with the Use of Human Samples form. Any request to changes in this section must be discussed with the central study team and the GSK Biologicals' ICF taskforce prior to finalization of the ICF.

As part of the study, you will be asked to give sample of your blood. **Your** blood **sample may be sent to GSK or other laboratories working with GSK including those outside [insert name of country] to**:

- measure how your body reacted to the study vaccine you received as a part of the 106316 (Tdap-0.3-007) study conducted ***approximately*** nine years ago.
- **ensure the quality of the tests we use for the study vaccine and/ or diseases.**
- **improve tests and develop new tests linked to the study vaccine and/or diseases. These tests will never include testing related to your genes' hereditary characteristics.**

Your samples will be given a code so that it does not directly identify you.

Your samples will be kept for a maximum of 20 **years from the end of the study**. **Any sample remaining at that time will be destroyed**.

Optional tests on your samples:

If you agree, your sample(s) may also be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board.

You can choose not to allow these optional tests and still be in the study.

What side effects or risks can you expect in this study?

When you give blood, you may feel like fainting, or locally experience mild pain, bruising, irritation or redness at the site where blood will be taken.

What benefits can you expect in this study?

- Information from this study may help researchers understand more about protecting adults against tetanus, diphtheria and pertussis diseases in the future.
- Being in this study will not help you.

Do you have to stay in the study?

You may choose to leave the study at any time, without giving a reason. If you do give a reason, then it may be recorded. Your choice will not change the medical care or other benefits you receive outside of this study.

We will share with you as soon as possible any new information that may change your choice to stay in the study.

Tell the study doctor if you no longer want to take part in the study.

GSK may choose to stop your participation in the study or the study doctor may choose to stop your participation in the study at any time. We will then tell you why. We may ask you to leave the study if:

- You do not follow study instructions
- The study doctor thinks it is in your best interest to stop, e.g. if you have specific health problems.

What happens if you leave the study?

Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in the Local ICF compared to the Model ICF, in response to a request from any source, these should be discussed with the central study team and GSK Biologicals ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection can be taken into account.

No more information about you will be collected after you leave the study. All the information and sample collected before you left the study will still be used.

If the doctor becomes aware of any relevant safety information about you after you left the study, this will be collected.

We may also contact you later for information. This is to help us better understand the safety profile of the vaccine.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations.

Informed Consent Form

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Persistence only

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information can be used as described here.

- Your personal and medical information may be checked by GSK and others [like agencies that approve and monitor studies for example Food and Drug Administration (FDA)]. This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labeled with a code number (for example, PPD It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - keep it electronically, and analyse it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - share it with regulatory agencies that approve new vaccines and medicines,
  - share it with people who check that the study is done properly (like the independent ethics committee or review boards),
  - combine it with results from other studies to learn more about the vaccine and other vaccines and these diseases and related diseases. This may help us to assess the risks and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,
  - publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.
  - share coded information with other companies, organisations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the trial may be moved to, stored and used in the country where you live or another country where GSK or those working with

GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this clinical trial will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the clinical study is conducted.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.

What happens if you get hurt while taking part in this study?

GSK will help pay for your care if you are hurt by the study vaccine or a procedure done to you as part of the study. GSK will pay for reasonable and necessary care for the injury that is not covered by the National Vaccine Injury Compensation Fund. GSK will not pay for any other expenses. To pay these medical expenses, GSK will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because GSK has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare. GSK will not use this information for any other purpose.

Signing this consent form does not change any legal rights you may have.

Will you be paid for being in the study?

This section should be completed locally.

You will not be paid for taking part in this study. **OR**

We will reimburse you for the cost of travelling to your study visit. You may receive up to **[amount]** for travel / per visit.

Do you have to pay anything to be in the study?

Authors note that this section is optional. This section should be completed locally.

You will get all the study tests and procedures for free **[or indicate if there is a cost]**.

Who should you contact if you have questions?

Identify who the subject should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: **name, address, telephone number.**

Person to contact about your rights: **name, address, telephone number.**

Person to contact in case of injury: **name, address, telephone number.**

Informed Consent Form Subject ID_____

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Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Persistence only

Consent statement

I,

_____

(Printed name of Subject)

- confirm that I have read the written information (or have had the information read to me) for study 110086 (Tdap-0.3-009 Ext: 007 Year 9), Version 02, 02/January/2015 , 9 pages **(to be updated locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the chance to ask questions about this study and I am satisfied with the answers and explanations that have been given.
- understand that I give access to data about me to authorised persons described in this information sheet.
- I know what will happen to my blood sample
- understand that by signing this form any of my identifiable medical information given to someone that is not a health care provider is not protected by the US federal privacy rules called the HIPAA Privacy Regulations.
- have been given time and opportunity to consider to take part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my family doctor will be told about my participation in the study.

☐ **Yes** ☐ **No**

Tick as appropriate

I agree that my biological sample may be used for future research. GSK will always ask approval for this research to an independent ethics committee or independent review board. I understand that if I select "No", I can still take part in the study.

☐ **Yes** ☐ **No**

I agree to take part in this study.

Signature of subject _____ Date: _____ day/ month/ year

Indicate version: i.e. Local **(specify country and subset if applicable)** ICF Version Number **NN**, Dated: **DD/MMM/YYYY**, based on Model ICF (Persistence only) Version Number 02, Dated: 02/JAN/2015

Informed Consent Form Subject ID_____

CONFIDENTIAL

Study Identification 110086 (Tdap-0.3-009 Ext: 007 Year 9) Persistence only

I confirm that I have conducted the consent process according to applicable regulations.

Printed name of person conducting consent _____

Signature of person conducting consent _____ Date: _____ day/ month/ year

Delete the following Appendix in the Final local ICF.

Appendix A GlaxoSmithKline Biologicals Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Biologicals internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator's study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject's confidentiality would be maintained for the retained samples, must be reported in the ICF.

The content of this section must be fully aligned with the Use of Human Samples form. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and

local regulations. To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account

Type of changes

Changes to the local ICF can be classified into 3 categories:

'Not permitted' changes

BOLD BLACK mandatory text in the model ICF should not be changed.

'Required' changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as **BOLD RED** text in the model ICF e.g. investigator details).

'Justified' changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.

ICF section	Type of changes	Rationale/Impact
Study Identification		
Check if study identification is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Study Title		
Check if study title is identical to Model ICF.	Not permitted	The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
ICF Version Number and Date		
Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
Company Name		
Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required	Justified	A change to this section is permitted if it is justified by local regulations.

ICF section	Type of changes	Rationale/Impact
by local regulations.		For some countries, the local GSK affiliate should be indicated as Company Name.
Subject/Patient Identification		
Check whether there is space foreseen to insert the subject ID.	Required	The subject/patient ID should be mentioned on the ICF to be able to link the subject/patient ID with the corresponding source documents and RDE entries.
Header		
Check if study identification in header is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Footer		
Indicate version of Local ICF and check if reference to the Model ICF version is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject/patient may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
What is consent?		
Explain the consent process and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	Freely given and written informed consent must be obtained from each subject/patient/LAR prior to study participation. Informed consent involves an education and information exchange that takes place between the researcher and

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
		the potential subject/patient. How the process of consenting looks like, needs to be explained in the ICF. The text can be simplified, if necessary.
Why is this study being done?		
Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
How is GSK involved?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The role of the sponsor should be explained in this section. The text can be simplified if necessary.
Who can join this study?		
Summarize the main inclusion and exclusion criteria. Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What does this study involve?		
Explain the approximate number of subjects/patients involved in the study, the study design and groups, the study procedures and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary
If subject cards are used, check if the text is identical to the Model ICF.	Not permitted	Subject cards provide information about the study which can be used in the event of a medical emergency. Provision of this

ICF section	Type of changes	Rationale/Impact
		information in the ICF ensures that the subject/patient is aware of the use of the subject card. This information will also indicate to the ethics committee that it is provided to the subject/patient.
What about pregnancy and breastfeeding?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
What will happen to samples taken in this study?		
Check if all mandatory wording from the Model ICF is present in the Local ICF.	Not permitted	If this text is changed, there is a risk to use human samples outside the subject‘s/patient’s consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data etc… .
Check if the content of this section is aligned with the Use of Human samples form (UHSF).	Not permitted	The text in the ICF should match 100% with the information documented in the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject’s/patient’s consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject‘s/ patient’s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

ICF section	Type of changes	Rationale/Impact
Check if the QA (Quality Assurance) on tests related to the study vaccine/ disease (type 2 testing) is reported in the Local ICF.	Not permitted	QA testing will be done at <u>all times</u>, assuming it is allowed as per individual subject's/patient's consent. If QA testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted.
Check local regulations regarding tests related to the product/disease under study (type 3a and 3b testing). [If there are concerns regarding this text then this should be discussed with the central team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since type 3a or 3b should be chosen according to local regulations. However, <u>the wording of the text itself, should not be changed</u>! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording. So if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject's consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Check Local regulations regarding storage duration. Check if the wording "for a maximum of 20 years" is not changed into "for 20 years". [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for "for a maximum of"20 years. Attention should be paid to the used wording "**for a maximum of**" 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the UHSF. This will allow the laboratory to take the appropriate measures for sample storage, "for a maximum of 20" years or as defined in the ICF and documented in the UHSF section called "other".
Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, the wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by the mean of the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF. This form allows the central project team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's/patient's consent and local regulations. If this text is changed, there is a risk to use human samples outside the

ICF section	Type of changes	Rationale/Impact
		subject‘s consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc….
What side effects or risks can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary. Refer to the GSK Position Paper on ‘Communication of Individual Immunological Assay Results to Study Sites’ for additional information.
Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.	Not permitted	The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The AID wording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.
Check if the text on Rotarix, if applicable, is identical to the Model ICF.	Not permitted	This text has been approved by GSK upper management following feedback from Authorities.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
What benefits can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary
Are there other products or treatment?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
Add currently available local alternatives, if applicable.	Required	This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.
Do you have to stay in the study?		
Explain voluntary participation and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
What happens if you leave the study?		
Check if the text on the use of data after subject/patient withdrawal is identical to the	Justified	The bold text in this section has been approved by Medical Governance. Changes to this

ICF section	Type of changes	Rationale/Impact
Model ICF. [Check local regulations and seek local legal advice] [If the text needs to be changed it should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF].		section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to GSK's Clarification Paper on 'Handling Data after Subject withdrawal' for additional information.
What about your personal and medical information?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]	Justified	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary.
What happens if you get hurt while taking part in this study?		
- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]	Justified	The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury
- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.	Justified	The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.

Best Practices Document for the Development of the Local ICF

ICF section	Type of changes	Rationale/Impact
Will you be paid for being in the study?		
Information related to this section is added at a regional or country level.	Required	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject/patient is well informed before consenting to participation. The anticipated prorated payment or other financial benefit, if any, to the subject for participating in the study should be mentioned in the ICF. Explain if expenses incurred by subjects for clinical visits made because of their participation in the study will be reimbursed or not.
Do you have to pay anything to be in the study?		
This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.	Justified	If appropriate for a study, include here information on cost/expenses that subject/patient will have to bear for taking part in the study i.e., whether the subject/patient or the subject's/patient's insurance will be charged for any study item or procedure. According to ICH-GCP, the anticipated expenses, if any, to the subject/patient for participating in the study should be mentioned.
Who should you contact if you have questions?		
Add local contact details.	Required	The content of this section is required by ICH-GCP. The subject/patient must have a contact person for further information regarding the study, his rights and who to contact in the event of trial-related injury.
Consent statement		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The consent statement should be aligned with ICH-GCP requirements. Omitting any of the information can have legal

ICF section	Type of changes	Rationale/Impact
		implications
Check local regulations regarding future research (type 4 testing). Check if the wording is identical to the wording in the body of the ICF. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Biologicals' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. This type of testing is optional for the subject/patient, meaning that if this testing is mentioned in the body of the ICF, a tick box should be available in the consent statement. The wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF by using the UHSF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the UHSF.

References

SOP_54823, Development and implementation of Informed Consent for clinical studies.

GUI_51905, Guidance for Informed Consent documents.

GUI-BIO-CLIN-0014, Guidance for the development of Informed Consent-related documents.

GSK's Position Paper on Communication of Individual Immunological Assay Results To Study Sites.

GSK's Clarification Paper on Handling Data after Subject withdrawal.

GSK's Clarification Paper on Future Use of Biospecimens

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Pages 657 to 740 have been removed - Out of Scope of phase 1 of Policy 0070 - Investigator CVs

Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals
Vaccines R&D
Investigator Approval Page

STUDY TITLE: A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9.

Study: 110086 (Tdap-0.3-009 EXT:007 Year 9) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Stephanie Powell
Affiliation /investigational centre:	PMG Research of Bristol, 1958 W. State St. Bristol, Tennessee, United States
Signature of Investigator:	_____
Date:	_____

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GlaxoSmithKline Biologicals
Vaccines R&D
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9.

Study: 110086 (Tdap-0.3-009 EXT:007 Year 9) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Narcisa Elena Mesaros
Title of Sponsor Signatory:	MD, Clinical and Epidemiology R&D Project Leader, DTP, Polio and Hib containing vaccines – R&D Centre Belgium, GlaxoSmithKline Biologicals
Signature:	
Date:	

For internal use only

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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Enrolled subjects received the following lot/batch numbers, per treatment group:

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
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Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
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Treatment Group	Batch (Lot) number
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Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
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Treatment Group	Batch (Lot) number
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Treatment Group	Batch (Lot) number
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Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
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Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
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Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
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Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@

Treatment Group	Batch (Lot) number
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
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Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB151C@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@

Treatment Group	Batch (Lot) number
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB117B@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@
Tdap	AC52VB118A@

Randomization list

Not Applicable

Audit Certificates

AUDIT CERTIFICATE

Study Number: 110086

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

Study Number	Type	Conducted by	Centre number	Country	Audit Date
110086	Investigator Site	GSK-CDQA	PPD	USA	22-24 Sep 2015
110086	Investigator Site	GSK-CDQA		USA	9-10 Dec 2015
110086	Investigator Site	GSK-CDQA		USA	2-4 March 2016
110086	Investigator Site	GSK-CDQA		USA	2-4 Feb 2016
110086	Investigator Site	GSK-CDQA		USA	27-29 Jul 2016

Clinical Development Quality Assurance hereby confirm that the audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

Name: PPD **Date:** 31 Oct 2016

Role: Senior Manager CDQA Vaccines

Clinical Development Quality Assurance
GlaxoSmithKline Research and Development

Documentation of statistical methods

Statistical Analysis Plan

Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080)
Tdap-0.3-009 Ext:007 Year 3 (110082)
Tdap-0.3-009 Ext:007 Year 5 (110084)
Tdap-0.3-009 Ext:007 Year 9 (110086)

Detailed Title:	A phase III, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of *Boostrix* as a second dose of Tdap, when administered at Year 9.
SAP version	Amendment 3
SAP date	19-Jul-2017
Scope:	All data pertaining to the above study at Year 1, 3, 5 and 9 time point.
Co-ordinating author:	PPD
Adhoc reviewers:	PPD (Safety Physician) PPD (Safety Scientist) PPD on behalf of PPD (Clin RA representative) PPD (Public disclosure)
Approved by:	PPD (Clinical Research and Development Lead), PPD (Lead Statistician), PPD (Statistician), PPD (Lead statistical analyst), PPD (Scientific Writer)

Statistical Analysis Plan

Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080)
Tdap-0.3-009 Ext:007 Year 3 (110082)
Tdap-0.3-009 Ext:007 Year 5 (110084)
Tdap-0.3-009 Ext:007 Year 9 (110086)

TABLE OF CONTENTS

PAGE

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

LIST OF TABLES

PAGE

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-To-Protocol
CI	Confidence Interval
D	Diphtheria
DTaP	Diphtheria, Tetanus, Acellular Pertussis Vaccine
eCRF	Electronic Case Report Form
EL.U/ml	ELISA unit per milliliter
ELISA	Enzyme-linked immunosorbent assay
Eli Type	Internal GSK database code for type of elimination code
FHA	Filamentous Hemagglutinin from Bordetella pertussis
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline
IU	International Units
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PRN	Pertactin from Bordetella pertussis
PT	Pertussis Toxoid from Bordetella pertussis
RCC	Reverse Cumulative distribution Curve
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

T	Tetanus
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid And Acellular Pertussis Vaccine Adsorbed
UL	Upper Limit of the confidence interval

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

1. DOCUMENT HISTORY

Date	Version	Description
20-FEB-2008	First version	
04-FEB-2010	Amendment 1.0	Persistency analysis for Y3, 5, or 10 is described in detail
05-AUG-2016	Amendment 2.0	Following are the main changes that have been made based on the protocol amendment 3 Administrative Change 2 Final: 03 February 2015. – , Analysis corresponding to the co-primary objective has been added to demonstrate that the immune response elicited by a second dose of Tdap vaccine, Boostrix (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination. – Throughout the analysis, the time point for the study for persistence and booster has been amended from year 10 to year 9.
19-JUL-2017	Amendment 3.0	see detail below

The statistical analysis plan was amended for 2 main reasons

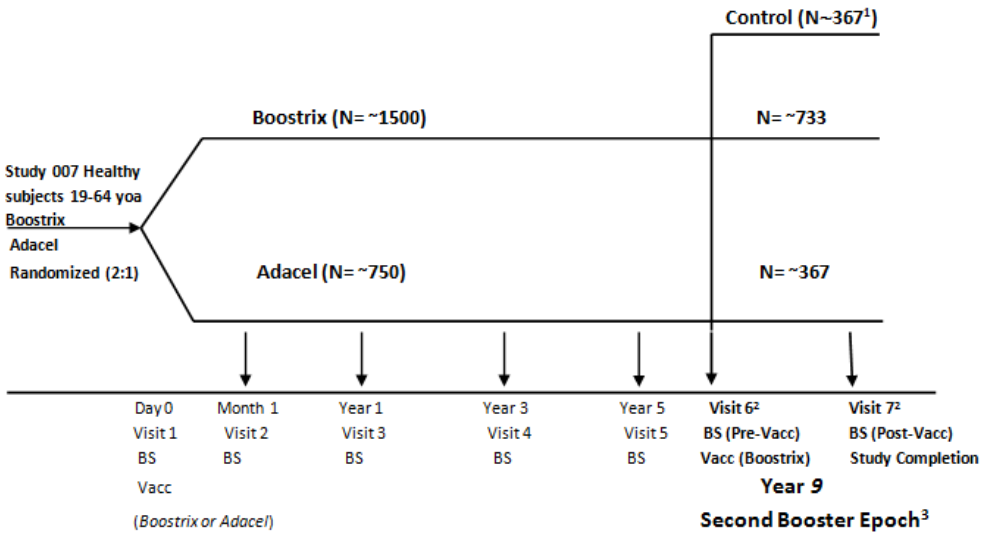
1. During the course of the study, the assays used to measure the anti-D, -T, -PT, -FHA and -PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISAs for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISAs in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA's have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/ml for anti-D, 0.043 IU/ml for anti-T, 2.693 IU/ml for anti-PT, 2.046 IU/ml for anti-FHA and 2.187 IU/ml for anti-PRN. The newly validated DTPa ELISA's were used for the Year 9 pre and post vaccination blood samples. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) and therefore the

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

clinical endpoints and anti-D and anti-T are unchanged. In the absence of a correlate of protection for the B. pertussis antigens, the pertussis endpoints were redefined based on the assay cut-off (see section 7.1 and section 4.2).

- The sensitivity analyses planned per protocol were based on imputation method. The method was replaced by a repeated mixed model which is a direct model not based on imputation.

2. STUDY DESIGN



Yoa= Year of Age
BS= Blood sample
Vacc= Vaccination
Although the second booster epoch is a non-randomized study, for practical purposes group ratio of 1:2:1 is assigned for the Control, Boostrix and Adacel groups respectively for the Year 9 time point.
[1]Subjects who were not part of the 106316 study will be recruited as the Control group.
[2]For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7.
[3]An epoch named second booster epoch has been added for practical purposes and it has no relation to the number of epochs in this study.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures, are essential and required for study conduct.

- Experimental design: A phase III, parallel, open-label, interventional, multicenter study with the same two parallel groups as in the 106316 study and one new Control group receiving the first dose of Tdap vaccine (*Boostrix*).
- Study groups:
  - Boostrix group: Subjects who had received GSK Biologicals' Tdap vaccine (*Boostrix*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Adacel group: Subjects who had received Sanofi Pasteurs' Tdap vaccine (*Adacel*) in study 106316 will receive a second dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).
  - Control group: Subjects in the Control group will receive the first dose of Tdap vaccine (*Boostrix*) in this study at Year 9 (Visit 6).

Table 1 Study groups foreseen in the study

Study Groups	Number of subjects	Age (Min - Max) (age unit)
Boostrix Group	Approximately 733	28 years-73 years
Adacel Group	Approximately 367	28 years-73 years
Control Group	Approximately 367	28 years-73 years

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups		
		Boostrix Group	Adacel Group	Control Group
Boostrix	Tdap	x	x	x

- Blinding: This study will be an open study since this is an extension of study 106316 (Tdap 0.3-007) which was unblinded at the time of primary analysis.
- Subjects who received *Boostrix* or *Adacel* in study 106316 will be analyzed as separate groups. Subjects in the Control group will also be analyzed as a separate group.
- Treatment allocation: Non-randomized, all the study groups will receive a single dose of *Boostrix* at Year 9 (Visit 6).

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- Control: Active control.
- Vaccination schedule: A single dose of *Boostrix* vaccine will be administered to all subjects participating in the vaccination phase at Visit 6 i.e. at Year 9 (For the Control Group although it will be their first and second visit for this study, the visits are named as Visit 6 and Visit 7 to keep it consistent with the visit numbering of Boostrix and Adacel groups. The study procedures will be similar across all groups at Visit 6 and Visit 7).
- Blood samples will be collected at the following time points: 1 year, 3 years, 5 years and 9 years [Visit 6 (pre-vacc) and Visit 7 (post-vacc for subjects who receive vaccination in this study)] for all the subjects.
- Duration of the study: Approximately 9 years for subjects who were enrolled in study 106316 and who participated in all phases of the study including Year 9 time point and approximately one month for the Control group.
- Data collection: Electronic Case Report Form (eCRF).

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	Boostrix Group	Subjects who had received GSK Biologicals' Tdap vaccine (Boostrix) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
2	Adacel Group	Subjects who had received Sanofi Pasteurs' Tdap vaccine (Adacel) in study 106316 and a second dose of Tdap vaccine (Boostrix) at Year 9 Visit 6
3	Control Group	Subjects who will receive the first dose of Tdap vaccine (Boostrix) at Year 9 Visit 6

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

3. OBJECTIVES

3.1. *Co*-Primary objectives

- To evaluate the persistence of antibodies to diphtheria toxoid (anti-D antibodies) and tetanus toxoid (anti-T antibodies) elicited by a single dose of Tdap vaccine (*Boostrix* and *Adacel*), at 1 year, 3 years, 5 years and 9 years.
- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to seroprotection rate against diphtheria and tetanus antigens, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limit of the 97.5% confidence interval (CI) for the difference between groups in the seroprotection rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).

  – One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the seroprotection rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria and tetanus antigens is greater than or equal to -10% (clinical limit for non-inferiority).
- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a three dose series of Infanrix vaccine in infants in the German household contact efficacy study APV-039, with respect to antibodies against pertussis toxoid (anti-PT), antibodies against filamentous hemagglutinin (anti-FHA) and antibodies against pertactin (anti-PRN) antibody concentrations, one month following vaccination.

  The criterion for meeting the above objective is defined as:

  – One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN geometric mean antibody concentrations (GMC) ratios (Boostrix group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- One month after vaccination, the lower limits of the 97.5% CI for the anti-PT, anti-FHA and anti-PRN GMC ratios (Adacel group divided by Infanrix group in APV-039) are greater than or equal to 0.67.

- To demonstrate that the immune response elicited by a second dose of Tdap vaccine, *Boostrix* (Boostrix group and Adacel group) is non-inferior to the immune response elicited by a first dose of Tdap vaccine (Control group), with respect to booster response[$] against diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month following vaccination.

  The criteria on for meeting the above objective is defined as:

  - One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Boostrix group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

  - One month after vaccination, the lower limit of the 97.5% CI for the difference between groups in the booster response rate [a second dose of Tdap (Adacel group) minus the first dose of Tdap (Control group)] against diphtheria, tetanus and pertussis antigens(PT, FHA and PRN) is greater than or equal to -10% (clinical limit for non-inferiority).

Refer to Section 4.1 for definition of the co-primary endpoints and the hierarchical approach used to assess success in reaching a study objective and to control the risk of erroneously concluding.

[$]Refer to Section 7.1 for the definition of booster response.

3.2. Secondary objectives

- To evaluate the persistence of antibodies to acellular pertussis antigens with respect to percentage of subjects with anti- PT, anti- FHA, and anti-PRN antibody concentrations ≥ the assay cut-off, 1 year, 3 years, 5 years and 9 years following a single dose of *Boostrix* and *Adacel*.
- To evaluate GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years, and 9 years after vaccination with *Boostrix* and *Adacel*.
- To assess the immunogenicity of *Boostrix* in terms of seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies, one month after vaccination.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- To assess the immunogenicity of *Boostrix* in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations, one month after vaccination.
- To explore the potential difference in terms of alternate booster response* to D, T, PT, FHA and PRN antigens between Boostrix group and Adacel group.
- To explore the potential difference in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations between a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group).
- To evaluate and compare the safety of a second dose of Tdap vaccine (Boostrix group and Adacel group) and a first dose of Tdap vaccine (Control group), with respect to solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

Refer to Section 4.2 for definitions of secondary endpoints.

*Refer to Section 7.1 for the definitions of booster response and alternate booster response.

4. ENDPOINTS

4.1. Co-Primary endpoints

- Subjects with anti-D antibody concentrations ≥ 0.1 IU/mL (ELISA) or ≥ 0.01 IU/mL (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL (ELISA) in the *Boostrix* and the *Adacel* vaccine groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at Year 9 time point.
  - Anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs, one month after vaccination.
  - Anti-pertussis (PT, FHA and PRN) GMCs evaluation one month after the third dose of Infanrix in Study APV-039.
  - Booster response to diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens, one month after vaccination.

Refer to Section 7.1 for the definition of booster response.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

4.2. Secondary endpoints

- Subjects with anti- PT, anti- FHA, and anti- PRN antibody concentrations ≥ assay cut-off in the *Boostrix* and *Adacel* groups, 1 year, 3 years, 5 years and 9 years following first Tdap vaccination.
- Immunogenicity with respect to components of the study vaccine at the Year 9 time point.
  - Anti-D* and anti-T antibody concentrations ≥ 0.1 IU/mL, anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL; anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody concentrations prior to and one month after vaccination.
  - Alternate booster response to the diphtheria, tetanus and pertussis (PT, FHA and PRN) antigens one month after vaccination (Refer to Section 7.1 for the definitions of booster response and alternate booster response).

  * Sera with ELISA concentrations < 0.1 IU/mL will be tested for neutralizing antibodies using a Vero-cell neutralization assay.
- Solicited local and general symptoms.
  - Occurrence of each solicited local and general symptom (any and Grade 3) during the 4 day (Day 0–3) follow-up period after vaccination.
  - Occurrence of large injection site reactions (defined as swelling with a diameter > 100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) during the 4 day (Day 0-3) follow-up period after vaccination.
- Unsolicited adverse events.
  - Occurrence of unsolicited Aes during the 31 day (Day 0–30) follow-up period after vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Serious adverse events.
  - Occurrence of serious adverse events from the administration of the vaccine dose and during the 31 day (Day 0–30) follow-up period following vaccination.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

5. STUDY POPULATION

5.1. Year X (1, 3, 5, 9) cohort

The Year X cohort is a subset of the total vaccinated cohort in 106316 study and is the cohort of subjects for whom serological results for at least one antigen is available after a blood sample taken X years after vaccination. The year 1 cohort consists in all subjects enrolled in study Tdap-0.3-009 at the year 1 visit.

5.2. According-To-Protocol (ATP) for analysis of immunogenicity Year X (1, 3, 5) cohort

The ATP Year X (1, 3, 5) cohort will include all subjects from Year X (1, 3, 5) cohort who were in the ATP cohort for analysis of immunogenicity in 106316 study and who did not meet the following elimination criteria:

- without administration of a Td or Tdap vaccine, or any registered or investigational vaccine utilizing a diphtheria toxoid or tetanus toxoid carrier after the vaccination in 106316 study.
- Diphtheria and/or tetanus and/or pertussis disease diagnosed after the vaccination in 106316 study.
- Administration of immunoglobulins and/or any blood products within 90 days of blood draw for the long-term time point.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within 90 days prior to each study visit. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 20 mg/day. Inhaled and topical steroids are allowed).
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

5.2.1. Additional cohorts defined for Year 9 analysis

5.2.1.1. Total Vaccinated Cohort (TVC) at Year 9

The TVC will include all subjects with a study vaccine administration dose documented:

- A safety analysis based on the TVC will include all vaccinated subjects.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- An immunogenicity analysis based on the TVC will include all vaccinated subjects for whom immunogenicity results are available.

5.2.1.2. ATP cohort for analysis of safety at Year 9

The ATP cohort for analysis of safety at Year 9 time point will include all eligible and vaccinated subjects.

- Who have received the dose of study vaccine.
- For whom administration site of study vaccine is known.
- Who did not receive a vaccine leading to elimination from an ATP analysis.

5.2.1.3. ATP cohort for analysis of immunogenicity at Year 9 (ATP Year 9)

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for analysis of safety:

- Who comply with the procedures and intervals defined in the protocol.
- Who do not meet any of the criteria for elimination from an ATP analysis during the study.
- For whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after Year 9 vaccination.

5.3. Adapted ATP cohort

When presenting different time points, the Adapted ATP cohort will be used to denote that for each time point, the corresponding ATP cohort for immunogenicity/persistence has been used.

More specifically,

- The analyses on the pre and post primary dose time points will be based on the ATP cohort for immunogenicity in study 106316
- The analysis on Year 1, 3, 5 time points will be based on the ATP cohort for persistence Year 1, 3, 5, respectively.
- The analysis on Year 9 (pre and post Tdap vaccination) will be based on the ATP cohort for immunogenicity at Year 9

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Criteria for eliminating subjects from the analyses.

Cohort	Elimination codes	Eli Type
Year X (1, 3, 5, 9) cohort	900	Y1, Y3, Y5
ATP for analysis of immunogenicity Year X (1,3,5) cohort	1030-2500	Y1, Y3, Y5
ATP cohort for analysis of safety at Year 9	1030-1500	BO
ATP cohort for analysis of immunogenicity at Year 9 (ATP Year 9)	1030-2500	BO

6. STATISTICAL METHODS

An analysis will be performed after each follow-up visit (Year 1, Year 3, Year 5 and Year 9) on cleaned data obtained through each Year X. A clinical study report (CSR) will also be written following each analysis.

For the current Year 9 persistence analysis, all previous time points including the initial study 106316 (Tdap 0.3 007), and follow up time points 110080 (Y1), 110082 (Y3), 110085 (Y5) will be pooled together to generate some of the demography and immunogenicity tables.

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age in years at vaccination in Tdap-0.3-009, time since last DT vaccination, gender, ethnicity, race and age stratum) of the ATP cohort for immunogenicity at year 9 and for the enrolled cohort at Year 1.

The number of subjects included in the total vaccinated cohort in 106316 study and in each follow-up cohort up to Year X (1, 3, 5 or 9) cohort and in the ATP Year X (1, 3, 5 or 9) cohort will be tabulated.

Time from the vaccination in 106316 study to the blood sampling at Year X (1, 3, 5, 9) (in years) will be summarized using descriptive statistics.

6.1.1. Analysis of persistence

The primary analysis will be based on the adapted ATP cohort.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

The following analyses will be performed:

Within group assessment:

For each vaccine group, at each time point for which a serological result is available:

- Seroprotection rates (percentage of subjects with anti-D/ anti-T antibody concentrations ≥ 0.1 IU/mL by ELISA) with exact 95% CI will be calculated by group. Overall seroprotection rates for anti-D (percentage of subjects with anti-D antibody concentrations ≥ 0.1 IU/mL by ELISA or ≥ 0.01 IU/mL by VERO cell assay when anti-D concentrations < 0.1 IU/mL by ELISA) with 95% CI, will be calculated by group.
- Seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies (with exact 95% CI) will be calculated by group.
- GMCs to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies (with 95% CI) will be tabulated by group.

In addition, at Year X 9 visit:

- Distribution of antibody concentrations for each antigen will be displayed using reverse cumulative distribution curves (RCC) by group at all persistence time points.

Above summaries will be provided for each level of the age stratum (Subjects age classified as 19 – 29 years, 30 – 49 years and 50-64 years at enrolment in study 106316) and by Gender.

Comparability between Groups - Exploratory analyses

- For anti-D antibody response, the two-sided asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA and in the overall seroprotection rates (percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO when anti-D concentrations < 0.1 IU/mL by ELISA), Year X (1, 3, 5, 9) after vaccination will be calculated.
- For anti-T antibody response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ 0.1 IU/mL by ELISA, Year X (1, 3, 5, 9) after vaccination will be calculated.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- For anti-PT, anti-FHA and anti-PRN, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) in the percentage of subjects with antibody concentrations ≥ assay cut-off, Year X (1, 3, 5, 9) after vaccination will also be calculated.

Sensitivity analysis for persistence

A sensitivity analysis will be performed to ensure that comparability between subjects in the Boostrix group and Adacel group is not biased by drop-out at the persistence time point.

The analysis will use a repeated mixed model on log-transformed titre accounting for results one month post-vaccination in study 106316, year 1, 3, 5, and 9 post initial vaccination in study Tdap-0.3-009. Analyses will be based on adapted ATP cohorts. The model will include the following fixed effects: the group effect, the age strata effect (agestratum1, agestratum2 referred below as being the age indicator for 19 – 29 years and 30 – 49 years interval at enrolment in study 106316, respectively) and the pre-vaccination titer (pre-vac variable referred below) in study 106316, the activity effect and the fixed activity-by-group effect. An unstructured covariance matrix will be used.

The following SAS-code will be applied to obtain prediction in term of log_{10}-transformed GMC:

```
*** base denotes the log-transformed titer pre-vaccination is study 106316;
PROC MIXED data=sero;
Class activity group;
MODEL logval=activity agestratum1 agestratum2  group activity*group pre-vac;
Repeated activity / subject=pid type=UN;
LSMEAN activity*group / CL cdiff;
RUN;
```

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

6.1.2. Analysis of immunogenicity at booster dose

The following analyses will be carried out after Year 9 vaccination, primarily on the ATP cohort for analysis of immunogenicity at Year 9 cohort. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC at Year 9 will be performed to complement the ATP analysis.

Within groups assessment

For each group and each antigen:

- Seropositivity/seroprotection rate at pre-vaccination and one month post-vaccination will be calculated with exact 95% CIs.
- GMCs or GMTs at pre-vaccination and one month post-vaccination will be tabulated with 95% Cis.
- Booster response rate one month post-vaccination will be calculated with exact 95% CIs.

In addition:

- the distribution of antibody concentrations for each antigen at pre-vaccination and one month post-vaccination will be displayed using RCCs by group.
- the above summaries will be provided for each level of the age stratum(28-38 years old, 39-58 years old and 59-73 years old) and by Gender.

Comparability between Groups – confirmatory analyses:

- For diphtheria and tetanus, the two-sided standardized asymptotic 97.5% CI of the group difference in seroprotection rate one month after vaccination (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be computed.
- For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.

Comparability between Groups – exploratory analyses:

- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN alternative booster response, the two-sided standardized asymptotic 97.5% CI for the group differences (Boostrix group minus Control group and Adacel group minus the Control group, respectively) will be calculated.
- For anti-D, anti-T antibody response, the two-sided 95% Cis of the GMC ratios between subjects in the Boostrix group and (divided by) the Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations, the pre-vaccination status in study 106316 will be used as co-variable leading to an Analysis of Co-variance (ANCOVA).
- For anti-PT, anti-FHA and anti-PRN antibody response, the two-sided 95% CI of the GMC ratios between subjects in the Boostrix group and Adacel group one month after vaccination will be computed using an ANOVA model on the logarithm_{10} transformation of the concentrations, the pre-vaccination status in study 106316 will be used as co-variable leading to an Analysis of Co-variance (ANCOVA).
- For anti-D, anti-T, anti-PT, anti-FHA and anti-PRN booster response, the two-sided standardized asymptotic 95% CI for the group differences (Boostrix group – Adacel group) will be calculated.

Sensitivity analysis following the booster dose

A sensitivity analysis will be performed to ensure that comparability between subjects in the Boostrix group and Adacel group is not biased by drop-out at the booster phase.

The analysis will use a repeated mixed model on log-transformed titre accounting for results one month post-vaccination in study 106316 and one month post-vaccination in study 110086. Analyses will be based on adapted ATP cohorts. The model will include the following fixed effects: the group effect, the age strata effect (agestratum1, agestratum2 referred below as being the age indicator for 19 – 29 years and 30 – 49 years interval at enrolment in study 106316, respectively) and the pre-vaccination titer (pre-vac variable referred below) in study 106316, the activity effect and the fixed activity-by-group effect. . An unstructured covariance matrix will be used.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

The following SAS-code will be applied to obtain prediction in term of log_{10}-transformed GMC:

```
*** base denotes the log-transformed titer pre-vaccination is study 106316;
PROC MIXED data=sero;
Class activity group;
MODEL logval=activity agestratum1 agestratum2  group activity*group pre-vac;
Repeated activity / subject=pid type=UN;
LSMEAN activity*group / CL cdiff;
RUN;
```

6.1.3. Analysis of safety

Persistence follow-up phase up to Year ***9*** time point:

The following is applicable to subjects who refuse vaccination at Year ***9*** time point:

No safety analysis will be performed during the persistence phase of this study. If GSK is informed by an investigator of an SAE that in his/her medical judgment could be reasonably related to the study vaccine administered in study 106316, or to participation in this persistence study, the pertinent clinical details will be summarized in the study report.

Vaccination phase at Year 9 time point:

The primary analysis will be based on the TVC at Year 9. If the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety at Year 9 is more than 5%, a second analysis based on this ATP cohort will be performed to complement the analysis of the TVC.

Safety data will be analyzed by subject incidence rates of solicited and unsolicited adverse events in the treatment groups, by solicited local and general symptoms and, for unsolicited AEs, by MedDRA preferred term and system organ class. Safety data will be summarized for all subjects by treatment group.

The incidence of solicited local and general symptoms occurring during the 4 day (Day 0-3) follow-up period after vaccination will be tabulated with exact 95% CI for each group. The same calculations will be performed for symptoms of any intensity, those with intensity grade ≥ 2, and those with intensity grade 3 (occurrence of fever will be reported per 0.5°C cumulative increments), as well as for solicited general with relationship to vaccination. All solicited local adverse events are considered to be causally related.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

The percentage of subjects who reports at least one unsolicited adverse event classified by MedDRA during the 31 day (Day 0-30) follow-up period after vaccination will be tabulated with exact 95% CI for each treatment group. The same tabulation will be performed for grade 3 unsolicited adverse events, AEs resulting in a medically attended visit, for unsolicited adverse events that are considered by the investigator to be possibly related to vaccination and for grade 3 unsolicited adverse events that are possibly related to vaccination.

Serious adverse events will be summarized from Day 0 to Day 30 post-vaccination.

Serious adverse events, large injection site reaction (defined as swelling with a diameter >100 mm, noticeable diffuse swelling or noticeable increase of limb circumference) and withdrawals due to adverse event(s) will be described in detail.

In addition, safety analysis for TVC at Year 9 will be performed separately for each level of the age stratum (Subjects age at Year 9 vaccination will be classified into three categories, 28-38 years old, 39-58 years old and 59-73 years old) and by Gender.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

- A seronegative subject is a subject whose antibody concentration is below the assay cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the assay cut-off value.
- Seroprotection rate is defined as the percentage of subjects with antibody concentrations greater than or equal (≥) the seroprotection cut-off value defined for that antibody (See Section 6.1.1 for description of the seroprotection cut-off value).
- The percentage of subjects with antibody concentrations ≥ 0.1 IU/mL (ELISA), percentage of subjects with antibody concentrations ≥ cut off (VERO) and anti-T antibody concentrations ≥ 0.1 IU/mL in the Boostrix and the Adacel vaccine groups, 1 year, 3 years, 5 years, and 9 years following vaccination will be derived to evaluate the primary objective.
- The percentage of subjects with anti-PT, anti-FHA, and anti-PRN antibody concentrations ≥ assay cut-off in the Boostrix and Adacel groups, 1 year, 3 years, 5

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

years and 9 years following vaccination will be derived to evaluate the first secondary objective.

- The GMC calculations are performed by taking the anti-$\log_{(10)}$ of the mean of the log antibody concentration transformations. Antibody concentration below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

- The GMCs of anti-D, anti-T, anti-PT, anti-FHA, and anti-PRN antibodies, 1 year, 3 years, 5 years and 9 years after vaccination with *Boostrix* will be derived to evaluate the other secondary objectives.

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

- The age stratum is derived, subjects classified as 19 – 29 years, 30 – 49 years and 50-64 years for primed subjects in the 106316 study and subjects are classified in to the following age stratum (28-38 years old, 39-58 years old and 59-73 years old) at enrolment in 110086 for the control group.

Booster responses to be considered for Year 9 time point:

- Booster response to D and T antigens is defined as:
  - for initially seronegative subjects with pre-booster antibody concentration below 0.1 IU/mL, an increase in antibody concentrations at least four times 0.1 IU/mL (i.e. 0.4 IU/mL), one month after vaccination, and
  - for initially seropositive subjects with pre-booster antibody concentration ≥ 0.1 IU/mL, an increase in antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
- Booster response to PT, FHA and PRN antigens is defined as:
  - initially seronegative subjects (pre-booster antibody concentration below the assay cut-off) with an increase of at least four times the assay cut-off one month after vaccination,
  - initially seropositive subjects with anti-body concentration < four times the assay cut-off with an increase of at least four times the pre-booster antibody concentration one month after vaccination

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

  - initially seropositive subjects with anti-body concentration ≥ four times the assay cut-off with an increase of at least two times the pre-booster antibody concentration one month after vaccination

- Alternative Booster response to D and T antigens is defined as:
  - for initially seronegative subjects (pre-booster antibody concentration below 0.1 IU/mL): antibody concentrations at least four times the 0.1IU/ML, one month after vaccination, and
  - for subjects with pre-booster antibody concentration ≥ 0.1 IU/mL and <1.0 IU/mL: antibody concentrations of at least four times the pre-booster antibody concentration, one month after vaccination.
  - for subjects with pre-booster antibody concentration ≥ 1.0 IU/mL and <6.0 IU/mL: antibody concentrations of at least two times the pre-booster antibody concentration, one month after vaccination.
  - Subjects with pre-booster antibody concentration ≥ 6.0 IU/mL are not evaluable for booster response.
- Alternative Booster response to PT, FHA and PRN antigens is defined as:
  - for initially seronegative subjects (pre-booster antibody concentration below the assay cut-off): antibody concentrations at least four times the assay cut-off one month after vaccination, and
  - for initially seropositive subjects with pre-booster antibody concentration □ assay cut-off and < 60 IU/mL: antibody concentration increase of at least 30 EL.U/mL from the pre-booster antibody concentration, one month after vaccination.
  - for initially seropositive subjects with pre-booster antibody concentration □ 60 EL.U/mL : at least 1.5 fold increase of antibody concentration from the pre-booster antibody concentration, one month after vaccination.

7.2. Handling of missing data:

Immunogenicity:

- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

Reactogenicity and Safety:

- For a given subject and for the analysis of solicited symptoms during the 4 day (Day 0-3) follow-up period post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the TVC will include only vaccinated subjects and doses with documented safety data (i.e. symptom screen completed).
- For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered. Subjects who did not report an event or a concomitant medication will be considered as subjects without an event or a concomitant medication respectively.
- For summaries reporting of both solicited symptoms and unsolicited adverse events, all vaccinated subjects will be considered. Subjects who did not report an event or a concomitant medication will be considered as subjects without an event or a concomitant medication respectively.

7.3. Number of decimals

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
Immunogenicity	GMT/C	1
Immunogenicity	Ratio of GMT/C	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	3

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

7.4. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413.

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, Statist Med. 1998; 17, 873-890. The standardised asymptotic method used is the method six.

The above methods will be used for the percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO when anti-D concentrations < 0.1 IU/mL by ELISA if all samples with anti-D concentrations < 0.1 IU/mL could be retested by VERO.

If some samples with anti-D concentrations < 0.1 IU/mL could not be retested by VERO, VERO will be treated as left censored at 0.1 IU/mL and the Greenwoood formula for censored data will be used to estimate the percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or anti-D concentrations ≥0.01 IU/mL by VERO and its associated CI and the CI for the group difference will obtained using the method G.Y. Zou and A. Donner [Stat Med. 2008 May 10;27(10):1693-702. Construction of confidence limits about effect measures: a general approach. Zou GY(1), Donner A.].

For anti-PT, anti-FHA and anti-PRN antibody response and each of the Boostrix group, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix group and (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for Boostrix group, one month after the third dose of Infanrix for Infanrix group in APV-039) using the method proposed by G.Y. Zou and A. Donner.

The 95% CI for GMTs/GMCs will be obtained within each group separately. The 95% CI for the mean of log-transformed titre/concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre/concentration.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Persistence data will be analyzed at each time point (Year 1, Year 3, Year 5 and Year 9) as available and reported separately. At Year 9 time point, immunogenicity and safety of vaccine administration will be reported. A separate TFL will be focusing on Year 9 time point analysis.

e-Track	Description	Analysis ID	Disclosure Purpose	Reference for TFL
110080	Final	E1_01	Final Analysis	DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y1 (110080) RAP
110082	Final	E1_01	Final Analysis	DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3 (110082) RAP (Amendment 1)
110084	Final	E1_01	Final Analysis	DTPA 0.3 (BOOSTRIX)-009 EXT 007 Y3 (110082) RAP (Amendment 1)_2
110086	CTRS Safety Analysis	E1_02	CTRS Safety and Demography Analysis	CTRS tables from TFL dated Jul-2016
110086	Final Analysis	E1_01	Final Analysis	TFL dated Aug-2017

8.2. Statistical considerations for interim analyses

No interim analysis was planned.

9. CHANGES FROM PLANNED ANALYSES

- For the within group assessement, a sub-group analysis for immunogenicity and reactogenicity by Gender was added to be consistent with year 1,3 and 5 analysis.
- For the sake of simplification the adapted ATP cohort was introduced to present integrated immunological summaries for time points from study 106316 (007), and follow up time points 110080 (Y1), 110082 (Y3), 110085 (Y5).
- For the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations, the two-sided 97.5% CIs of the GMC ratios between subjects in the Boostrix group and Adacel group (divided by) the Infanrix Group in APV-039 one month after vaccination (one month after vaccination for <Boostrix group> < Adacel group>, one month after the third dose of Infanrix for Infanrix group in APV-039) will be computed using the method proposed by G.Y. Zou and A. Donner [Zou, 2008] in order to account heterogeneity of variance between this study and APV-039.

Statistical Analysis Plan	
Study alias & e-track number(s): Tdap-0.3-009 Ext:007 Year 1 (110080) Tdap-0.3-009 Ext:007 Year 3 (110082) Tdap-0.3-009 Ext:007 Year 5 (110084) Tdap-0.3-009 Ext:007 Year 9 (110086)	

- A sensitivity analysis was proposed in the protocol to compare immunogenicity post-vaccination in study 110086. The context of the sensitivity analysis was clarified to be limited to comparison between the Boostrix and Adacel group as defined in study 106316. In addition the imputation method proposed in the protocol was replaced by a mixed model which is direct and allows accounting for ANCOVA model covariates used in study 106316.
- During the course of the study, the assays used to measure the anti-D, -T, -PT, -FHA and -PRN IgG concentrations were re-developed and re-validated and both assay units and assay cut-offs were adapted. The new ELISAs for PT, FHA and PRN were calibrated against the WHO International Standard (NIBSC 06/140). This allowed the expression of concentrations measured with the new ELISAs in international units per milliliter (IU/mL) instead of the formerly used ELISA units per milliliter (ELU/mL). The newly validated DTPa ELISA's have a lower assay cut-off as compared to the one described in the protocol. The current assay cut-off is 0.057 IU/ml for anti-D, 0.043 IU/ml for anti-T, 2.693 IU/ml for anti-PT, 2.046 IU/ml for anti-FHA and 2.187 IU/ml for anti-PRN. The newly validated DTPa ELISA's were used for the Year 9 pre and post vaccination blood samples. An agreement between the old and new ELISAs was shown with regards to the two thresholds of clinical relevance for the DI/TE response (0.1 IU/mL and 1.0 IU/mL) and therefore the clinical endpoints and anti-D and anti-T are unchanged. In the absence of a correlate of protection for the B. pertussis antigens, the pertussis endpoints were redefined based on the assay cut-off (see section 7.1and section 4.2).
- The incidence of solicited general symptom 'fever' will be presented in °C instead of °F.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not Applicable

Publications based on the study

Not Applicable

Important publications referenced in the report

Blatter MM, Friedland LR, Weston WM, Li P, Howe B. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid, and 3-component acellular pertussis vaccine in adults 19–64 years of age. Vaccine 2009; 27: 765–772.

Camargo ME, Silverira L, Furuta JA, et al. Immunoenzymatic assay of anti-diphtheria toxin antibodies in human serum. J Clin Microbiol. 1984;20:72-4.

Campins-Marti M, Cheng HK, Forsyth K, et al. Recommendations are needed for adolescent and adult pertussis immunisation: rationale and strategies for consideration. Vaccine. 2002;20:641-6.

Centers for Disease Control and Prevention (CDC) Pertussis (Whooping cough) Outbreaks, 2017

https://www.cdc.gov/pertussis/outbreaks/trends.html. Accessed: 14 December 2017.

Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Accessed: 19 December 2017.

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf. Accessed: 19 December2017.

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) ‘adopted at Community level in May 2006); http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed: 19 December 2017.

GlaxoSmithKline Biologicals Study Report 110084 [Tdap 0.3-009 EXT: 007 Year 5]. A phase IIIb, controlled, multicenter study to evaluate antibody persistence at 1, 3, 5 and 10 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007). GSK Biologicals’ data on file.

GlaxoSmithKline Biologicals Annex Report 208355 (APV) 022. Double-blind, randomised comparative assessment of the immunogenicity and reactogenicity of three different lots of GSK Biologicals’combined diphtheria, tetanus, acellular pertussis vaccine (PT 25mcg + FHA 25mcg + 69kDa 8mcg). The vaccines were administered to healthy infants as a primary vaccination course of three consecutive doses at 3, 4 and 5 months of age. GSK Biologicals’ data on file.

Greco D, Salamaso S, Manstrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. New Eng. J. Med. 1996; 334:341-8.

Melville-Smith ME, Seagroatt VA and Watkins JT. A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralization test in mice as a method for the estimation of tetanus antitoxin in human sera. J Biol Stand 1983; 11: 137-44.

Schmitt HJ, Schuind A, Knuf M. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22, 505 infants. J. Pediatr. 1996a; 129:695-701.

Schmitt HJ, Wirsig von Koning CH, Neiss A. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA. 1996b; 275:37-41.

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine in Adults Aged 65 Years and Older — Advisory Committee on Immunization Practices (ACIP), 2012. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6125a4.htm?s_cid=mm6125a4_w. Accessed: 19 December 2017.

Weston W, Messier M. Friedland LR, et al. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. Vaccine 2011; 29(47): 8483-86.

Zou GY, Donner A. Construction of confidence limits about effect measures: a general approach, Statistics in Medicine 2008; 27:1693-1702.

CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

Pages 802 to 1111 have been removed - Out of Scope of phase 1 of Policy 0070 - CRF/eCRFs

Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals
Vaccines R&D
Investigator Approval Page

STUDY TITLE: A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9.

Study: 110086 (Tdap-0.3-009 EXT:007 Year 9) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Stephanie Powell
Affiliation /investigational centre:	PMG Research of Bristol, 1958 W. State St. Bristol, Tennessee, United States
Signature of Investigator:	PPD
Date:	19 Jan 2018

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GlaxoSmithKline Biologicals
Vaccines R&D
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A phase III, controlled, multicentre study to evaluate antibody persistence at 1, 3, 5 and 9 years following administration of a single dose of Tdap vaccine to healthy subjects, 19 years of age and older in the study 106316 (Tdap 0.3-007) and to evaluate the immunogenicity and safety of Boostrix as a second dose of Tdap, when administered at Year 9.

Study: 110086 (Tdap-0.3-009 EXT:007 Year 9) Development Phase: III

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Narcisa Elena Mesaros

Title of Sponsor Signatory: MD, Clinical and Epidemiology R&D Project Leader, DTP, Polio and Hib containing vaccines

PPD e Belgium, GlaxoSmithKline

Signature: PPD

Date: PPD 11-01-2018

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