Statistical Analysis Plan

A Phase 2a Randomized, Double-blind, Placebo-controlled, Parallel-designed Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamic Effects of MEDI5884 in Subjects with Stable Coronary Heart Disease

Protocol Number: D7870C00002

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody
AE	Adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
[redacted]	[redacted]
apoB	Apolipoprotein B
ATC	anatomical therapeutic chemical
BMI	Body mass index
CHD	coronary heart disease
CI	Confidence interval
ECG	Electrocardiogram
EL	endothelial lipase
HDL-C	HDL Cholesterol (High density lipoprotein – cholesterol)
[redacted]	[redacted]
hsCRP	High-sensitivity C-reactive protein
IXRS	Interactive voice/web response system
LDL-C	LDL Cholesterol (Low density lipoprotein – cholesterol)
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	ECG interval measured from the onset of the P wave to the onset of the QRS complex
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the offset of the T-wave
QTc	cardiac QT interval corrected for heart rate
QTcB	cardiac QTc interval corrected for heart rate by the formula of Bazett
QTcF	cardiac QTc interval corrected for heart rate by the formula of Fridericia
RR	The time between corresponding points on 2 consecutive R waves on the ECG
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	MedDRA system organ class
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document describes the statistical analysis for protocol D7870C00002 (Amendment 2, 28Nov2017), a trial of MEDI5884 in a Phase 2a randomized, double-blind, placebo-controlled, parallel-design study to evaluate the safety, PK, pharmacodynamics (PD), and immunogenicity of multiple subcutaneous (SC) doses of MEDI5884 in subjects with stable CHD who are currently receiving high-intensity statin therapy. This document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table, listing, and figure templates and specifications is planned to be created in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

Evaluate the safety and tolerability of repeated [redacted] dosing with MEDI5884 in subjects with stable CHD

2.1.2 Secondary Study Objectives

- Establish the PK profile of MEDI5884 following repeat dosing
- Evaluate the effect of MEDI5884 on HDL-C and apoB
- Assess immunogenicity

2.1.3 Exploratory Study Objectives

- [redacted]

2.2 Study Design

This is a Phase 2a randomized, double-blind, placebo-controlled, parallel-design study to evaluate the safety, PK, PD, and immunogenicity of multiple SC doses of MEDI5884 in subjects with stable CHD who are currently receiving high-intensity statin therapy. At least 120 subjects are planned to be randomized across approximately 25 study sites in the United States of America to evaluate up to 5 dose levels of MEDI5884 via SC injection ([redacted],

[redacted]) compared to placebo (Figure 2.2-**1**). Subjects will be dosed once monthly for [redacted] and will be randomized in a [redacted] ratio to receive MEDI5884 ([redacted]) or placebo (volume matched for [redacted] MEDI5884). Subjects will be followed for [redacted] post last dose (up to [redacted]).

Figure 2.2-1 Study Flow Diagram

2.3 Treatment Assignment and Blinding

An (Interactive voice/web response system) IXRS will be used for randomization to a treatment group and assignment of blinded investigational product. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized in a [redacted] ratio to receive MEDI5884 ([redacted]) or placebo (volume matched to [redacted] MEDI5884).

This is a double-blind study in which MEDI5884 and placebo are visually distinguishable until SC doses are prepared. Neither the subject nor any of the investigator or sponsor staff

who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9).

In order to maintain the blind, an unblinded pharmacist will be responsible for dose preparation including preparation of volume matched placebo injections.

Once prepared, MEDI5884 and placebo are indistinguishable. A blinded qualified designee will administer investigational product to subjects via SC injection.

2.4 Sample Size

[redacted]

3 STATISTICAL METHODS

3.1 General Considerations

Data will be provided in listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product unless otherwise specified.

When last observation carried forward (LOCF) is used to impute for missing post-baseline data, only post-baseline data will be carried forward (e.g., baseline data will not be carried forward).

All statistical tests will be 2-sided at an alpha = 0.05 significance level unless stated otherwise.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC).

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
As-treated population	Subjects who receive any study investigational product will be included in the as-treated population and subjects will be analyzed according to the treatment they actually received.
PK population	Subjects who received any amount of MEDI5884 with at least one detectable post treatment serum concentration measurement
ADA evaluable population	Subjects who have non-missing baseline ADA data and at least one non-missing post-treatment ADA assessment

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization as well as treatment group received (including summary of subjects randomized but not treated) will be provided. In addition, disposition of subjects throughout the study will be provided with respect to completion of treatment, discontinuation of treatment, and discontinuation of study.

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics may include, but not be limited to, total cholesterol, HDL-cholesterol, LDL-cholesterol (direct and Friedewald equation), apoB, apoA1, and background statin.

3.3.3 Study Drug Exposure

The number of study drug (investigational product) doses received will be summarized by treatment group.

3.3.4 Concomitant Medications

Concomitant medications (administered during or after treatment) will be coded using the current WHO Drug Dictionary. Concomitant medications will be summarized using frequency count and percentage by the highest anatomical therapeutic chemical (ATC) class and preferred term. All concomitant medications will be presented in a data listing.

3.4 Efficacy Analyses

There are no efficacy endpoints in this study.

3.5 Pharmacodynamic Endpoint(s) and Analyses

All pharmacodynamic analyses will be based on the As-treated population.

3.5.1.1 Secondary Pharmacodynamic Endpoint(s)

- Change in apoB (mg/dL) from baseline to [redacted]
- Percent change in HDL-C from baseline to [redacted]

3.5.1.2 Analysis of Secondary Pharmacodynamic Endpoint(s)

PD analysis will be based on the As-treated population. The secondary PD endpoints, change from baseline to [redacted] in apoB and percent change from baseline to [redacted] in HDL-C, will be summarized by treatment group. Statistical comparisons of these endpoints between each MEDI5884 treatment group and placebo will be performed using an analysis of covariance (ANCOVA) by adjusting baseline value and treatment group with last-observation-carried forward (LOCF) approach to handle any missing data. A one-sided upper 95% confidence interval comparing each MEDI5884 treatment group to placebo for change from baseline to [redacted] in apoB will be provided. There will be no adjustment for multiple comparisons or multiple endpoints.

3.5.1.3 Exploratory Pharmacodynamic Endpoint(s)

- [redacted]

- [redacted]

[redacted]

3.5.1.4 Analysis of Exploratory Pharmacodynamic Endpoint(s)

[redacted]

[redacted]

3.6 Other Additional Analyses

[redacted]

- [redacted]
- [redacted]

[redacted]

3.7 Safety Analyses

All safety analyses will be based on the As-treated population. The primary safety endpoints are the safety and tolerability of MEDI5884 as measured by the incidence of TEAEs and TESAEs. Investigators are to record clinically important changes in physical examination, laboratory values, 12-lead ECGs, and vital signs as AEs. In addition, numeric values from clinical laboratory tests, ECGs and vital signs will be summarized descriptively. Other safety parameters, such as descriptive ECG readings and physical examination entries will be provided as listings.

The evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance. No formal statistical comparisons will be performed for the safety summaries.

3.7.1 Adverse Events and Serious Adverse Events

Treatment emergent AEs (TEAEs) and Treatment emergent serious AEs (TESAEs) are events that had an onset after the first dose of investigational product. TEAEs and TESAEs will be coded with the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the incidence, severity and relationship to investigational product will be summarized by treatment group and MEDI5884 overall for each MedDRA system organ class and preferred term reported. Adverse events leading to discontinuation, AEs leading to death, and deaths will also be summarized. Specific AEs will be counted once for each subject when calculating percentages. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship observed will be reported. All TEAEs and TESAEs will be summarized overall, as well as categorized by MedDRA system organ class and preferred term. Injection site assessments (redness, swelling, and pain) regardless reported as AEs or not will also be summarized.

Subjects with potential immunogenicity related TEAEs for immune complex diseases, allergic reactions, and injection site reactions according to Standardized MedDRA Queries (SMQ) will be summarized. The US Food and Drug Administration has requested that safety data be analyzed for this study according to the following SMQs: Systemic lupus erythematosus (broad and narrow terms); vasculitis (broad and narrow terms); Guillain-Barre syndrome (narrow terms) and allergic reactions (narrow SMQs for anaphylactic reaction, angioedema, severe cutaneous adverse reaction, anaphylactic/anaphylactoid shock conditions and hypersensitivity). Injection site reactions will be assessed using the following high level MedDRA (HLT) terms: administration site reactions, application and instillation site

reactions, infusion site reactions, and injection site reactions. These terms will be updated to the current version of MedDRA.

3.7.2 Adverse Events of Special Interest

The following AESI has been identified specifically for this protocol:

- Hepatic function abnormality meeting the definition of Hy's law

The AESIs will be summarized by treatment group and MEDI5884 overall, as well as by MedDRA system organ class and preferred term.

3.7.3 Deaths and Treatment Discontinuations due to Adverse Events

Death and AEs resulting in permanent discontinuation from the study drug will be summarized by treatment group and MEDI5884 overall as well as by MedDRA system organ class and preferred term.

3.7.4 Clinical Laboratory Evaluation

The hematology and serum chemistry parameters as well as their changes from baseline will be summarized with descriptive statistics by treatment group at each of the scheduled visits. In addition, hematology and serum chemistry values will also be classified as low, normal, or high with respect to the laboratory reference range for the parameter. The shift from baseline category to each post-baseline visit category for each parameter will be summarized at each post-baseline visit by treatment group as well as for MEDI5884 overall.

The urinalysis categorical results will be classified as normal or abnormal with respect to the laboratory reference range for the parameter. The shift from baseline category to the post-baseline category will be summarized by treatment group and MEDI5884 overall at each post-baseline visit.

3.7.4.1 Physical Examinations

Subjects with abnormalities in each body system examined will be presented for each scheduled evaluation in data listings.

3.7.4.2 Vital Signs

Vital sign parameters (systolic and diastolic blood pressure, pulse rate, respiration rate, and temperature) will be summarized with descriptive statistics for each scheduled evaluation by

treatment group and MEDI5884 overall. Change from baseline to each post baseline evaluation will also be summarized. In addition, changes from pre-dose to 1 hour post-dose will be summarized for each dosing visit.

3.7.4.3 Electrocardiogram

The following ECG parameters will be summarized: Heart rate, RR, PR, QRS and QT intervals as well as derived parameters QT corrected interval parameters, QTcB (Bazett's formula) and QTcF (Fridericia's formula). The results at each visit: Baseline (average of the 3 triplicate ECG averages taken on [redacted] and at each post-baseline visit (average of ECG triplicate) will be summarized as well as the change from baseline. In addition, the number of subjects having the following notable ECG interval values will be summarized.

- Maximum QTcF and QTcB intervals > 450 ms, > 480 ms, > 500 ms
- Maximum uncorrected QT intervals > 500 ms
- Maximum changes from baseline in QTcF and QTcB > 30, >60 and > 90 ms

The percent of subjects with an abnormal ECG evaluation and specific ECG abnormalities observed at each visit will be summarized by treatment group and MEDI5884 overall.

3.8 Immunogenicity

The immunogenicity analyses will be based on the ADA evaluable population. ADA incidence rate and titer will be tabulated for each treatment group. Samples confirmed positive for ADA will be tested and analyzed for nAb titer and summarized similarly. For overall post-baseline summary, persistent positive is defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment; transient positive is defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥2 post-baseline assessments (with <16 weeks between first and last positive).

3.9 Pharmacokinetics

The pharmacokinetic analyses will be based on the PK population. Descriptive statistics of serum MEDI5884 concentration data will be provided. Individual and mean serum concentration-time profiles of MEDI5884 for each treatment group will be generated. Non-compartmental PK data analysis will be performed and PK parameters such as C_{max}, AUC_{0-inf}, $t_{1/2}$ will be generated.

4 INTERIM ANALYSIS

An interim analysis is planned after all subjects have completed their [redacted] visit. MedImmune personnel will be unblinded at the interim analysis; study subjects, the investigator, and site staff who are involved in the treatment or clinical evaluation of subjects will remain blinded until the end of study.

5 REFERENCES

Bretz F, Pinheiro J, Branson M. Combining Multiple Comparisons and Modelling Techniques in Dose-Response Studies. *Biometrics* 2005; 61:738-748

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	14DEC2017	Initial document	Initial document