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

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Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC, One MedImmune Way, Gaithersburg, Maryland, 20878, USA

Medical Monitor: [redacted]

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PROTOCOL SYNOPSIS

TITLE

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

HYPOTHESES

Primary Hypothesis: Repeated [redacted] dosing of MEDI5884 exhibits an acceptable safety and tolerability profile in subjects with stable coronary heart disease (CHD)

Secondary Hypotheses:

1. MEDI5884 demonstrates a pharmacokinetic (PK) profile that supports once [redacted] dosing
2. MEDI5884 increases high-density lipoprotein cholesterol (HDL-C) without raising apolipoprotein B (apoB)

OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
Evaluate the safety and tolerability of repeated [redacted] dosing with MEDI5884 in subjects with stable CHD	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) and clinically important changes in electrocardiograms (ECGs), vital signs, clinical laboratory evaluations and physical examination up to end of study ([redacted]).
Secondary	
Establish the PK profile of MEDI5884 following repeat dosing	• Maximum serum concentration (C_{max}) of MEDI5884, area under the curve (AUC), terminal half-life ($t_{1/2}$).
Evaluate the effect of MEDI5884 on HDL-C and apoB	• Change in apoB (mg/dL) from baseline to [redacted]. • Percent change in HDL-C from baseline to [redacted].
Assess immunogenicity	• Antidrug antibody incidence and titer at [redacted]
Exploratory	
[redacted]	• [redacted]
[redacted]	• [redacted]

STUDY DESIGN

This is 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. 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] compared to placebo. Subjects will [redacted] will be randomized [redacted] to receive MEDI5884 [redacted] or placebo (volume matched for [redacted] MEDI5884).

Subjects will undergo a screening period of up to [redacted]. Subjects will arrive at the study center the morning of each visit. Subjects will be followed for [redacted] after last dose (up to [redacted]). Additional follow-up visits will be required if a subject's ADA value is > the Baseline value at the last visit, if a subject's directly measured LDL-C value at the last visit is ≥ the Baseline value + 30 mg/dL, or if a subject's triglyceride value is > 1000 mg/dL at the last visit.

TARGET SUBJECT POPULATION

Adult males or females, aged 45 through 80 years inclusive, with stable CHD who are currently receiving high-intensity statin therapy. Females of childbearing potential and lactating females will be excluded.

TREATMENT GROUPS AND REGIMENS

Cohort	Dose Level	Number of Doses & Dosing Frequency	Number of Subjects
1	[redacted]	[redacted]	20
2	[redacted]	[redacted]	20
3	[redacted]	[redacted]	20
4	[redacted]	[redacted]	20
5	[redacted]	[redacted]	20
6	[redacted]	[redacted]	20

STATISTICAL METHODS

Sample size: [redacted]

Statistical analyses: Safety analysis will be based on the As-treated Population. 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 by MedDRA System Organ Class and Preferred Term. Other safety data, such as vital signs and clinical laboratory data will be descriptively summarized by treatment group at each time point. Change from Baseline to each postbaseline time point in these data will also be summarized, where appropriate. ECG parameters will also be assessed and summarized descriptively. Injection site reactions, regardless of being recorded as AEs or not, will also be summarized.

Descriptive statistics of serum MEDI5884 concentration data will be provided. Individual and mean serum concentration-time profiles of MEDI5884 per treatment group and/or visit will be generated. Non-compartmental PK data analysis will be performed and PK parameters such as C_{max}, AUC, $t_{1/2,}$ will be generated. Additional PK and PK/PD analyses may be conducted as appropriate.

Immunogenicity incidence rate and titers will be summarized for each treatment group.

PD analysis will be based on the As-treated Population. The primary PD endpoints, including change from Baseline to [redacted] in apoB and percent change from Baseline to [redacted] in HDL-C, will be summarized by treatment group and analyzed by comparing each MEDI5884 treatment group and placebo using an analysis of covariance by adjusting baseline value and treatment group. A one-sided upper 95% confidence interval comparing each MEDI5884 treatment group versus placebo for change from Baseline to [redacted] in apoB will be provided. [redacted]

Interim analysis: An interim analysis is planned after all subjects have completed their [redacted] visit.

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LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
[redacted]	[redacted]
apoB	apolipoprotein B
AST	aspartate transaminase
AUC	area under the concentration-time curve
BP	blood pressure
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CL	clearance
C_{max}	maximum observed concentration
CV	cardiovascular risk
dECG	digital electrocardiogram
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EDV	early discontinuation visit
EL	endothelial lipase
FSH	follicle-stimulating hormone
GCP	good clinical practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
IC_{50}	half of the maximal inhibitory concentration
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IRB	Institutional Review Board
IXRS	interactive voice or web response system
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic(s)

PK	pharmacokinetic(s)
PR(PQ)	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 end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAD	single ascending dose
SC	subcutaneous
SD	standard deviation
SID	subject identification
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse events
TG	triglycerides
ULN	upper limit of normal
[redacted]	[redacted]
WHO	World Health Organization

1 INTRODUCTION

1.1 Disease Background

Coronary heart disease (CHD) remains the leading cause of death worldwide (world health organization, [WHO, 2017]). Despite highly effective low-density lipoprotein cholesterol (LDL-C) lowering therapies, high-density lipoprotein (HDL) is a key mediator of reverse cholesterol transport, a system that removes cholesterol from the vessel wall. In epidemiologic studies, low plasma levels of high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of major adverse cardiovascular events while elevated levels are associated with lower cardiovascular (CV) risk (Prospective Studies Collaboration et al., 2007). However, existing pharmacological approaches to raising plasma HDL-C, for example by cholesteryl ester transfer protein (CETP) inhibition have not been convincingly shown to reduce CV risk (Aim-High Investigators et al., 2011; Barter et al., 2007; Hps Timi Reveal Collaborative Group et al., 2017; Schwartz et al., 2012). Lowering risk may require improving HDL-C function as well as quantity, and employing a mechanism which promotes reverse cholesterol transport.

Endothelial lipase (EL) is a circulating phospholipase A1 enzyme that hydrolyzes HDL-C phospholipids and increases the catabolism of HDL-C and its loss through the kidney resulting in low HDL-C levels. Partial and complete loss-of-function EL gene mutations result in elevated HDL-C, increased cholesterol efflux, and CV risk reduction in otherwise healthy individuals. MEDI5884 is a high affinity and selective human EL neutralizing antibody. Studies of MEDI5884 in nonhuman primates demonstrate increases in HDL particle numbers and ATP-binding cassette transporter 1 mediated cholesterol efflux. It is hypothesized that MEDI5884 will inhibit EL resulting in an increase in HDL-C levels and improved HDL function in humans.

1.2 MEDI5884 Background

MEDI5884 is briefly described below. Refer to the current Investigator's Brochure for details.

[redacted]

[redacted]

1.3 Summary of Nonclinical Experience

[redacted]

1.4 Summary of Clinical Experience

[redacted]

[redacted]

1.5 Rationale for Conducting the Study

Safety, PK, and PD data following multiple dose administrations of MEDI5884 will confirm target engagement and support dose selection for subsequent studies. Stable CHD subjects are chosen in order to assess the effects of EL inhibition in subjects with known cardiovascular disease.

1.6 Benefit-Risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

[redacted]

General risks based on the administration of biologics include injection site reactions, hypersensitivity, anaphylactic type reactions, and development of antidrug antibodies (ADA).

To mitigate against these risks, this study will be conducted at clinical sites that have experience in managing clinical studies with biologic investigational products. Appropriate drugs and medical equipment to treat acute anaphylactic and serious allergic reactions will be immediately available, and study personnel will be trained to recognize and treat anaphylaxis. Subjects will be closely monitored after the administration of investigational product on [redacted] for immediate drug reactions or other adverse effects.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

1. Repeated [redacted] dosing of MEDI5884 exhibits an acceptable safety and tolerability profile in subjects with stable CHD

1.7.2 Secondary Hypotheses

1. MEDI5884 demonstrates a PK profile that supports once [redacted] dosing
2. MEDI5884 increases HDL-C without raising apolipoprotein B (apoB)

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 2.1-1 Primary Objective and Associated Endpoints

Type	Objective	Endpoint
Safety	Evaluate the safety and tolerability of repeated [redacted] dosing with MEDI5884 in subjects with stable CHD	• Occurrence of TEAEs and TESAEs and clinically important changes in ECGs, vital signs, clinical laboratory evaluations and physical examination up to end of study ([redacted])

CHD = coronary heart disease; ECG = electrocardiogram; TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse events

2.2 Secondary Objectives and Associated Endpoints

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
PK	Establish the PK profile of MEDI5884 following repeat dosing	• Maximum serum concentration (C_{max}) of MEDI5884, area under the curve (AUC), terminal half-life ($t_{1/2}$).
PD	Evaluate the effect of MEDI5884 on HDL-C and apoB	• Change in apoB (mg/dL) from Baseline to [redacted]. • Percent change in HDL-C from Baseline to [redacted].
Immunogenicity	Assess immunogenicity	• Antidrug antibody incidence and titer at [redacted].

ApoB = apolipoprotein B; HDL-C = high-density lipid cholesterol; PD = pharmacodynamic; PK = pharmacokinetics

2.3 Exploratory Objectives and Associated Endpoints

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

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 [redacted]

Subjects will undergo a screening period of up to [redacted]. Subjects will arrive at the study center the morning of each visit. Subjects will be followed for [redacted] (up to [redacted] Figure 3.1.1-1). Additional follow-up visits will be required if a subject's ADA level is > Baseline at the last visit, if a subject's directly measured LDL-C at the last visit is ≥ Baseline + 30 mg/dL, or if a subject's triglyceride value is > 1000 mg/dL at the last visit (Section 4.2.3).

Concomitant Statin Therapy Required

The endpoints to be measured in this study are described in Section 2.

3.1.2 Treatment Regimen

Table 3.1.2-1 Treatment Regimen

Cohort	Dose Level	Number of Doses & Dosing Frequency	Number of Subjects
1	[redacted]	[redacted]	20
2	[redacted]	[redacted]	20
3	[redacted]	[redacted]	20
4	[redacted]	[redacted]	20
5	[redacted]	[redacted]	20
6	[redacted]	[redacted]	20

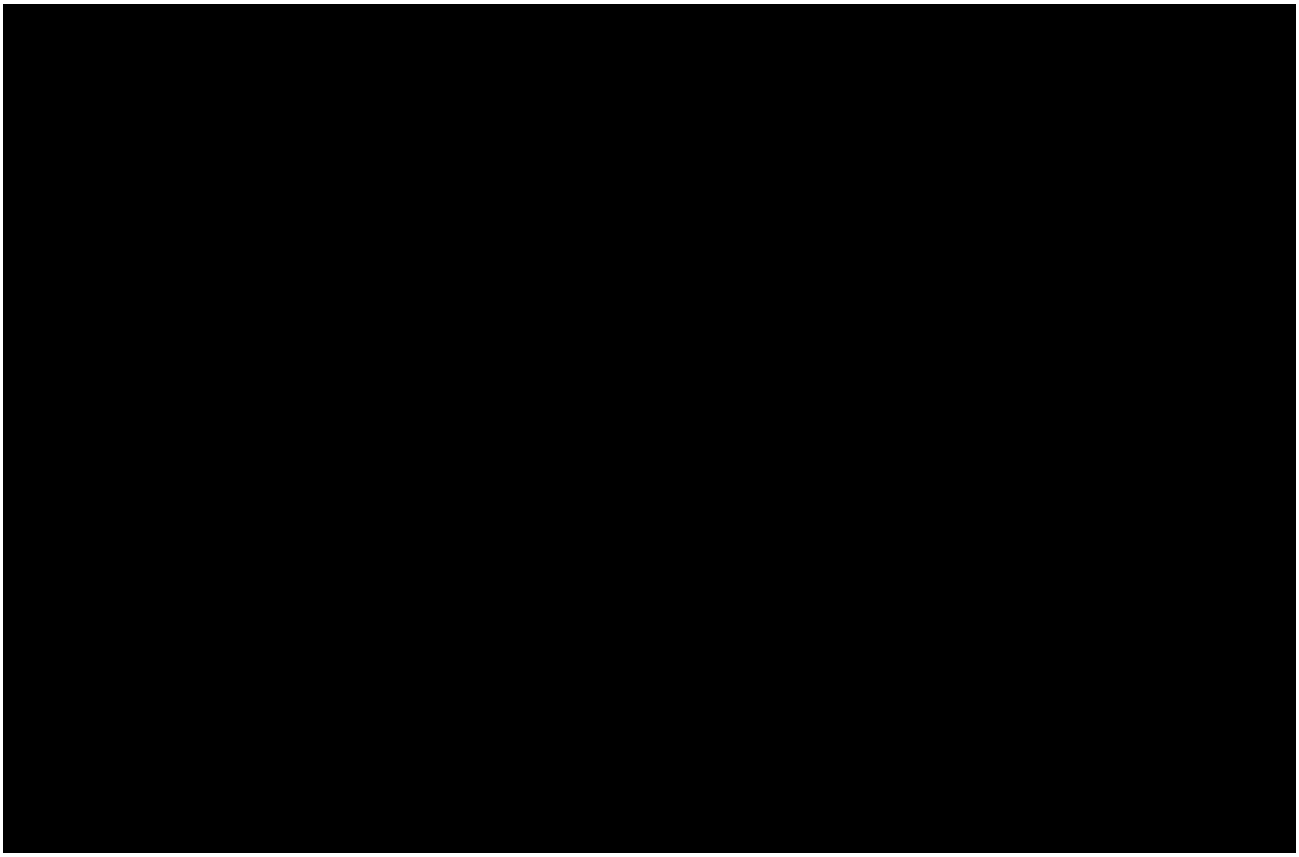
3.2 Rationale for Dose, Population, and Endpoints

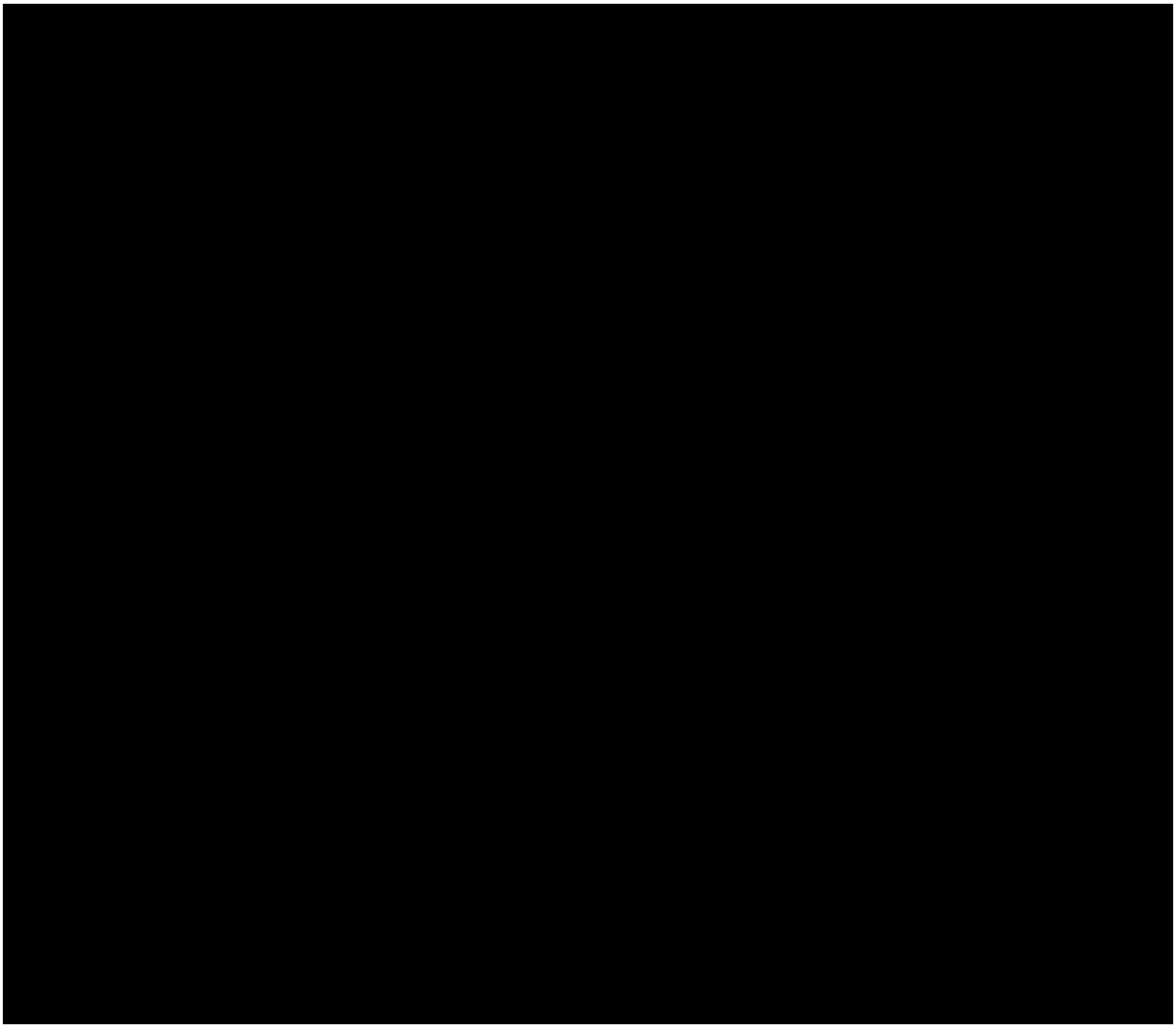
3.2.1 Dose Rationale

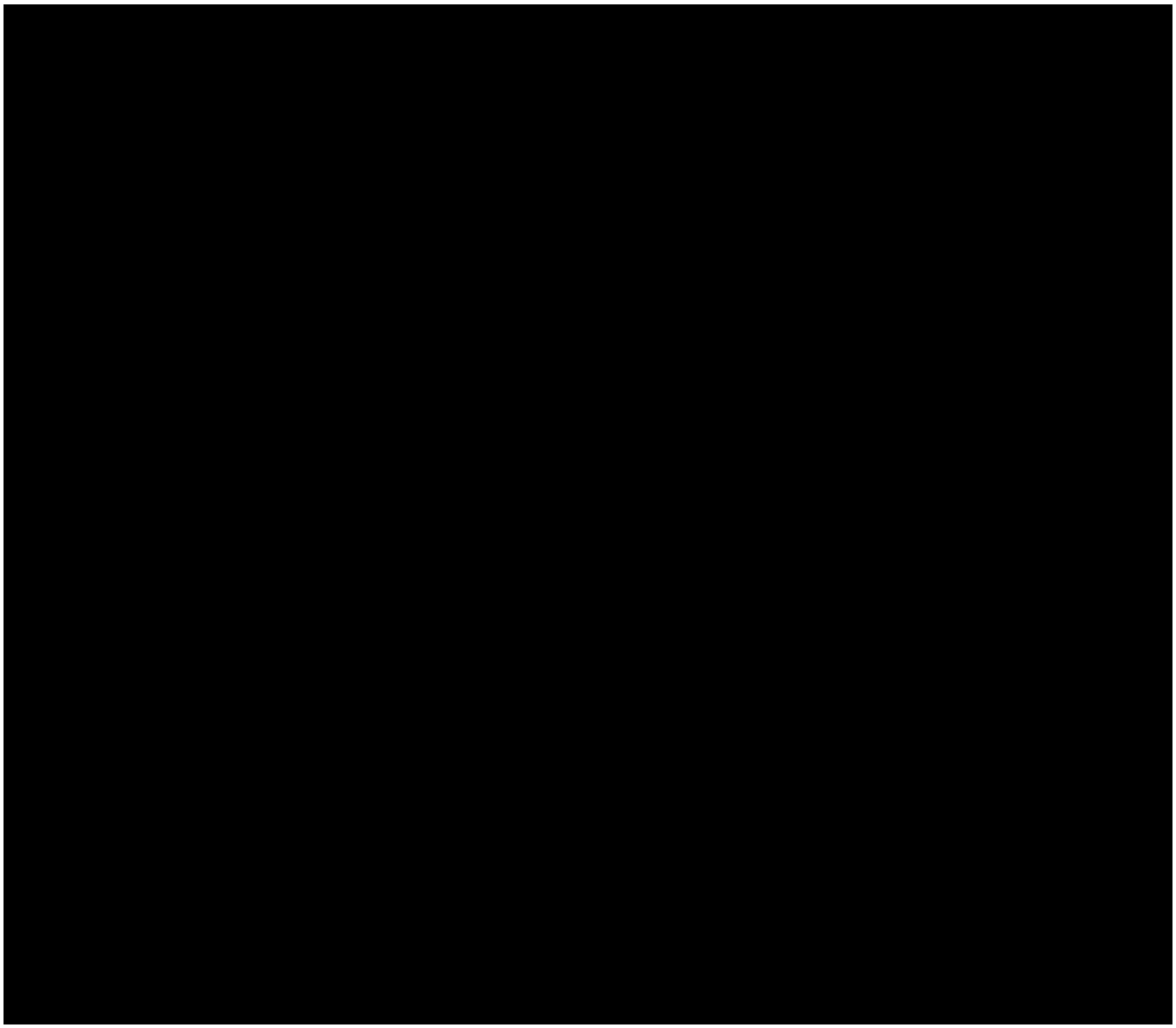
Doses for this study have been selected based on the preliminary results of PK/PD (Cohorts 1 to 3) data from the ongoing Phase 1 SAD study of MEDI5884 (D7870C00001).

A PK/PD model was developed to describe MEDI5884 PK and the corresponding HDL changes over time using an indirect response model. Model estimates were based on fitting PK/PD data simultaneously in healthy volunteers [redacted]

MEDI5884 PK appeared nonlinear. A 2 –compartment population PK model with linear and nonlinear clearance described the data of all 3 cohorts well. The estimated PK parameters are presented in Table 3.2.1-1 and Figure 3.2.1-2.







[redacted]

In summary, the proposed doses of MEDI5884 in this study are expected to be well tolerated, and the collected PK/PD data will be appropriate to fulfill the objectives of this study. The follow-up duration is sufficient to evaluate the potential immunogenic profile of MEDI5884 and monitor any potential impact on PD markers as a result of neutralizing ADA.

3.2.2 Rationale for Study Population

The study population consists of adults with CHD who are clinically stable and taking a high-intensity statin. [redacted]

Subjects will be required to be on a stable high-intensity statin regimen (≥40-mg atorvastatin or ≥20-mg rosuvastatin for non-Asian subjects; ≥10-mg rosuvastatin for Asian subjects) for ≥28 days as is the standard of care for atherosclerotic disease, with LDL-C levels ≤100 mg/dL at Screening.

3.2.3 Rationale for Endpoints

3.2.3.1 Primary Endpoints

Safety and tolerability endpoints including TEAEs, TESAEs, ECGs, vital signs, clinical laboratory evaluations, and physical examinations are standard measures.

3.2.3.2 Secondary Endpoints

Pharmacokinetic Profile

Serum MEDI5884 concentrations will be used to establish the PK profile of MEDI5884, to characterize exposure, and relate to toxicological exposures. The PK may also be used to develop dose-exposure-PD response relationships to help inform dose selection for future clinical studies.

High-density Lipoprotein Cholesterol and Apolipoprotein B

Percent change in HDL-C from Baseline to [redacted] and change in apoB (mg/dL) from Baseline to [redacted] are the primary PD endpoints in this study. Based on large prospective studies of CV risk factors, low HDL-C levels have been shown to be an independent and inverse predictor of atherosclerotic heart disease (Emerging Risk Factor Collaboration et al., 2009). However, increasing evidence suggests that measures of HDL function in contrast to HDL-C levels are better predictors for atherosclerotic burden

(Bhatt and Rohatgi, 2016; Khera et al., 2011; Rohatgi et al., 2014). [redacted]

[redacted]

In the extensive lipid literature, apoB has more consistently predicted CV risk than LDL-C. For example, in the Treating to New Targets study which randomized 9251 patients with CHD to atorvastatin 10 mg or 80 mg, 729 CV events were identified after median 4.9 year follow up. In univariate analysis, many variables including LDL-C, HDL-C, apoA1, and apoB were associated with subsequent CV events. In multivariable analysis, apoB independently predicted CV events whereas LDL-C did not (Mora et al., 2012). This is an established concept; the American Association for Clinical Chemistry issued a position paper in 2009 stating "apoB is a better measure of circulating LDL particle concentration and is a more reliable indicator of risk than LDL-C" (Contois et al., 2009).

Immunogenicity

ADA incidence rate and titer will be tabulated for each subject to monitor immunogenicity. Tiered analyses will be performed to include screening, confirmatory and titer assay components; samples confirmed positive for ADA will be tested and analyzed for antibody titer and reported and may be utilized for further characterization of the ADA response.

[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

At least 120 subjects are planned to be randomized across approximately 25 study sites in the United States of America as described in Sections 3.1.1 and 3.1.2.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female adult aged 45 through 80 years, inclusive, at the time of Screening
2. Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
3. Written informed consent if participating in the optional future use research or genetic research. Declining to participate in this part of the study will not result in penalty or loss of benefit to the subject
4. Ability to meet all eligibility requirements for randomization within up to [redacted] after signing the informed consent form
5. Ability and willingness to adhere to visit/protocol schedule and complete the follow-up period
6. Diagnosis of stable CHD documented prior to Screening defined as a history of at least one of the following:
   a. prior myocardial infarction,
   b. coronary revascularization,
   c. coronary atherosclerosis diagnosed >3 months prior to Screening, based on invasive or non-invasive imaging,
   d. abnormal stress testing diagnostic of CHD
7. Currently receiving any high-intensity statin (≥40-mg atorvastatin or ≥20-mg rosuvastatin for non-Asian subjects; ≥10-mg rosuvastatin for Asian subjects) at a stable dose for ≥30 days prior to Screening and intending to remain at a stable dose throughout the study duration.
8. Females must not be of childbearing potential and must not be lactating (see Section 10.2 for definition of females of childbearing potential)
9. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from [redacted] through the end of their participation in the study. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as described in Section 10.2.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Unstable cardiovascular conditions, including acute coronary syndrome, stroke or transient ischemia attack, critical limb ischemia, arterial revascularization, life-threatening arrhythmias, or heart failure hospitalization within [redacted] of Screening
2. Any planned arterial revascularization (coronary, peripheral or carotid)
3. New York Heart Association Class III or IV congestive heart failure or treatment with advanced therapies (cardiac transplant, ventricular assist device, cardiac resynchronization therapy, and/or chronic intravenous ionotropic support)
4. Severe valvular heart disease
5. Fasting laboratory values at Screening for any of the following:
   a. Triglycerides >500 mg/dL
   b. LDL-C >100 mg/dL (by direct measure)
6. Clinically significant BP abnormalities at Screening after 10 minutes supine rest:
   a. Systolic BP <90 or >160 mmHg
   b. Diastolic BP >100 mmHg

   Note: BP may be retested one time at the discretion of the investigator.
7. ECG results from the central lab report at Screening, demonstrating:
   a. Prolonged QTcF >460 milliseconds based on reported mean of any ECG, or
   b. QRS >160 milliseconds based on reported mean of any ECG
8. Family history of long QT, or any clinically significant ECG finding as judged by the investigator (at [redacted]) that may interfere with the interpretation of serial ECG and QT interval changes
9. Current or previous use of lipid-lowering medications within [redacted] prior to Screening, except for statins and/or <100-mg/day niacin, and/or 10-mg/day ezetimibe, and/or <2-g/day fish oil
10. History of any of the following:
    a. Documented genetic disorder of cholesterol metabolism
    b. Chronic kidney disease stage 4-5, defined by estimated glomerular filtration rate <30 mL/min/1.73 m^2 by the modification of diet in renal disease equation, or end stage renal disease treated with kidney transplant or renal replacement therapy
    c. History of clinically overt chronic liver disease or biochemical evidence of liver disease (eg, aspartate transaminase [AST] or alanine transaminase [ALT] >1.5 × upper limit of normal [ULN] and/or total bilirubin [TBL] >ULN [unless due to Gilbert's syndrome])
    d. Poorly controlled endocrine disorder including Type 1 or Type 2 diabetes mellitus with glycated hemoglobin >10% as assessed at Screening
    e. Uncontrolled thyroid disorder defined as thyroid stimulating hormone >1.5 × ULN and abnormal free T4; subjects with thyroid deficiency should have received a stable dose of thyroid hormone for >6 weeks prior to Screening

f. Current or previous use of systemic corticosteroids within [redacted] prior to Screening. Topical, intra-articular, intranasal, inhaled, and ophthalmic steroid therapies are permitted
g. History of severe infection or ongoing febrile illness within [redacted] of Screening
h. Positive hepatitis B surface antigen or positive hepatitis C virus (HCV) antibody serology
i. History of active malignancy within 5 years (subjects with non-melanotic skin cancer may be included)
j. Any other disease or condition or laboratory value that, in the opinion of the investigator or medical monitor, would place the subject at an unacceptable risk or interfere with the evaluation of the investigational product. Note: abnormal laboratory values may be re-tested one time only if, in the investigator's judgment, the values are not representative of the subject. The rationale for retest must be documented in source documents.

11. History of alcohol or recreational substance abuse within the past 6 months, with abuse defined in accordance with the judgment of the investigator
12. Known allergy/hypersensitivity to any component of the investigational product formulation, other biologics, plastics, adhesive or silicone, or ongoing clinically important allergy/hypersensitivity as judged by the investigator
13. Pregnant females (a negative urine pregnancy test is required at Screening and [redacted] and lactating females are excluded.
14. An employee, or close relative of an employee, of AstraZeneca, MedImmune, the contract research organization, or the study site, regardless of the employee's role
15. Either:
    - Use of any biological agent within 6 months or 5 half-lives of its dosing prior to Screening, whichever is longer
    - Receipt of any investigational drug therapy within 5 half-lives of its dosing prior to Screening
    - Concurrent enrollment in an interventional study

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IXRS], and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized (if applicable) or receive investigational product. Subjects who are randomized but do not receive MEDI5884 or placebo may be rescreened.

Subjects may be rescreened once to permit eligibility based on time-dependent factors including:

- Not being on a stable dose of high-intensity statin therapy for the required [redacted] (inclusion criterion 7)
- Not being at least [redacted] since an unstable cardiovascular condition (exclusion criterion 11)
- To permit a change in antihypertensive therapy so that clinically significant bp abnormalities have resolved ([redacted])
- To be at least [redacted] out from lipid-lowering medication not permitted in [redacted]
- To be on a stable dose of thyroid hormone for at least [redacted] prior to screening ([redacted])
- To have been off of systemic corticosteroids for at least [redacted] prior to screening ([redacted])
- To avoid having had a severe infection or ongoing febrile illness within [redacted] of screening ([redacted]).

Rescreening to meet laboratory- or ECG-based enrollment criteria is not permitted with the following exception:

- Subjects who were excluded based on fasting triglyceride or LDL-C levels may be rescreened once if their lipid-lowering therapy has been increased; rescreening must be [redacted] after change in therapy.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any adverse events (AEs). If the subject is willing, the subject will be seen and assessed by the investigator. Adverse events will be followed up; and all study medications should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent from further treatment with investigational product or lost to follow-up
2. An AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing
3. Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing investigational product might constitute a safety risk
4. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
5. Pregnancy in any female subject
6. Any of the following liver function abnormalities: ALT or AST ≥3 × ULN and total bilirubin >2 × ULN
7. Subject's most recent apoB value, obtained at least [redacted] after the subject's previous dose, exceeds his or her baseline ([redacted] predose) level by ≥30 mg/dL. ApoB testing may be repeated once within the protocol-specified dosing window for Doses 2 or 3, and if that value is <30 mg/dL higher than the baseline value, the subject may be dosed. If the subject's apoB level is ≥30 mg/dL above the baseline level the subject cannot be dosed but will remain in the study to be followed for safety.
8. Subject's pre-dose triglyceride value is ≥ 1000 mg/dL.

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments, including follow-up of any AEs, unless consent is withdrawn from further study participation (Section 4.1.5).

4.1.7 Replacement of Subject

Subjects who do not complete dosing per randomization for any reason other than for safety (which includes subjects who withdrew due to an AE or by having met withdrawal criteria for withdrawal of investigational product (Section 4.1.6) may be replaced if deemed necessary by the medical monitor to ensure that safety and PK data are collected from a sufficient number of subjects and to maintain the balance of the study.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

4.1.8.1 Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor the safety of the subject.

4.1.8.2 Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number linked to the SID number but will not be labeled with personal identifiers such as the subject's name. If the subject withdraws consent for participating in genetic research or future research, the sponsor will locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted DNA will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at Screening.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws.

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	V1
Procedure/Study Day	[redacted]
Main study informed consent / assignment of SID number	X
Future use informed consent (optional)	X
Genetic research informed consent (optional)	X
Medical History	X
Body Weight	X
Height	X
Physical Examination (Detailed)	X
Vital Signs	X
dECG[a]	X
Serum Chemistry and Hematology	X
Thyroid Stimulating Hormone	X
HbA1c	X
Lipids for Eligibility[b]	X
Urinalysis	X
FSH[c]	X
Urine Pregnancy Test[c]	X
Hepatitis and HIV	X
Assessment of AEs and SAEs	X
Assessment of Concomitant Medications	X
Verify Eligibility Criteria	X
EL Mass and Exploratory Biomarkers[b]	X

[redacted]

c [redacted]

4.2.2 Randomized Treatment Period and Follow-up

Table 4.2.2-1 shows all procedures to be conducted at the treatment and follow-up periods.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

Table 4.2.2-1 Schedule of Randomized Treatment Period and Follow-up Procedures

Study Period	Treatment Period															Follow-up	LDL-C or Triglycerides Follow-up[c]		
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[a]**	**V9[b]**	**V10**	**V11[a]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**
[redacted]	[redacted]																		
Medical history	X																		
Body weight	X															X			
Physical examination (abbreviated)	X						X			X				X					
Vital signs[d]	X	X	X		X		X			X	X	X		X	X	X			
dECG[e]	X						X			X	X	X		X		X			
Serum chemistry and hematology	X						X			X				X		X			
Urinalysis	X						X			X				X		X			
Urine pregnancy test[f,g]	X																		
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X																		
[redacted]	[redacted]																		

Table 4.2.2-1 Schedule of Randomized Treatment Period and Follow-up Procedures

Study Period	Treatment Period															Follow -up	LDL-C or Triglycerides Follow-up[c]		
Visit	V2	V3	V4	V5	V6	V7	V8[a]	V9[b]	V10	V11[a]	V12	V13	V14	V15	V16	V17	V18	V19	V20
[redacted]	[redacted]																		
Total cholesterol, nonHDL-C, LDL-C (direct and Friedewald), HDL-C, VLDL-C, triglycerides, [redacted]	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
ApoA1 and ApoB blood sample[i,j]	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
[redacted]																			

Table 4.2.2-1 Schedule of Randomized Treatment Period and Follow-up Procedures

Study Period	Treatment Period															Follow -up	LDL-C or Triglycerides Follow-up[c]		
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[a]**	**V9[b]**	**V10**	**V11[a]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**
[redacted]																			
Future use blood sample	X						X			X				X		X			
Genetic research sample	X																		
Randomization	X																		
[redacted]																			
Assessment of injection sites[m]	X	X					X	X		X	X								
Physical examination (detailed)																X			

[redacted]

Table 4.2.2-1 Schedule of Randomized Treatment Period and Follow-up Procedures

Study Period	Treatment Period															Follow -up	LDL-C or Triglycerides Follow-up[c]		
Visit	V2	V3	V4	V5	V6	V7	V8[a]	V9[b]	V10	V11[a]	V12	V13	V14	V15	V16	V17	V18	V19	V20

4.2.2.1 Early Discontinuation Visit or Unscheduled Study Visit

Study procedures should be completed as per [redacted]/early discontinuation visit for subjects who prematurely discontinue from the study and for subjects who require an unscheduled study visit. Subjects should be encouraged to remain in the study for follow-up.

4.2.3 Additional Follow-up

[redacted]

Subjects whose direct LDL-C at the [redacted] visit is ≥30 mg/dL above their baseline ([redacted] predose) value will return [redacted] after their last visit for repeat LDL-C testing, and, for continued elevation of LDL-C ≥30 mg/dL above Baseline, again on [redacted] and [redacted] for LDL-C testing (see Table 4.2.2-1).

Subjects whose triglyceride value at the [redacted] visit is > 1000 mg/dL will return for a repeat triglyceride testing on [redacted]. If the triglyceride value remains > 1000 mg/dL on [redacted], an additional follow-up visit ([redacted]) will occur for repeat testing (Table 4.2.2-1).

4.3 Description of Study Procedures

4.3.1 Efficacy

No efficacy assessments are being conducted in this study. PD assessments related to the effects of MEDI5884 are described in Section 4.3.6.

4.3.2 Medical History, Physical Examination, Height, Weight, Vital Signs, Electrocardiogram, and Injection Site Reaction Assessment

4.3.2.1 Medical History

A complete history will include medical and disease history, current medical conditions, smoking and alcohol history, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders. A medical and disease history will be performed at Screening and [redacted]

4.3.2.2 Physical Examination, Height, and Weight

A detailed physical examination will be performed at Screening and at last follow-up visit. The full physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, heart, lung, abdomen, musculoskeletal system, endocrine system, and nervous system. An abbreviated physical exam will be performed as outlined in Table 4.2.2-1. The abbreviated physical exam will include examination of: general appearance, skin, heart, lung, and abdomen, at a minimum. Each clinically significant abnormal finding will be recorded for all physical examinations. Weight and height will be measured as outlined in Table 4.2.1-1 and Table 4.2.2-1.

4.3.2.3 Vital Signs

Vital signs (BP, HR, respiratory rate, and body temperature) will be obtained at Screening and on study days as outlined in Table 4.2.2-1. With respect to dosing, vital signs (BP, HR, respiratory rate, and body temperature) on [redacted] should be collected predose (within 60 minutes prior to start of dosing) and 1 hour (± 15 minutes) postdose. Predose vital signs should not be clinically significantly different from the subject's screening value according to the judgment of the investigator. All vital sign measurements will be measured with the subject in a supine position having rested for at least 10 minutes before each reading, and should be taken before any blood draws scheduled in close proximity

4.3.2.4 Electrocardiogram

At the visits specified in Table 4.2.1-1 and Table 4.2.2-1, 12-lead ECGs will be obtained after 10 minutes supine rest. Predose triplicate digital ECG on [redacted] should be collected at 3 different time points (3 × 3 replicates) prior to dosing; each triplicate must be separated by at least 5 minutes. On all other days of ECGs, they will be captured in triplicate, up to 5 minutes apart. In addition, a 10-second paper ECG print-out from the 12-lead ECGs will be taken predose, for overall evaluation (normal/abnormal) before administration and during study days. Subjects with predose ECGs showing clinically significant abnormalities, according to the judgment of the investigator, should not be dosed.

The same recorder will be used for each subject at each time point, if possible. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement.

The following variables will be reported: heart rate, RR, PR, QRS and QT intervals from the primary lead of the digital 12-lead ECG. Derived parameters (QTcF, QTcB, and others, as applicable) will also be calculated.

The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

4.3.2.5 Injection Site Reaction Assessment

Assessment of the injection sites for injection site reactions should be conducted as specified in Table 4.2.2-1.

Subjects will be given a tape measure and an injection site worksheet. They will be instructed to record onto the worksheet whether or not an injection site reaction has occurred at any injection site during the 24 hours after each dose of investigational product. If an injection site reaction has occurred, the subject is to record the measured maximal redness and swelling and a graded assessment of pain (per Table 4.3.2.5-1) for the maximum observation at any injection site. Measurements <¼ inch at the largest diameter should be recorded as 0 inches. Measurements ≥¼ inch but <1 inch would result in a subject recording "yes" to injection site reaction, but the reaction would not be graded (< Grade 1). The subject will report injection site reactions to the Investigational Site and this information will be recorded in the electronic data capture (EDC) system. The subject should return the worksheet to the site to be included in the subject's investigational records. If the subject fails to return the worksheet, the site should query the subject, and, if the subject is able to report the information, it should be recorded, even if incomplete.

Table 4.3.2.5-1 Tables for Clinical Abnormalities: Local Reactions to Injectable Product as Reported by Subjects in their Injection Site Reaction Assessments

Local Reaction to Injectable Product	Reaction Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Erythema/redness[a]	1-2 inches	>2-4 inches	>4 inches	Necrosis or exfoliative dermatitis
Induration/swelling[b]	1-2 inches	>2-4 inches	>4 inches	Necrosis

Local Reaction to Injectable Product	Reaction Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

ER = emergency room

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement

Injection site reactions that occur beyond the 24 hours of collection will be recorded as AEs according to the criteria described in Section 5.1.

Investigators may choose to enter significant injection site reactions occurring during the first 24 hours postdose as AEs, but reporting of injection site reactions as an AE is not required during the first 24 hours postdose and may not occur for low-grade reactions. Injection site reaction data are recorded separately by patient reported injection site reaction assessments and also by investigator reported injection site reactions. These data will be reported separately and may not be identical.

4.3.3 Clinical Laboratory Tests

A laboratory manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests, including urine pregnancy tests, will be performed in a licensed clinical laboratory. Urine pregnancy test will be conducted at Screening and on [redacted] Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant (as determined by the investigator) abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed:

4.3.3.1 Serum Chemistry

- Calcium
- Phosphorus
- Chloride
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- ALP
- Total bilirubin
- Gamma glutamyl transferase
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Creatinine kinase

Note: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. Please refer to Section 10.5 if a subject shows an AST or ALT ≥3 × ULN or total bilirubin ≥2 × ULN.

4.3.3.2 Hematology

- White blood cell count with differential (% and absolutes)
- Red blood cell count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

4.3.3.3 Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Leukocyte esterase
- Bilirubin
- Urobilinogen
- Nitrite
- Urine microscopy and urine casts (as required if dipstick at central laboratory is abnormal)

4.3.3.4 Pregnancy Test (Females Only)

- Urine human chorionic gonadotropin (hCG)

4.3.3.5 Lipids for Eligibility at Screening (Fasting for a Minimum of 8 Hours)

- Triglycerides
- LDL-C (by direct measure)
- HDL-C

4.3.3.6 Other Safety Tests (Screening Only)

- Thyroid stimulating hormone
- Follicle stimulating hormone (FSH; females only)
- Hepatitis B surface antigen, Hepatitis C antibody
- HIV-1, -2 antibodies
- Glycated hemoglobin

4.3.3.7 Other Tests:

- [redacted]
- TC
- HDL-C
- NonHDL-C
- LDL-C (direct and Friedewald equation)
- Very-low-density lipoprotein cholesterol (VLDL-C)
- Triglycerides
- ApoA1
- ApoB

[redacted]

4.3.4 Pharmacokinetic Evaluation and Methods

Blood samples will be collected to evaluate PK of MEDI5884 in serum (see Section 4.2.2 for collection time points). The PK of MEDI5884 in serum will be measured utilizing a validated immunoassay method. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate ADA response to MEDI5884 (see Section 4.2.2 for collection time points). These evaluations will be performed utilizing a validated immunoassay method. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the site.

If a subject's final scheduled immunogenicity sample is > Baseline, the subject will return to the study site as described in Section 4.2.3.

Serum samples collected for ADA should be stored for 2 years after marketing approval, and they may be utilized for further characterization of the antibody response.

4.3.6 Pharmacodynamic Evaluation and Methods

Blood samples will be collected to evaluate the PD response to MEDI5884 (see Section 4.2.2 for collection time points). PD endpoints may include HDL-C, TC, nonHDL-C, LDL-C (direct and Friedewald equation), VLDL-C, triglycerides, [redacted]

[redacted]. HDL-C, TC, nonHDL-C, LDL-C, VLDL-C, triglycerides, [redacted] will be measured by using a validated assay. [redacted], apoB, and apoA1 will be measured by using a qualified immunoassay method. [redacted]

Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the site.

4.3.7 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected per subject is presented in Table 4.3.7-1. Additional blood samples may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an AE.

Table 4.3.7-1 Estimate of Blood Volume to be Collected

Visit Day	Estimated Blood Volume (mL)
[redacted]	15.0
[redacted]	102.0
[redacted]	8.5
[redacted]	10.5
[redacted]	8.5
[redacted]	8.5
[redacted]	8.5
[redacted]	32.5
[redacted]	3.0
[redacted]	32.5
[redacted]	8.5
[redacted]	8.5
[redacted]	8.5
[redacted]	40.5
[redacted]	10.5
[redacted]	32.5
[redacted]	3.0
[redacted]	3.0
[redacted]	6.0
Total	350.5

[a] [redacted] blood draws will occur only for subjects who require additional follow-up (See Section 4.2.3)

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Anaphylaxis in any subject assessed as related to MEDI5884
3. Subject enrollment is unsatisfactory
4. Noncompliance that might significantly jeopardize the validity or integrity of the study
5. Sponsor decision to terminate development of the investigational product for this indication

If MedImmune determines that temporary suspension or permanent termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

[redacted]

[redacted]

[redacted]

[redacted]

4.5.1.1 Investigational Product Handling

[redacted]

[redacted]

[redacted]

4.5.1.2 Investigational Product Inspection

[redacted]

[redacted]

4.5.1.3 Dose Preparation Steps

[redacted]

4.5.1.4 MEDI5884 Reconstitution Procedure

[redacted]

[redacted] **Calculations**

1. [redacted]

3. [redacted]

4.5.1.6 Subcutaneous Dose Preparation:

1. [redacted]

3. [redacted]

[redacted]

[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

4.5.1.7 Treatment Administration

[redacted]

[redacted]

[redacted]

4.5.1.8 Monitoring of Dose Administration

[redacted]

4.5.1.9 Reporting Product Complaints

[redacted]

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

[redacted]

[redacted]

4.5.3 Labeling

[redacted]

4.5.4 Storage

[redacted]

4.5.5 Treatment Compliance

[redacted]

4.5.6 Accountability

[redacted]

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An 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.

[redacted]

Investigational product (MEDI5884 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately

4.6.2 Methods to Ensure Blinding

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. Volume matched placebo injections will be prepared as per Table 4.5.1.6-1. Once prepared, MEDI5884 and placebo are indistinguishable. A blinded qualified designee will administer investigational product to subjects via SC injection.

The investigational product manager/unblinded study personnel must ensure that only the unblinded team members (ie, study pharmacist) have access to the areas of the pharmacy where the investigational product is being prepared. An independent investigational product monitor will also be unblinded to perform investigational product accountability. In the event that treatment allocation for a subject becomes known to the investigator or other study personnel involved in the management of the study subject, the sponsor must be notified immediately. If the identity of a treatment needs to be unblinded for a subject in order to treat that individual subject for an AE, the investigator must notify the sponsor immediately. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

4.6.2.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In most cases, the management of a medical emergency would be the same whether the investigational product was received by the subject or not. In such cases, the identity of the investigational product should remain blinded.

MedImmune retains the right to unblind the treatment allocation for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.2.2 Unblinding for the Interim Analysis

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.

4.6.2.3 Unblinding for Pharmacokinetic and Immunogenicity Analysis

A small number of clinical bioanalytical personnel, who will not be involved in the treatment or clinical evaluation of subjects, will be unblinded to subject treatment allocation to analyze PK and immunogenicity samples. Local standard operating procedures will govern maintenance of the blind and information on treatment allocation will not be communicated outside of these personnel.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of Screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Subjects must be on high-intensity statin (≥40-mg atorvastatin or ≥20-mg rosuvastatin for non-Asian subjects; ≥10-mg rosuvastatin for Asian subjects), at a stable dose for ≥30 days prior to Screening and intend to remain at a stable dose throughout the study duration.

4.7.2 Prohibited Concomitant Medications

Current or previous use of lipid-lowering medications within [redacted] prior to Screening, except for statins and/or <100-mg/day niacin, and/or 10-mg/day ezetimibe, and/or <2-g/day fish oil, is prohibited. Enrolled subjects should intend to maintain their prescribed dose of lipid-lowering medications through the course of the study; however, subjects whose lipid-lowering medications have been changed should stay in the study and may be dosed in

accordance with the study, but these medication changes must be recorded in the Concomitant Medication eCRF.

Current or previous use of systemic corticosteroids within [redacted] prior to Screening is prohibited. Topical, intra-articular, intranasal, inhaled, and ophthalmic steroid therapies are allowed.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

4.8 Statistical Evaluation

4.8.1 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. Details of endpoint analyses will be described in the statistical analysis plan.

Analysis Populations

The As-treated Population includes all subjects who receive any investigational product analyzed according to the treatment they actually receive.

The PK Population includes subjects who received any amount of MEDI5884 with at least one detectable posttreatment serum concentration measurement.

4.8.2 Sample Size

[redacted]

[redacted]

4.8.3 Safety

4.8.3.1 Analysis of Adverse Events

Safety analysis will be based on the As-treated Population. Adverse event 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 by MedDRA System Organ Class and Preferred Term. Adverse events leading to discontinuation, AEs leading to death, and deaths will also 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. Injection site reactions, regardless of being recorded as AEs or not, will also be summarized.

4.8.3.2 Analysis of Clinical Laboratory Parameters, Vital Signs, and Electrocardiograms

Clinical laboratory data and vital signs will be summarized at each time point by treatment group. Change from Baseline to each postbaseline time point in these data will also be summarized, where appropriate. ECG parameters will also be assessed and summarized by treatment group descriptively.

4.8.4 Efficacy

No efficacy data are being collected in this study.

4.8.5 Analysis of Immunogenicity and Pharmacokinetics

4.8.5.1 Immunogenicity Analysis

ADA incidence rate and titer will be tabulated for each treatment group and the placebo group. Samples confirmed positive for ADA may be further characterized and summarized similarly.

4.8.5.2 Pharmacokinetic Analysis

Descriptive statistics of serum MEDI5884 concentration data will be provided. Individual and mean serum concentration-time profiles of MEDI5884 per treatment group and/or visit will be generated. Non-compartmental PK data analysis will be performed and PK parameters such as C_{max}, AUC, $t_{1/2}$ will be generated.

Additional PK and PK/PD analysis may be conducted when appropriate.

4.8.6 Pharmacodynamic Analysis

PD analysis will be based on the As-treated Population. The primary 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 approach to handle missing data. A one-sided upper 95% confidence interval comparing each MEDI5884 treatment group versus placebo for change from Baseline to [redacted] in apoB will be provided.

[redacted]

4.8.7 Interim Analysis

An interim analysis is planned after all subjects have completed their [redacted] visit.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6 (R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from Baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of 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 may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic function abnormality meeting the definition of Hy's Law is considered an AESI. See Section 5.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see Section 5.5). See Section 5.2 for the definition of SAEs and Section 10.3 for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

Adverse event collection begins after the subject signs the informed consent document and lasts until the end of the study.

All SAEs will be recorded from the time of informed consent.

For nontreatment-emergent AEs (ie, AEs that occur during the period from the time informed consent is signed but prior to the subject receiving investigational product), only AEs associated with protocol-related procedures should be reported. After the start of treatment, all TEAEs (Section 5.1) should be reported.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.5 Reporting of Serious Adverse Events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product greater than that specified in the current study protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a MedImmune investigational product occurs during the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

5.6.2 Hepatic Function Abnormality

Cases in which a subject may show elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Section 10.5 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.6.3 Pregnancy

5.6.3.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to the Sponsor.

The designated sponsor representative will work with the investigator to ensure that all relevant information is provided within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Any subject who becomes pregnant during the study will be followed so that pregnancy outcome can be determined and reported to the sponsor and the regulatory authorities.

5.6.3.2 Paternal Exposure

Nonsterilized male study subjects who are sexually active with a female partner of childbearing potential must use condom and spermicide from [redacted] through the end of the study follow-up period.

Male subjects should refrain from fathering a child or donating sperm from [redacted] through the end of the study follow-up period.

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from [redacted] through the end of the study follow-up period should be followed up and documented. Information on the pregnancy of a subject's partner must be obtained directly from the subject's partner. Therefore, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the protocol and related documents with the investigational staff and train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the laboratory manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of investigational product that were received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

An electronic data capture system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document

incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7.2 Ethics and Regulatory Review

The IRB responsible for each site must review and approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The IRB must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB, and distributing them to the study site staff.

The opinion of the IRB must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrolment of any subject into the study.

MedImmune should approve any substantive modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IRB, and principal investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core informed consent form for use by all investigators in the clinical study. MedImmune must

approve any modifications to the informed consent form that are needed to meet local requirements.

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

Substantial changes must be documented in a study protocol amendment. MedImmune will distribute amended versions of the protocol to the principal investigator(s). Before implementation, amended protocols must be approved by relevant IRB (see Section 7.2) and according to local requirements, the national regulatory authority approval. The IRB must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

If local regulations require, any unsubstantial changes will be communicated to or approved by each IRB.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded,

analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 4, 29May2018

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4.

Table 9.1-1 Summary of Revisions to the Protocol (Amendment 4)

Key Details of the Amendment	Reason for Amendment
Amendment 4 (29May2018)	
Protocol Synopsis	Updated to align with changes to main body.
Section 3.1.1 (Overview)Table 4.2.2-1 (Schedule of Randomized Treatment Period and Follow-up Procedures), Section 4.2.3 (Additional Follow-up)	Text and footnote added to reflect additional follow-up visits if a subject's triglyceride level exceeded 1000 mg/dL at the last visit and is in response to feedback from the FDA.
Section 4.1.6 (Discontinuation of Investigational Product)	Text added to exclude from dosing any subject whose pre-dose triglyceride value was ≥ 1000 mg/dL. This amendment is occurring after all subjects have completed dosing, but the amendment is recorded for clarity of the protocol. The exclusion was previously instituted by means of a memorandum to sites dated 16Mar2018 that was subsequently approved by the IRB.

FDA = Food and Drug Administration

9.2 Protocol Amendment 3, 27Feb2018

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. Changes to the protocol were made for clarification and to improve minor administrative/language inconsistencies throughout. Changes are summarized in Table 9.2-1.

Table 9.2-1 Summary of Revisions to the Protocol (Amendment 3)

Key Details of the Amendment	Reason for Amendment
Amendment 3 (27Feb2018)	
Protocol Synopsis	Updated to align with changes to main body.
Usage of greater than / greater than or to equal language and symbols revised throughout document	Revised throughout for accuracy/clarity: • For ADA, follow-up if assessment value > baseline value • For ApoB, no dosing if value ≥ baseline value + 30 mg/dL • For LDL, additional visits required if value ≥ baseline value + 30 mg/dL
Section 1.1 (Introduction Disease Background)	Text added for clarity: World Health Organization (WHO) definition was added (first use in text body) and added to List of Abbreviations.

Table 9.2-1 Summary of Revisions to the Protocol (Amendment 3)

Key Details of the Amendment	Reason for Amendment
Amendment 3 (27Feb2018)	
Section 1.1 (Introduction Disease Background)	Text deleted: Subjects will be encouraged to maintain a healthy lifestyle, including diet and exercise, during the study period.
Section 3.1.1 (Study Design, Overview)	The term "up to" was deleted for accuracy/clarity: [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Section 4.1.2 (Inclusion Criteria)	Text revised for accuracy: Criterion 7: [redacted] prior to Screening.
Section 4.1.5 (Withdrawal from the Study)	Text revised throughout for accuracy/clarity: Subjects who withdraw consent will be asked about the reason(s) and about the presence or absence of any adverse events (AEs). The statement "subjects must withdraw if unblinded" was removed.
Section 4.1.7 (Replacement of Subjects)	Text revised for clarity: Subjects who do not complete dosing per randomization for any reason other than for safety (which includes subjects who withdrew due to an AE or by having met withdrawal criteria for withdrawal of investigational product (Section 4.1.6) may be replaced if deemed necessary by the medical monitor to ensure that safety and PK data are collected from a sufficient number of subjects and to maintain the balance of the study.
Section 4.2.1, Enrollment/Screening Period	Text revised to the following: Table 4.2.1-1 shows all procedures to be conducted at Screening. Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. Two sentences deleted: Assessments should be performed in the order shown in the table. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.
Section 4.2.2 (Randomized Treatment Period and Follow-up)	Text revised for clarity: Table 4.2.2-1 shows all procedures to be conducted at the treatment and follow up periods.

Table 9.2-1 Summary of Revisions to the Protocol (Amendment 3)

Key Details of the Amendment	Reason for Amendment
Amendment 3 (27Feb2018)	
	The last sentence, (assessments should be performed in the order shown in the table), was deleted.
Section 4.2.2 (Table 4.2.2-1, Schedule of Randomized Treatment Period and Follow-up Procedures)	Table note (a) added for clarity: [a] Subjects should dose within dosing windows; however, to minimize data loss, subjects who are unable to return within dosing windows but are otherwise able and eligible to dose outside the window may be dosed with the permission of the sponsor. In such cases, subsequent visits may need to be adjusted to maintain their relationship to dosing but wherever possible, visits should conform to those in Table 4.2.2-1. Note: All subsequent table notes (sequential lettering corresponding to each correct note) were updated within the table and in the list of table notes to remain accurate.
Section 4.3.2.3 (Vital Signs)	Text added for clarity: Predose vital signs should not be clinically significantly different from the subject's screening value according to the judgment of the investigator. All vital sign measurements will be measured with the subject in a supine position having rested for at least 10 minutes before each reading, and should be taken before any blood draws scheduled in close proximity.
Section 4.3.2.4 (Electrocardiogram)	Additional text added for clarity: Predose triplicate digital ECG on [redacted] should be collected at 3 different time points (3 × 3 replicates) prior to dosing; each triplicate must be separated by at least 5 minutes, and subjects with predose ECGs showing clinically significant abnormalities, according to the judgment of the investigator, should not be dosed.
Section 4.3.2.5 (Injection Site Reaction Assessment)	Text revised for clarity: Measurements <¼ inch at the largest diameter should be recorded as 0 inches. Measurements ≥¼ inch but <1 inch would result in a subject recording "yes" to injection site reaction, but the reaction would not be graded (< Grade 1).
Section 4.3.2.5 (Table 4.3.2.5-1)	Table title revised for clarity: Tables for Clinical Abnormalities: Local Reactions to Injectable Product as Reported by Subjects in their Injection Site Reaction Assessments.
Section 4.3.2.5 (Injection Site Reaction Assessment)	Text revised for clarity: Injection site reaction data are recorded separately by patient reported injection site reaction assessments and also by investigator reported injection site reactions. These data will be reported separately and may not be identical.
Section 4.3.3 (Clinical Laboratory Tests)	Text revised for clarity (removed as a table note and added into table text): Urine microscopy and urine casts (as required if dipstick at central laboratory is abnormal).

Table 9.2-1 Summary of Revisions to the Protocol (Amendment 3)

Key Details of the Amendment	Reason for Amendment
Amendment 3 (27Feb2018)	
Section 4.5.1.3 (Dose Preparation Steps) Section 4.5.1.6 (Subcutaneous Dose Preparation)	Text revised where applicable for clarity/accuracy: A 2- or 3-mL polypropylene or polycarbonate syringe with an 18-, 19-, or 20-G 1½ inch needle should be used to extract 1.3 mL of sterile water from the single use vial for reconstitution of MEDI5884.
Section 4.5.2 (Additional Study Medications) Section 4.7.1 (Permitted Concomitant Medications) Section 4.7.2 (Prohibited Concomitant Medications)	Text revised for accuracy: Stable dose for [redacted] prior to screening was revised to [redacted] was added to body text.

9.3 Protocol Amendment 2, 28Nov2017

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Changes to the protocol were made in response to feedback from the Food and Drug Administration, for the purpose of clarification, and to correct previous oversights. Changes are summarized in Table 9.3-1.

Table 9.3-1 Summary of Revisions to the Protocol (Amendment 2)

Key Details of the Amendment	Reason for Amendment
Amendment 2 (28Nov2017)	
Protocol Synopsis	Updated to align with changes to main body.
Section 3.1.1 (Overview), Figure 3.1.1-1 (Study Flow Diagram), and Table 4.2.2-1 (Schedule of Randomized Treatment Period and Follow-up Procedures)	Text and footnote updated to reflect addition of follow-up visits or if a subject's directly measured LDL-C at the last visit is ≥ Baseline + 30 mg/dL in response to feedback from the FDA. The requirement for additional ADA follow-up if a subject's ADA level is not at or below Baseline at the last visit was clarified. The schedule of procedures was amended to reflect the addition of LDL-C follow-up.
Section 3.2.1 (Dose Rationale)	Abbreviations in footnotes and figure titles amended to correct previous oversights.
Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria), Section 4.5.2 (Additional Study Medications), and Section 4.7.1 (Permitted Concomitant Medications)	The requirement to be at a stable dose of high-intensity statin was reduced from [redacted] prior to Screening to [redacted] prior to Screening, to aid recruitment. Relevant text was updated to reflect this.
Section 4.1.3 (Exclusion Criteria)	Criterion 5b amended to LDL-C >100 mg/dL (by direct measure) in response to feedback from the FDA.

Table 9.3-1 Summary of Revisions to the Protocol (Amendment 2)

Key Details of the Amendment	Reason for Amendment
Amendment 2 (28Nov2017)	
	Criterion 9 amended to clarify that current or previous use of 10-mg/day ezetimibe and/or <2-g/day fish oil within [redacted] prior to [redacted] is not exclusionary.
Section 4.1.4 (Subject Enrollment and Randomization)	Text amended to clarify the circumstances under which a subject may be rescreened.
Section 4.1.6 (Discontinuation of Investigational Product)	Discontinuation criterion 6 was amended from "ALT or AST >3 × ULN" to "ALT or AST ≥3 × ULN" to correct a previous oversight.
Section 4.1.6 (Discontinuation of Investigational Product) and Table 4.2.2-1 (Schedule of Randomized Treatment Period and Follow-up Procedures)	A discontinuation criterion based on increased apoB levels was added in response to feedback from the FDA. A visit on [redacted] was added to measure apoB for a decision regarding dosing at [redacted].
Section 4.2.1 (Enrollment/Screening Period) and Table 4.2.1-1 (Schedule of Screening Procedures)	New section created to present the schedule of screening procedures separately for clarity.
Section 4.2.2 (Randomized Treatment Period and Follow-up) and Table 4.2.2-1 (Schedule of Randomized Treatment Period and Follow-up Procedures)	Study procedures that occurred during Screening only were removed due to redundancy. Section and table titles were updated to better reflect the contents. The definition of a day for Visits 2 to 5 was added to the footnotes for clarification. A telephone visit (V9) was added to for the capture of injection site reaction symptoms and measurements from subjects and footnote a was added to reflect this. Footnote i added to clarify that the results of HDL-C, apoA1 and calculated (Friedewald) LDL-C will not be provided to the sites. Footnote k added to clarify that subjects should be closely observed for 1 hour postdose on [redacted].
Table 4.2.2-1 (Schedule of Randomized Treatment Period and Follow-up Procedures) and Section 4.3.2.5 (Injection Site Reaction Assessment)	Text added to provide detail on subject's measurement of injection site reactions over the 24 hours after investigational product administration in response to feedback from the FDA. Footnote l was added to schedule of procedures to reflect this.
Section 4.2.3 (Additional Follow-up)	Text added to reflect the addition of LDL-C follow-up visits.
Section 4.3.3 (Clinical Laboratory Tests) and Section 4.5.1.5 (Monitoring of Dose Administration)	Text added to specify that tryptase should be collected within 30 minutes for anaphylaxis or anaphylaxis-like reactions, if feasible, in response to feedback from the FDA.
Table 4.3.7-1 (Estimate of Blood Volume to Be Collected)	Table updated to reflect changes to the study design.

Table 9.3-1 Summary of Revisions to the Protocol (Amendment 2)

Key Details of the Amendment	Reason for Amendment
Amendment 2 (28Nov2017)	
Section 4.5.1.3 (Dose Preparation Steps)	Text added to clarify instructions for the MEDI5884 reconstitution process.
Section 4.5.2 (Additional Study Medications)	Text added to clarify that any change in statin type or dose must be recorded in the Concomitant Medication section of the electronic case report form.
Section 4.6.2.1 (Unblinding in the Event of a Medical Emergency)	The text "If a subject's investigational product allocation is unblinded to the blinded staff, the subject should be discontinued from investigational product" was removed to correct a previous oversight.
Section 4.7.2 (Prohibited Concomitant Medications)	Text updated to reflect the change to Exclusion Criterion 9 and to clarify that subjects whose lipid-lowering medications have been changed should stay in the study and may be dosed in accordance with the study, but these medication changes must be recorded in the Concomitant Medication eCRF.
Section 4.8.3.1 (Analysis of Adverse Events)	Text amended to clarify that injection site reactions, regardless of being recorded as AEs or not, will also be summarized.

ADA = antidrug antibody; AEs = adverse events; ALT = alanine transaminase; apoA1 = apolipoprotein A1; apoB = apolipoprotein B; AST = aspartate transaminase; eCRF = electronic case report form; FDA = Food and Drug Administration; HDL = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein; ULN = upper limit of normal.

9.4 Protocol Amendment 1, 05Oct2017

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The Original Protocol (03Oct2017) was not submitted to a regulatory agency or IRB. Changes to the protocol are summarized in Table 9.4-1.

Table 9.4-1 Summary of Revisions to the Protocol (Amendment 1)

Key Details of the Amendment	Reason for Amendment
Amendment 1 (05Oct2017)	
[redacted]	[redacted]

10 APPENDICES

10.1 Appendix 1 - Signatures

Sponsor Signature(s)

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.

I agree to the terms of this protocol.

Signature and date: Electronic Signature is attached

[redacted]

Clinical Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: -1-301-398-0645

10.2 Appendix 2 – Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal defined as 12 months with no menses without an alternative medical cause and have a follicle-stimulating hormone level in the laboratory's normal range for post-menopausal phase at Screening.
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 10.2-1.
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 90 days after the final dose of investigational product.

Table 10.2-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system or implant; eg, Mirena®)[a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

10.3 Appendix 3 - Additional Safety Guidance

10.3.1 Further Guidance on the Definition of a Serious Adverse Event (SAE)

10.3.1.1 Life threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

10.3.1.2 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

10.3.1.3 Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

10.3.1.4 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.3.1.5 Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as TESAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

10.4 Appendix 4 - National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s Baseline

10.5 Appendix 5 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

10.5.1 Introduction

This appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

10.5.2 Definitions

10.5.2.1 Potential Hy's Law

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

10.5.2.2 Hy's Law

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For potential Hy's Law and Hy's Law, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

10.5.3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

In cases where a subject may meet any of the abnormal laboratory identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to sponsor study representative).

The investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the investigator will:

- Notify the sponsor study representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets potential Hy's Law criteria (see Section 10.5.2) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

10.5.4 Follow-up

10.5.4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the investigator will:

- Inform the study representative that the subject has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

10.5.4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the investigator will:

- Notify the sponsor study representative who will then inform the study team

The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. This includes deciding which the tests available in the Hy's Law laboratory kit should be used.
- Complete the Liver CRF Modules as information becomes available.
- If at any time (in consultation with the medical monitor) the potential Hy's Law case meets serious criteria, report it as an SAE using standard reporting procedures.

10.5.5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the investigational product. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to the sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are met. Update the SAE report according to the outcome of the review

10.6 References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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