Division: Worldwide Development
Retention Category: GRS019
Information Type: Summary Document Analysis Plan

Title:	Summary Document Analysis Plan for the Integrated Analysis of Cardiovascular Risk Among Type II Diabetes Subjects Exposed to GSK716155 in the Phase III Program

Compound Number: GSK716155

Effective Date: 31-MAY-2012

Description: This reporting and analysis plan presents the statistical analyses of cardiovascular safety data among type II diabetic subjects who participate in the GlaxoSmithKline (GSK) albiglutide program as amended from the final version of 15DEC2011. Results of these analyses will be reviewed by the regulatory agencies to rule out excess cardiovascular risk of albiglutide relative to combined comparators.

Subject: Cardiovascular risk analysis; type II diabetes mellitus

Author: [redacted] Associate Director of Biostatistics, PPD, Inc.

[redacted] Principal Statistician, Discovery Statistics Metabolic, GSK R&D

[redacted] Principal Statistical Scientist, PPD, Inc.

Approved by:

[redacted]

31 May 2012
Date

Head, Biostatistics and Data Science
Alternative Development Program
GlaxoSmithKline

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
CEC	Clinical Endpoint Committee
CI	Confidence interval
CVE	Cardiovascular events
DPP4	Dipeptidyl peptidase-4
EDC	Electronic data capture
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
KM	Kaplan-Meier
MACE	Major cardiovascular events
MACE+	Major cardiovascular events plus
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
PPD	PPD Development, LP
PH	Proportional hazards
SAE	Serious adverse event
SU	Sulfonylureas
TZD	Thiazolidinedione
WHODRUG	World Health Organization Drug Dictionary

1. ADMINISTRATIVE STRUCTURE

The clinical studies covered by this document are being conducted under the sponsorship of GlaxoSmithKline PLC. The clinical monitoring, data management and statistical analysis are being performed under contract with PPD, in collaboration with GSK.

2. INTRODUCTION

Albiglutide is a novel analogue of human GLP-1 designed to retain the therapeutic actions of GLP-1 while having an extended duration of action to treat type 2 diabetes mellitus (GlaxoSmithKline, 2008).

Starting in 2009, several randomized, double-blind, placebo- and active-controlled, multi- and parallel-group, multicenter studies have been initiated to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide by itself or in combination with currently approved antidiabetic therapy. An Independent Data Monitoring Committee (IDMC) reviews on an ongoing basis accumulating safety data to ensure the safety of subjects in all of the studies.

This reporting and analysis plan presents details of planned interim and end-of-study analysis of all cardiovascular events (CVE) as well as CVE adjudicated by a Clinical Endpoints Committee (CEC) for albiglutide Phase III studies. This plan includes the statistical approach as well as examples of the layout of data presentation including the shells for tables, listings and figures. These analyses will be submitted to the relevant regulatory authorities and will also be the basis for final safety analysis.

3. STUDY OBJECTIVES AND CARDIOVASCULAR EVENTS ENDPOINTS

3.1. Study Objectives

The primary objective of the analysis is to evaluate whether albiglutide alters the risk of cardiovascular events in subjects with type 2 diabetes relative to all comparators that comprise standard of care in the albiglutide Phase III program.

The secondary objective is to evaluate separately the albiglutide cardiovascular risk relative to active comparators plus background therapy and placebo plus background therapy.

3.2. Cardiovascular Events Endpoint(s)

Following the recent US Food and Drug Administration (FDA) issuance of an industry guidance for evaluating cardiovascular risk in new antidiabetic treatments (December, 2008), with the recommendations included in the Food and Drug Administration (FDA) letters dated 08 November 2008, 30 June 2009 and 1 and 12 July 2010 and extensive

deliberation by the program's CEC, the primary cardiovascular safety endpoint for albiglutide Phase III program is selected to be adjudicated "MACE Plus" event.

The following cardiovascular events comprise MACE:

- Acute Myocardial Infarction (MI)
- Stroke
- Cardiovascular death
    - Sudden cardiac death
    - Death due to acute MI
    - Death due to heart failure
    - Death due to stroke
    - Death due to other cardiovascular causes (e.g. pulmonary embolism, CV procedure-related, other CV event)
    - Presumed CV death (all deaths not attributed to the above categories of CV death and not attributed to a non-CV cause as indicated in the CEC charter)

The "MACE plus" ("MACE +") is defined as MACE events listed above plus

- hospitalization(s) for unstable angina.

3.3. Primary Comparison

The primary comparison will be incidence rate and relative hazard of the first occurrence of the adjudicated Major Cardiovascular Events plus (MACE+), as defined above, for albiglutide versus combined comparators. These comparators for integration consist of metformin, sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4(DPP4) inhibitors, long- and short-acting insulin, and placebo. In addition, MACE (as defined above) events will be analyzed similarly.

Other supportive analyses and comparisons include:

- Incidence rates and hazard ratios for adjudicated first MACE+ /MACE overall, by protocol and type of events for albiglutide versus combined comparators
- Incidence rates and hazard ratios for adjudicated first on-therapy MACE+/MACE overall and by protocol for albiglutide versus combined comparators
- Probability of occurrence of adjudicated first MACE+ /MACE at selected time points for albiglutide versus combined comparators
- Relative risks for adjudicated first MACE+/MACE for albiglutide versus combined comparators overall and by type of events
- Relative risk for all occurrences of adjudicated MACE+/MACE for albiglutide versus combined comparators overall and by type of events

Heterogeneity of albiglutide effects versus combined comparators on first MACE+ among selected subgroups will also be evaluated.

All TIAs will be reviewed by the CEC to check for any missed stroke events. Silent MI, hospitalization due to other angina, hospitalization for other chest pain, hospitalization for heart failure, subdural/extradural hemorrhages, and non-CV deaths will also be adjudicated by the CEC. These events and their adjudicated results will be descriptively summarized by individual study and integrated data as well. Furthermore, all cardiovascular related events including the events that have been submitted to CEC for adjudication will also be descriptively summarized by individual study and integrated data.

Full details of the meta analyses of the cardiovascular safety events are provided in Section 11.2. Supportive analyses including summary statistics on cardiovascular adverse events and serious adverse events by protocol and across protocols are in Section 12.

3.4. Statistical Hypothesis

Per the FDA guidance for evaluating cardiovascular risk in new anti-diabetic therapies to treat type 2 diabetes, the hypothesis of non-inferiority of the new antidiabetic therapy relative to all comparators with respect to cardiovascular risk will be tested at the time of the initial filing for market application as well as at the end of all the studies. A group sequential approach using non-binding boundaries for controlling the type I error will be used with an initial BLA filing when approximately 90 unique subject events are available and a final analysis when all studies are completed.

At initial BLA filing, the following hypothesis for CEC-adjudicated MACE+ hazard rate will be tested:

H_0 (null hypothesis): Albiglutide group is inferior to (worse than) the combined comparators with hazard ratio margin of 1.8; versus

H_a (alternative hypothesis): Albiglutide group is non-inferior to (not worse than) the combined comparators group.

For the initial BLA filing, GSK will perform statistical analysis of adjudicated MACE+ events to calculate estimated RR (relative risk) and 2-sided 97.55% CI. If the upper bound of the 2-sided 97.55% CI is less than 1.8, then this will provide unequivocal evidence of CV safety. If with 90 events, the upper bound of the 2-sided 97.55% CI for RR is above 1.8, the final analysis will be performed when all studies are completed. The final analysis will use a 2-sided 97.45% CI interval. If the upper bound of the 2-sided 97.45% CI for final analysis is below 1.8, the data will also provide definitive proof of CV safety for albiglutide.

Details of the power to detect the above alternative hypothesis as well other statistical hypotheses to be tested during the initial filing and at the completion of all the studies are in section 4.2.

Supporting analyses will be performed with their associated statistical hypotheses tested. Results from such analyses will be interpreted with great caution.

4. STUDIES IN SCOPE FOR ANALYSIS

The analysis of cardiovascular event safety will include data from the following studies:

- Five phase III studies for which subject enrollment started in the first quarter of 2009, and which continue for up to 3 years
- Three phase III studies for which subject enrollment started in the first half of 2010.
- Japan phase IIb study for which subject enrollment started in the first quarter of 2010.

These are studies that enroll subjects with type 2 diabetes and include a control group, both being essential for testing the statistical hypotheses. At the time of the meta-analysis, the 5 Phase III studies having 3 year duration will be ongoing. At the time of the regulatory filing, available cardiovascular data from all enrolled subjects from above 9 protocols will be used.

4.1 Details of studies in scope

The analysis of cardiovascular event safety will include data from the following randomized, placebo- and active-controlled, multi- and parallel-group, multicenter studies.

Phase III studies (enrollment started in the first quarter of 2009, and continue for up to 3 years):

- GLP112753 is a randomized, double-blind, placebo- and active-controlled, 4 parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin as compared with metformin +sitagliptin, metformin + glimepiride, and metformin + placebo among subjects with type 2 diabetes whose glycemia is not adequately controlled with their current regimen of metformin. About 1000 subjects were randomized to each of the 4 treatment groups in 3:3:3:1 ratio with metformin alone as the smaller group.
- GLP112754 is randomized, open-label, 2 parallel-group, multicenter study to evaluate the efficacy and safety of a subcutaneously weekly injected 30 mg dose of albiglutide (uptitrated to 50 mg weekly, if needed) as compared with insulin glargine in subjects with type 2 diabetes mellitus who are inadequately controlled on their current regimen of metformin alone or metformin + sulfonylurea. About 750 subjects were randomized to each of the 2 treatment groups in 2:1 ratio with insulin glargine as the smaller group.

- GLP112755 is a randomized, double-blind, placebo-controlled, 2 parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin) among subjects with a historical diagnosis of type 2 diabetes mellitus whose glycemia is inadequately controlled on their current regimen of pioglitazone alone or metformin + pioglitazone. About 300 subjects were randomized to each of the 2 treatment groups in 1:1 ratio.

- GLP112756 is a randomized, double-blind, placebo-controlled, 3 parallel-group, multicenter study to evaluate the efficacy and safety of weekly subcutaneously injected albiglutide in subjects with type 2 diabetes mellitus whose glycemia is inadequately controlled on their current regimen of diet and exercise and have received less than 7 contiguous days of treatment with any antidiabetic therapy within the 3 months before screening. There will be albiglutide treatment groups, one in which the albiglutide dose remains fixed at 30mg weekly, and the other in which the albiglutide 30mg weekly dose is titrated to 50mg weekly, to be compared with matching placebo group. A total of 315 subjects will be randomly assigned to each of the 3 treatment groups in a 1:1:1 ratio.

- GLP112757 is randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin + glimepiride compared with metformin + glimepiride alone and metformin + glimepiride + pioglitazone in subjects with type 2 diabetes mellitus whose glycemia is inadequately controlled with their current regimen of metformin plus a sulfonylurea. A total of 600 subjects were randomized to each of the 3 treatment groups in a 5:5:2 ratio with the metformin + placebo add on as the smaller group of 100 subjects.

Phase III studies (subject enrollment started in the first half of 2010):

- GLP108486 is a randomized, open-label, active-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of a weekly subcutaneously injected dose of albiglutide in combination with insulin glargine as compared with the combination of insulin glargine and preprandial lispro insulin in subjects with type 2 diabetes mellitus. Subjects with a historical diagnosis of type 2 diabetes mellitus who are inadequately controlled despite the use of insulin glargine or other intermediate- or long-acting insulins for ≥6 months but <5 years, with or without oral antidiabetic medications, who are unable to achieve an glycosylated hemoglobin value of <7% will be recruited into the study. A total of 500 subjects were randomly assigned to each treatment group in a 1:1 ratio.

- GLP114130 is a randomized, double-blind, active-controlled, 2 parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide as compared with sitagliptin. Subjects who are renally impaired with a historical diagnosis of type 2 diabetes mellitus and whose glycemia is inadequately controlled on their current regimen of diet and exercise

or their antidiabetic therapy of metformin, thiazolidinedione, sulfonylurea, or any combination of these oral antidiabetic medications will be recruited into the study. A total of 500 subjects were randomly assigned to each treatment group in a 1:1 ratio.

- GLP114179 is a randomized, open-label, multicenter, 2 parallel-group study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide as compared with liraglutide. Subjects with a historical diagnosis of type 2 diabetes mellitus and whose glycemia is inadequately controlled on their current regimen of metformin, thiazolidinediones, sulfonylureas, or combination of these oral antidiabetics will be recruited into the study. A total of 800 subjects were randomly assigned to each treatment group in a 1:1 ratio.

Japan phase IIb (subject enrollment started in the first quarter of 2010).

- GLP110932 is a Phase IIb, randomized, double-blind, placebo-controlled, multicenter, 4-parallel-group, dose ranging, superiority study evaluating the dose response, efficacy and safety of weekly and every other week subcutaneously injected GSK716155 in subjects with type 2 diabetes mellitus. A total of 200 subjects were randomly assigned to each treatment group in a 1:1:1:1 ratio.

The above nine protocols will enrol a total of 4985 subjects, 2475 of whom will be exposed to albiglutide.

4.2 Sample Size and Power

The ongoing and completed 9 Phase II/III albiglutide studies were expected to enroll a total of 4985 subjects, with approximately 2475 exposed to albiglutide. At the time of the initial filing, it was predicted that there would be around 9000 total patient-years of exposure for these studies. The MACE rate was originally predicted for each Phase III study using a modified United Kingdom Prospective Diabetes Study (UKPDS) model (Stewart, Ye and Yang, 2010) which took into account the demographics, risk factors, and exposure time for subjects recruited in the corresponding study.

Table 4.2.1 presents the predicted MACE rate for each study. Per the Modified UKPDS model prediction, the 8 Phase III studies were expected to accumulate a total of approximately 94 MACE at the time of initial filing. The number of MACE+ (MACE and hospitalizations(s) for unstable angina) was estimated to be approximately 1.1- to 1.4-fold the number of MACE based upon the review of the literature. With the previous assumption, the total number of MACE+ at the time of initial filing was estimated to be approximately 105 to 130, which provided 85% to 91% power to rule out RR risk of at least 1.

Table 4.2.2 presents the estimated events and the power to rule out RR 1.8. The person-years were based on person-years used at the time of initial filing.

Table 4.2.1 Estimated CV Event Rate by Protocol

Protocol Number	Study description	Total Subjects	Total Albiglutide Subjects	Estimated event rate per year MACE
Phase IIIa – First wave of 5 core studies (1Q09 start)				
112753	Add-on to metformin	1000	300	0.9%
112754	Albiglutide vs. insulin	750	500	1.0%
112755	Add-on to TZD (+/- metformin)	300	150	0.9%
112756	Monotherapy	315	210	1.1%
112757	Add-on to metformin + SU	600	250	1.0%
Phase IIIa – Second wave of 3 core studies				
114179	Head to head with liraglutide	800	400	0.9%
114130	Renally impaired, albiglutide vs sitagliptin	500	250	2.1%
108486	Add-on to basal insulin	500	250	1.3%
Phase IIb – Japan Study				
110932	Proof of Concept (Japan)	220	165	NA
	Overall	**4985**	**2475**	**1.03%**
Total exposure at initial filing (person-years)		9123	4223	
Total exposure at the end (person-years)		10605	4928	

Table 4.2.2 Estimated CV Events and Power for Albiglutide Clinical program

	Person year at initial filing	Expected Number of events at initial filing	Power to rule out 1.8 RR	Person years at the end of Study	Expected number of events at the end of studies	Power to rule out 1.8 RR
MACE+	9013	105-130	85%-91%	10495	119-151	89%-95%
MACE	9013	94	81%	10495	108	86%

CV = cardiovascular; MACE = major adverse cardiovascular events; MACE+ = major adverse cardiovascular events plus; RR = risk ratio; UKPDS = United Kingdom Prospective Diabetes Study.
Note: Event prediction based on modified UKPDS model and available demographic data from subjects enrolled into the Phase III studies. The total number of subjects in this prediction exercise is less than the total number of subjects enrolled in the study.

GSK originally planned to cut the clinical and EventNet (includes CEC adjudication result) databases for assessment of MACE+ events when around 125 events would have been observed (which was predicted to be June 2012 based on event onset time). 125 events would provide 90% power to rule out a RR of 1.8 and above assuming a true relative risk of 1.0. However, the event rate has been lower than predicted. It was expected that there would be only around 90 events accumulated at the planned time of data analysis for the initial BLA filing. Considering the recent data on the GLP-1 class suggesting that the true relative risk could be less than 1.0 (e.g 0.9), 85 to 90 events expected for the data analysis in June 2012 would have power that ranges from 82% to 85% to rule out RR of 1.8 with 0.025 significance level if the true RR was 0.9. With

reasonable power to rule out RR of 1.8 as well as practical consideration to have sufficient time to process and adjudicate the CV events, GSK decided to perform the data analysis in June 2012 as originally planned by adopting a group sequential approach using non-binding boundaries for controlling the type I error.

As originally planned, subjects are being followed up to three years, and CV events continue to be accumulated, adjudicated and analyzed for the final filing. Group sequential approach would allow an early evaluation CV safety (with ~ 90 events) while accumulating more events to the end of the study and controlling overall type I error.

The confidence interval boundaries of early evaluation and final evaluation will be determined by Lan-DeMets method. Alpha =0.0245 will be assigned to the early evaluation and alpha=0.0255 will be assigned to the final evaluation. This alpha allocation is based on a power error spending function with exponent 2 for information fraction t=0.70 (e.g. $\alpha(t)=\alpha t^2$). The information fraction t=0.7 is equal to the proportion of the number of events during the initial filing out of the total projected events at the final filing.

The testing procedures are described below:

- For the BLA filing with approximately 90 unique subject events, GSK will perform statistical analysis of adjudicated MACE+ events to calculate estimated RR and 97.55% CI. If the upper bound of 97.55% CI is less than 1.8, there will be unequivocal evidence of CV safety at the time of submission of the initial filing. GSK will still endeavour to make available the final result during the BLA review (the last subject last visit for the Phase III program will be in March 2013), even if the data at the time of submission using the Year 2 study results provide definitive proof of CV safety for albiglutide.
- If with 90 events, the upper bound of 97.55% CI for RR is above 1.8, the final analysis will be performed when all studies are completed. The final analysis will use 97.45% CI interval. If the upper bound of 97.45% CI for final analysis is below 1.8, the data will also provide definitive proof of CV safety for albiglutide.

The above approach should establish CV safety earlier with 90 events when there is very strong evidence to support the conclusion and retain the legitimacy of the final assessment if there is not sufficient number of events for early evaluation. If the noninferiority of the albiglutide CV safety is established with noninferiority margin of 1.8 either at the initial or final filing, further noninferiority test with noninferiority margin of 1.3 will be performed at the final filing. A superiority test will be performed following a statistically significant noninferiority test with 1.3 margin.

The table below shows the power of the initial and final filing using the allocated alpha at each time point assuming the true RR is either 1.0 or 0.9.

Predicted Number of Events at Initial Filing	Power for Initial Analysis with 97.55% CI Interval (RR = 1.0/0.9)	Predicted Number of Events at End of Study	Power for Final Analysis with 97.45% CI Interval (RR = 1.0/0.9)
100	75%/89%	135	88%/96%
90	70%/85%	120	83%/94%
85	67%/82%	110	80%/92%
80	64%/80%	100	75%/89%

Should the total number of events at the final filing be substantively lower than the projected total of over 125 events, an adjustment to the alpha used for the final analysis will be made to account for the shortfall.

4.3 MACE+/CV Events Safety Data Collection and Review Process

The overall adjudicated MACE+ events/CV events safety data collection and review process includes various components that are implemented using PPD's clinical database (Oracle Clinical Remote Data Capture), PPD's event adjudication system (EventNet), GSK's adverse event coding system and OmniTrace, a vendor that follows up the vital status of study participants. An overview of the various components follows below.

Special eCRFs at each visit are used to ensure that all data related to MACE+ events are properly collected and reported. This includes a CV-event reminder CRF at each visit, which asks the investigator if a MACE+ event has occurred since the last visit. All events are included in the clinical database.

An event where a narrative describes a possible MACE+ event or other event to be adjudicated by the CEC will be identified during regular medical monitor review and periodic data review by project physicians. In addition, GSK and PPD will use Standard MeDRA Queries (SMQ) to ensure that all MACE+ events are fully captured in the studies. All events whose coded terms match preferred terms listed within an SMQ will be uploaded to PPD's EventNet. EventNet is an electronic system outside of the clinical database that is utilized to facilitate the review process by the CEC, collates information about adverse events from various sources, including but not limited to the clinical database, manages the process flow of the review, and provides interface for the CEC to enter their adjudication classifications. Further details of the overall data collection and review process are in the Cardiovascular Analysis Plan for the Albiglutide Clinical Development Program (2009). This plan was submitted to the US Food and Drug Administration.

In addition, the clinical operations group of PPD has contracted OmniTrace, a third party vendor, who will assess from existing records vital status of subjects who are lost to follow-up. Data from this review of existing records will be integrated with the CV analysis database and could lead to more precise estimate of events, if there are any, and person years for subjects who are lost to follow-up.

5. PLANNED ANALYSES

5.1. Frequency of Analyses

The analyses of cardiovascular events will be performed at the time of initial filing and at the time when all current ongoing and planned phase III studies are completed. At the time of the submission of regulatory marketing applications, all subjects would complete at least 2 years of follow-up in the 5 core studies, and subjects from additional planned 3 Phase III studies would have approximately 6 months to 1 year of exposure. Subjects will continue to receive double-blind investigational product for up to 3 years, after which additional analyses of cardiovascular events and other safety data will be performed.

The analyses of cardiovascular events will rely on data from both the clinical database and EventNet system. At the time of initial filing, the data cut-off for both databases will be targeted for June 2012 when approximately 90 events will be obtained. Due to the time lag in the CEC adjudicating events there will be some cases pending adjudication at the time of the initial submission. All cases will be adjudicated for the final analysis.

In addition, GSK established an IDMC for the albiglutide phase III development program. All CV event data, together with other safety data, will be sent to the IDMC for review at approximately every 6 months after the first subject has been randomized to receive treatment. This frequency may be adjusted, if deemed necessary by the IDMC, depending on the enrolment rates and the rate of safety events. The IDMC will review not only the data from individual protocols but also the integrated data across all protocols. IDMC charter, reporting and procedures are outlined in separate documents.

5.2. Masked Analyses

At the time of the submission of regulatory marketing applications, the analyses of cardiovascular events for the ongoing 3 year studies will be conducted in a masked fashion by the designated submission team. The designated submission team will be unblinded to treatment code but will not have access to the actual subject identifier. This approach is intended to minimize the potential impact on the ongoing studies and ensure integrity of the analyses. The process for maintaining the blind and assuring data integrity for the Phase 3 studies that continue for 3 years has been agreed with the regulatory authorities and is described in separate documents. For the IDMC analyses, open and closed reports are prepared by separate unblinded and blinded analysis teams, respectively.

5.3. Overview of Statistical Methods

For continuous variables, descriptive summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Additional supportive listings and figures will also be provided. Additional details of these summaries are described in the presentation of key endpoints in the appropriate sections below.

For the analysis of CVE data, frequencies and product-limit estimates of events at selected time points will be provided for each protocol and for the integrated data combining all protocols. Inferential hypothesis testing including stratified log-rank testing and proportional hazards (PH) modeling as described in Section 11.1 will be performed.

If the data indicate insufficient number of events to support the proposed primary statistical analysis method of time to event/PH model/log-rank test, exact test method with the adjustment of protocol/stratification will be considered. GSK will communicate with FDA if that is the case.

6. ANALYSIS POPULATION

The Randomized population will include all subjects randomly assigned to receive study treatment regardless of whether or not they received a dose of study medication.

The Safety population will be used through the entire report of the cardiovascular risk analyses. The Safety population consists of all randomized subjects who received at least one dose of study treatment. The Safety subject will be analyzed according to treatment received.

7. TREATMENT COMPARISONS

For the integrated analysis of CVE data, treatment comparisons will include:

Primary comparison:

- Albiglutide versus all comparators;

Supportive comparisons:

- Albiglutide versus active comparators
- Albiglutide versus placebo comparators.

Studies with active comparators will be grouped for albiglutide versus active comparators comparison. Similarly, studies with placebo control will be grouped for albiglutide versus placebo comparison. Studies with both active control and placebo will be included into both groups. Details of the grouping of treatment groups into the comparison groups for the integrated safety analysis are in table 7 below.

The comparison of albiglutide versus individual comparator will be done at study level as further supportive analysis. Other than the overall comparison, all grouped analyses and within study analyses with no pre-specified hypotheses and power are of supportive nature to support the overall primary analysis. Results from these supportive analyses need to be interpreted with great caution.

Table 7 Grouping of Protocol-Specific Treatments into Integrated Analysis Comparison Groups

Protocol Number / Short Name	Protocol Specific Treatment Groups	Integrated Analysis Comparison Groups: Albiglutide + Background Therapy	Active Control + Background Therapy	Placebo Control + Background Therapy	All Comparators + Background Therapy
		n	n	n	n
GLP108486					
Add-on to insulin glargine	Albiglutide + insulin glargine	250			
	Preprandial insulin + insulin glargine		250		250
	Sub-total	250	250	0	250
GLP112753					
Add on to Metformin	Albiglutide + Metformin	300			
	Sitagliptin + Metformin		300		300
	Glimepiride + Metformin		300		300
	Metformin + Placebo			100	100
	Sub-total	300	600	100	700
GLP112754					
Albiglutide vs Insulin	Albiglutide	500			
	Insulin Glargine		250		250
	Sub-total	500	250	0	250
GLP112755					
Add on to TZD (+/- Metformin)	Albiglutide + TZD (+/- Metformin)	150			
	Placebo + TZD (+/- Metformin)			150	150
	Sub-total	150	0	150	150
GLP112756					
Monotherapy	Albiglutide 30 mg	105			
	Albiglutide 30 mg with up-titration to 50 mg at Week 12	105			
	Placebo			105	105
	Sub-total	210	0	105	105
GLP112757					
Add on to Metformin +Sulfonylureas	Metformin + Glimepiride + Pioglitazone		250		250
	Metformin + Glimepiride + Albiglutide	250			
	Metformin + Glimepiride + Placebo			100	100
	Sub-total	250	250	100	350

Table 7 Grouping of Protocol-Specific Treatments into Integrated Analysis Comparison Groups

Protocol Number / Short Name	Protocol Specific Treatment Groups	Integrated Analysis Comparison Groups: Albiglutide + Background Therapy	Active Control + Background Therapy	Placebo Control + Background Therapy	All Comparators + Background Therapy
		n	n	n	n
GLP114179					
Head-to-Head vs. Liraglutide	Albiglutide (30 mg with up-titration to 50 mg at Week 6) + Metformin, Pioglitazone, Glimepiride or combination	400			
	Liraglutide + Metformin, Pioglitazone, Glimepiride or combination		400		400
	Sub-total	400	400	0	400
GLP114130					
Renal Impairement Albiglutide + Sitagliptin	Albiglutide+ Sitagliptin Matching Placebo	250			
	Sitagliptin+ Albiglutide Matching Placebo		250		250
	Sub-total	250	250	0	250
GLP110932					
Proof of Concept (Japan)	Albiglutide 15mg weekly	55			
	Albiglutide 30mg weekly	55			
	Albiglutide 30mg biweekly	55			
	Placebo			55	55
	Sub-total	165	0	55	55
Total		**2475**	**2000**	**510**	**2510**

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All analyses will be conducted using SAS Version 9.1 or higher.

8.1. Multicenter Studies

The analyses will be pooled across sites within each individual study.

8.2. Multiple Comparisons and Multiplicity

No additional adjustments, other than those presented in Section 4.2 are planned. Analyses of adjudicated cardiovascular events aggregated across protocols provide the IDMC information in considering early study termination of the albiglutide program

based on safety and not efficacy consideration. In the circumstance of albiglutide having a superior benefit versus comparators on CV events (placebo/active control, overall superiority, i.e., not driven by isolated studies or populations based on Lan-DeMets group sequential boundary (Roboussin et al., 2000)), the IDMC will assess this finding and may make a recommendation in the setting of the overall risk/benefit profile of albiglutide and overall study/development program objectives.

8.3. Examination of Subgroups

The following demographic and baseline variables have been identified to be of general interest for subgroup comparison :

- Gender (Male, Female)
- Race/Ethnicity (Non-hispanic African American, Non-hispanic White, Hispanic, Asian, Other)
- Age at randomization: (<65 years, ≥65 to <75 years, ≥75 years)
- Baseline BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 to <35 kg/m^2, ≥35 kg/m^2)
- Region
  - Europe = {France, Germany, Spain, and United Kingdom}
  - Asia = {Hong Kong, Philippines, India, Korea, Taiwan, Japan}
  - Rest of World (ROW) = {Australia, Brazil, Columbia, Israel, Mexico, Peru, Russian Federation, South Africa}
  - USA – North
  - USA – South Atlantic
  - USA – South Central
  - USA – West
- Duration of diabetes (<5 years, 5 to <10 years, ≥10 years)
- Background therapies: (None, Met, Met+SU, Met+SU+TZD, Met+TZD, SU, TZD, SU+TZD)
- Baseline HbA1c (<8.0%, ≥8.0% to <9.0%, ≥9.0%)
- Smoking status (Never Used, Current User, Former User)
- Prior CV History (Yes, No): defined as yes for subjects with any of the following medical history conditions: past myocardial infarction, stroke, cardiac arrest, unstable angina, current ischaemic heart disease without cardiomyopathy, or current ischaemic heart disease with cardiomyopathy

Other factors such as background medication may also be considered when applicable.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal

Every effort will be made to keep subjects on their active treatment for as long as the protocol requires, and to have the subjects complete the study for at most three years since randomization. The reasons for subjects not completing their active treatment or not completing the study will be recorded. Subjects who stop their active treatment or who prematurely withdraw will still be followed up to ensure that no cardiovascular events have occurred since the last contact and throughout the whole study duration. Subjects who are withdrawn from the study will not be replaced.

9.2. Derived and Transformed Data

9.2.1. Person Years

Total person years (MACE+/MACE)

For the analysis of first MACE+ events, the person time is equal to:

- For subjects with any CEC-adjudicated events the total number of days between the date of the first CEC-adjudicated event occurrence as recorded in EventNet and the date of first dose plus 1.

- For subjects with no CEC-adjudicated event (e.g. subjects who are censored), the person time is equal to the number of days between the date of the last contact and the date of first dose plus 1. For these subjects, the date of the last contact equals date of last contact from the clinical database.

For subjects who are lost to follow-up with vital status (dead or alive) tracked by OmniTrace the date of last contact as recorded in the clinical database will still be considered the date of last contact. This approach is used because it is uncertain whether or not MACE+ events occurred for subjects who are lost to follow-up.

To obtain the person years, the person time in days is divided by 365.25.

Total person-years is calculated as the sum of all person years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment).

It is expected that the CEC adjudication will consider whether all related occurrences of events that occur within a short period of time may be single or multiple events. For example, a stroke followed by death within a day can be considered as a single event instead of two separate events. The date of the occurrence of the first CV event will be based on the date designated by the CEC.

Total on-therapy person years (MACE+/MACE)

The on-therapy person time will include time between the last dose date and the first dose date plus 57 and is derived as follows:

- For subjects who withdraw from study treatment early with CEC-adjudicated on-therapy events, the on-therapy person time is equal to the total number of days between the date of the first CEC-adjudicated event occurrence and the date of first dose plus 57.

- For subjects with no CEC-adjudicated on-therapy event (e.g. subjects who are censored, or whose adjudicated events occur after withdrawal from treatment), the person time is equal to the number of days between the date of the last dose and the date of first dose plus 57.

Because of the expected long half-life of albiglutide, 56 days past the last dose date is added to the person time. This adjustment in person time among subjects in the albiglutide arm will also be made for person time of subjects in the non-albiglutide arms of the trials. The on-therapy person years will exclude follow-up time past the last dose date + 57 days. As in the calculation of overall person years above, the date of the occurrence of the first CV event will be based on the date designated by the CEC. To obtain the on-therapy person years, the on-therapy person time in days is divided by 365.25.

Total on-therapy person-years is calculated as the sum of all on-therapy person years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment).

Total person years and on-therapy person years will be calculated for each of the composite events (MACE+ or MACE) and for each component event.

Total all-cause mortality person years (All-cause mortality)

For the analysis of all-cause mortality events, the person time is equal to:

- For subjects that died, the total number of days between the date of death as recorded in the clinical database and the date of first dose plus 1. Any deaths recorded in the OmniTrace database will also be recorded in the clinical database.

- For subjects that have not died (e.g. subjects who are censored), the person time is equal to the number of days between the date of the last contact and the date of first dose plus 1. For subjects that are not lost to follow-up, the date of the last contact equals date of last contact from the clinical database. For subjects who are lost to follow-up but are located by OmniTrace to be alive, the last date of contact is the date of lost follow-up as recorded in OmniTrace.

To obtain the all-cause mortality person years, the all-cause mortality person time in days is divided by 365.25.

Total all-cause mortality person-years is calculated as the sum of all all-cause mortality person-years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment).

9.2.2. Censoring Variables

Subjects who experienced an event (MACE, MACE+, all-cause mortality) will be assigned a value of 1 for the censoring variable and those with no events will be assigned a value of 0. Censoring variables will be constructed for each of the composite events as well as the component event. This censoring variable together with the person-years will be used in the CVE time-to-event analysis.

10. SUMMARY POPULATION

10.1. Disposition of Subjects

The study disposition of subjects in each protocol and across protocols will be reported based on the randomized analysis population. The number and percentage of subjects who have completed the protocol-mandated visits will be summarized by treatment group. To be reported by protocol–specific treatment groups, and integrated analysis comparison groups are the numbers of subjects with respect to:

- completion of active treatment (e.g. completed, terminated early or ongoing active treatment) together with reasons for early treatment termination
- completion up to study conclusion together with reasons for not completing the study follow-up visits
- completion for the primary endpoint (e.g completed follow-up for CV events to data cut-off or had a primary event before being lost to follow-up)
- vital status (dead/alive/unknown) of subjects who are lost to follow-up
- subject disposition with respect to inclusion in the safety analysis population

The percentages of subjects within treatment groups will also be reported.

10.2. Disposition of Potential CV Events

The total number of events that potentially define a MACE/MACE+ event and their designation as actual MACE/MACE+ events, other (definitely not MACE/MACE+), or pending ajudication status, will be presented by protocol-specific treatment groups and integrated comparison groups.

10.3. Protocol Deviations/Violations

Major protocol violations will be tabulated by protocol-specific treatment groups and integrated analysis comparison groups.

10.4. Demographic and Baseline Characteristics

Continuous variables, such as age at randomization, body mass index, baseline HbA1c, weight, height and duration of diabetes will be summarized using descriptive statistics for each treatment comparison grouping. Some variables will be categorized, such as age (<65, ≥65 to <75, and ≥75 years). These and other categorical variables including sex, race/ethnicity, baseline HbA_{1c} category, duration of diabetes category, background anti-hyperglycemia medication category, and prior MI will be summarized by reporting the number and percentage of subjects in each category for each treatment comparison grouping. All summaries will be performed using the safety population.

10.5. Cardiovascular Medical History

The number and percentage of subjects with current and/or past cardiovascular medical history will be presented in decreasing order within the albiglutide treatment group. In addition, by subject listings of cardiovascular history will be presented. All summaries will be performed using the safety population.

10.6. Risk Factors for Cardiovascular Events

Descriptive summary statistics on selected risk factors (demographics, smoking status, baseline and previous medical history as per Section 8.3) will be presented by treatment comparison grouping.

10.7. Concomitant Medications

The GSK drug dictionary, based on the World Health Organization Drug Dictionary (WHODRUG), will be used to code all medications. Summaries of all medications with approved indication to prevent and/or treat CVE will be identified via medical review and will be summarized by treatment comparison groupings. Generic terms will be provided in relation to treatment phase (prior medication, concomitant medication, or post-therapy medication). Prior medications are those started before the first dose of study drug. Concomitant medications are those taken at any time on or after the day of the first dose of study drug and within 56 days after the last dose of study drug, including those medications that were started prior to randomization but were continued into the study period. Post-therapy medications are those taken more than 56 days after the day of the last dose of study drug.

Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. In the case of a completely missing start date, the start date will be assumed to be prior to date of the first administration of study drug. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, the medication will be assumed to be ongoing.

11. CARDIOVASCULAR SAFETY ANALYSES

11.1. Extent of Exposure and Treatment Compliance

Descriptive summary statistics including the number of subjects, mean, standard deviation, minimum and maximum study drug exposure will be reported by treatment. The duration of exposure is defined as the number of days between the date of the last dose and the date of the first dose plus 1. Exposure and treatment compliance will be reported for the investigational product and not on the background therapies.

For subjects who receive albiglutide or double-blind albiglutide placebo, treatment compliance will be calculated as total number of administered doses divided by total number of doses which should have been taken based on the date of the last dose administered. Treatment compliance will be summarized for all subjects in addition to being summarized separately for subjects who have terminated treatment early, subjects who have completed active treatment, and subjects who are continuing active treatment. Summary statistics for treatment compliance percentages, as well as the number and percentage of subjects who are <80%, and ≥80% compliant will be reported.

Background therapy cardiovascular events as reported by the sites in the electronic data capture (EDC) system will be reviewed periodically. However, recommendations for continuation/discontinuation of the program based on CVE review will be based on CEC-adjudicated MACE+ events only. The incidence of MACE+ events is the primary CVE endpoint. All adjudicated MACE+ events will be reported in integrated manner across protocols. MACE only events will also be reviewed and reported in integrated manner across protocols.

11.2. Integrated CVE Analysis

An integrated inferential analysis of MACE+ events will be conducted as the primary analysis of CVE. The estimated hazard ratios together with their 95% confidence intervals will be reported from a Cox proportional hazards (PH) model for the first event occurrence where the key study treatment covariate is a two-level identification of albiglutide versus all comparators (albiglutide versus active or placebo control plus background therapy), stratified by protocols. This analysis will also be performed where albiglutide will be compared separately with active comparators plus background therapy and placebo control plus background therapy. The 2-sided p-value for the test of the significance of effect of albiglutide versus comparators on CVE will be reported. However, in support of the non-inferiority hypothesis that CV risk of albiglutide is non-inferior to all comparators with 1.8 non-inferiority margin, one-sided test with 0.0125 significance level will be performed during the initial filing. The equivalent two-sided 97.55% CIs will be reported for the albiglutide versus all comparators only.

The Cox PH model will be fitted to the time of the first MACE+ aggregated outcome, as well as to the time of occurrence of each type of CVE. The Cox-model estimate of the log hazard ratio and its standard error will be used to construct a model-based estimate of the confidence limits on the hazard ratio. The confidence limits are first constructed for the log hazard ratio and then exponentiated to provide the corresponding confidence limits on the hazard ratio scale. It is to be noted that the logrank test (without ties) could

be derived as an efficient score test in a proportional hazards regression model with a single binary covariate to represent treatment group (Lachin 2000). Per literature, the Efron approximation for the likelihood under tied failure times in proportional hazards regression performs far better than Breslow approximation (Hertz-Picciotto 1997). Therefore, in case of ties in reported survival time, Efron's adjustment will be used instead of the default setting of Breslow adjustment.

The descriptive statistics including the number of first events (equal to the number of subjects with events), total person years and incidence rate by integrated analysis comparison groups will be presented together with the Cox model hazard ratio and its 95% CI and p-value. The analogous information will be provided where albiglutide is compared with placebo control and active control. Also reported are p-values for testing the significance of effect of albiglutide versus the integrated comparators obtained in running the Cox model for each of the protocols.

The descriptive statistics and results of Cox models where the outcome is time to the first occurrence of each type of CVE (acute MI, stroke, cardiovascular death, and hospitalizations for unstable angina) will be presented where the effects of albiglutide on time to first occurrence of specific CVE are compared with all comparators, placebo control and active control, respectively.

The hazard ratios and their 95% CIs, for the overall MACE+ will be presented graphically for each of the three comparisons described above. Similarly, the hazard ratios and their 95%CI for each of the MACE+ component will be presented graphically for each of the three comparisons above.

The product-limit estimates of the probabilities (and their standard errors) of first MACE+ over time after first dose up to 3 years of study follow-up as obtained from Kaplan-Meier (KM) survival curves will be presented where albiglutide is compared with all comparators, placebo control and active control. The KM curves will also be presented corresponding to the above comparisons.

The total number of all MACE+ or any of its components, total person years (up to the last contact with subjects), total on-therapy person years and incidence rate per 100 person years, relative risks and their 95% CI calculated from Poisson regression models, number of subjects who experienced at least one event, 2 or 3 or more MACE+ or its components will be presented by integrated comparison groups.

The heterogeneity of albiglutide effects will be assessed in Cox PH model stratified by protocol where the explanatory variables include indicator for treatment/comparison groups, covariate level indicator and treatment by covariate interaction. The p-values for testing the heterogeneity of the treatment effects across levels of covariate together with the hazard ratios and 95% CI and descriptive statistics at each level of the covariate will be presented for comparison of albiglutide with all comparators, placebo control and active control. The covariates to be modelled parametrically include the randomization stratification factors as described in Section 8.3.

The effects of the covariates on the MACE+ hazard for albiglutide will be presented based on a model that includes all of the key covariates of interest. These covariates

include CVE experience prior to randomization, age at randomization, baseline HbA1c, sex, race, and regional grouping of sites.

The following analyses will be repeated for MACE:

- Incidence rates and hazard ratios for adjudicated first MACE overall and by protocol
- Incidence rates and hazard ratios for adjudicated first on-therapy MACE overall and by protocol
- Probability of occurrence of adjudicated First MACE by type of event
- Relative risk for adjudicated first MACE and for all occurrences of MACE

The following analyses will be repeated for all-cause of mortality:

- Incidence rates and hazard ratios for all-cause mortality overall and by protocol
- Relative risk for all-cause mortality

The hazard ratio and their 95% CI for overall MACE+ and MACE will also be presented graphically by pre-defined subgroups and individual studies.

The details of model fitting and some sample programming codes are in Appendix A.

The number and percent of subjects who experienced coronary revascularizations, type of procedures used and sequelae of the procedure will be reported by comparison groups.

11.3. Assessment of PH Assumption

Both the stratified log-rank test and stratified Cox PH model have the greatest power to detect the differences in survival curves among treatment groups when the proportional hazard assumptions hold in the data. Stratification in Cox model allows for proportional hazards assumptions to hold in the specified strata, and not for the aggregate of study subjects. In addition to having the greatest power to detect differences in survival curves, the logrank test is a form of Cochran-Mantel-Haenszel test, and performs well even for sparse data.

The log hazard ratio estimate obtained from the Cox proportional hazards model is a consistent (asymptotically unbiased) estimate. However, the Cox model-based estimate of the standard error is biased when the PH model assumption does not apply. A test of whether the PH model assumption is consistent with the data will be done by fitting a Cox model where a function of time like logarithm of time is included in the model in addition to the treatment effect. If the coefficient associated with the function of time is nominally significant at the 0.10 level, then the robust information sandwich (Lin and Wei, 1989; cf. Lachin, 2000) will be employed to provide a consistent estimate of the variance of the log hazard ratio estimated from the Cox PH model. The resulting robust confidence limits on the hazard ratio will then have the desired coverage probability even though the PH assumption may not apply for the treatment effect.

Graphical assessments of proportional hazards assumption will be performed by plotting the log(-log) of the probability of survival versus time or logarithm of time for each

integrated comparison group. If the hazards are indeed proportional, the difference in the plots of log(-log) of the probability of survival versus time will more or less be constant across time.

In the case of the data not being consistent with the proportional hazards assumptions as indicated by the results of PH modelling and graphical assessments, alternative stratified statistical tests of the association of hazards and treatment will be performed. In particular, Peto's one-step method would be considered which is based on quantities that are required for the calculation of the Mantel-Haenszel test. Peto's one-step method computes an approximation of the log-odds from the ratio of the efficient score to the Fisher information and weighted log-odds by the Fisher information before taking exponential transformation. The method of Peto was evaluated as most appropriate coverage for event rates of 1% or below (Bradburn et al.2007).

11.4. Within-Protocol CVE Analysis

An overview of the CVE analysis within each protocol is as follows:

- Present incidence rates (including the total number of events and total person years up to the event) and hazard ratios and their 95% CI for adjudicated first MACE+, MACE, on-therapy MACE+, on-therapy MACE, all-cause mortality.
- Hazard ratios for adjudicated first MACE+ will be presented for the key pairwise treatment comparisons of interest in protocols with more than two treatment groups. The p-value from the Cox PH model for testing whether hazard rates are equal between treatment groups will be presented.
- Adjudicated non-MACE+ events

12. GENERAL CARDIOVASCULAR ADVERSE EVENT ANALYSIS

In addition to the analysis of CEC-adjudicated MACE+/MACE events, on-therapy and post-therapy cardiovascular related adverse events will be summarized and compared across treatment groups as supportive analysis.

The therapy periods will be defined as:

- **Pre-therapy:** The onset date of the AE is before the start date of study medication. If the onset date of the AE is on the start date of study medication, the AE will be considered as on-therapy.
- **On-therapy (Treatment-emergent):** The onset date of the AE is on or after the start date of study medication and within 56 days after the date of last dose.
- **Post-therapy:** The onset date of the AE is more than 56 days after the last date of study medication.

If only partial information is available for the onset date of an AE, then the AE will be included in the most conservative therapy period that is consistent with the therapy period

definitions above and the available AE onset and resolution date information. (Here most conservative therapy period means on-therapy > post-therapy > pre-therapy.)

The scope of general cardiovascular safety data ranges from:

- all cardiovascular adverse events which would be sent to adjudication committee for adjudication,
- all adjudicated MACE/MACE+ events, and
- all events selected as cardiovascular events based on MedDRA dictionary coding

Included among cardiovascular adverse events sent to the adjudication committee are silent MI, hospitalizations due to other angina, hospitalizations for other chest pain, hospitalizations for heart failure, other cerebrovascular events including subdural/extradural haemorrhages and non-cardiovascular deaths. Events will be grouped by type based on the standard MeDRA queries that correspond to cardiovascular and cerebrovascular events. Their adjudication results will be summarized by event type for the comparison groups.

To ensure that all events that require adjudication have been identified, all the AEs/SAEs will be regularly reviewed to ensure that site investigators have completed the required eCRF pages. An AE that appears to be a potential endpoint or a symptom of a potential endpoint will be identified based on prospectively identified rules and follow up with the Investigator will be completed and a documented action will be noted. The details on the process/ rules for screening and identifying of above events will be provided in separate document.

All of the general cardiovascular adverse events will be tabulated by event type and treatment group for individual protocols. In addition, the general cardiovascular events will be aggregated across protocols where the proportions of subjects who experienced each CVE between the albiglutide and comparator groups will be tested for equality using the Cochran-Mantel-Haenzsel test with protocols as the stratification factor. The reported p-values will be used as IDMC's screening tool; in the event of signal, the IDMC may perform detailed evaluation of the safety events.

The total of general cardiovascular events that occurred while on therapy and post-therapy will also be presented by comparison groups.

By subject listing of cardiovascular events will be generated for each protocol. The CVE listing will include the seriousness, severity, relationship to the study drug, whether event is a reason for early study drug discontinuation or study withdrawal, whether the event was sent to CEC and the event was adjudicated as MACE+/MACE.

13. REFERENCES

Bradburn M.J., Deeks J.J., Berlin J.A. and Localio A. Russell, Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med, 26 (2007), pp. 53–77.

DeMets DL, Lan KKG: "Interim analysis: The alpha spending function approach". *Statistics in Medicine*, 13:1341-1352, 1994.

Food and Drug Administration (USA) 2008. Guidance for Industry:Diabetes Mellitus — Evaluating Cardiovascular Risk in New AntidiabeticTherapies to Treat Type 2 Diabetes. Downloaded on 14May2009 from http://www.fda.gov/cder/guidance/8576fnl.pdf.

GlaxoSmithKline Document Number RM2006/00602/03. Investigator's brochure: GSK716155. 25-Nov-2008.

Hertz-Picciotto I and Rockhill B. Validity and Efficiency of Approximation Methods for Tied Survival Times in Cox Regression. Biometrics, 53, No. 3 (Sep., 1997), 1151-1156.

Lachin, JM. Biostatistical Methods: The Assessment of Relative Risks. John Wiley and Sons. NY. 2000.

Lan KKG, DeMets DL: "Discrete sequential boundaries for clinical trials". *Biometrika*, 70(3):659-663, 1983.

Lin, D. Y. (1991). Goodness-of fit analysis for the Cox regression model based on a class of parameter estimators. J. Amer. Statist. Assoc., 86, 725-728.

Lin, D. Y. and Wei, L. J. (1989). The robust inference for the Cox proportional hazards model. J. Amer. Statist. Assoc., 84, 1074-1078.

Reboussin DM, DeMets DL, Kim K, Lan KKG. Computations for group sequential boundaries using the Lan–DeMets spending function method. Controlled Clinical Trials 2000; 21:190 –207.

Thall PF and Lachin JM. Assessment of stratum-covariate interactions in Cox's proportional hazards regression model. Stat Med, 1986, 5, 73-83.

Ye J, Yang F, Stewart M. Modification of the UKPDS Risk Engine to Evaluate Cardiovascular Event Rates in Controlled Clinical Trials. Diabetes. 2010;59 (Suppl 1):A-192, 704-P

APPENDIX A: SAMPLE PROGRAMS FOR CVE ANALYSIS

A1. Variables for Integrated CVE Analysis:

These variable names are for the illustrative purpose to run the Kaplan-Meier and Cox proportional hazards models for the integrated analysis of time to first cardiovascular event.

SURV is the failure time variable (i.e. time to event or censoring).

STATUS is the censoring variable and takes the value of either 0 or 1; 0 refers to the censored observation and 1 to the observation who experienced an event.

TREAT_A is an indicator variable where 1 is for albiglutide and 0 is for all comparators.

TREAT_3 is a 3-level nominal variable where 1 if for albiglutide treatment group, 2 for control comparators and 3 for active comparators.

PROTOCOL is a categorical variable that nominally names the protocols from 1, 2…,k for each of the k protocols in the albiglutide program. PROTOCOL is a stratification variable in the integrated CVE analysis, allowing for baseline hazards to vary by protocol.

COV_X is a generic name that refers to the randomization variables entered for testing the heterogeneity of treatment effects across levels of covariates.

XXX is a generic name that refers to the dataset processed for a specified model.

Outputs for each of the specified model will be directed to ODS files which are then used to generate the TLFs of interest. Details of these will be provided in the TLF specifications.

All modelling runs will be made using SAS 9.1.3 or higher.

A2. Model Specifications for the Primary Analysis for Comparing Albiglutide versus All Comparators:

Primary Analysis: Model 1 as specified below will be fitted for the primary analysis. Model 1 will provide an unadjusted estimate of albiglutide effects under the proportional hazards assumption with baseline hazards set to vary by protocol as indicated in the STRATA statement.

The 95% CI for the hazard ratio will be reported using the ‘risklimits’ option. In case of ties in reported survival time, Efron’s adjustment will be used. Both the model-based and robust covariance will be reported by using the option ‘covs’.

/* **Model 1** */

```
proc tphreg data=XXX covs(aggregate);

model SURV*STATUS(0)=TREAT_A/ risklimits  ties=Efron;

strata PROTOCOL;
```

title 'Unadjusted HR stratified by protocol with robust variance and assessment of PH assumption for treatment effect';

Model 2 provides additional test of whether the data are consistent with proportional hazards assumption. This test is for the statistical significance of the coefficient associated with the interaction of survival time and treatment group. This specification came from the GSK template for the analysis of survival data. Log of time instead of time per se may also be used in the time by treatment group interaction. Other procedures like the assessment of the parallel log(-log) of survival curves between group as obtained from the Kaplan-Meier procedure will also be used to assess the PH assumption.

```
/* Model 2 */

proc tphreg data=XXX covs;

model SURV*STATUS(0)=TREAT_A TRT_TIME/ risklimits  ties=Efron

strata PROTOCOL;

TRT_TIME=TREAT_A*log(SURV);
```

Model 3 provides KM estimates of probability of first event by treatment groups. The request for plot for survival, log of survival and log of log negative survival further provides evidence or lack of evidence of proportional hazard assumption. The log rank test obtained in this procedure is approximately equal to the score test in the Cox PH model if the PH assumption holds.

```
/*Model 3: KM Estimate* /

proc lifetest data=XXX method=KM  plot=(s,ls,lls);

time surv*status(0);

strata TREAT_A;
```

Model 4 provides model to test whether treatment effects are homogeneous across levels of covariates. The p-value for the test of the significance of the interaction of treatment by covariate is a test of the statistical significance of the coefficient associated with the treatment by covariate interaction term.

To implement model 4, add to model 1, COVX, and COVX by treatment variable, TRTCOVX (e.g. TRTCOVX=TREAT_A*COVX), and assess whether the coefficient associated with TRTCOVX is significant. For a dichotomous covariate, the estimated Hazard Ratio comparing treatments for each level of COVX will be reported. For a quantitative covariate, the treatment group hazard ratio per unit change in the covariate will be reported.

```
/*Model 4 */

proc tphreg data=XXX covs;

model SURV*STATUS(0)=TREAT_A COVX  TRTCOVX/ risklimits  ties=Efron;

 strata PROTOCOL;

TRTCOVX=TREAT_A*COVX;
```

Model 5 will then test whether the treatment effect is homogeneous across strata. This is a special case of testing for a stratum-covariate interactions in Cox's proportional hazards regression using the likelihood ratio test as described in Thall and Lachin (1986) comparing models C versus B therein. This model would be fit as follows:

```
/*  Model 5 */

proc tphreg data=XXX covs;

model SURV*STATUS(0)=TREAT_A1 .... TREAT_A5 / risklimits  ties=Efron;

 strata PROTOCOL;

TREAT_A1 = 0; IF PROTOCOL = 1 THEN TREAT_A1 =1;

TREAT_A2 = 0; IF PROTOCOL = 2 THEN TREAT_A2 =1;

.....

TREAT_A5 = 0; IF PROTOCOL = 5 THEN TREAT_A5 =1;
```

In this model there is a separate treatment effect variable TREAT_A1 ... TREAT_A5 for each protocol, the protocols numbered 1 – 5. The test of homogeneity of treatment effects is then obtained as a likelihood ratio test computed as the difference in the -2logL value from model 5 versus model 1 above.

A.3. By Protocol Analysis

For the IDMC, Model 1 and Model 3 will be fitted by protocol to obtain the protocol-specific HR using the integrated grouping of comparison groups. In addition, these models will be fitted to compare the survival curves and hazard ratios specific to each protocol.

A.4 Model Specifications Using PROC TPHREG

The experimental PROC TPHREG allows for CLASS and CONTRAST statements and will be used. The last category is the default reference category but this default can be overridden by specifying the reference category in the class statement. The current version of TPHREG does not allow assessment of PH assumption. Thus, PH assumption and calculation of HR will be based on procedures specified above.

The specification below provides comparison of level 1 (albiglutide) with level 3 (active comparators), and level 2 (placebo) with level 3.

The first contrast statement provides an HR for albiglutide versus active comparators. The second contrast statement provides an HR for albiglutide versus placebo comparators. As in PHREG, model-based and robust covariance are provided by specifying 'covs' option.

```
proc data=XXX covs (aggregate);

class TREAT_3 ;

model SURV*STATUS(0) =TREAT_3;

strata PROTOCOL;

contrast 'Key Comparisons'

        TREAT_3 1  0  , /* Albiglutide vs active comparator*/

        TREAT_3 1  -1  /* Albiglutide vs placebo comparator*/

              / estimate=exp;

run;
```

APPENDIX B: PREDICTION OF CV EVENT RATES IN ALBIGLUTIDE PHASE III STUDIES BASED ON DEMOGRAPHIC AND CV RISK FACTORS

To ensure sufficient numbers of MACE+ and MACE CV events will be observed in the albiglutide Phase III studies, all of the Phase III protocols are designed to include "enriched" patient populations such as the elderly, those with previous MI and those with some degree of renal impairment. GSK also closely monitors subjects enrolled in albiglutide studies with respect to various risk factors for CV events. These CV risk factors from UKPDS risk prediction model are listed in Table 1 below. To predict the MACE+/MACE event rates based on subjects' demographic and baseline characteristics, GSK uses a modified UKPDS model (Stewart, Ye and Yang, 2010). The modifications are made in discussion with the UKPDS group that originated the CV risk prediction model. The modified UKPDS model is used to predict CV events at interims and end of recruitment of subjects into the albiglutide program.

Table 1 provides descriptive summary of the demographics and risk factors based on the subjects recruited into the 8 phase III albiglutide studies. For comparison, Table 2 summarizes the key demographics and risk factors for recently published outcome studies. Also included in Table 2 are study-specific MACE/"MACE+" event rates.

Overall, the characteristics of albiglutide subjects enrolled in 8 Phase III studies appear to be similar to those of subjects in the RECORD study. The albiglutide subjects experienced less previous CVD and have lower average BP than RECORD subjects.

Table 1: Baseline and Demographic Characteristics of Albiglutide Randomized Subjects

UKPDS Risk Factors (Mean/%)	No previous CV history (n=4522)	With Previous CV History (n=451)	Total
Age (years)	55.1	61.8	55.7
Duration of DM (years)	8.1	9.7	8.2
Male	50.7%	65%	58%
Race (% Black)	12.6%	8.0%	12.2%
Smoker (%)	13.8%	14.4%	13.9%%
Baseline A1c (%)	8.22	8.18	8.21
SBP (mm/HG)	128.5	132.5	129
Total Cholesterol to/HDL ratio	4.1	4.0	4.1

Table 2: Baseline and Demographic Characteristics of Subjects and MACE+/MACE Event Rates from Outcome Studies

	ACCORD	ADVANCE	VADT	PROactive	ADOPT	BARI-2D	RECORD
Population	North America	Europe /Asia	US	Europe	North America /Europe	America /Europe	Europe / Australia
Male	62%	58%	97%	66.1%	57.7%	70.4%	52%
Age group Mean age	40-79 62.2	>55 yrs 66	>40yrs 60.5	35-75 61.8	30-75 57	>25 62.4	40-75 58.5
Non-Hispanic White Ethnic Representation	27% Hispanic, African Am	37% Asian	38% Hispanic, African Am, Native Am	98.5% White	88.5% White	70.4% White	99% White
Duration DM	10 yrs	8 yrs	11.5 yrs	9.5 yrs	<3 yrs	10.4 yrs	7 yrs
Baseline A1c	8.3	7.5	9.4	8.1	7.4	7.7	7.9
Smoker	14%	15%	17%	13.8%	14.6%	12.5%	16%
Prior CVD	35%	32%	62%	100%		100%	21%
SBP	136.4	145	132	143.4	133	131.7	138.5
Total Cholesterol/ HDL	4.3	4.0	5.1	4.0	4.3	4.5	4.1
Observed Rates							
MACE	~2.2	~2.1	~ 4.2	~3.6	~0.81	~4.69	~ 1.45
MACE+	~2.9	~2.9		~4.2			

* "MACE+" event rate in ACCORD/ADVANCE/PRO active study is defined as Fatal and non-fatal MI, stroke, congestive heart failure/heart failure and coronary events. Other than heart failure, this definition is similar to the current definition of MACE+ used in the albiglutide study. MACE+ event rates in the outcome studies in this table, in general, are about 1.1/1.4 fold compare to MACE event rates.

The original UKPDS CV risk model provides risk prediction for stroke and coronary heart diseases only (e.g. these are mostly MACE events). Because the primary CV endpoint for the albiglutide is MACE+, the predicted CV risk calculated from the original UKPDS is modified to account for a more extensive CV coverage in the albiglutide program. The modified UKPDS model accounts for the increased CV risk for subjects with previous CVD history. In particular, it is expected that the predicted event rate among subjects with previous CVD history is about 2 fold compared to the event rate for subjects without CVD history. In addition, based on the observed MACE and MACE+ rates from the published outcome studies above, the MACE+ event rate is expected to be 1.1 – 1.4 fold compare to MACE event rate.

Based on the modified UKPDS predicted CV risk for the enrolled subjects in the eight phase III studies, the MACE event rate is 1.04%. This predicted albiglutide MACE event rate is consistent with the observation that the albiglutide subjects have similar demographic and risk factors as the RECORD study subjects. The MACE+ event rate is

projected to be 1.14% -- 1.46% (assuming 1.1 –1.4 fold increase compare to MACE event rate).

With the estimated MACE event rate of 1.04,%, it is expected that there would be around 94/108 MACE events at the time of filing /when all studies have been completed. The predicted MACE+ event at the time of filing and when all studies are completed are 105/119 assuming 1.1 fold increase compared to MACE event, and, 130/151 event assuming 1.4 increase of MACE+ event compared to MACE event, respectively. These projected numbers of CV events should provide sufficient power to rule out the hazard risk ratio of 1.8 at the time of initial market application and at the end of the studies

Table 3: Estimated CV Events and Power for Albiglutide Clinical program

	Person year at initial filing	Expected Number of events at initial filing	Power to rule out 1.8 RR	Person years at the end of Study	Expected number of events at the end of studies	Power to rule out 1.8 RR
MACE+	9013	105/130	85%/91%	10495	119/151	89%95%
MACE	9013	94	81%	10495	108	86%

MACE+ = MACE (non-fatal MI, non-fatal stroke and cardiovascular death) + hospitalization due to unstable angina CV = cardiovascular; MACE = major adverse cardiovascular events; MACE+ = major adverse cardiovascular events plus; RR = risk ratio; UKPDS = United Kingdom Prospective Diabetes Study

Note: Event prediction based on modified UKPDS model and available demographic data from subjects enrolled into the Phase III studies.

In summary, GSK closely monitors subjects enrolled in the Phase III studies with respect to various risk factors for CV events and uses a modified UKPDS risk model (with modifications made in discussion with the UKPDS group) to quantitatively predict MACE+/MACE event rates and counts based on characteristics of actual subjects (at interim and end of recruitment) recruited into the albiglutide studies.

14. AMENDMENT 1

This amendment describes the specific modifications to the reporting and analysis plan for Integrated Analysis of Cardiovascular Risk applied in the amended RAP.

GSK Integrated Analysis of Cardiovascular Risk Reporting Analysis Plan Amendments ("*Was-is*" Summary Table)

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
Section 3.2 Cardiovascular Event Endpoints	

The following cardiovascular events comprise MACE:
• Myocardial Infarction (MI)
• Stroke
• Cardiovascular death
  ○ Death due to acute MI
  ○ Death due to heart failure
  ○ Death due to stroke
  ○ Death due to other cardiovascular causes
 	
The "MACE plus" ("MACE +") is defined as MACE events above plus hospitalization(s) for unstable angina.
	The following cardiovascular events comprise MACE:
	• Acute Myocardial Infarction (MI)
	• Stroke
	• Cardiovascular death
	  ○ Sudden cardiac death
	  ○ Death due to acute MI
	  ○ Death due to heart failure
	  ○ Death due to stroke
	  ○ Death due to other cardiovascular causes (e.g. pulmonary embolism, CV procedure-related)
	  ○ Presumed CV death (all deaths not attributed to the above categories of CV death and not attributed to a non-CV cause as indicated in the CEC charter)
	
	The "MACE plus" ("MACE +") is defined as MACE events listed above plus
	• hospitalization(s) for unstable angina.

Section 3.4 Statistical Hypothesis	
The null hypothesis for CEC-adjudicated MACE+ hazard rate at initial filing is that albiglutide group is inferior to (worse than) the combined comparators with hazard ratio margin of 1.8. The alternative hypothesis is the albiglutide group is non-inferior to (not worse than) the combined comparators group. For non-inferiority to be established, it is required that the upper limit of the 95% confidence interval for the hazard ratio (one-sided α = 0.025) falls below 1.8 at the time of initial filing for market application.	A group sequential approach using non-binding boundaries for controlling the type I error will be used with an initial BLA filing when approximately 90 unique subject events are available and a final analysis when all studies are completed. At initial BLA filing, the following hypothesis for CEC-adjudicated MACE+ hazard rate will be tested: H_0 (null hypothesis): Albiglutide group is inferior to (worse than) the combined comparators with hazard ratio margin of 1.8; versus H_a (alternative hypothesis): Albiglutide group is non-inferior to (not worse than) the combined comparators group.

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
	For the initial BLA filing, GSK will perform statistical analysis of adjudicated MACE+ events to calculate estimated RR (relative risk) and 2-sided 97.55% CI. If the upper bound of the 2-sided 97.55% CI is less than 1.8, then this will provide unequivocal evidence of CV safety. If with 90 events, the upper bound of the 2-sided 97.55% CI for RR is above 1.8, the final analysis will be performed when all studies are completed. The final analysis will use a 2-sided 97.45% CI interval. If the upper bound of the 2-sided 97.45% CI for final analysis is below 1.8, the data will also provide definitive proof of CV safety for albiglutide.
Section 4.2 Sample Size and Power	
Currently the ongoing and completed 9 Phase II/III albiglutide protocols enrolled a total of 5188 subjects (a bit larger than projected), approximately 2475 of whom were exposed to albiglutide. At the time of the initial filing, there will be around 9000 total patient years exposure for the 9 phase II/III studies. Assuming there is no difference for cardiovascular risk between albiglutide group and comparator group, 125 MACE+ events would allow 90% power for the determination of the potential effect of albiglutide on the occurrence of cardiovascular risk by ruling out RR of 1.8 and above, as outlined in the FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (FDA - CDER, 2008). The MACE event rate was predicted for each phase III study using a modified UKPDS model (Stewart, Ye and Yang, 2010; see details in Appendix B) which takes into account the demographics, risk factors and exposure time for patients recruited in the corresponding study. Table 4.2.1 presents the predicted MACE rate for each study. Per UKPDS model prediction, the eight phase III studies are expected to accumulate about a total of 94 MACE events at time of initial filing. The number of MACE+ (MACE and hospitalization(s) for unstable angina) was estimated about 1.1 to 1.4 fold the number of MACE based upon the review of the literatures. With the above assumption, the total number of MACE+ events at time of initial filing is estimated to be about 105 to 130, which will provide 85% to	The ongoing and completed 9 Phase II/III albiglutide studies were expected to enrol a total of 4985 subjects, with approximately 2475 exposed to albiglutide. At the time of the initial filing, it was predicted that there would be around 9000 total patient-years of exposure for these studies. The MACE rate was originally predicted for each Phase III study using a modified United Kingdom Prospective Diabetes Study (UKPDS) model (Stewart, Ye and Yang, 2010) which took into account the demographics, risk factors, and exposure time for subjects recruited in the corresponding study. Table 4.2.1 presents the predicted MACE rate for each study. Per the Modified UKPDS model prediction, the 8 Phase III studies were expected to accumulate a total of approximately 94 MACE at the time of initial filing. The number of MACE+ (MACE and hospitalizations(s) for unstable angina) was estimated to be approximately 1.1- to 1.4-fold the number of MACE based upon the review of the literature. With the previous assumption, the total number of MACE+ at the time of initial filing was estimated to be approximately 105 to 130, which provided 85% to 91% power to rule out RR risk of 1.8 and above. Table 4.2.2 presents the estimated events and the power to rule out RR 1.8. The person-years were based on person-years used at the time of initial filing. GSK originally planned to cut the clinical and EventNet (includes CEC adjudication result) databases for assessment of MACE+ events when around 125 events would have been observed (which was predicted to be June 2012 based on event onset time). 125 events would provide 90% power to rule out a RR of 1.8 and above assuming a true relative risk of 1.0. However, the event rate has been lower than

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
91% power to rule out RR risk of 1.8 and above. Table 4.2.2 presents the estimated events and the power to rule out RR 1.8 Both MACE events and hospitalization due to unstable angina will be adjudicated according to specified criteria defined in the CEC charter (consistent with FDA suggested definitions).	predicted. It was expected that there would be only around 90 events accumulated at the planned time of data analysis for the initial BLA filing. Considering the recent data on the GLP-1 class suggesting that the true relative risk could be less than 1.0 (e.g 0.9), 85 to 90 events expected for the data analysis in June 2012 would have power that ranges from 82% to 85% to rule out RR of 1.8 with 0.025 significance level if the true RR was 0.9. With reasonable power to rule out RR of 1.8 as well as practical consideration to have sufficient time to process and adjudicate the CV events, GSK decided to perform the data analysis in June 2012 as originally planned by adopting a group sequential approach using non-binding boundaries for controlling the type I error. As originally planned, subjects are being followed up to three years, and CV events continue to be accumulated, adjudicated and analyzed for the final filing. Group sequential approach would allow an early evaluation CV safety (with ~ 90 events) while cumulating more events to the end of the study and controlling overall type I error. The confidence interval boundaries of early evaluation and final evaluation will be determined by Lan-DeMets method. Alpha =0.0245 will be assigned to the early evaluation and alpha=0.0255 will be assigned to the final evaluation. This alpha allocation is based on a power error spending function with exponent 2 for information fraction t=0.70 (e.g. $\alpha(t)=\alpha t^2$). The information fraction t=0.7 is equal to the proportion of the number of events during the initial filing out of the total projected events at the final filing. The testing procedures are described below: • For the BLA filing with approximately 90 unique subject events, GSK will perform statistical analysis of adjudicated MACE+ events to calculate estimated RR and 97.55% CI. If the upper bound of 97.55% CI is less than 1.8, there will be unequivocal evidence of CV safety at the time of submission of the initial filing. GSK will still endeavour to make available the final result during the BLA review (the last subject last visit for the Phase III program will be in March 2013), even if the data at the time of submission using the Year 2 study results provide definitive proof of CV safety for albiglutide.

<table>
<tr><th>Reporting Analysis Plan (RAP)
Effective 15DEC2011</th><th>Amendment
Effective 31MAY2012</th></tr>
<tr><td></td><td>
If with 90 events, the upper bound of 97.55% CI for RR is above 1.8, the final analysis will be performed when all studies are completed. The final analysis will use 97.45% CI interval. If the upper bound of 97.45% CI for final analysis is below 1.8, the data will also provide definitive proof of CV safety for albiglutide.
The above approach should establish CV safety earlier with 90 events when there is very strong evidence to support the conclusion and retain the legitimacy of the final assessment if there is not sufficient number of events for early evaluation. If the noninferiority of the albiglutide CV safety is established with noninferiority margin of 1.8 either at the initial or final filing, further noninferiority test with noninferiority margin of 1.3 will be performed at the final filing. A superiority test will be performed following a statistically significant noninferiority test with 1.3 margin.

The table below shows the power of the initial and final filing using the allocated alpha at each time point assuming the true RR is either 1.0 or 0.9.

<table>
<tr><th>Predicted Number of Events at Initial Filing</th><th>Power for Initial Analysis with 97.55% CI Interval (RR = 1.0/0.9)</th><th>Predicted Number of Events at End of Study</th><th>Power for Final Analysis with 97.45% CI Interval (RR = 1.0/0.9)</th></tr>
<tr><td>100</td><td>75%/89%</td><td>135</td><td>88%/96%</td></tr>
<tr><td>90</td><td>70%/85%</td><td>120</td><td>83%/94%</td></tr>
<tr><td>85</td><td>67%/82%</td><td>110</td><td>80%/92%</td></tr>
<tr><td>80</td><td>64%/80%</td><td>100</td><td>75%/89%</td></tr>
</table>

Should the total number of events at the final filing be substantively lower than the projected total of over 125 events, an adjustment to the alpha used for the final analysis will be made to account for the shortfall.
</td></tr>
<tr><td colspan="2">Section 5.2 Masked Analyses</td></tr>
<tr><td>The blinded biostatistics team at PPD will produce blinded tables, listing and figures to be reviewed by the GSK safety group.</td><td>References to blinded and unblinded analyses are removed. Only masked analyses will be provided.

At the time of the submission of regulatory marketing</td></tr>
</table>

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
At the time of the submission of regulatory marketing applications, the analyses of cardiovascular events will be conducted in a masked unblinded fashion by the designated BLA submission team. The designated BLA submission team will be unblinded to treatment code but will not have access to the actual subject identifier. This approach is intended to minimize the potential impact on the ongoing trials and ensure integrity of the analyses. The process for maintaining the blind and assuring data integrity for the Phase III studies that continue for 3 years has been agreed with the regulatory authorities and is described in separate documents. The unblinded biostatistics team at PPD will produce coded unblinded reports to be reviewed by the IDMC. In the unblinded reports, treatment groups will be randomly assigned letters (A, B, C, etc.). The PPD unblinded statistician will have the decode for the coded unblinded treatment groups (A, B, C, etc.) available should the IDMC need this information during the closed session.	applications, the analyses of cardiovascular events for the ongoing 3 year studies will be conducted in a masked unblinded fashion by the designated submission team. The designated submission team will be unblinded to treatment code but will not have access to the actual subject identifier. This approach is intended to minimize the potential impact on the ongoing studies and ensure integrity of the analyses. The process for maintaining the blind and assuring data integrity for the Phase 3 studies that continue for 3 years has been agreed with the regulatory authorities and is described in separate documents. For the IDMC analyses, open and closed reports are prepared by separate unblinded and blinded analysis teams, respectively.
Section 5.3 Overview of Statistical Methods	
	References to IDMC analyses have been removed, as this RAP concentrates on analyses for the submission.
Section 7 Table 7	
	Updated Integrated analysis comparisons groups for consistency with IAS (Integrated Analyses of Safety) RAP.
Section 8.3 Examination of Subgroups	
The following demographic and baseline variables have been identified to be of general interest for subgroup comparison • Baseline HbA_{1c} (<8.0%, ≥8.0%) • Gender (male, female) • Race (white, black, other non-white) • Ethnicity (Hispanic/Latino, Not Hispanic/Latino) • Age at randomization (<65 years, ≥65 years) • Baseline BMI (<25 kg/m^2, ≥25 to <30	*This section has been updated for consistency with ISS (Integrated Analyses of Safety) and ISE (Integrated Analyses of Efficacy) analyses.* The following demographic and baseline variables have been identified to be of general interest for subgroup comparison : • Gender (Male, Female) • Race/Ethnicity (Non-hispanic African American, Non-hispanic White, Hispanic,

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
kg/m^2, ≥30 to <35 kg/m^2, ≥35 kg/m^2) • Region (Ex-US, USA – North, USA – South Atlantic, USA – South Central, USA – West) • Duration of diabetes (<5 years, 5 to <10 years, ≥10 years) • Prior CV history Other factors such as background medication may also be considered when applicable.	Asian, Other) • Age at randomization: (<65 years, ≥65 to <75 years, ≥75 years) • Baseline BMI (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 to <35 kg/m^2, ≥35 kg/m^2) • Region o Europe = {France, Germany, Spain, and United Kingdom} o Asia = {Hong Kong, Philippines, India, Korea, Taiwan, Japan} o Rest of World (ROW) = {Australia, Brazil, Columbia, Israel, Mexico, Peru, Russian Federation, South Africa} o USA – North o USA – South Atlantic o USA – South Central o USA – West • Duration of diabetes (<5 years, 5 to <10 years, ≥10 years) • Background therapies: (None, Met, Met+SU, Met+SU+TZD, Met+TZD, SU, TZD, SU+TZD) • Baseline HbA1c (<8.0%, ≥8.0% to <9.0%, ≥9.0%) • Smoking status (Never Used, Current User, Former User) • Prior CV History (Yes, No): defined as yes for subjects with any of the following medical history conditions: past myocardial infarction, stroke, cardiac arrest, unstable angina, current ischaemic heart disease without cardiomyopathy, or current ischaemic heart disease with cardiomyopathy Other factors such as background medication may also be considered when applicable.
Section 9.2.1 Person-Years	
Total person years For the analysis of first MACE+ events, the total	*Updated definition of total person years (MACE+/MACE) and added definition for Total all-*

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
person time is equal to the total number of days between the date of the first CEC-adjudicated event occurrence and the date of first dose plus 1. For subjects with no CEC-adjudicated event (e.g. subjects who are censored), the person time is equal to the number of days between the date of the last contact and the date of first dose plus 1. The date of the last contact will come from the clinical database for subjects who completed the three-year follow up time, or from the OmniTrace database for subjects who are lost to follow-up. In case no contact date is obtained by OmniTrace, the last contact date in the clinical database will be used. To obtain the total person years, the total person time in days is divided by 365.25. For the analysis of all occurrences of MACE+ events, the total person time is set to the total number of days between the date of last contact and the date of first dose plus 1. It is expected that the CEC adjudication will consider whether all related occurrences of events that occur within a short period of time may be single or multiple events. For example, a stroke followed by death within a day can be considered as a single event instead of two separate events. The date of the occurrence of the first CV event will be based on the date designated by the CEC. On-therapy person years The on-therapy person time will include time between the last dose date and the first dose date plus 57. For subjects who withdraw from study treatment early with CEC-adjudicated on-therapy events, the on-therapy person time is equal to the total number of days between the date of the first CEC-adjudicated event occurrence and the date of first dose plus 57. For subjects with no CEC-adjudicated on-therapy event (e.g. subjects who are censored, or whose adjudicated events occur after withdrawal from treatment), the person time is equal to the number of days between the date of the last dose and the date of first dose plus 57. Because of the expected long half-life of albiglutide, 56 days past the last dose date is added to the person time. This adjustment in person time among subjects in the albiglutide arm will also be made for person time of subjects in	*cause mortality person years (All-cause mortality)* Total person years (MACE+/MACE) For the analysis of first MACE+ events, the person time is equal to: • For subjects with any CEC-adjudicated events the total number of days between the date of the first CEC-adjudicated event occurrence as recorded in EventNet and the date of first dose plus 1. • For subjects with no CEC-adjudicated event (e.g. subjects who are censored), the person time is equal to the number of days between the date of the last contact and the date of first dose plus 1. For these subjects, the date of the last contact equals date of last contact from the clinical database. For subjects who are lost to follow-up with vital status (dead or alive) tracked by OmniTrace the date of last contact as recorded in the clinical database will still be considered the date of last contact. This approach is used because it is uncertain whether or not MACE+ events occurred for subjects who are lost to follow-up. To obtain the person years, the person time in days is divided by 365.25. Total person-years is calculated as the sum of all person years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment). It is expected that the CEC adjudication will consider whether all related occurrences of events that occur within a short period of time may be single or multiple events. For example, a stroke followed by death within a day can be considered as a single event instead of two separate events. The date of the occurrence of the first CV event will be based on the date designated by the CEC. Total on-therapy person years (MACE+/MACE) The on-therapy person time will include time between the last dose date and the first dose date plus 57 and

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
the non-albiglutide arms of the trials. The on-therapy person years will exclude follow-up time past the last dose date + 57 days. As in the calculation of overall person years above, the date of the occurrence of the first CV event will be based on the date designated by the CEC. To obtain the on-therapy person years, the on-therapy person time in days is divided by 365.25. Total person years and on-therapy person years will be calculated for each of the composite events (MACE+ or MACE) and for each component event. Since a subject may still be followed for CVE after terminating randomized treatment, the calculated person years may differ from the actual duration of exposure to randomized treatment. In particular, subjects who are lost to follow-up but are located by OmniTrace to be alive with no CV events by the time that would have completed the three-year follow will have larger person years calculated than person years of exposure.	is derived as follows: • For subjects who withdraw from study treatment early with CEC-adjudicated on-therapy events, the on-therapy person time is equal to the total number of days between the date of the first CEC-adjudicated event occurrence and the date of first dose plus 57. • For subjects with no CEC-adjudicated on-therapy event (e.g. subjects who are censored, or whose adjudicated events occur after withdrawal from treatment), the person time is equal to the number of days between the date of the last dose and the date of first dose plus 57. Because of the expected long half-life of albiglutide, 56 days past the last dose date is added to the person time. This adjustment in person time among subjects in the albiglutide arm will also be made for person time of subjects in the non-albiglutide arms of the trials. The on-therapy person years will exclude follow-up time past the last dose date + 57 days. As in the calculation of overall person years above, the date of the occurrence of the first CV event will be based on the date designated by the CEC. To obtain the on-therapy person years, the on-therapy person time in days is divided by 365.25. Total on-therapy person-years is calculated as the sum of all on-therapy person years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment). Total person years and on-therapy person years will be calculated for each of the composite events (MACE+ or MACE) and for each component event. Total all-cause mortality person years (All-cause mortality) For the analysis of all-cause mortality events, the person time is equal to: • For subjects that died, the total number of days between the date of death as recorded in the clinical database and the date of first dose plus 1. Any deaths recorded in the OmniTrace database will also be recorded in

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
	the clinical database. • For subjects that have not died (e.g. subjects who are censored), the person time is equal to the number of days between the date of the last contact and the date of first dose plus 1. For subjects that are not lost to follow-up, the date of the last contact equals date of last contact from the clinical database. For subjects who are lost to follow-up but are located by OmniTrace to be alive, the last date of contact is the date of lost follow-up as recorded in OmniTrace. To obtain the all-cause mortality person years, the all-cause mortality person time in days is divided by 365.25. Total all-cause mortality person-years is calculated as the sum of all all-cause mortality person-years for subjects in the integrated safety population (all subjects who received at least one dose of study treatment).
Section 10.3 Protocol Deviations/Violations	
Major protocol violations and protocol deviations will be tabulated by protocol-specific treatment groups and integrated analysis comparison groups A by subject listing will be produced to include subjects who fail to fulfil the inclusion-exclusion criteria and other major protocol deviations or violations.	*Listing of protocol violations was removed.* Major protocol violations will be tabulated by protocol-specific treatment groups and integrated analysis comparison groups.
Section 10.4 Demographic and Baseline Characteristics	
Continuous variables, such as age, body mass index, weight and height will be summarized using mean, standard deviation, median, minimum, and maximum for each treatment group. Some variables will be categorized, such as age (<65, ≥65 years). These and other categorical variables such as sex and ethnicity will be summarized by reporting the number and percentage of subjects in each category for each treatment group. All summaries will be performed using the safety population.	*Updates made for consistency with ISS ((Integrated Analyses of Safety) RAP analyses.* Continuous variables, such as age at randomization, body mass index, baseline HbA1c, weight, height and duration of diabetes will be summarized using descriptive statistics for each treatment comparison grouping. Some variables will be categorized, such as age (<65, ≥65 to <75, and ≥75 years). These and other categorical variables including sex, race/ethnicity, baseline HbA_{1c} category, duration of diabetes category, background anti-hyperglycemia medication category,

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
	and prior MI will be summarized by reporting the number and percentage of subjects in each category for each treatment comparison grouping. All summaries will be performed using the safety population.
Section 10.5 Cardiovascular Medical History	
The number and percentage of subjects with current and/or past cardiovascular history or medical procedures related to cardiovascular conditions will be reported for each treatment group.	The number and percentage of subjects with current and/or past cardiovascular medical history will be presented in decreasing order within the Albiglutide treatment group.
Section 10.6 Risk Factors for Cardiovascular Events	
Descriptive summary statistics about the baseline risk factors for cardiovascular events will be presented by treatment group at the protocol level and by comparison groups for the integrated analysis. The selected risk factors include some demographic characteristics, previous cardiovascular conditions and some laboratory measures associated with CV risks.	Descriptive summary statistics on selected risk factors (demographics, smoking status, baseline and previous medical history as per Section 8.3) will be presented by treatment comparison grouping.
Section 10.7 Concomitant Medications	
The WHODrug drug dictionary will be used to code drug names. Generic drug names will also be grouped by the ATC codes. Tabular and by subject listing of prior and concomitant medications will be produced. Prior medications are those started before randomization, concomitant medications are those taken at any time after randomization (i.e. on or after the first date of study medication dosing) and prior to or on the day after the last dose of study medication (including those started prior to randomization which were continued during the study period). Any medications taken after the day of last dose of study medication are considered to be post-therapy. All summaries will be performed using the safety population. All medications with approved indication to prevent and/or treat CVE will be identified via medical review and summarized accordingly. For the integrated CVE analysis, prior, concomitant and post-therapy cardiovascular medications will	*Updated the definitions of prior, concomitant and post-therapy for consistency with ISS (Integrated Analyses of Safety) RAP and individual studies.* The GSK drug dictionary, based on the World Health Organization Drug Dictionary (WHODRUG), will be used to code all medications. Summaries of all medications with approved indication to prevent and/or treat CVE will be identified via medical review and will be summarized by treatment comparison groupings. Generic terms will be provided in relation to treatment phase (prior medication, concomitant medication, or post-therapy medication). Prior medications are those started before the first dose of study drug. Concomitant medications are those taken at any time on or after the day of the first dose of study drug and within 56 days after the last dose of study drug, including those medications that were started prior to randomization but were continued into the study period. Post-therapy medications are those taken more than 56 days after the day of the last dose of study drug. Partial start dates of prior and concomitant medications

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
be summarized separately from the reporting of all concomitant medications.	will be assumed to be the earliest possible date consistent with the partial date. In the case of a completely missing start date, the start date will be assumed to be prior to date of the first administration of study drug. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, the medication will be assumed to be ongoing.
Section 11.1 Extent of Exposure and Treatment Compliance	
Descriptive summary statistics including the number of subjects, mean, standard deviation, minimum and maximum study drug exposure will be reported by treatment. The duration of exposure is defined as the number of days between the date of the last dose and the date of the first dose plus 1. Exposure and treatment compliance will be reported for the investigational product and not on the background therapies. During the interim review of safety data, subjects will be at different duration of study participation. To account for this varying duration of study participation, treatment compliance will be reported up to the last visits subjects have made. Among those subjects still participating in the study, treatment compliance is defined as the percentages of doses subjects have taken over the total doses up to the completed visits. Summary statistics on percentage of treatment compliance as well as the number and percentage of subjects who are <75%, 75-85% and greater than 85% compliant will be reported. Duration and compliance of subjects who either have terminated treatment early or have completed treatment will be reported separately from those continuing in the study. Treatment compliance reported by principal investigators to be <80% or ≥80% for non-albiglutide therapies during visits will be summarized by protocol-specific treatment groups and integrated comparison groups. In addition, summary statistics on the number of visits with at least 80% compliance with the non-albiglutide therapies will be reported by protocol-specific treatment groups and integrated comparison groups.	*Updated compliance categories and definitions for consistency with ISS(Integrated Analyses of Safety) RAP and individual studies.* Descriptive summary statistics including the number of subjects, mean, standard deviation, minimum and maximum study drug exposure will be reported by treatment. The duration of exposure is defined as the number of days between the date of the last dose and the date of the first dose plus 1. Exposure and treatment compliance will be reported for the investigational product and not on the background therapies. For subjects who receive albiglutide or double-blind albiglutide placebo, treatment compliance will be calculated as total number of administered doses divided by total number of doses which should have been taken based on the date of the last dose administered. Treatment compliance will be summarized for all subjects in addition to being summarized separately for subjects who have terminated treatment early, subjects who have completed active treatment, and subjects who are continuing active treatment. Summary statistics for treatment compliance percentages, as well as the number and percentage of subjects who are <80%, and ≥80% compliant will be reported.

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
Section 11.2 Integrated CVE Analysis	
An integrated inferential analysis of MACE+ events will be conducted as the primary analysis of CVE. The estimated hazard ratios together with their 95% confidence intervals will be reported from a Cox proportional hazards (PH) model for the first event occurrence where the key study treatment covariate is a two-level identification of albiglutide versus all comparators (albiglutide versus active or placebo control plus background therapy), stratified by protocols. This analysis will also be performed where albiglutide will be compared separately with active comparators plus background therapy and placebo control plus background therapy. The p-value for the test of the significance of effect of albiglutide versus comparators on CVE will be reported as screening tool and may serve as signal for further evaluation of protocol-specific and aggregated events.	An integrated inferential analysis of MACE+ events will be conducted as the primary analysis of CVE. The estimated hazard ratios together with their 95% confidence intervals will be reported from a Cox proportional hazards (PH) model for the first event occurrence where the key study treatment covariate is a two-level identification of albiglutide versus all comparators (albiglutide versus active or placebo control plus background therapy), stratified by protocols. This analysis will also be performed where albiglutide will be compared separately with active comparators plus background therapy and placebo control plus background therapy. The 2-sided p-value for the test of the significance of effect of albiglutide versus comparators on CVE will be reported. However, in support of the non-inferiority hypothesis that CV risk of albiglutide is non-inferior to all comparators with 1.8 non-inferiority margin, one-sided test with 0.0125 significance level will be performed during the initial filing. The equivalent two-sided 97.55% CIs will be reported for the albiglutide versus all comparators only.
Section 12 General Cardiovascular Adverse Event Analysis	
In addition to the analysis of CEC-adjudicated MACE+/MACE events, general cardiovascular related adverse events will be summarized within protocols and compared across treatment groups as supportive analysis.	*1st paragraph – updated to include definitions for pre-therapy, on-therapy and post-therapy adverse events.* In addition to the analysis of CEC-adjudicated MACE+/MACE events, on-therapy and post-therapy cardiovascular related adverse events will be summarized and compared across treatment groups as supportive analysis. The therapy periods will be defined as: • **Pre-therapy:** The onset date of the AE is before the start date of study medication. If the onset date of the AE is on the start date of study medication, the AE will be considered as on-therapy. • **On-therapy (Treatment-emergent):** The onset date of the AE is on or after the start date of study medication and within 56 days after the date of last dose. • **Post-therapy:** The onset date of the AE is more than 56 days after the last date of study

Reporting Analysis Plan (RAP) Effective 15DEC2011	Amendment Effective 31MAY2012
	medication. If only partial information is available for the onset date of an AE, then the AE will be included in the most conservative therapy period that is consistent with the therapy period definitions above and the available AE onset and resolution date information. (Here most conservative therapy period means on-therapy > post-therapy > pre-therapy.)
Updated Breslow test to Efron test	
	A2. Model Specifications for the Primary Analysis for Comparing Albiglutide versus All Comparators *Updated Breslow test to Efron:* Per literature, the Efron approximation for the likelihood under tied failure times in proportional hazards regression performs far better than Breslow approximation (Hertz-Picciotto 1997). Therefore, in case of ties in reported survival time, Efron's adjustment will be used instead of the default setting of Breslow adjustment.

-- END OF AMENDMENTS --