Statistical Analysis Plan

A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of MEDI6012 in Subjects with Stable Atherosclerotic Cardiovascular Disease

Protocol Number: D5780C00005

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
apoAI	apolipoprotein AI
apoAII	apolipoprotein AII
apoB	apolipoprotein B
apoCIII	apolipoprotein CIII
apoE	apolipoprotein E
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration curve
$AUC_{0\text{-}96h}$	area under concentration curve from 0 to 96 hours
$AUC_{0\text{-}168h}$	area under concentration curve from 0 to 168 hours
BMI	Body mass index
CAD	coronary artery disease
CE	cholesteryl ester
CHD	coronary heart disease
CL	systemic clearance
C_{max}	observed maximum concentration
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DEC	Dose Escalation Committee
ECG	electrocardiogram
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HDL-CE	high-density lipoprotein-cholesteryl ester
HDL-UC	high-density lipoprotein-unesterified cholesterol
HIV	human immunodeficiency virus
IV	intravenous(ly)
IXRS	interactive voice/web response system
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein

Abbreviation or Specialized Term	Definition
LDL-C	low-density lipoprotein-cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
PD	pharmacodynamics
PK	pharmacokinetics
rhLCAT	recombinant human lecithin-cholesterol acyltransferase
R_{max}	maximum biomarker response
SAE	serious adverse event
SAP	statistical analysis plan
SPP	Statistical programming plan
$t_{1/2}$	terminal half-life
TC	total cholesterol
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TG	triglyceride(s)
T_{max}	time of maximal concentration
UC	unesterified cholesterol
ULN	upper limit of normal
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein-cholesterol

1 INTRODUCTION

This document describes the statistical analysis for Protocol D5780C00005, *A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of MEDI6012 in Subjects with Stable Atherosclerotic Cardiovascular Disease*. Some background information and an overview of the study design are provided in Section 2. Section 3 and onwards of the document details the statistical summaries relating to each study objective as well as describing general conventions and definitions. A separate statistical programming plan (SPP), containing table templates and specifications, has also been created to be used in conjunction with this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

1. The primary safety objective is to evaluate the safety of MEDI6012 following repeat dosing in subjects with stable atherosclerotic cardiovascular disease (CVD) over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).

   Primary Safety Endpoints: Safety and tolerability of MEDI6012 as measured by the incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) and clinically important changes in 12 lead electrocardiogram, vital signs, and clinical laboratory evaluations over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).

2. The primary PD objective is to establish that repeat dosing with MEDI6012 results in a sustainable and reversible dose-dependent response for HDL-C, HDL-CE, and CE.

   Primary PD Endpoint: Baseline adjusted area under the concentration-time curve from time 0 to 96 hours post dose 3 ($AUC_{0\text{-}96hr}$) for HDL-C, HDL-CE, and CE.

2.1.2 Secondary Study Objectives

1. To establish the PK profile of MEDI6012 following repeat dose administration.
2. To establish the PD effect of MEDI6012 following an initial loading dose followed by a dose at 48 hours and 1 week later (Cohort 4 only).
3. To evaluate the effect of MEDI6012 on a range of PD biomarkers following repeat dose administration.

4. To evaluate the immunogenicity potential of MEDI6012.

Secondary Endpoints:

1. PK for MEDI6012 mass and activity
2. Serum concentration of other key lipids and lipoproteins: CE, HDL-CE, HDL-unesterified cholesterol (HDL-UC), non-HDL-C, non HDL CE, non-HDL-UC, low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apoB), triglycerides (TG), very low-density lipoprotein-cholesterol (VLDL-C), and apolipoprotein A1 (apoA1), apoAII, apoCIII, apolipoprotein E (apoE), pre-beta1 high-density lipoprotein (preβ1-HDL).
3. Anti-drug antibodies (ADA) and nAb development, with concomitant decreases in HDL-C

2.1.3 Exploratory Study Objectives

2.2 Study Design

This is a Phase 2a randomized, blinded (subject/investigator blinded, MedImmune unblinded), placebo-controlled, dose-escalation study to evaluate the PK/PD, safety and immunogenicity of repeat doses of MEDI6012 in adult subjects with stable atherosclerotic CVD. At least 32 subjects are planned to be randomized across approximately 10 study sites in the United States of America (USA) to evaluate 3 dose levels of MEDI6012 (40, 120, 300 mg, and an IV push dosing regimen that includes a loading dose of 300 mg followed by a 150 mg maintenance dose at 48 hours and a 100 mg maintenance dose 7 days later) of MEDI6012 (Figure 2.2-1). For each cohort, 8 subjects are planned for randomization in a 6:2 ratio to receive MEDI6012 or placebo. Investigational product will be administered as a 1-hour IV infusion (Cohorts 1-3) or an IV push (Cohort 4).

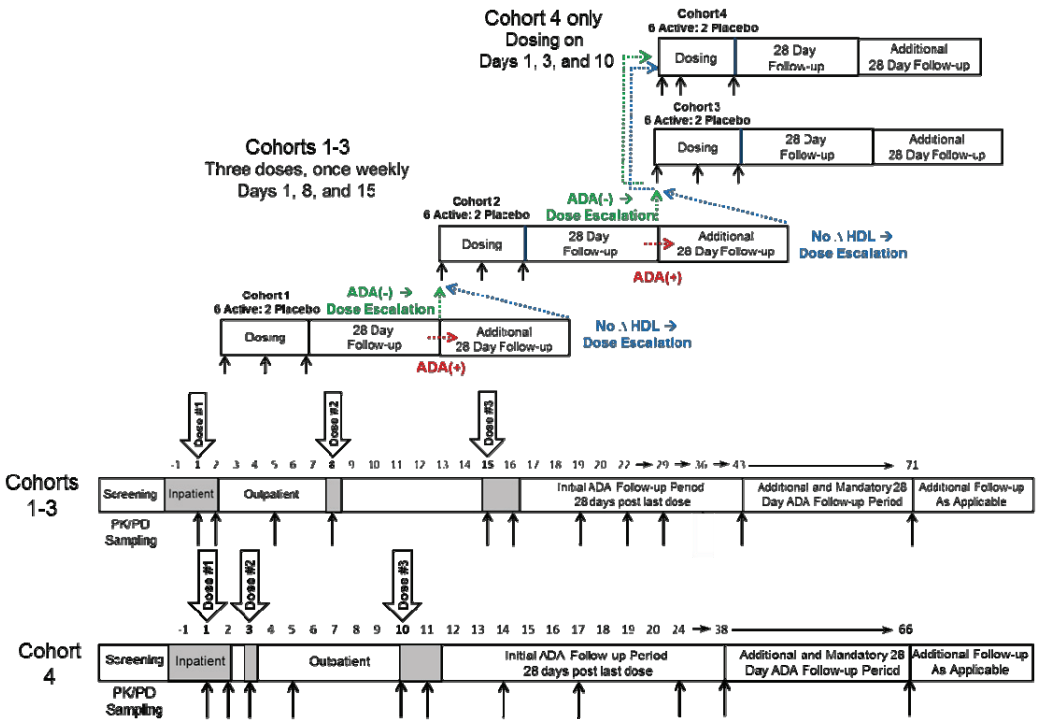


Figure 2.2-1 Study Flow Diagram and Additional Design Details

ADA = anti-drug antibody; Δ HDL = change in high density lipoprotein; PD = pharmacodynamics; PK = pharmacokinetics; IV = intravenous.

Subjects may be admitted to the study center the evening prior to randomization and first dose administration (Day -1) and prior to third dose administration (Day 15 for Cohorts 1-3 or Day 10 for Cohort 4) and remain at the study center, for 24-36 hours. In lieu of overnight admission, outpatient arrangements such as a hotel stay near the study center or a return to home may alternatively be provided. For Cohort 4, outpatient arrangements may be provided through Day 4. In addition, sites may admit the evening of Day 14 for Day 15 dosing (Cohorts 1-3) or Day 9 for Day 10 dosing (Cohort 4).

Subjects in Cohorts 1-3 will be administered investigational product weekly via IV infusion. Cohort 4 subjects will be administered investigational product via IV push using a loading dose of 300 mg (Day 1) of MEDI6012 followed by a 150 mg maintenance dose 48 hours later (Days 3) and a maintenance dose of 100 mg one week later (Day 10).

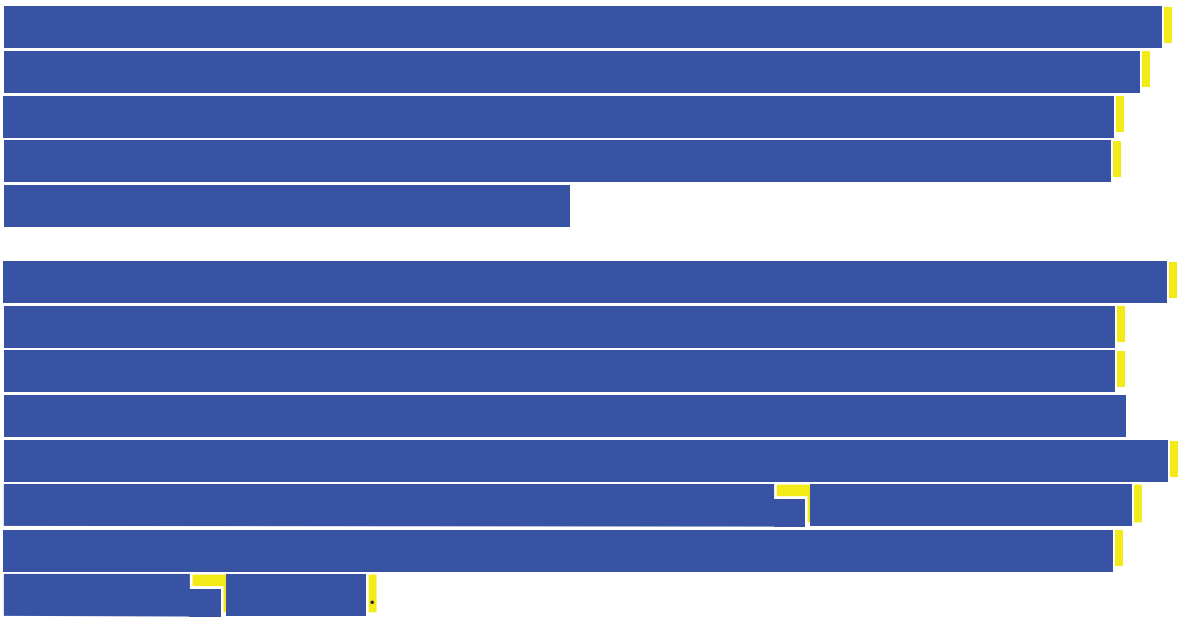
2.3 Treatment Assignment and Blinding

An IXRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. 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.

For each cohort, 8 subjects will be randomized in a 6:2 ratio to receive MEDI6012 or placebo.

This is a blinded study in which the subjects and investigator and contract research organization personnel are blinded to investigational product, and MedImmune staff involved in the study are unblinded.

2.4 Sample Size



3 STATISTICAL METHODS

3.1 General Considerations

Data will be provided in listings sorted by cohort, treatment group and subject number. Tabular summaries will be presented by cohort and treatment group with placebo group combined when appropriate. 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.

Data analyses will be conducted using the SAS® System Version 9.3 or higher (SAS Institute Inc., Cary, NC) unless otherwise specified. All analysis outputs will be validated according to MedImmune SAS programming standards and MedImmune validation procedures.

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 receive.
PK population	Subjects in the as-treated population who have at least one detectable LCAT serum concentration measurement
Immunogenicity population	Immunogenicity population includes all subjects in the as-treated population who have at least one serum sample for immunogenicity testing

The primary analysis of the safety and PD endpoints will be assessed based on As-treated population. The PK data will be analyzed in PK population. Immunogenicity data will be assessed using immunogenicity population.

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 with respect to completion of treatment and follow-up will be provided.

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 characteristics may include, but not be limited to medical history and cardiovascular disease history.

3.3.3 Study Drug Exposure

The number of subjects who received investigational product at Days 1, 8, and 15 for Cohorts 1-3 and at Days 1, 3, and 10 for Cohort 4 will be summarized descriptively by the amount of the product received (i.e., entire dose vs entire dose not administered) and the reasons subject did not receive entire dose (i.e., AEs vs other) will also be summarized descriptively.

3.3.4 Concomitant Medications

Concomitant medications will be coded using the latest available version of AstraZeneca Drug Dictionary and summarized by preferred term with frequency and percentage by

treatment group. In addition, concomitant medications will summarized by Anatomical Therapeutic Chemical (ATC) Classification System.

3.4 Pharmacodynamic Endpoint(s) and Analyses

3.4.1 Pharmacodynamic Endpoint(s)

The PD parameters of primary interest are the baseline-adjusted HDL-C, HDL-CE, and CE $AUC_{0\text{-}96hr}$ following Dose 3 administration ($AUC_{0\text{-}96hr\ Dose\ 3}$).

Other endpoints including $AUC_{0\text{-}96hr\ Dose\ 1}$, $AUC_{0\text{-}96hr\ Dose\ 3}$, $AUC_{0\text{-}168hr\ Dose\ 1}$, $AUC_{0\text{-}168hr\ Dose\ 3}$, and $AUC_{1\text{-}22d}$ (AUC from time 0 on Day 1 through 168 hours after Dose 3) for HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C (by direct measure), TG, VLDL-C, apoA1 and apoB.

For Cohorts 1-3, preβ1-HDL will be reported at baseline, 12 hours post dose 1, day 2, prior to dose 3 and 12 hours post dose 3, days 16, 19, and 22. ApoAII, apoCIII, and apoE will be reported at baseline, day 19, and day 22.

For Cohorts 4, preβ1-HDL will be reported at baseline, 12 hours post dose 1, day 2, day 5, prior to dose 3 and 12 hours post dose 3, days 11, 14, and 17. ApoAII, apoCIII, and apoE will be reported at baseline, day 14, and day 17.

3.4.2 Analysis of Pharmacodynamic Endpoint(s)

AUC will be calculated using the trapezoidal rule. Statistical comparison with regard to AUC between treatment groups will be conducted using analysis of covariance (ANCOVA) by adjusting baseline values and treatment group comparing each active treatment against placebo. The dose-response profile with regard to HDL-C may be explored using MCP-MOD procedure.

Change and the percent change from baseline at each time point for serum concentration of HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C (by direct measure), TG, VLDL-C, apoA1, preβ1-HDL, apoAII, apoCIII, apoE, and apoB will be analyzed and compared using ANCOVA by adjusting baseline values and treatment. Descriptive statistics will be provided by treatment group for maximum response (R_{max}) and time to maximum response [$(R)T_{max}$].

For ANCOVA, if the data is not normally distributed, the analyses will be conducted on rank-transformed data.

3.5 Safety Analyses

The primary safety endpoints are the safety and tolerability of MEDI6012 following repeat-weekly dosing as measured by the incidence of TEAEs and TESAEs, and clinically important changes in 12-lead ECG, vital signs, and clinical laboratory evaluations over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).

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.

3.5.1 Adverse Events and Serious Adverse Events

AE collection begins after the subject signs the informed consent document and lasts until the end of the study. TEAEs and TESAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity and relationship to investigational product will be summarized. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular 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 and by severity and relationship to investigational product.

Infusion site reactions for local reactions will be checked. Infusion site related AEs will be summarized.

3.5.2 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI, which is defined in Sections 5.3 and 5.6.2 of the protocol as hepatic function abnormality meeting the definition of Hy's law, may be serious or non-serious. Treatment-emergent AESIs will be summarized together with other AEs/SAEs. No separate summary tables will be produced.

3.5.3 Deaths and Treatment Discontinuations due to Adverse Events

Number of subjects who died or discontinued from the treatment due to AEs will be summarized by treatment group.

3.5.4 Clinical Laboratory Evaluation

Clinical laboratory safety tests including serum chemistry, hematology, urinalysis, and others will be summarized using descriptive statistics at each time point by treatment group. Change from baseline to each post baseline time point and shift from baseline relative to normal range will also be summarized, where appropriate.

3.5.5 Other Safety Evaluations

3.5.5.1 Vital Signs

Vital sign (blood pressure, respiratory rate, pulse, pulse oximetry, and body temperature) results and change from baseline will be summarized using descriptive statistics at each time point by treatment group.

3.5.5.2 Electrocardiogram

ECG parameters as well as change from baseline for quantitative measurements (RR, PR, QRS, QT, QTcF, QTcB, and heart rate) will be assessed and summarized descriptively by treatment group at each time point..

3.6 Immunogenicity

ADA incidence rate and titer will be tabulated for each treatment group at baseline and post-baseline visits. 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).

3.7 Pharmacokinetics

Non-compartmental analysis will be performed for MEDI6012 treated subjects. Serum MEDI6012 mass and activity concentration-time profiles will be summarized by dose cohort. The PK parameters to be reported include C_{max}, time to reach C_{max} (T_{max}), AUC, accumulation ratio, and $t_{1/2}$. Descriptive statistics for PK parameters will be provided.

Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the clinical study report.

The PK analysis will be performed by the Clinical Pharmacology DMPK department (CPD), MedImmune LLC. Results, discussions and data interpretations of the PK analysis will be presented in a report separate from the CSR.

3.8 Exploratory Endpoints

4 INTERIM ANALYSIS

A primary analysis of the safety, immunogenicity, PK, and PD data will be conducted after the last subject has completed or dropped out prior to the last scheduled visit (Day 71 visit [Cohorts 1-3] or Day 66 [Cohort 4]) and will be reported in the CSR. The long-term follow-up data will be reported as an addendum to the CSR.

5 REFERENCES

N/A