A Randomized, Placebo-controlled Phase 2b Study to Evaluate the Safety and Efficacy of MEDI6012 in Acute ST Elevation Myocardial Infarction

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Investigational Product: MEDI6012 [redacted]

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

Medical Monitor: [redacted] MBBS, MRCP, PhD
[redacted], Clinical Development, MedImmune

Study Chair: [redacted] MD, MPH
Chairman, [redacted]
[redacted] MD, [redacted]
Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School

Principal/Coordinating Investigator: [redacted] MD, MPH
Investigator, [redacted]
Associate Physician, Brigham and Women's Hospital
Assistant Professor, Harvard Medical School

Contract Research Organization: [redacted]

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PROTOCOL SYNOPSIS

TITLE

A Randomized, Placebo-controlled Phase 2b Study to Evaluate the Safety and Efficacy of MEDI6012 in Acute ST Elevation Myocardial Infarction

HYPOTHESES

Primary Hypothesis: MEDI6012 will reduce myocardial infarction (MI) size compared to placebo.

Secondary Hypotheses:

Compared with placebo,

1 MEDI6012 will improve left ventricular systolic function (ejection fraction [EF])
2 MEDI6012 will induce regression/reduce progression of non-calcified coronary plaque
3 MEDI6012 will reduce adverse remodeling of the left ventricle (LV).
4 MEDI6012 will exhibit an acceptable safety and immunogenicity profile in subjects with acute ST segment elevation myocardial infarction (STEMI).

OBJECTIVES

Primary objective: To evaluate the effect of MEDI6012 on infarct size compared with placebo.

Secondary objectives:

1 To evaluate the effect of MEDI6012 on LV systolic function compared to placebo.
2 To evaluate the effect of MEDI6012 on non-calcified coronary plaque regression/progression from baseline to 10-12 weeks compared with placebo.
3 To evaluate the effect of MEDI6012 on remodeling of the LV measured by myocardial mass and volumes.
4 To evaluate the safety and tolerability of MEDI6012.
5 To describe the pharmacokinetics (PK) and immunogenicity of MEDI6012.

Exploratory objectives:

1 [redacted]

STUDY ENDPOINTS

Primary endpoints:

- Infarct size as a percentage of LV mass measured on delayed-enhanced (CV magnetic resonance [CMR]) imaging 10-12 weeks post-MI compared to placebo.

Secondary endpoints:

- EF measured by cine magnetic resonance imaging (MRI) at 10-12 weeks post-MI compared to placebo.
- Change in NCPV in the coronary arteries from index computed tomography angiography (CTA) to 10-12 weeks post-MI compared with placebo.
- Myocardial mass and LV volumes at end-systole and end-diastole.
- Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs).
- Lecithin-cholesterol acyltransferase (LCAT) mass and anti-drug antibodies (ADAs).

Exploratory endpoints:

- [redacted]

STUDY DESIGN

This is a Phase 2b randomized, blinded (subject/MedImmune blinded, investigator unblinded), placebo-controlled study to evaluate the efficacy, safety, PK/pharmacodynamic, and immunogenicity of repeat doses of MEDI6012 in adult subjects presenting with acute STEMI. Approximately 540 subjects are planned to be randomized across approximately 43 study sites in approximately 10 countries, to evaluate a [redacted] regimen and a [redacted] regimen of MEDI6012. The study will enrol subjects presenting with acute STEMI within 6 hours of symptom onset who are planned for pPCI. Following initial screening, subjects will be randomized in a 1:1 ratio to a [redacted] or [redacted] regimen and then randomized within that dose regimen to a 2:1 ratio to receive MEDI6012 or placebo.

For both the [redacted] and the [redacted] regimens, the first two doses of investigational product will be administered in the inpatient setting on study Days 1 and 3. Subjects randomized to the [redacted] regimen will receive standard of care treatment post pPCI. Subjects randomized to the [redacted] regimen will receive standard of care treatment post pPCI and additional administration of investigational product on Days 10, 17, 24, and 31. For all subjects, an end of study CMR will be performed at 10-12 weeks (70-84 days following Dose 1). Subjects randomized to the [redacted] regimen will also undergo an index (Days 3-5) and an end of study CTA (70-84 days following Dose 1).

If a subject's Day 70-84 immunogenicity sample is confirmed as ADA positive and there is a > 30% decrease from baseline in HDL-C or a neutralizing antibody (nAb) is present, the subject will return for additional assessments. Safety data for subjects ongoing in Extended Follow-up at database lock will be reported in a clinical study report (CSR) addendum.

TARGET SUBJECT POPULATION

Subjects 30-80 years of age inclusive, presenting with acute STEMI.

TREATMENT GROUPS AND REGIMENS

Cohort A: [redacted]

Cohort B: [redacted]

STATISTICAL METHODS

Sample size:

Statistical analyses:

Intention-to-Treat Population: all subjects who are randomized, analyzed according to randomized treatment assignment.

As-treated Population: all randomized subjects who receive any investigational product. Subjects who receive any dose of MEDI6012 will be assigned to the MEDI6012 group. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive any dose of MEDI6012 will be analyzed with the MEDI6012 group. Safety analyses will be performed on the As-treated Population.

Primary Efficacy Analysis Population: all randomized subjects with of investigational product. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive doses of MEDI6012 will be analyzed with the MEDI6012 group.

Efficacy Analysis Population all randomized subjects with investigational product. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive of MEDI6012 will be analyzed with the MEDI6012 group.

Efficacy Analysis Population - all randomized subjects with investigational product. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive of MEDI6012 will be analyzed with the MEDI6012 group.

The CTA Analysis Population: randomized subjects in the regimen who receive a full treatment course of investigational product and are eligible for performed. The subjects who receive doses will be analyzed with the placebo group; conversely, subjects who receive doses of MEDI6012 will be analyzed with the MEDI6012 group.

Immunogenicity Population: includes all subjects in the As-treated Population who have at least one serum sample for immunogenicity testing.

PK Population: includes all subjects in the As-treated Population who have at least one detectable serum concentration measurement for LCAT mass.

The primary efficacy endpoint of infarct size will be analyzed using t-test with log-transformation of the data based on the primary efficacy analysis population. The primary endpoint of infarct size will also be analyzed based on the Efficacy Analysis Population - TIMI 2-3, the Efficacy Analysis Population - TIMI 0-3, and the Intent-To-Treat population.

Secondary efficacy endpoints include EF measured by cine MRI at 10-12 weeks post-MI, change in NCPV in the coronary arteries from index CTA to 10-12 weeks post-MI, and myocardial mass and left ventricular

volumes at end-systole and end-diastole. EF, myocardial mass, and left ventricular volumes will be analyzed similarly to infarct size without the log-transformation of the data. Change from index CTA in NCPV will be analyzed using t-test based on CTA analysis population.

Safety analysis will be based on the As-treated Population. Adverse event (AE) collection will begin after the subject signs the informed consent document and lasts until the end of the study. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All TEAEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, SAEs, and treatment discontinuations due to AEs will be provided.

Clinical laboratory safety tests including serum chemistry and hematology parameters will be summarized using descriptive statistics at each time point by treatment group with placebo group combined when appropriate. Change from baseline to each post baseline time point in these data will also be summarized, where appropriate. A shift table will be provided for these clinical laboratory parameters as well where possible.

Vital sign results will be summarized using descriptive statistics at each time point by treatment group.

ADA incidence rate and titer will be tabulated for each treatment group.

Serum MEDI6012 mass concentration time profiles will be summarized for MEDI6012 treated subjects by dose cohort.

The following PD markers will be collected: . The PD markers measured at each time point and change from baseline each post baseline time point will be summarized using descriptive statistics by treatment group with placebo group combined when appropriate.

Interim analysis: interim analyses are planned. The objective of the interim analysis will be for It will be conducted after 30% of the initially planned Primary Efficacy Analysis Population (N = 74) is enrolled and will require that > 50% of subjects (N > 37) and . The interim analysis will be conducted through the Data Monitoring Committee with details in the DMC charter. The interim analysis is planned to accelerate decision on future development options for MEDI6012 and will be performed once 60% of the revised Primary Efficacy Analysis Population (N = 162) is enrolled and will require that > 50% of subjects (N > 81) have and . Details of the interim analyses will be specified in the interim analysis plan. The sponsor and Principal Investigator will monitor the statistical assumptions in a blinded fashion and decide the exact time for interim analyses.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibody
AE	adverse event
ALT	alanine transaminase
[redacted]	[redacted]
[redacted]	[redacted]
AST	aspartate transaminase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from 0 to infinity
AUC_{0-72h}	area under the concentration-time curve from 0 to 72 hours
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
[redacted]	[redacted]
C_{max}	maximum plasma concentration
[redacted]	[redacted]
COVID-19	coronavirus disease
CrCl	creatinine clearance
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	electronic case report form
EDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FAAN	Food and Allergy Anaphylaxis Network
FC	free cholesterol
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HDL-CE	High-density lipoprotein-cholesterol ester
[redacted]	[redacted]
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialized Term	Definition
IV	intravenous(ly)
IXRS	Interactive response system
[redacted]	[redacted]
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LV	left ventricle
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MR	magnetic resonance
MRI	magnetic resonance imaging
nAb	neutralizing antibody
NCPV	non-calcified plaque volume
NO	nitric oxide
NOAEL	no-observed-adverse-effect-level
pPCI	primary percutaneous coronary intervention
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
RCT	reverse cholesterol transport
rhLCAT	recombinant human lecithin-cholesterol acyltransferase
SAE	serious adverse event
SID	subject identification
SOC	system organ class
STEMI	ST segment elevation myocardial infarction
sWFI	sterile water for injection
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
USA	United States of America

1 INTRODUCTION

1.1 Disease Background

Acute coronary syndrome (ACS) comprises a spectrum of life-threatening clinical conditions that include unstable angina and non-ST-segment elevation myocardial infarction (non-STEMI) and ST-segment elevation myocardial infarction (STEMI). STEMI patients generally have larger infarcts and are at higher risk for subsequent heart failure and death (Stone et al, 2016). Efforts to limit infarct size have focused on reducing door-to-balloon time and maintaining culprit artery patency after primary percutaneous coronary intervention (pPCI). Therapies that decrease infarct size or increase left ventricular ejection fraction (EF) are associated with reductions in cardiovascular (CV) death and heart failure (Breathett et al, 2016; Kramer et al, 2010). However, no acute drug therapies have demonstrated cardioprotection in humans.

Infusion of high-density lipoprotein (HDL) or apolipoprotein A1 (apoA1) has demonstrated reductions in infarct size and improve hemodynamics in preclinical models of acute STEMI (Gomaraschi et al, 2016). Cross-sectional epidemiology studies (Framingham Study) demonstrated post-infarct EF is lower in patients with low HDL cholesterol, even after excluding baseline coronary heart disease (CHD) (Kempen et al, 1987; Wang et al, 1998). However, HDL and apoA1 infusions have not been tested for the purpose of cardioprotection in humans.

In addition to cardioprotection, acute STEMI patients could benefit from a therapy that rapidly removes plaque cholesterol, stabilizes vulnerable plaque, and thereby reduces the likelihood of subsequent ischemic events (Chen et al, 2010; Krause and Remaley, 2013; Libby and Aikawa, 2003; Shah, 2007). Therapies that increase HDL-cholesterol (HDL-C) or apoA1 have the potential to regress atheroma.

1.2 MEDI6012 Background

MEDI6012 is briefly described below. Refer to the current Investigator's Brochure (IB) for details.

MEDI6012 (formerly ACP501) [redacted]. Lecithin-cholesterol acyltransferase (LCAT) is the rate-limiting enzyme in lipid metabolism that esterifies free cholesterol (FC) to cholesteryl ester (CE) and facilitates the maturation of HDL particles. [redacted] EDI6012 relative to ACP501. In clinical studies (further described below), single and multiple doses of MEDI6012 increased HDL-C, HDL-C ester (HDL-CE), CE, and apoA1. In addition, in clinical and clinical *ex vivo* studies, MEDI6012 improves HDL function.

1.3 Summary of Nonclinical Experience

Nonclinical pharmacology, pharmacokinetic (PK), pharmacodynamic (PD), and toxicology studies were conducted as part of the nonclinical program for MEDI6012. The nonclinical pharmacology data, summarized in the IB, show that MEDI6012 [redacted] In the 6-week repeat-dose toxicity study of MEDI6012 in [redacted] This corresponded to mean maximum plasma concentration (C_{max}) and area under the concentration-time curve from 0 to 72 hours (AUC_{0-72h}) values of 904 µg/mL and 14200 µg·hr/mL, respectively, following Day 43 of dosing.

1.4 Summary of Clinical Experience

Two completed studies with ACP501 are summarized in the IB (ACP501-01 and 13-H-0060).

Study D5780C00002, was a Phase 2a study to evaluate the safety, PK, and PD of single doses of MEDI6012 in subjects with stable coronary artery disease (CAD). Forty-eight subjects were administered a single dose of MEDI6012 of 24, 80, 240, or 800 mg by 1-hour infusion or by SC injection at doses of 80 or 600 mg, or placebo (6:2 ratio).

Study D5780C00005 was a Phase 2a study to evaluate the safety, PK, and PD of multiple doses of MEDI6012 in subjects with stable atherosclerotic cardiovascular disease. In this study, 32 subjects were administered multiple doses of MEDI6012 or placebo (6:2 ratio). MEDI6012 or placebo was administered three times weekly at 3 dose levels (1-hour IV infusion of 40, 120, or 300 mg on Days 1, 8, and 15) and a 4th cohort tested an IV push dosing regimen that included a loading dose of 300 mg followed by 150 mg second dose at 48 hours followed by a 100 mg maintenance dose 7 days later.

1.4.1 Efficacy

Dose-dependent increases in HDL-C that were statistically significant at the 80, 240, and 800 mg IV and the 600 mg SC dose levels were observed after [redacted] doses in Study D5780C00002. In addition, the study demonstrated: 1) dose dependent, statistically significant increases in [redacted] at all IV dose levels and at the 600 mg SC dose; 2) statistically significant increase in [redacted] only at the highest IV dose level (800 mg); and 3) a statistically significant decrease in [redacted] across all IV dose levels indicating a decrease in the number of [redacted] particles.

After multiple doses of MEDI6012 in Study D5780C00005, the primary PD endpoints of sustainable and reversible dose-dependent response for HDL-C, HDL-CE and CE were met. In addition, the study demonstrated dose dependent, statistically significant increases in

and statistically significant increase in LDL-C at the dose levels with no increase in .

1.4.2 Safety

In Study D5780C00002, single doses of MEDI6012 were generally well tolerated. There were no treatment-emergent serious adverse events (TESAEs), deaths, or life-threatening treatment-emergent adverse events (TEAEs), or TEAEs leading to withdrawal from the study. Non-serious TEAEs were reported by 55.6% of all MEDI6012-treated subjects and 41.7%) placebo-treated subjects. The majority of TEAEs were of mild or moderate severity. At the preferred term (PT) level, the most frequent TEAEs in all MEDI6012 subjects were headache ( ), injection site reaction), and injection site erythema, medical device site irritation, and constipation). There were no clinically relevant changes in vital signs, electrocardiogram (ECG), or standard safety laboratory parameters. Of the subjects treated with MEDI6012, subjects (14%) tested positive for treatment-emergent anti-drug antibodies (ADAs) at 1 or more timepoints. None of these ADAs were neutralizing.

In study D5780C00005, multiple doses of MEDI6012 were generally well tolerated. There was TESAE of atrial fibrillation felt due to external factors unrelated to Investigational Product or study procedures. There were no deaths, or life-threatening TEAEs or TEAEs leading to withdrawal from the study. Non-serious TEAEs were reported by 52% (all MEDI6012-treated subjects and 43%) of all placebo-treated subjects. All TEAEs were of mild or moderate intensity. At the PT level, the most frequent TEAEs in all MEDI6012 subjects were dyspnea), injection site reaction ( ), non-cardiac chest pain ( ) and diarrhea ( ). There were no clinically relevant changes in vital signs, ECG, or standard safety laboratory parameters. No subject treated with MEDI6012 tested positive for treatment-emergent ADA.

1.4.3 Pharmacokinetics

After doses, exposure to MEDI6012 increased with the increase in IV dose level from and exhibited linear PK with peak exposure (C_{max}) generally increasing proportionally with increasing dose and systemic plasma area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) increasing proportionally between and IV doses. The bioavailability derived based on mean dose-normalized $AUC_{0-\infty}$ between SC and IV dose was 49.8%. The PK profile of MEDI6012 supported IV dosing.

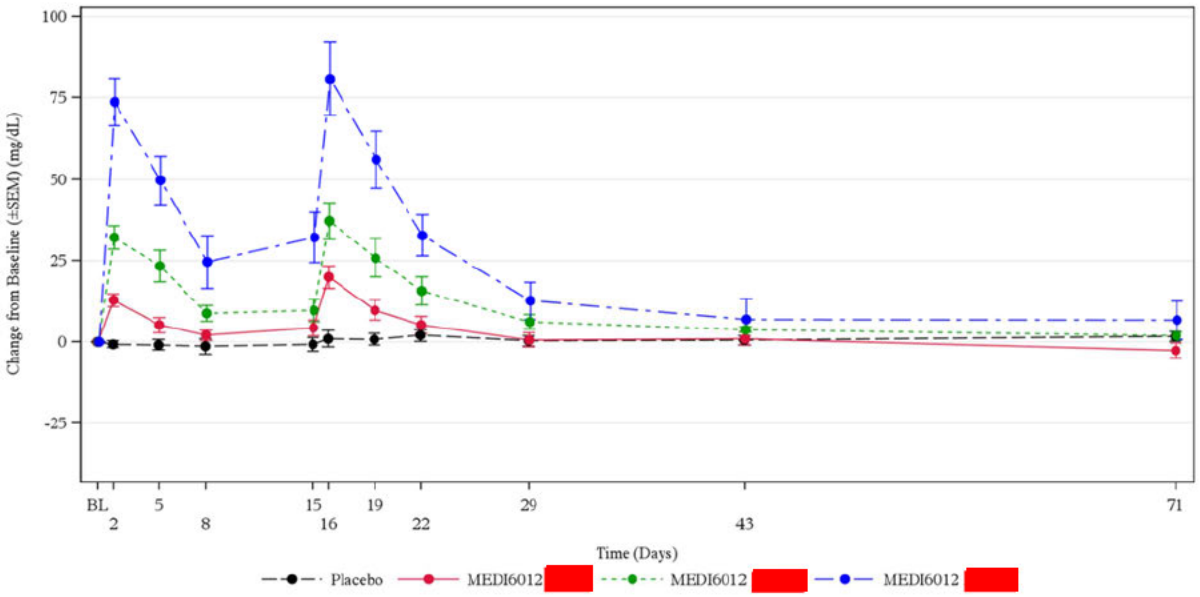
No multiple dose pharmacokinetic data are available at the time of writing.

1.5 Rationale for Conducting the Study

MEDI6012 increases HDL-C, HDL-CE, and CE consistent with its mechanism of action (Table 1 and Table 2). In addition, MEDI6012 increases apoA1 after both single and multiple

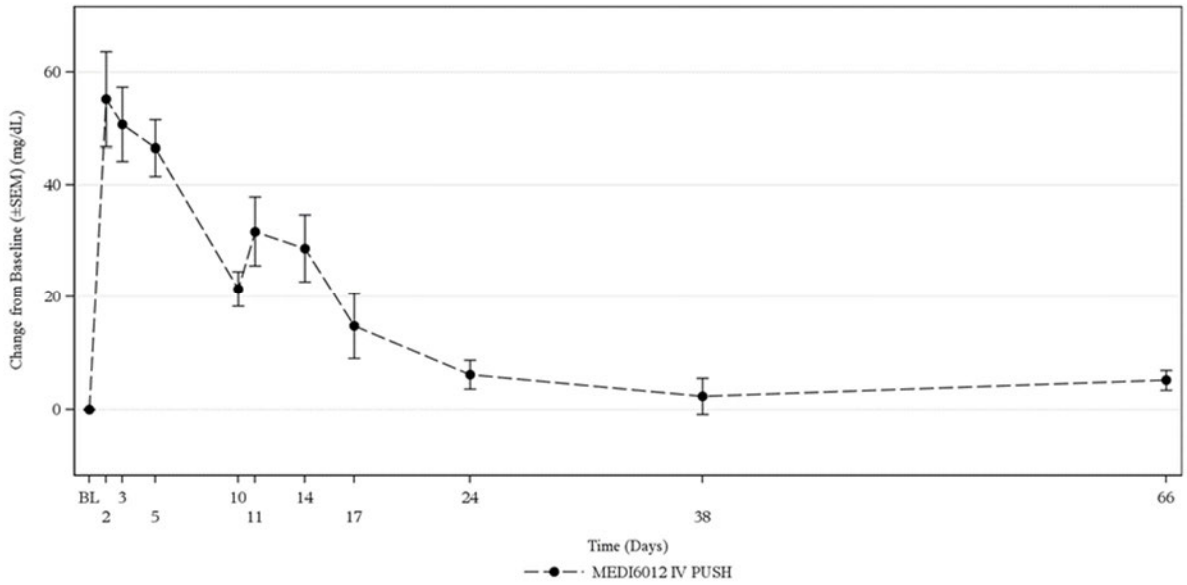
ascending doses, shown to be cardioprotective in nonclinical studies and atheroprotective in clinical studies. The increase in HDL-C is rapid, enabling MEDI6012 to induce HDL-C mediated cardio-protection in the acute STEMI setting (Figure 1 and Figure 2).

Figure 1 **Mean Change from Baseline in Serum HDL-C After Ascending [redacted] IV Doses of MEDI6012**



apoA1 = apolipoprotein A1; apoB = apolipoprotein B; HDL-C = high-density lipoprotein-cholesterol; IV = intravenous; LDL-C = low-density lipoprotein-C; SEM = standard error of the means.

Figure 2 **Mean Change from Baseline in Serum HDL-C After an IV Push Regimen of (Day 1 – [redacted], Day 3 – [redacted], and Day 10 – [redacted]) MEDI6012**



apoA1 = apolipoprotein A1; apoB = apolipoprotein B; HDL-C = high-density lipoprotein-cholesterol; IV = intravenous; LDL-C = low-density lipoprotein-C; SEM = standard error of the means.

Table 1 Baseline Adjusted $AUC_{0\text{-}96h}$ for Key PD Parameters After Ascending [redacted] Doses of MEDI6012 – As-treated Population

	Placebo N = [redacted]	MEDI6012 [redacted] N = [redacted]	MEDI6012 [redacted] N = [redacted]	MEDI6012 [redacted] N = [redacted]	MEDI6012 Total N = [redacted]
HDL Cholesterol (mg.h/dL)					
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-81.97	794.46	2450.86	5214.73	2820.02
SD	213.88	420.30	871.01	1575.91	2127.37
Median	3.82	917.76	2588.25	5419.23	2588.25
(Min, Max)	(-360.1, 104.9)	(72.3, 1228.0)	(1134.6, 3223.9)	(3339.3, 7575.5)	(72.3, 7575.5)
LS Mean	-102.09	794.46	2502.60	5183.11	2832.22
95% CI of LS Mean	(-904.10, 699.92)	(-6.04, 1594.97)	(1692.21, 3312.98)	(4378.90, 5987.32)	(1905.61, 3758.82)
P-value		0.114	<0.001	<0.001	0.003
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-6.72	1355.64	2874.86	6465.05	3394.60
SD	467.59	576.94	1232.21	2074.77	2502.22
Median	-106.23	1498.99	2974.75	5951.50	2062.32
(Min, Max)	(-434.3, 894.8)	(380.5, 2062.3)	(1524.8, 4079.0)	(3962.4, 9630.9)	(380.5, 9630.9)
LS Mean	-15.49	1357.98	2905.80	6435.63	3406.41
95% CI of LS Mean	(-1074.52, 1043.54)	(300.13, 2415.83)	(1832.29, 3979.31)	(5263.89, 7607.37)	(2284.12, 4528.71)
P-value		0.070	<0.001	<0.001	0.004
LDL-C (Direct) (mg h/dL)					
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 1 **Baseline Adjusted $AUC_{0\text{-}96h}$ for Key PD Parameters After Ascending [redacted] Doses of MEDI6012 – As-treated Population**

	Placebo N = [redacted]	MEDI6012 [redacted] N = [redacted]	MEDI6012 [redacted] N = [redacted]	MEDI6012 [redacted] mg N = [redacted]	MEDI6012 Total N = [redacted]
Mean	-442.28	397.52	667.47	1203.37	756.12
SD	440.57	277.06	603.85	1219.22	828.12
Median	-369.14	398.70	637.00	1028.80	686.26
(Min, Max)	(-1120.6, 89.5)	(-42.7, 699.5)	(-190.5, 1484.0)	(-572.3, 3032.0)	(-572.3, 3032.0)
LS Mean	-433.38	404.72	648.33	1206.41	753.77
95% CI of LS Mean	(-1077.75, 211.00)	(-237.40, 1046.83)	(-19.24, 1315.90)	(567.81, 1845.02)	(372.71, 1134.83)
P-value		0.067	0.027	0.001	0.004
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-55.96	1125.45	1043.39	3056.76	1664.52
SD	886.81	872.40	700.00	1765.33	1424.58
Median	-34.88	655.85	934.47	3964.80	1133.15
(Min, Max)	(-1531.9, 1057.4)	(397.8, 2335.0)	(252.4, 2223.2)	(325.1, 4573.8)	(252.4, 4573.8)
LS Mean	-18.56	1156.28	972.92	3059.45	1658.98
95% CI of LS Mean	(-985.42, 948.30)	(193.20, 2119.36)	(-23.49, 1969.34)	(2013.22, 4105.68)	(974.31, 2343.66)
P-value		0.084	0.159	<0.001	0.017
Cholesteryl Ester (mg.h/dL)					
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-153.71	1094.80	3132.86	5735.04	3320.90
SD	619.13	546.46	864.84	1889.19	2275.08
Median	-167.29	993.13	3111.81	5495.73	3111.81
(Min, Max)	(-1126.7, 493.0)	(583.9, 1958.7)	(1772.4, 4084.7)	(3537.0, 9106.6)	(583.9, 9106.6)

Table 1 Baseline Adjusted $AUC_{0\text{-}96h}$ for Key PD Parameters After Ascending [redacted] Doses of MEDI6012 – As-treated Population

	Placebo N = [redacted]	MEDI6012 40 mg N = [redacted]	MEDI6012 120 mg N = [redacted]	MEDI6012 300 mg N = [redacted]	MEDI6012 Total N = [redacted]
LS Mean	-135.76	1130.14	3054.01	5760.60	3315.29
95% CI of LS Mean	(-1107.39, 835.87)	(153.33, 2106.95)	(2049.91, 4058.11)	(4787.11, 6734.08)	(2303.30, 4327.28)
P-value		0.069	<0.001	<0.001	0.002
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	373.04	2267.37	4047.38	9004.31	4877.06
SD	1060.76	1126.43	1314.67	2086.47	3187.51
Median	350.00	1930.24	3937.06	9011.63	4022.03
(Min, Max)	(-871.3, 2011.5)	(1055.0, 4022.0)	(2836.0, 5450.1)	(6987.1, 12261.2)	(1055.0, 12261.2)
LS Mean	389.20	2296.77	3989.87	9018.65	4873.95
95% CI of LS Mean	(-855.77, 1634.17)	(1044.31, 3549.23)	(2707.55, 5272.18)	(7656.07, 10381.23)	(3405.99, 6341.90)
P-value		0.035	<0.001	<0.001	0.004
Apolipoprotein A1 (mg.h/dL)					
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	309.57	1453.24	1856.43	2704.57	2004.75
SD	347.45	354.56	972.15	1086.94	974.88
Median	378.52	1333.08	1965.04	2755.66	1792.63
(Min, Max)	(-229.6, 795.7)	(1214.6, 2146.1)	(424.2, 2864.7)	(1102.8, 4386.3)	(424.2, 4386.3)
LS Mean	309.82	1454.45	1855.46	2704.09	2004.57
95% CI of LS Mean	(-365.32, 984.95)	(778.65, 2130.26)	(1179.91, 2531.01)	(2028.87, 3379.31)	(1566.93, 2442.21)
P-value		0.021	0.003	<0.001	<0.001

Table 1 Baseline Adjusted $AUC_{0\text{-}96h}$ for Key PD Parameters After Ascending [redacted] Doses of MEDI6012 – As-treated Population

	Placebo N = [redacted]	MEDI6012 40 mg N = [redacted]	MEDI6012 120 mg N = [redacted]	MEDI6012 300 mg N = [redacted]	MEDI6012 Total N = [redacted]
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	821.33	2440.48	3740.59	5302.87	3741.22
SD	1465.70	1021.34	1508.93	1739.86	1786.30
Median	922.45	2276.28	3409.54	5672.88	3254.78
(Min, Max)	(-1221.0, 2371.7)	(1258.4, 4005.6)	(2288.8, 5590.6)	(3254.8, 7331.4)	(1258.4, 7331.4)
LS Mean[a]	823.07	2444.76	3739.15	5297.36	3738.99
95% CI of LS Mean	(-446.63, 2092.77)	(1173.03, 3716.50)	(2469.58, 5008.72)	(3903.24, 6691.48)	(2852.35, 4625.62)
P-value		0.074	0.003	<0.001	0.002
Apolipoprotein B (mg.h/dL)					
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-273.27	-205.08	-229.88	-817.97	-417.64
SD	279.82	176.37	279.63	734.34	525.08
Median	-269.46	-176.92	-300.37	-592.84	-296.84
(Min, Max)	(-609.6, 60.2)	(-526.5, 4.9)	(-485.5, 263.8)	(-2144.1, -139.5)	(-2144.1, 263.8)
LS Mean	-272.38	-173.50	-277.40	-802.92	-417.97
95% CI of LS Mean	(-630.45, 85.69)	(-535.15, 188.15)	(-643.52, 88.73)	(-1161.81, -444.03)	(-649.86, -186.07)
P-value		0.689	0.984	0.041	0.521
Post [redacted]					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	-82.95	-40.06	145.42	-374.38	-72.93
SD	667.65	477.21	283.62	588.54	479.14

Table 1 Baseline Adjusted AUC_{0-96h} for Key PD Parameters After Ascending [redacted] Doses of MEDI6012 – As-treated Population

	Placebo N = 6	MEDI6012 40 mg N = 6	MEDI6012 120 mg N = 6	MEDI6012 300 mg N = 6	MEDI6012 Total N = 18
Median	-213.81	-121.10	36.39	-388.77	-91.85
(Min, Max)	(-1047.1, 744.8)	(-577.2, 629.5)	(-99.3, 558.3)	(-1107.2, 458.6)	(-1107.2, 629.5)
LS Mean	-76.29	16.97	72.64	-363.46	-75.41
95% CI of LS Mean	(-498.68, 346.09)	(-410.52, 444.46)	(-358.08, 503.35)	(-826.25, 99.33)	(-327.34, 176.51)
P-value		0.748	0.611	0.348	0.998

CI = confidence interval; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; LS = least squares; Max = maximum; Min = minimum; N = number of total subjects; n = number of subjects for assessment; PD = pharmacodynamic; SD = standard deviation.

Table 2 Baseline Adjusted AUC_{0-96h} for Key PD Parameters After IV push dosing regimen ([redacted] mg loading dose followed by [redacted] mg at 48 hours and [redacted] mg 7 days later) - As-treated Population

	Placebo IV PUSH N = [redacted] [a]	MEDI6012 IV PUSH N = [redacted]
HDL Cholesterol (mg.h/dL)		
Post [redacted]		
n	[redacted]	[redacted]
Mean	-675.69	4125.69
SD	NA	552.08
Median	-675.69	4402.63
(Min, Max)	(-675.7, -675.7)	(3184.1, 4585.9)
Post [redacted]		
n	[redacted]	[redacted]
Mean	266.68	1803.12
SD	NA	1684.32

Table 2 Baseline Adjusted AUC_{0-96h} for Key PD Parameters After IV push dosing regimen (mg loading dose followed by mg at 48 hours and mg 7 days later) - As-treated Population

	Placebo IV PUSH N = [a]	MEDI6012 IV PUSH N =
Median	266.68	658.73
(Min, Max)	(266.7, 266.7)	(353.1, 4308.4)
LDL-C (Direct) (mg h/dL)		
Post		
n		
Mean	-616.78	890.25
SD	NA	840.94
Median	-616.78	871.57
(Min, Max)	(-616.8, -616.8)	(-192.5, 2334.8)
Post		
n		
Mean	-78.79	1364.12
SD	NA	2375.93
Median	-78.79	302.30
(Min, Max)	(-78.8, -78.8)	(-152.0, 6542.5)
Cholesteryl Ester (mg.h/dL)		
Post		
n		
Mean	-1316.90	4574.76
SD	NA	708.37
Median	-1316.90	4633.84
(Min, Max)	(-1316.9, -1316.9)	(3546.7, 5418.1)

Table 2 Baseline Adjusted AUC_{0-96h} for Key PD Parameters After IV push dosing regimen [redacted] mg loading dose followed by [redacted] mg at 48 hours and [redacted] mg 7 days later) - As-treated Population

	Placebo IV PUSH N = [redacted][a]	MEDI6012 IV PUSH N = [redacted]
Post [redacted]		
n	[redacted]	[redacted]
Mean	371.75	2649.56
SD	NA	3039.83
Median	371.75	761.94
(Min, Max)	(371.8, 371.8)	(303.0, 8374.1)
Apolipoprotein A1 (mg.h/dL)		
Post [redacted]		
n	[redacted]	[redacted]
Mean	-1208.16	1669.34
SD	NA	691.14
Median	-1208.16	2007.14
(Min, Max)	(-1208.2, -1208.2)	(603.0, 2334.6)
Post [redacted]		
n	[redacted]	[redacted]
Mean	-20.42	2399.42
SD	NA	2611.21
Median	-20.42	744.70
(Min, Max)	(-20.4, -20.4)	(401.0, 6694.4)
Apolipoprotein B (mg.h/dL)		
Post [redacted]		

Table 2 Baseline Adjusted AUC_{0-96h} for Key PD Parameters After IV push dosing regimen (mg loading dose followed by mg at 48 hours and mg 7 days later) - As-treated Population

	Placebo IV PUSH N = [a]	MEDI6012 IV PUSH N =
n		
Mean	-651.36	-681.99
SD	NA	543.82
Median	-651.36	-779.18
(Min, Max)	(-651.4, -651.4)	(-1279.0, 381.1)
Post		
n		
Mean	-239.17	73.01
SD	NA	864.30
Median	-239.17	-209.54
(Min, Max)	(-239.2, -239.2)	(-403.4, 2017.4)

CI = confidence interval; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; LS = least squares; Max = maximum; Min = minimum; N = number of total subjects; n = number of subjects for assessment; PD = pharmacodynamic; SD = standard deviation.

[a] Analysis of LCAT levels in the placebo subject reveal that on day 10, the subject received MEDI6012 and not placebo

In a separate study in acute STEMI patients, endogenous LCAT mass and activity levels were evaluated acutely, 48, and 72 hours after myocardial infarction (MI). Compared with baseline, LCAT mass and activity levels were significantly decreased at 48 and 72 hours post-MI and plasma from those patients demonstrated impaired HDL-induced nitric oxide (NO) production. NO production remained impaired for 30 days post-MI. Incubation of the plasma samples with MEDI6012 restored HDL function as measured by HDL-induced NO production. Together, this study provides supportive evidence that HDL function is impaired in acute STEMI patients and MEDI6012 can restore this function (Ossoli A).

Epidemiologic and pre-clinical studies have established that higher levels of HDL-C are cardioprotective in patients post-MI and infusions of HDL or apoA1 mimetics reduce myocardial infarct size and improve left ventricular systolic function in animal models of acute MI. Specifically, 1) post-infarct EF is lower in patients with low HDL-C, even after excluding baseline CHD (Kempen et al, 1987; Wang et al, 1998); infusion of the apoA1 mimetic CSL-111 in two different mouse models of acute MI demonstrated an increase in viable myocardium of 54% - 61%, a reduction in infarct size by 21% - 26%, and a reduction in the recruitment of leukocytes and neutrophils in the area of infarction (Heywood et al, 2017); 2) infusion of the apoA1 mimetic ETC-216 in a rabbit model of ischemia-reperfusion resulted in a marked reduction in infarct size (Marchesi et al, 2004); 3) adenoviral transfer of apoA1 2 weeks prior to MI in a mouse model achieved apoA1 levels 1.5× controls and showed increased survival (~ 2×), attenuated infarct expansion, inhibition of left ventricle (LV) dilation, and improved hemodynamics (Gordts et al, 2013); 4) infusion of HDL vs HDL and its constituent sphingosine-1-phosphate in a mouse model of ischemia-reperfusion showed a 20% reduction in infarct size with HDL alone and a 40% reduction in infarct size when HDL and S1P (Theilmeier et al, 2006); and 5) apoA1 infusions reduced infarct size in Wistar rats via the RISK/SAFE pro-survival kinase pathways (Akt, ERK1/2, STAT-3) (Kalakech et al, 2014). The increases in apoA1 seen with the study by Gordts and Marchesi et al are similar to those increases seen with MEDI6012. Based on these data, this study will determine if acute treatment with MEDI6012 can reduce myocardial infarct size by increasing levels of HDL-C and apoA1.

In addition to myocardial protection following acute MI, MEDI6012 also has the potential to regress coronary atherosclerosis and exhibit vasculo-protective properties. In rabbits that express endogenous CETP, transgenic overexpression of LCAT has been shown to protect against diet-induced atherosclerosis (Hoeg et al, 1996). Similarly, IV administration of rhLCAT to wild-type rabbits has also been shown to protect against atherosclerosis (Zhou M, 2009). Clinical data have further suggested that low levels of LCAT may be associated with an increased incidence and/or severity of CAD (Asztalos et al, 2000; Lamon-Fava et al, 2008; Miida et al, 1996; Sethi et al, 2010; Solajic-Bozicevic et al, 1994; Tashiro et al, 2009). In the single ascending dose study (D5780C00002) in of patients with stable CHD on statin therapy, MEDI6012 decreased small atherogenic LDL particles by 41%, 88%, and 79% at 80, 240, and

800 mg respectively, supporting the potential that MEDI6012 may be beneficial in atherosclerosis.

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, and applicable regulatory requirements.

This study will test MEDI6012 in acute STEMI patients. Patients with acute STEMI are at risk of future major adverse CV events, including death, MI, stroke, and heart failure. MEDI6012's mechanism of action gives it the [redacted] with a favourable benefit-risk ratio.

Nonclinical studies have established that therapies that increase HDL-C and/or apoA1 have the potential to protect the heart from ischemia/reperfusion injury that occurs during an acute STEMI. Reductions in ischemia reperfusion injury decrease infarct size and improved heart function. Nonclinical studies of MEDI6012 demonstrate that MEDI6012 [redacted] In addition, nonclinical studies have established that MEDI6012 [redacted]. These nonclinical studies have supported clinical studies in patients with atherosclerotic CV disease.

Acute STEMI patients have decreases in LCAT mass and activity and HDL from acute STEMI patients is impaired in its ability to induce nitric oxide production. Treatment of plasma from acute STEMI patients with MEDI6012 [redacted]. Clinical studies of MEDI6012 have demonstrated that IV infusions of MEDI6012 result [redacted] and MEDI6012 can improve the function [redacted]. MEDI6012 is being developed so it can be administered rapidly as an IV push, [redacted] in the acute STEMI setting.

Clinical studies have demonstrated that single and multiple doses of MEDI6012 are generally well tolerated. Two identified risks with MEDI6012 are injection site reactions, which were observed at low frequencies when administered by IV, and ADAs. ADAs were observed in the MEDI6012 SAD study in [redacted] (14%) subjects. No ADAs were observed in the MEDI6012 MAD study when MEDI6012 was given IV, only, and in lower doses. A theoretical risk of MEDI6012 is [redacted] has been detected in clinical studies of MEDI6012. In addition, the transient rise [redacted] with MEDI6012 is accompanied [redacted]

[redacted], and is expected consistent with LCAT's mechanism of action. Subjects enrolled in this study will undergo therapies which include LDL-C lowering with statins.

Acute STEMI is a major contributor to the development of heart failure (HF) and death in patients with CHD. The risk of HF and death is related to the size of the MI and the impact it has on heart function. Furthermore, the extent of coronary plaque burden is directly related to the risk of death and MI. The only therapy shown to reduce infarct size in humans with acute STEMI is pPCI. In addition, statins and proprotein convertase subtilisin kexin 9 inhibitors have demonstrated a reduction in the progression of coronary atheroma and reductions in major adverse CV events. MEDI6012, with its ability to [redacted], has the potential to be the first therapeutic that [redacted] Taken together, [redacted] a favourable benefit-risk ratio.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

MEDI6012 will reduce MI size compared to placebo.

1.7.2 Secondary Hypotheses

Compared with placebo,

1 MEDI6012 will improve left ventricular ejection fraction (EF)
2 MEDI6012 will induce regression/reduce progression of non-calcified coronary plaque
3 MEDI6012 will reduce adverse remodeling of the LV
4 MEDI6012 will exhibit an acceptable safety and immunogenicity profile in subjects with acute STEMI

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective and associated endpoint is presented in Table 3.

Table 3 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To evaluate the effect of MEDI6012 on reduction of infarct size compared with placebo.	Infarct size as a percentage of LV mass measured on delayed-enhanced CMR imaging 10-12 weeks post-MI compared to placebo.

CMR = cardiovascular magnetic resonance; LV = left ventricle; MI = myocardial infarction.

2.1.2 Secondary Objectives

Secondary objectives and associated endpoints are presented in Table 4.

Table 4 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint(s)
Efficacy	To evaluate the effect of MEDI6012 on systolic function of the LV compared to placebo.	EF measured by cine MRI at 10-12 weeks post-MI compared to placebo.
Efficacy	To evaluate the effect of MEDI6012 on non-calcified coronary plaque regression/progression from baseline to 10-12 weeks compared with placebo.	Change in NCPV in the coronary arteries from index CTA to 10-12 weeks post-MI compared with placebo.
Efficacy	To evaluate the effect of MEDI6012 on remodeling of the left ventricle measured by myocardial mass and volumes.	Myocardial mass and LV volumes at end-systole and end-diastole.
Safety	To evaluate the safety and tolerability of MEDI6012.	Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs).
PK, and Immunogenicity	To describe the PK and immunogenicity of MEDI6012.	LCAT mass and presence of ADAs.

ADAs = anti-drug antibodies; CTA = computed tomography; EF = ejection fraction; LCAT = lecithin-cholesterol acyltransferase; LV = left ventricular; MI = myocardial infarction; MRI = magnetic resonance imaging; NCPV = non-calcified plaque volume; PK = pharmacokinetic(s); TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

2.1.3 Exploratory Objectives

Exploratory objectives and associated endpoints are presented in Table 5.

Table 5 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint(s)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

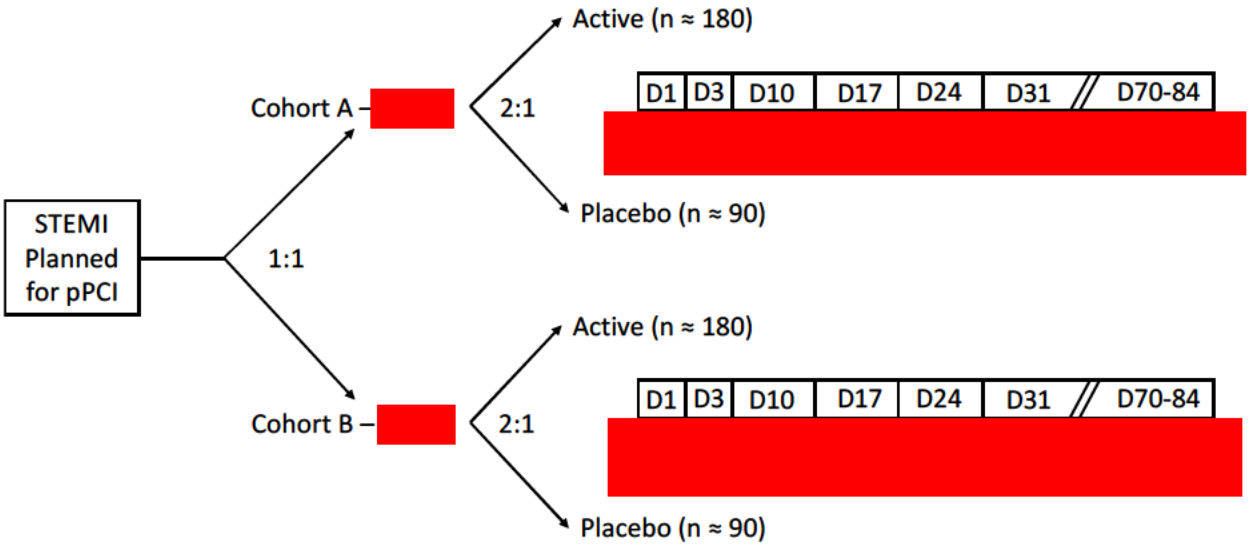
3.1.1 Overview

This is a Phase 2b, randomized, placebo-controlled study to evaluate the efficacy, safety, PK/PD, and immunogenicity of repeat doses of MEDI6012 in adult subjects presenting with acute STEMI. In this study, the subject and MedImmune staff will be blinded. Sites will be trained to keep the investigator blinded. However, due to the acute nature of the study, members of the research team and, possibly, the investigator may be unblinded.

Approximately 540 subjects are planned to be randomized across approximately 43 study sites in around 10 countries to evaluate a [redacted] regimen and a [redacted] regimen of MEDI6012.

Due to the acute nature of this study, there will be a very short screening period. The study will enroll subjects presenting with acute STEMI within 6 hours of symptom onset who are planned for emergent pPCI. After obtaining verbal or written informed consent (as per local regulations), subjects will be assessed for eligibility and, if considered eligible, will be randomized in a 1:1 ratio into either Cohort A ([redacted]) or Cohort B ([redacted]) (Figure 3). Within each cohort/dose regimen, subjects will be randomized in a 2:1 ratio to receive MEDI6012 or placebo prior to pPCI. In the event a dose regimen (Cohort A or Cohort B) is dropped at the interim analysis, subjects will be randomized in a 1:1 ratio to receive MEDI6012 or placebo for the remaining dose regimen.

Figure 3 Overall Study Schema



CMR = cardiovascular magnetic resonance (imaging); CTA = computed tomography angiography; D = study day; N = number of subjects; pPCI = primary percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

Inpatient Phase – Cohorts A and B

Both Cohorts A and B will receive their [redacted] doses in the inpatient setting.

Following verbal or written informed consent (per local regulations) and prior to dosing, an assessment will be made of vital signs, and blood samples will be collected for clinical laboratory assessment, PK, PD, and immunogenicity. The [redacted] of investigational product should be administered via IV infusion over 1-2 minutes prior to pPCI on Day 1 as soon as possible prior to the first pPCI procedure, defined as the time that the first angioplasty wire crosses the culprit lesion. Following dosing and pPCI, study procedures will be conducted in accordance with the Schedule of Study Procedures. On Day 3 (48±8 hours post [redacted] subjects will receive a [redacted] dose of investigational product and additional study procedures will be conducted according to the Schedule of Study Procedures.

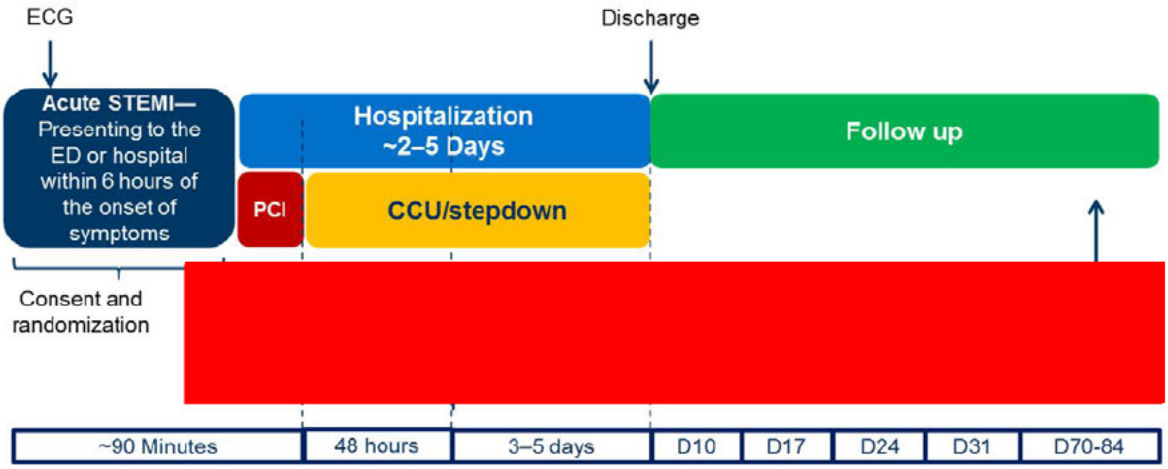
For Cohort B only, those subjects with creatinine clearance (CrCl) $\geq$ 60 mL/min (Cockcroft Gault equation) within 6 hours will undergo an index coronary computerized tomography angiography (CTA) no earlier than 40 hours following the [redacted] dose. It is preferred that the index CTA occur 48-72 hours post Dose [redacted], but it may be done up to 5 days post Dose [redacted]. Subjects may be discharged following Day 3 assessments, if considered acceptable by the clinical team and investigator.

Following Doses [redacted] and [redacted] (Cohort A) or Doses [redacted] through [redacted] (Cohort B), subjects will be monitored for 2 hours in a location with personnel trained in Adult Advanced Life Support with proper resuscitation equipment available.

Outpatient Phase – Cohort A

Subjects randomized to Cohort A [redacted] regimen) will undergo standard of care treatment post pPCI (Figure 4) and will follow-up according to the Schedule of Assessments. An end of study cardiovascular magnetic resonance (CMR) will be performed at 10-12 weeks (70-84 days post Dose 1).

Figure 4 Study Flow Diagram for Cohort A: [redacted] Regimen

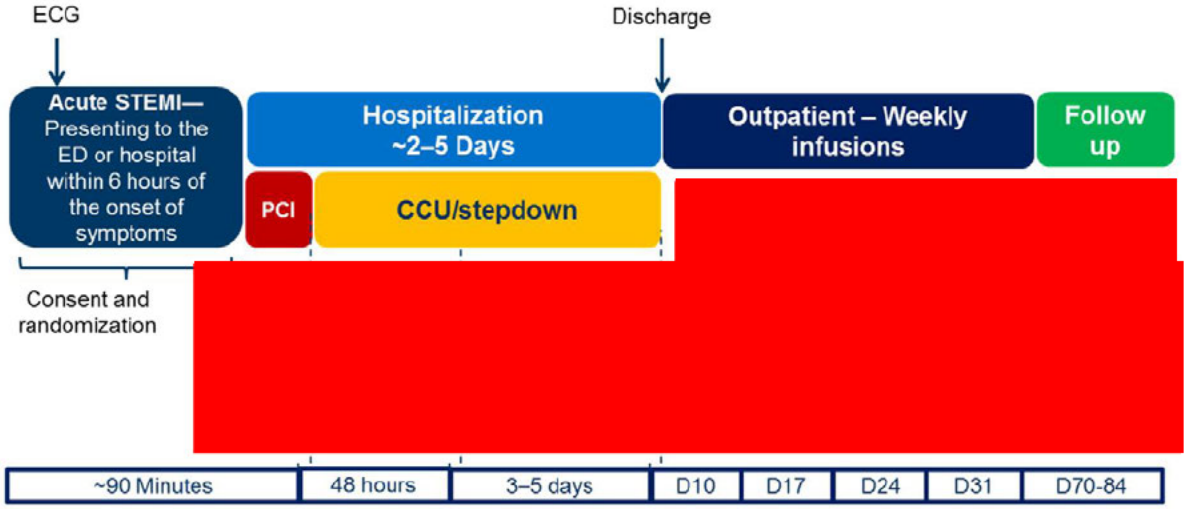


CCU = cardiac care unit; CMR = cardiovascular magnetic resonance (imaging); D = day; ECG = electrocardiogram; ED = emergency department; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

Outpatient Phase – Cohort B

Subjects randomized to Cohort B ([redacted] regimen) will undergo standard of care treatment post pPCI (Figure 5) and will undergo remaining study procedures according to the Schedule of Assessments. Following the initial [redacted] doses, subjects will receive investigational product at [redacted] intervals (± 1 day) for 4 weeks. While it is most likely these additional doses will occur in the outpatient setting, subjects with prolonged hospitalizations may undergo further dosing as an inpatient. At the end of the study, an end of study CMR and coronary CTA will be performed at 10-12 weeks (70-84 days post Dose [redacted]. Subjects who did not undergo index CTA for any reason, will not undergo the CTA at the end of the study.

Figure 5 Study Flow Diagram for Cohort B - [redacted] Regimen



CCU = cardiac care unit; CMR = cardiovascular magnetic resonance (imaging); CTA = computed tomography angiography; D = day; ECG = electrocardiogram; ED = emergency department; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

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

Note: for Cohorts A and B, if there is a clinical indication for an intracardiac device (ie, pacemaker, implantable cardioverter-defibrillator), the CMR can be scheduled at an earlier time point, but not prior to 30 days post Dose [redacted]. In addition, if the end of study CMR is determined to be of inadequate image quality by the CMR core laboratory, the subject may return for a repeat CMR within 4 weeks of the end of study window (up to 112 days post Dose [redacted]). In both cases, CMR data acquired 30 to 112 days post Dose [redacted] will be included in the analysis of endpoints. Coronary CTA will not be repeated due to image quality issues.

3.1.2 Treatment Regimen

Enrolment of approximately 540 subjects is planned to evaluate the [redacted] dosing regimens (Cohort A: [redacted] regimen and Cohort B: [redacted] regimen) as follows:

Cohort A

- MEDI6012, [redacted] (n ~ 180)
- Placebo, [redacted] (n ~ 90)

Cohort B

- MEDI6012, [redacted] (n ~ 180)
- Placebo, [redacted] (n ~ 90)

Inpatient Phase Dosing

Both Cohort A and Cohort B inpatient dosing will consist of a [redacted] loading dose of Investigational Product administered on Day 1, followed on Day 3 by a [redacted] second dose, both administered in the inpatient setting (Table 6 and Table 7). Dosing for Cohort A will be completed at this point.

Table 6 Dosing for Cohort A: [redacted] Regimen

[redacted]

For Cohort B, additional maintenance doses of [redacted] mg will be administered at weekly intervals on Days 10, 17, 24, and 31 (Table 7). These doses will be administered in the outpatient setting.

Table 7 Dosing for Cohort B: [redacted] Regimen

[redacted]

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

Since this study will involve treating acute STEMI subjects in the acute setting, the aim is to increase [redacted]. The rate of [redacted] 1 increase with MEDI6012 are [redacted]. Therefore, on Day 1 a loading dose of MEDI6012 [redacted] or placebo will be administered to achieve a [redacted]. Based on PK modeling, [redacted] is expected to increase ~50% in 90 minutes and ~100% in 6 hours (assuming a mean [redacted] in acute STEMI patients). In addition, improved [redacted] L function is expected based on cholesterol efflux capacity data from study D5780C00002. A [redacted] dose of [redacted] of MEDI6012 or placebo will be administered 48 hours [redacted] following the [redacted] dose to maintain [redacted] during the acute and

sub-acute phases of MI. For the [redacted] regimen, dosing will be complete. For the [redacted], subjects will receive 4 additional weekly [redacted] doses as an outpatient. A maintenance dose of [redacted] was selected to [redacted] at a level conferring benefit in epidemiology studies and at a level, predicted by PD/PK modeling from study D5780C00002 and D5780C00005, not to result in an appreciable accumulation of [redacted]. Increases in [redacted]

3.2.2 Rationale for Study Population

The current study is intended to examine the cardioprotective and atherosclerotic effects of MEDI6012 in subjects with acute STEMI. In comparison to acute non-STEMI, patients with acute STEMI, particularly acute anterior STEMI, experience larger myocardial infarcts that result in greater reductions in EF. Since it is likely that subjects with larger infarcts will be more likely to benefit from MEDI6012, the study population is planned to have > 50% of subjects with acute anterior STEMI and > 60% with pre-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) 0-1. However, this study will evaluate the effect of MEDI6012 in non-anterior STEMI and those with pre-PCI TFG 2-3 to fully characterize the potential efficacy of MEDI6012.

3.2.3 Rationale for Endpoint(s)

3.2.3.1 Rationale for Primary Endpoints

The primary endpoint is assessment of infarct size as a percentage of LV mass measured on delayed-enhanced CMR imaging at 10-12 weeks post MI.

Infarct size measured at 10-12 weeks reflects final infarct size after remodeling of the LV and will reflect both the early and late effects of treatment with MEDI6012 (Mather et al, 2011). Infarct size is an independent predictor of secondary major adverse CV events, including mortality and hospitalization for heart failure (Stone et al, 2016; Wu et al, 2008). For every 5% increase in infarct size, there is a 19% increase risk of all-cause mortality, 20% increase risk of heart failure hospitalization, and a 20% increase in the combined endpoint of death and heart failure hospitalization (Stone et al, 2016). CMR is considered the gold standard for the evaluation of infarct size and is considered the most relevant endpoint in cardioprotection trials (Hausenloy et al, 2013).

3.2.3.2 Rationale for Secondary Endpoints

Safety and tolerability of MEDI6012 as measured by the incidence of TEAEs, and TESAEs, and immunogenicity measured by ADAs, and nAbs over time to last study visit (Days 70-84), will support further drug development.

EF measured by cine magnetic resonance (MR) imaging at 10-12 weeks post-MI compared to placebo was selected since EF is a well-established measurement of the systolic function of

the LV. Additionally, pharmacologic improvements in EF have been linked to decreases in mortality and heart failure hospitalizations (Breathett et al, 2016; Kramer et al, 2010). EF will be calculated as the ratio of stroke volume divided by end-diastolic volume.

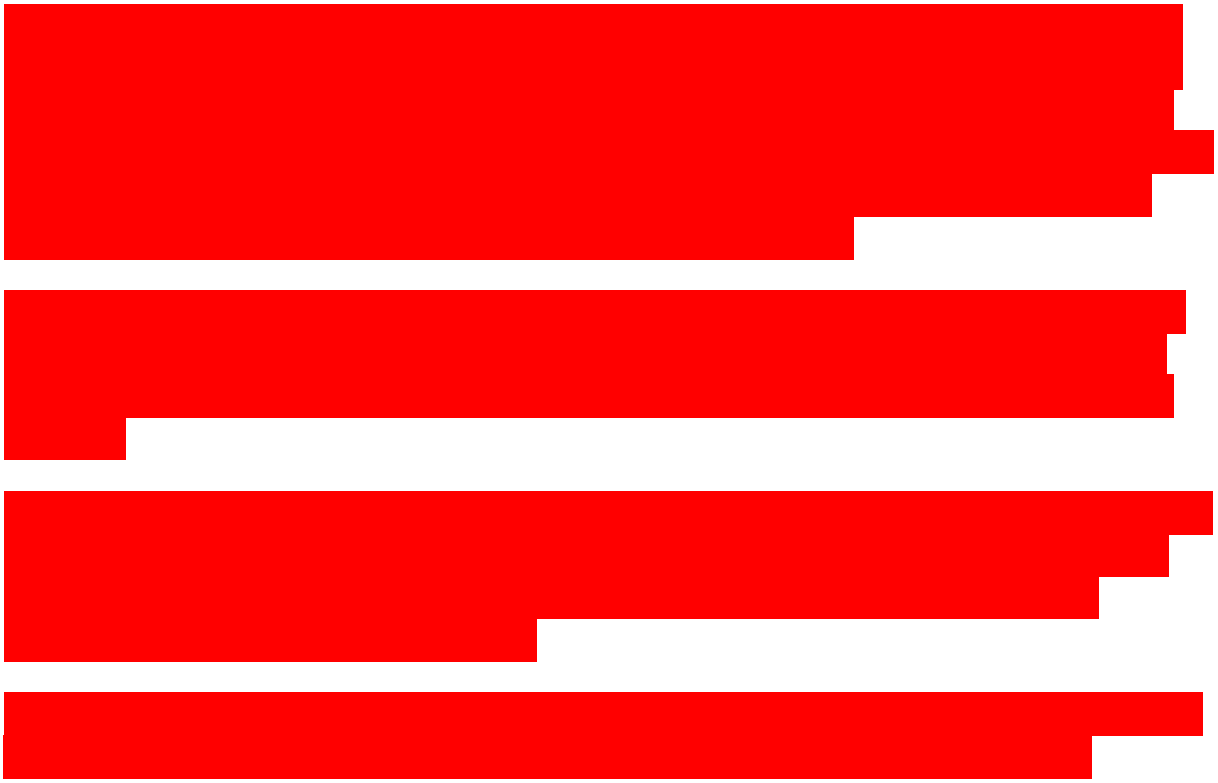
Change in non-calcified plaque volume (NCPV) in the coronary arteries from index computed tomography angiography (CTA) to 10-12 weeks post-MI compared with placebo was selected as a secondary endpoint over calcified and total plaque volume. When studied in ACS, specifically non-STEMI ACS, NCPV is a better predictor of major adverse cardiac events when compared to Agatston calcium score and total plaque volume (Kristensen et al, 2011). NCPV will be measured in all vessels ≥ 2 mm in diameter and expressed in mm^3. Coronary segments with stents or otherwise deemed uninterpretable will be excluded from analysis.

Myocardial mass and LV volumes at end-systole and end-diastole are included since they are well-established predictors of clinical outcomes and will be measured by CMR. Ventricular volumes and myocardial mass will be measured in mL and g, respectively, and indexed to body surface area.

3.2.3.3 Rationale for PK Endpoints

Serum concentration of MEDI6012 (mass) will be used to characterize MEDI6012 exposure. The PK may also be used to develop dose-exposure-PD response relationships to help inform dose selection for future clinical studies.

3.2.3.4 Rationale for Exploratory Endpoints



[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 540 subjects are planned as described in Section 3.1.2.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Men and women without child-bearing potential (for definitions see Section 10.2) aged 30-80 years of age who are capable and willing to provide informed consent.
2 Acute STEMI diagnosed by ST elevation (≥ 0.1 mV) in 2 contiguous leads
3 Planned for pPCI
4 Ischemic symptoms for ≤ 6 hours
5 Capable of completing study visits

4.1.3 Exclusion Criteria

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

1 Pre-randomization cardiogenic shock or cardiopulmonary resuscitation
2 Fibrinolytic administration for index event
3 Known prior MI or prior coronary artery bypass graft (CABG) surgery
4 Known pre-existing cardiomyopathy
5 History of anaphylaxis
6 Suspected non-thrombotic etiology (ie, vasospasm, dissection, Takotsubo cardiomyopathy)

7 Other condition or severe illness that the investigator feels would limit the prognosis of the patient (eg, malignancy with life-expectancy < 3 months) or would make the patient otherwise unsuitable for enrollment (eg, pose a hazard or undue burden to the patient [known chronic renal or hepatic impairment, recent (< 30 days), cerebrovascular accident or transient ischemic attack] unable to complete study visits)

8 Known contraindication to MR imaging (eg, metallic implant, claustrophobia, implantable cardioverter-defibrillator [ICD], pacemaker), known CrCl $\leq$ 30 mL/min (Cockcroft Gault equation)

9 Pregnant women and/or breastfeeding women.

10 Current or previous participation within the last 30 days in a study using an investigational therapy or device

4.1.4 Additional Study Procedure Requirements

After randomization and prior to study-related imaging procedures, subjects will be required to meet the following criteria for CMR and CTA imaging.

Administration of Gadolinium Contrast for Cardiovascular MRI

MRI is allowed if there is no contraindication to MR imaging (eg, metallic implant, claustrophobia, ICD, pacemaker), but in order for subjects to receive gadolinium contrast, the following requirements must also be met:

1 CrCl $\geq$ 30 mL/min (Cockcroft Gault equation) within 7 days prior to the procedure

2 No known allergy to gadolinium contrast agents

Coronary CTA

1 CrCl $\geq$ 60 mL/min (Cockcroft Gault equation) within no more than 6 hours prior to index CTA and no more than 7 days prior to follow up CTA

2 Women must be 40 years of age or older

3 No known allergy to iodinated contrast

4 No known history of contrast induced nephropathy

5 No contraindication to heart rate lowering using betablockers to allow for high quality, low-radiation dose CTA (per-protocol). Please note, if heart rate is well-controlled allowing for a high quality, low radiation CTA without betablocker, then a contraindication to betablocker does not exclude the subject from coronary CTA.

6 For follow-up CTA at the end of the study, subjects would need to have undergone index CTA

4.1.5 Subject Enrollment and Randomization

Subjects will be enrolled while they are having an acute STEMI. The time for consent, screening, randomization, and administration of the first dose of investigational product in this setting will require an efficient process that accomplishes this in a timely fashion. Typically, the standard of care in acute STEMI is to have a door-to-balloon time of 90 minutes or less from when a patient enters a healthcare facility (door time) to when they have pPCI (balloon time). Therefore, acute STEMI trials often use a short form consent (or verbal assent, depending on local regulations) to consent patients for the first dose of investigational product. This study will allow informed consent/verbal processes that include: 1) one-stage informed consent where full informed consent is obtained prior to required study procedures, 2) two stage informed consent where the first stage, obtained prior to study procedures, uses a short-form consent that covers day 1 dosing and study procedures and a second stage informed consent, obtained prior to all subsequent procedures, that covers the remaining doses and study procedures, and 3) two stage informed consent where the first stage uses verbal consent, obtained prior to study procedures, that covers day 1 dosing and study procedures and a second stage informed consent, obtained prior to all subsequent procedures, that covers the remaining doses and study procedures. Verbal and short-form consent will only be applied when applicable to local regulations and standards. A one- or two-stage informed consent, that may or may not include a verbal option (depending on local regulations), will be undertaken for this study, depending on local standards and preferences. In addition, next of kin or an impartial physician may be included in the consenting process according to local regulations and standards. A subject may consent for study procedures that occur on Day 1 and decline subsequent consent of further study procedures.

Study participation begins on study Day 1 (ie, a subject is “enrolled”) once the first consent, whether written or verbal is obtained. Following first consent, evaluations to assess study eligibility (inclusion/exclusion criteria) will be performed. A SID (subject identification) number will be used to identify the subject. Dose 1, as assigned following randomization by a central system (eg, an interaction response system [IXRS], which includes interactive voice response system and interactive web response system) may be given once the pre-screening procedures have been completed.

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 and/or are not randomized), 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.

Randomization will be stratified by infarct location, ensuring balanced randomization to active treatment vs placebo within the anterior group and the non-anterior MI groups. In

addition, the distribution of subjects with anterior vs non-anterior MIs will be monitored over the course of the study. The goal is that >50% of the final randomized population will be anterior MI. Therefore, the number with non-anterior MI will be monitored via the IXRS and capped by the study team.

4.1.6 Withdrawal from the Study

Subjects are free to withdraw consent from the study (which means permanent discontinuation of investigational product and all follow-up assessments) at any time without prejudice to further treatment. Discontinuation of investigational product in and of itself is not considered withdrawal of consent.

Withdrawal of consent should only occur if the subject refuses any further assessments or contact whatsoever. Subjects who do not want regular in-person follow-up after cessation of investigational product should be offered alternative methods of follow-up including periodic telephone follow-up, contact at study closure, or assessment of health status via treating physicians or medical records. Such subjects would then not be viewed as withdrawal of consent.

The investigator must explain to the subject all options for continued participation, and document which options were refused by the subject and the reason for refusal. Withdrawal of consent to all follow-up must be ascertained and documented in writing by the investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF and medical records.

Subjects who withdraw consent to all follow-up will be asked about the reason(s), and will be assessed for the presence of any adverse events. For confirmed withdrawal of consent subjects, direct ascertainment of health status at the end of the study or vital status via public records will be performed in compliance with local privacy laws/practices.

4.1.7 Discontinuation of Investigational Product

Subjects are free to discontinue investigational product at any time, without prejudice to further treatment. Subjects who choose to discontinue investigational product are expected to continue in the study according to the schedule of study procedures for the remainder of the study.

The investigator and/or medical monitor may determine that an individual subject will not receive any further investigational product if any of the following occur in that subject:

1 Safety reasons as judged by the investigator and/or sponsor where continued treatment may put patient at undue risk, eg,

(a) Severe adverse immune reaction (e.g., anaphylactic-type reactions, immune complex disease) deemed related to investigational product.

(b) Infusion site reaction assessed as intolerable and related to investigational product.

2 Incorrectly randomized patient in whom inclusion/exclusion criteria violation would put the patient at undue risk.

3 Before or after initial dosing, it is discovered that the subject has no coronary artery disease (obstructive or non-obstructive) on invasive angiography.

4 Subject noncompliance that, in the opinion of the investigator or Sponsor, warrants treatment discontinuation for safety reasons (e.g., refusal or inability to adhere to scheduled visits).

5 Pregnancy in any female subject.

Cases where subjects are incorrectly randomized (ie the subject does not meet the required inclusion/exclusion criteria for the study) should be discussed with the TIMI Hotline prior to any actions being taken with discontinuation of investigational product or follow up. Upon review by the TIMI Hotline or medical monitor, subjects found after randomization to have met an exclusion that is unrelated to safety may continue study treatment. For patients randomized but subsequently determined to not have a qualifying STEMI and who are therefore not planned to receive continued study treatment, follow up may be restricted to safety only at the discretion of the Sponsor. For subjects who never receive investigational product, follow up will consist of a minimum of a single phone call at the end of the study; however, visits are allowed at the discretion of the subject and investigator.

Discontinuation of investigational product does not mean discontinuation of follow-up. 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 specifically from further study participation (Section 4.1.6), the subject is lost to follow-up (Section 4.1.8), or the subject is enrolled in another clinical study.

A subject who decides, and/or is recommended by treating physician or the investigator to permanently discontinue investigational product, will always be asked about the reason(s) for discontinuation and about the presence of any AEs. All efforts must be taken to ensure that the subject will be seen and assessed by an investigator and, as scheduled for other subjects, all end-of-treatment visit assessments should be completed at the time of discontinuation of investigational product.

Following discontinuation of investigational product, regularly scheduled study visits and follow-up procedures are expected to continue as planned. The follow-up visits should preferably be in-person and should include all procedures and assessments listed in the Schedules of Study Procedures. Alternatively, if the subject does not agree to the in-person

follow-up visit option, a modified follow-up through regular telephone contacts or a contact at study closure should be arranged. Regardless of whether a subject comes to the site for an in-person follow-up visit or is contacted by telephone, once a possible event that may require adjudication is noted, medical records must be obtained and submitted to the CEC for adjudication of the event.

In the setting of acute MI, transaminases used to monitor for liver toxicity (alanine transaminase [ALT] and aspartate transaminase [AST]) can be elevated and of cardiac origin. Section 10.6 describes actions to be taken.

4.1.8 Lost to Follow-up Subjects

To prevent subjects being lost to follow-up, their contact details, including next of kin contacts should be collected by the site staff or representative. The investigator should educate the subject on the importance of contact with the investigator throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for subjects who are potentially lost to follow-up. A subject will be classified as confirmed lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, email, certified letter, or through subject locator agencies (if allowed by national regulation). Where permissible by local law, the informed consent forms will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost subjects using publicly available sources.

4.1.9 Replacement of Subjects

Subjects who are discontinued from further dosing or follow-up procedures from the study, or who withdraw their informed consent to all follow-up, prior to the end-of-study visit may be replaced, if deemed necessary, by the medical monitor to ensure that safety, PK, PD, and imaging data are collected from a sufficient number of subjects. The medical monitor should be notified within 48 hours if a subject is discontinued from the study or withdraws consent to all follow-up. A determination whether to replace the subject will be made jointly between the principal investigator and medical monitor.

4.1.10 Withdrawal of Informed Consent for Data and Biological Samples

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 safety of the subject.

Samples Obtained for Future Research

Samples obtained for 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 the 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 future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) 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 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 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 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, Treatment, and Follow-up Periods

Due to the acute nature of the first treatment in this study, the screening period takes place on study Day 1, immediately prior to receiving investigational product. All procedures to be conducted during the screening, treatment, and follow-up periods are presented in the Schedule of Study Procedures (Table 8 and Table 9).

4.2.1.1 Study Procedure Modifications in Response to the COVID-19 Pandemic

The modifications listed below are designed to enable safety monitoring of subjects enrolled in the trial through an extended blood sampling window as well as to maintain trial integrity for the primary and secondary endpoints by enrolling all remaining patients in Cohort B (to obtain both the CMR and CTA as well as extended dosing data), which has had a greater dropout rate further impacted by COVID-19.

1 If the Visit 6 (Day 70-84) follow-up visit cannot be conducted in person due to the coronavirus disease (COVID-19) pandemic, the following study procedure modifications are permissible:

(a) Where possible, a subject should return to the clinic as soon as possible after the planned Visit 6 (Day 70-84) visit but no more than 150 days post dose 1 for blood sample collection (except for future use samples), including immunogenicity, PK, and PD, as listed in the Schedule of Study Procedures (Table 8 and Table 9) for Day 70-84.

(b) However, assessment of AEs/SAEs and concomitant medications should be done via telephone contact within the originally specified window for Visit 6 (ie, Day 70-84).

(c) If a subject returns to the clinic for blood sample collection within the extended window, any AEs/SAEs that occur between the telephone contact and the date of this visit should also be recorded.

The modifications in study procedures listed above (1a-c) are only permitted due to COVID-19-related constraints impacting the subject, site, or health system; otherwise, the study procedures should be conducted within the timeframes originally specified in the Schedule of Study Procedures (Table 8 and Table 9).

2 All subjects will be randomized into Cohort B [redacted] Regimen). Subjects will be randomized in a 1:1 ratio to receive MEDI6012 or placebo. This modification will remain in place until the end of the study.

Table 8 Treatment Period and Follow-up Procedures: Cohort A [redacted] Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (Inpatient)						V2	V3	V4	V5	V6
Procedure / Study Day	Day 1					Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (±1 day) Phone	Day 17 (± 1 day)	Day 24 (± 1 day) Phone	Day 31 (± 1 day)	Days 70-84 [a]
	Screening	Pre-PCI	[redacted]	[redacted]	[redacted]							
Written or verbal informed consent	X											
Verify eligibility criteria	X											
Screening ECG (clinical) [b]	X											
Abbreviated medical history review	X											
Assignment of SID number and randomization		X [c]										
Record vital signs	X [d]	X [e]	X [f]		X		X [e,f]					X
Investigational product administration		[redacted]										
Full informed consent, if not done at screening, for Dose 2 and procedures on or after Day 3						X						
Full medical history review						X						
Physical examination (full)						X						X

Table 8 Treatment Period and Follow-up Procedures: Cohort A ([redacted] Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (Inpatient)						V2	V3	V4	V5	V6
Procedure / Study Day	Screening	Day 1 Pre-PCI	Day 1 [redacted]	Day 1 [redacted]	Day 1 [redacted]	Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (±1 day) Phone	Day 17 (± 1 day)	Day 24 (± 1 day) Phone	Day 31 (± 1 day)	Days 70-84 [a]
Assess for infusion site reaction		[redacted]										
Assessment of AEs/SAEs [i]		X	X				X	X	X	X	X	X
Post-dose observation [j]		[redacted]										
Concomitant medications	X	X [c]	X				X	X	X	X	X	X
Weight						X						X
Height						X						
12-lead ECG												X
Serum chemistry, creatinine [k], GLDH, CK and troponin		X [c]					X [e]		X		X	X
Hematology, cystatin C, NT-proBNP		X [c]					X [e]					X
PK blood sample		X [c]	X [l]				X [e,f]		X		X	X
PD blood sample		X [c]		X [m]			X [e,m]		X [m]		X [m]	X [m]
Immunogenicity blood sample		X [c]							X		X	X
LH/FSH							X					

Table 8 Treatment Period and Follow-up Procedures: Cohort A [redacted] Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (Inpatient)						V2	V3	V4	V5	V6
Procedure / Study Day	Day 1					Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (±1 day) Phone	Day 17 (± 1 day)	Day 24 (± 1 day) Phone	Day 31 (± 1 day)	Days 70-84 [a]
	Screening	Pre-PCI [redacted]	[redacted]	[redacted]	[redacted]							
Future use blood sample, if consented [n]		X [c]					X [e,m]					X [m]
Verify additional procedure requirements for CMR imaging (10-12 week [70-84 days post Dose 1] follow-up imaging)												X
CMR												X [o]

AE = adverse event; CCU = cardiac care unit; CK = creatine kinase; CK-MB = creatine kinase-MB; CMR = cardiovascular magnetic resonance (imaging); COVID-19 = coronavirus disease; CTA = computed tomography angiography; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; GLDH = glutamate dehydrogenase; LH = luteinizing hormone; NT-proBNP = N-terminal pro b-type natriuretic peptide; PCI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SID = subject identification; TIMI = Thrombolysis in Myocardial Infarction; V = visit

[a] See Section 4.2.1.1 for COVID-19 permissible modifications.

[b] Only if diagnostic ECG not of sufficient quality

[c] Within 2 hours prior to PCI [redacted]

[d] Where applicable for the screening vital signs, the vital signs taken as part of standard of care can be used if taken within 30 minutes [redacted] due to the acute nature of the study. The screening vital signs assessments and the [redacted] vital signs assessments do not need to be duplicated as long as one assessment is made within 30 minutes prior to [redacted]. If the [redacted] vital signs measurements are more than 30 minutes prior to [redacted] these must be repeated.

[e] [redacted]

[f] 10 minutes (± 5 minutes) [redacted]

Table 8 Treatment Period and Follow-up Procedures: Cohort A [redacted] Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (Inpatient)						V2	V3	V4	V5	V6
Procedure / Study Day	Day 1					Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (±1 day) Phone	Day 17 (± 1 day)	Day 24 (± 1 day) Phone	Day 31 (± 1 day)	Days 70-84 [a]
	Screening	Pre-PCI and Dose 1	Immediately Post-Dose/PCI	1-1.5 hr Post-Dose	12-18 hr Post-Dose							

[g] Should be prior to PCI, preferably >10 minutes prior

[h] Visits or missed doses that will potentially fall outside of the window specified in this table must be discussed with the TIMI Hotline as early as possible in order to adjust visit/dosing schedule.

[i] AE collection begins after randomization and lasts until the end of the study. SAE collection begins after the subject signs the informed consent document and lasts until the end of the study.

[j] For [redacted] observation, subjects will be monitored for 2 hours in a location with personnel trained in Adult Advanced Life Support with proper resuscitation equipment available.

[k] Local values for creatinine can be used for imaging eligibility (in addition to collecting central samples). Creatinine values must be measured and reviewed prior to CMR and CTA within the timeframe specified in Section 4.1.4.

[l] Within 20 minutes [redacted]

[m] Fasting for 1-1.5 hours at the 1-1.5 hour timepoint, fasting for ≥6 hours on Days 3-70

[n] Future use samples will only be obtained if the subject gives consent. Aliquots of future use samples will be stored at the core laboratory and the TIMI biobank.

[o] In the case of a clinical indication for an intracardiac device (ie, pacemaker, implantable cardioverter-defibrillator), the CMR can be scheduled at an earlier time point, but not prior to 30 days [redacted]. In addition, if the end of study CMR is determined to be of inadequate image quality by the CMR core laboratory, the subject may return for a repeat CMR within 4 weeks of the end of study window (up to 112 days post Dose 1).

Table 9 Treatment Period and Follow-up Procedures: Cohort B (Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (In-patient)						V2	V3	V4	V5	V6
Procedure / Study Day	Screening	Day 1 Pre-PCI	Day 1	Day 1	Day 1	Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (± 1 days)	Day 17 (± 1 days)	Day 24 (± 1 days)	Day 31 (± 1 days)	Day 70-84 [a]
Written or verbal informed consent	X											
Verify eligibility criteria	X											
Screening ECG (clinical) [b]	X											
Abbreviated medical history review	X											
Assignment of SID number and randomization		X [c]										
Record vital signs	X [d]	X [e]	X [f]		X		X [e,f]	X [e,f]	X [e,f]	X [e,f]	X [e,f]	X
Investigational product administration												
Full informed consent, if not done at screening, for Doses and procedures on or after Day 3						X						
Full medical history review						X						
Physical examination (full)						X						X
Assess for infusion site reaction												
Assessment of AEs/SAEs [i]		X	X				X	X	X	X	X	X
Post-dose observation [j]												
Concomitant medications	X	X [c]	X				X	X	X	X	X	X

Table 9 Treatment Period and Follow-up Procedures: Cohort B [redacted] Regimen)

Study Period		Treatment Period										Follow-up
Visit Number		V1 (In-patient)						V2	V3	V4	V5	V6
Procedure / Study Day	Day 1					Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (± 1 days)	Day 17 (± 1 days)	Day 24 (± 1 days)	Day 31 (± 1 days)	Day 70-84 [a]
	Screening	Pre-PCI	[redacted]	[redacted]	[redacted]							
Weight						X						X
Height						X						
12-lead ECG												X
Serum chemistry, creatinine [k], GLDH, CK and troponin		X [c]					X [e]		X [e]		X [e]	X
Hematology, cystatin C, NT-proBNP		X [c]					X [e]					X
PK blood sample		X [c]	X [l]				X [e,f]		X [e,f]		X [e,f]	X
PD blood sample		X [c]		X [m]			X [e,m]		X [e,m]		X [e,m]	X [m]
Immunogenicity blood sample		X [c]							X		X	X
LH/FSH							X					
Future use blood sample, if consented [n]		X [c]					X [e,m]					X [m]
Verify additional procedure requirements for CTA imaging							X [k]					
Verify additional procedure requirements for CMR and CTA imaging (10-12 week [70-84 days post Dose 1] follow-up imaging)												X [k]

Table 9 Treatment Period and Follow-up Procedures: Cohort B [redacted] Regimen)

Study Period		Treatment Period									Follow-up
Visit Number		V1 (In-patient)						V2	V3	V4	V5	V6
Procedure / Study Day	Day 1					Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (± 1 days)	Day 17 (± 1 days)	Day 24 (± 1 days)	Day 31 (± 1 days)	Day 70-84 [a]
	Screening	Pre-PCI [redacted]										
CMR												X [o]
Coronary CTA							X [p]					X [q]

AE = adverse event; CABG = coronary artery bypass graft; CCU = cardiac care unit; CK = creatine kinase; CK-MB = creatine kinase-MB; CMR = cardiovascular magnetic resonance (imaging); COVID-19 = coronavirus disease; CTA = computed tomography angiography; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; GLDH = glutamate dehydrogenase; LH = luteinizing hormone; NT-proBNP = N-terminal pro b-type natriuretic peptide; PCI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SID = subject identification; TIMI = Thrombolysis in Myocardial Infarction; V = visit

[a] See Section 4.2.1.1 for COVID-19 permissible modifications.

[b] Only if diagnostic ECG not of sufficient quality

[c] Within 2 hours prior to PCI [redacted]

[d] Where applicable for the screening vital signs, the vital signs taken as part of standard of care can be used if taken within 30 minutes [redacted] due to the acute nature of the study. The screening vital signs assessments and the pre-dose vital signs assessments do not need to be duplicated as long as one assessment is made within 30 minutes prior to [redacted]. If the [redacted] vital signs measurements are more than 30 minutes prior [redacted] these must be repeated.

[e] [redacted]

[f] 10 minutes (± 5 minutes) [redacted]

[g] Should be prior to PCI, preferably >10 minutes prior

[h] Visits or missed [redacted] that will potentially fall outside of the window specified in this table must be discussed with the TIMI Hotline as early as possible in order to adjust [redacted] schedule.

[i] AE collection begins after randomization and lasts until the end of the study. SAE collection begins after the subject signs the informed consent document and lasts until the end of the study.

[j] For [redacted] subjects will be monitored for 2 hours in a location with personnel trained in Adult Advanced Life Support with proper resuscitation equipment available.

[k] Local values for creatinine can be used for imaging eligibility (in addition to collecting central samples). Creatinine values must be measured and reviewed prior to CMR and CTA within the timeframe specified in Section 4.1.4.

Table 9 Treatment Period and Follow-up Procedures: Cohort B (Regimen)

Study Period		Treatment Period									Follow-up
Visit Number		V1 (In-patient)						V2	V3	V4	V5	V6
Procedure / Study Day	Screening	Day 1 Pre-PCI				Anytime between Days 1-3	Day 3 (48 ± 8 hours)	Day 10 (± 1 days)	Day 17 (± 1 days)	Day 24 (± 1 days)	Day 31 (± 1 days)	Day 70-84 [a]

[l] Within 20 minutes

[m] Fasting for 1-1.5 hours at the 1-1.5 hour timepoint, fasting for ≥6 hours on Days 3-70

[n] Future use samples will only be obtained if the subject gives consent. Aliquots of future use samples will be stored at the core laboratory and the TIMI biobank.

[o] In the case of a clinical indication for an intracardiac device (ie, pacemaker, implantable cardioverter-defibrillator), the CMR can be scheduled at an earlier time point, but not prior to 30 days post Dose 1. In addition, if the end of study CMR is determined to be of inadequate image quality by the CMR core laboratory, the subject may return for a repeat CMR within 4 weeks of the end of study window (up to 112 days post Dose 1).

[p] Index CTA will preferably be performed between 48-72 hours post Dose 1 (may be done up to 5 days post Dose 1) but no earlier than 40 hours post Dose 1. The index CTA scan should not be performed if CABG surgery was carried out prior to the index CTA time point or if one is planned.

[q] Follow-up coronary CTA imaging will be done only for subjects with index CTA and can occur on a separate visit from CMR imaging, if needed for scheduling purposes. In subjects who have CABG surgery planned, index and follow-up CTA should not be performed. If a subject completes 6 doses of investigational product and is scheduled for CABG surgery, follow-up CTA can be performed earlier to ensure that CTA occurs prior to the CABG surgery, upon approval from the TIMI Hotline or Sponsor. For subjects who have received fewer than 6 doses of investigational product or if CABG surgery has already been performed prior to the CTA time point, the CTA scan should not be performed.

4.2.2 Extended Follow-up Period for Subjects Testing Positive for Anti-Drug Antibodies Plus > 30% Decrease from Baseline in HDL-C at Day 70 to 84 or Presence of a Neutralizing Antibody on Day 70 to 84

Table 10 shows all procedures to be conducted during the Extended Follow-up period for subjects testing positive for ADAs plus > 30% decrease from baseline in HDL-C at Day 70 to 84) or presence of nAb on Day 70 to 84). Assessments should be performed in the order shown in the table. During the Extended Follow-up period, if either the ADA test result becomes negative or the HDL-C is no longer > 30% decreased compared with baseline, the subject does not need to return for any additional Extended Follow-up visit(s) and will be considered as having completed the Extended Follow-up period.

Table 10 Extended Follow-up Procedures for Subjects Testing Positive for Anti-Drug Antibodies Plus > 30% Decrease from Baseline in HDL-C at Day 70 to 84 or Presence of a Neutralizing Antibody on Day 70 to 84

Study Period	Extended Follow-up Period		
Visit Number	**Visit 7**	**Visit 8**	**Visit 9**
Procedure / Study Day or Week	**Week 25 ±2 Week**	**Week 39 ±2 Week**	**Week 52 ±2 Week**
Targeted Physical examination	X	X	X
Vital signs	X	X	X
PK blood sample	X	X	X
Immunogenicity blood sample	X	X	X
PD blood sample	X	X	X
Assessment of AEs/SAEs	X	X	X
Concomitant medications	X	X	X

AE = adverse event; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event.

4.3 Description of Study Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. 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 (with the exception of Visit 1 [Day 1], where the order of vital signs and then blood draws may not be possible due to the acute nature of this visit and as the subject may have invasive blood pressure measurements). The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.3.1 Medical History and Physical Examination, Weight, and Vital Signs

A brief and targeted medical history screening will be performed focusing on inclusion/exclusion criteria.

A full physical examination will be conducted anytime between Day 1 and 3 prior to administration of [redacted] and at the final study visit (Day 70-84).

Physical examinations will be performed by a physician or a qualified designee with examination of the following body systems: respiratory; CV; gastrointestinal; musculoskeletal; focused neurologic (to the extent of determining whether or not the subject is willing and able to cooperate with the required study procedures in the investigator's judgment); dermatologic; hematologic/lymphatic. When a targeted physical exam is required, evaluation of selective body systems will be at the judgement of the physician or qualified designee based on subject presentation.

Any focal deficit identified at baseline should be documented in the electronic case report form (eCRF). Clinically significant abnormal findings will be recorded at baseline and follow-up.

Weight will be measured immediately following PCI once feasible with regards to equipment availability and appropriateness for the patient's clinical status. Height can be measured anytime between Days 1 and 3 and weight repeated on the days specified in the Schedules of Procedures.

Vital sign measurements (blood pressure [BP], respiratory rate, heart rate, and body temperature) will be measured at the time points specified in the Schedules of Procedures. Invasive blood pressure measurements may be recorded when intra-arterial monitoring is available. When non-invasive blood pressures are taken, the subject should be supine and the subject's arm must be at the same height (at the level of their heart) during each BP measurement.

Subjects should refrain from smoking or drinking caffeinated beverages within 4 hours prior to vital signs measurements.

4.3.2 ECG

ECGs will be conducted at the time points presented in the Schedules of Procedures.

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. Scheduled ECGs and any ECGs done for safety purposes should be scanned for digital storage.

4.3.3 Systemic/Local Tolerability

Site staff will check the injection site(s) for local reactions and assess for systemic reactions at the times specified in the Schedules of Procedures. Local and systemic reactions will be recorded as AEs according to the criteria described in Section 5.4.

4.3.4 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 will be performed in a central clinical laboratory, unless specified as "local labs" in the schedule of procedures. Abnormal laboratory results should be followed up at the principal investigator's discretion.

The following clinical laboratory tests will be performed:

Serum Chemistry

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Gamma glutamyl transferase
- Creatinine
- Glucose
- Albumin
- Blood urea nitrogen

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell count with automated differential (by central laboratory)
- Red blood cell count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

Other Laboratory Tests

- Cystatin C
- Glutamate Dehydrogenase
- Creatine Kinase (CK)
- Troponin
- NT-proBNP
- Luteinizing Hormone [a]

- Follicle Stimulating Hormone [a]

[a] Female subjects only.

4.3.5 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of MEDI6012 in serum. Sampling within the specified time window around the specified time will not be considered a protocol deviation but the exact time of sampling must be recorded. The blood samples for PK taken at Visit 3 (Day 17), Visit 5 (Day 31) and Visit 6 (Day 70-84) from Cohort A, and Visit 6 (Day 70-84) from Cohort B will be collected and will only be measured for MEDI6012 PK if the resulting analyses are deemed to be useful to further evaluation of MEDI6012 based on emerging study data (ie, assessment of immunogenicity). PK of MEDI6012 in serum will be measured by immunoassay.

4.3.6 Pharmacodynamic Evaluation and Methods

Blood samples for key [redacted] will be collected at time points as presented in the Schedules of Procedures. The PD markers of primary interest are [redacted]; however, additional lipids and lipoproteins will also be collected and analyzed to fully describe the effect of MEDI6012 on the cholesterol pathway including but not limited to other measures in the lipid profile. Sampling within the specified time window around the specified time will not be considered a protocol deviation but the exact time of sampling must be recorded.

PD blood sample for key [redacted]

4.3.7 Immunogenicity Evaluation and Methods

As with any [redacted], administration of MEDI6012 may [redacted]. Because MEDI6012 is the [redacted]

Blood samples for ADA will be collected at time points specified in the Schedules of Procedures. A screening assay will be used to determine ADA-positive samples. This will be in the form of a traditional ligand-binding “bridging” assay using electrochemiluminescence.

Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI6012 investigational product. Titer evaluation will be performed on samples that are confirmed positive for ADA, and these samples will be further characterized as either a neutralizing or a non-nAb response using an enzymatic assay that determines the ability of LCAT to esterify a fluorescent analogue of cholesterol.

In addition, subjects whose follow up (Day 70-84) immunogenicity sample is confirmed as ADA positive plus > 30% decrease from baseline in HDL-C or presence of a nAb will return to the study site on Weeks 25, 39, and 52 for additional assessments (Table 10). However, during the Extended Follow-up period if the ADA test result becomes negative or the HDL-C is no longer > 30% decreased compared with baseline, the subject does not need to return for additional Extended Follow-up visit(s) and will be considered as having completed the Extended Follow-up period. These additional visits and assessments will be reported as an addendum to the clinical study report.

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

4.3.8 Imaging Biomarker Evaluation and Methods

Research CMR and coronary CTA imaging will be used for the primary endpoint and select secondary endpoints. CMR and coronary CTA imaging will be analyzed in separate, blinded, and independent core laboratories. Imaging personnel and equipment will undergo certification by the core laboratories. Clinical invasive angiograms will be evaluated locally by the principal investigator and de-identified images will be transferred to a central repository for future analysis, if necessary.

CMR

Subjects randomized to the [redacted] regimens will undergo CMR imaging at Visit 6 (Day 70-84). If the end of study CMR is determined to be of inadequate image quality by the CMR core laboratory, the subject may return for a repeat CMR within 4 weeks of the end of study window (up to 112 days post Dose 1). If CMR and CTA are scheduled on the same day, CMR should always be performed before coronary CTA and before the administration of betablockers for coronary CTA. For CMR, subjects will be required to meet the Additional Study Requirements listed in Section 4.1.4 including no contraindication to MR imaging (eg, metallic implant, claustrophobia, ICD, pacemaker) and, for the administration of gadolinium-based contrast, confirmation of CrCl ≥ 30 mL/min (Cockcroft Gault equation) is required. Prior to the scan, subjects will have a peripheral IV line placed for the administration of gadolinium-based contrast. Late Gadolinium-enhanced images will be obtained 15 minutes after an IV bolus injection of ionic, non-linear gadolinium contrast agent to identify regional fibrosis. Scan duration is estimated to be approximately 1 hour. The details of the imaging

protocol will be outlined in the CMR imaging manual. The imaging protocol will be refined to accommodate differences in imaging platforms at sites. The following imaging methods and evaluations will be performed:

Cine MRI for Quantification of LV Function and Volumes

- Left Ventricular Ejection Fraction
- [redacted]
- Left Ventricular End Diastolic Volume
- Left Ventricular End Systolic Volume
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Late-gadolinium Enhancement MRI for Myocardial Scar Quantification

- [redacted]
- [redacted]
- Scar Burden Expressed as a percentage of LV Mass [redacted]
- [redacted]
- [redacted]
- [redacted]

Coronary CTA

Coronary CTA will be performed in subjects randomized to the [redacted] regimen only during the inpatient hospitalization. The index CTA will preferably be performed between 48-72 hours post Dose 1 (may be done up to 5 days post Dose 1) but no earlier than 40 hours post Dose 1. The follow-up CTA will be performed 70-84 days following randomization. If CTA and CMR are done on the same day, CTA should always be performed after CMR. Follow-up coronary CTA imaging will be done only for subjects with index CTA and can occur on a separate visit from CMR imaging, if needed for scheduling purposes. In subjects who have CABG surgery planned, index and follow-up CTA should not be performed. If a subject completes [redacted] of investigational product and is scheduled for CABG surgery, follow-up CTA can be performed earlier to ensure that CTA occurs prior to the CABG surgery, upon approval from the TIMI Hotline or Sponsor. For subjects who have received fewer than [redacted] of investigational product or if CABG surgery has already been performed prior to the CTA time point, the CTA scan should not be performed. Subjects will be required

to meet the Additional Study Requirements listed in Section 4.1.4, including confirmation of an estimated CrCl ≥ 60 mL/min (Cockcroft Gault equation). Subjects will undergo heart rate lowering, if necessary, with oral and/or IV betablockers at least 60 minutes prior to the scan. Additional betablocker given prior to CTA for the purposes of CTA imaging should not be given prior to CMR. Subjects will have a 16-18 gauge IV placed, preferably, in the right antecubital fossa. Subjects will undergo a contrast-enhanced CTA performed with 50-100 mL of iodinated contrast. Scan coverage will extend from the right pulmonary artery to the diaphragm, to cover the full extent of the heart and coronary arteries. Imaging will be performed with prospective-ECG triggering, when feasible to lower radiation dose. For most subjects undergoing prospective-ECG triggered CTA, participation in the study will be associated with an estimated cumulative radiation exposure of approximately 11 mSv with a maximum dose of about 16 mSv (median radiation exposure per exam: 5.6 mSv, range 3-8 mSv). Follow-up and radiation safety escalation plan will occur in the event of single CT exposure in excess of 12 mSv. When prospective ECG-triggering is not feasible, secondary to higher heart rates or availability of technology, tube-current dose modulation will be used to limit radiation exposure. For subjects undergoing retrospective ECG-gated CTA with tube current modulation, participation in the study will be associated with an estimated cumulative radiation exposure of approximately 24 mSv with a maximum dose of about 30 mSv (median radiation exposure per exam: 12 mSv, range 8-15 mSv). Follow-up and radiation safety escalation plan will occur in the event of single CT exposure in excess of 15 mSv. Radiation dose will be estimated base on dose length product using a K factor of 0.014. Details of the imaging protocol will be outlined in the CTA imaging manual. The imaging protocol will be refined to accommodate differences in imaging platforms at sites. The following imaging methods and evaluations will be performed:

Measurements from Index and Follow-up CTAs

- [redacted]
- NCPV – in mm^3 [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Measurement from Index CTA, only:

- [redacted]
- [redacted]

4.3.9 Estimate of Volume of Blood to be Collected

The maximum volume of blood to be collected from each subject from Day 1 to the end of the study (Day 70-84) is estimated to be 225 mL. Subjects who consent to collection of future use samples will have an additional 60 mL of blood drawn throughout the study for a total blood volume estimation of 285 mL. Additional blood may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an AE. Furthermore, subjects with positive ADA test results plus > 30% decrease from baseline in HDL-C on Day 70 to 84 or presence of nAb on Day 70 to 84 will return on Weeks 25, 39, and 52 as applicable (depending on ADA and HDL-C results at these visits; Section 4.2.2) and have blood drawn for a volume estimated to be 25 mL per visit.

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 study may be terminated if, in the judgement of the sponsor, trial patients are placed at undue risk. The judgement may be based on recommendations from the Data Monitoring Committee (DMC)
2 Subject enrollment is unsatisfactory
3 Non-compliance that might significantly jeopardize the validity or integrity of the study
4 Sponsor decision to terminate development of the investigational product for this indication
5 Sponsor decision to terminate the study based on a planned futility analysis

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)/Independent Ethics Committee (IEC) 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/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product using designated distribution centers (Table 11).

Table 11 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI6012	MedImmune	[redacted]
Placebo	MedImmune	[redacted]

sWFI = sterile water for injection; w/v = weight by volume.

The MEDI6012 drug product [redacted]

Placebo is provided as a sterile colorless to slightly yellow solution.

Investigational product will be supplied to the site in cartons containing a single vial of either MEDI6012 drug product or placebo

Every investigational product vial assigned by the IXRS is to be used for dose preparation. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the vial within the carton).

4.5.1.1 Investigational Product Handling

Dedicated study staff preparing MEDI6012 and placebo should do so in an area that is out of sight of other study and clinical staff, wherever possible. Although this is a single-blind study, caution should be taken to not reveal any information regarding the randomized treatment administered to other catheterization laboratory staff or to the subject at all times. Once prepared for administration, MEDI6012 and placebo remain potentially indistinguishable.

The MEDI6012 investigational drug product and placebo must be stored at 2°C to 8°C (36°F to 46°F) at all times unless they are being used for dose preparation.

- MEDI6012 drug product
- The
- The

Each IV push dose will be delivered .

The MEDI6012 drug product and placebo do not contain preservatives and any unused portion must be discarded. The total in-use storage time from needle puncture of the first investigational product vial(s) to start of IV push administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from a new vial(s).

4.5.1.2 Investigational Product Inspection

The MEDI6012 drug product

If there are any defects noted with the investigational product, the Investigator and Site Monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.5) for further instructions.

4.5.1.3 Dose Preparation Steps

The dose of MEDI6012 or placebo for IV push administration must be prepared by the unblinded Investigational Product Manager or other qualified professional using aseptic technique. Only remove from storage the required MEDI6012 or placebo vials required for subject dosing.

MEDI6012 and placebo does not contain preservatives and any unused portion must be discarded. [redacted] Total in-use storage time from [redacted] of investigational product or needle puncture of the investigational product vial to start of IV push administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If in-use storage time before dose administration exceeds these limits, a new dose must be prepared from new vial(s).

For each MEDI6012 or placebo dose level delivered, Table 12 describes the delivery volume (mL), the required number of vials, and the number of syringes required for each dose.

Table 12 MEDI6012 and Placebo Product Delivery Volume and Vial Usage

Dose (mg)	Total Delivery Volume (mL)		Number of Vials Required		Syringes Required for Administration	
	MEDI6012	Placebo	MEDI6012	Placebo	MEDI6012	Placebo
[redacted]						

MEDI6012 or placebo is pooled in the appropriate syringe and dose prepared based on delivery volume. The IV push will be administered over 1-2 minutes and followed by a 10 mL normal saline flush.

4.5.1.4 Treatment Administration

The first day of dosing is considered Day 1. On Day 1, investigational product will be administered following verbal or written informed consent and should be prior to pPCI (as soon as possible prior to pPCI, defined as the time that the first angioplasty wire crosses the culprit lesion). In rare cases when investigational product is not administered prior to PCI in a subject who has already been randomized, then the first dose will be administered as soon as possible post-PCI. Subsequent doses will be administered following an overnight fast for a minimum of 6 hours, as soon as is practicable after rising. Subjects should be instructed on whether their regular medications can be taken while fasting.

Investigational product will be administered by IV push over approximately 1-2 minutes, inclusive of flush.

4.5.1.5 Monitoring of Dose Administration

Vital signs and ECG assessments will be performed according to the Schedules of Study Procedures.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, following Doses [redacted] (Cohort A) or Doses [redacted] (Cohort B), subjects will be monitored for 2 hours in a location with personnel trained in Adult Advanced Life Support with proper resuscitation equipment available. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105

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

4.5.2 Additional Study Medications

Subjects should undergo standard of care treatment and follow-up per local standards including high intensity statin therapy.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at 2°C to 8°C (36°F to 46°F).

4.5.5 Treatment Compliance

Investigational product is administered IV by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomization to a treatment regimen. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria. Subjects will be randomized in a 1:1 ratio to one of 2 cohorts, Cohort A ( ) and Cohort B ( ). Within each dose regimen, subjects will be randomized in a 2:1 ratio to receive MEDI6012 or placebo:

Cohort A

- MEDI6012, (n ~ 180)
- Placebo, (n ~ 90)

Cohort B

- MEDI6012, (n ~ 180)
- Placebo, (n ~ 90)

In the event that a dose regimen is dropped at the interim analysis, subjects will be randomized in a 1:1 ratio to receive MEDI6012 or placebo for the remaining dose regimen.

Infarct location will be controlled during the randomization process, ensuring a similar distribution of anterior vs. non-anterior infarcts between the active and placebo groups. In addition, the distribution of subjects with anterior versus non-anterior MIs will be monitored over the course of the study. The goal is that > 50% of the final randomized population will be anterior MI. Therefore, the number with non-anterior MI will be monitored via the IXRS and capped by the study team.

Investigational product (MEDI6012 or placebo) must be administered as soon as possible before pPCI (preferably > 10 minutes prior) and no later than 4 hours from the time investigational produce is reconstituted. 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 blinded study in which MEDI6012 and placebo are nearly identical in appearance. The subject/legal representative and the Sponsor will not be aware of the treatment received (ICH E9) (see Section 4.6.3.2 for unblinding related to interim and planned analysis). The unblinded individual preparing the first dose of investigational product for administration in the catheterization laboratory will be aware of the treatment received. The unblinded administrator will be trained to not reveal treatment assignment to the investigator or other clinical and study staff. The site will be asked to take reasonable steps to maintain the blind. However, due to the acute nature of the study, members of the research team, and possibly the investigator, may be unblinded. Subsequent doses after Dose 1 will be prepared by an unblinded pharmacist. Sites are encouraged to take all reasonable steps to keep site staff involved in follow up assessments after Day1 blinded to randomization group.

4.6.3 Methods for Unblinding

4.6.3.1 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 the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

4.6.3.2 Unblinding for Interim Analysis Purposes

The objective of the [redacted] interim analysis will be for futility and potentially dropping a dose regimen. It will be conducted through the Data Monitoring Committee with details in the DMC charter. The [redacted] interim analysis is planned to accelerate decision on future development options for MEDI6012 and will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. An Unblinded Review Committee (URC) will be formed to review the second interim analysis according to standard operating procedure. Details of the second interim analyses will be specified in the interim analysis plan prior to unblinding.

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. Specifically, subjects should receive full supportive care during the study in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

There are no prohibited concomitant medications.

4.8 Statistical Evaluation

4.8.1 General Considerations

An initial database lock for the purpose of clinical study analysis and reporting will be performed when the last randomized subject completes the Day 70 to 84 visit or is discontinued prior to that visit; if no subjects are ongoing in the Extended Follow-up period, then this database lock will be considered the final database lock for the study.

If subjects are ongoing in the Extended Follow-up period, a second database lock will occur after all subjects who entered the Extended Follow-up period have completed their Week 25, 39, or 52 visits as needed (see Section 4.2.2) or are discontinued prior to these visits, and this will be considered the final database lock. If the last Extended Follow-up visit occurs before the last Day 70 to 84 visit on the study, the second database lock will not be needed.

The study will be unblinded to the sponsor at the time of initial database lock. The site, subjects, and local CRO personnel will remain blinded to treatment assignment until the final database lock is declared.

Safety data will be generated for the Extended Follow-up period and summarized as an addendum to the clinical study report.

Data will be provided in listings sorted by treatment group, and subject number. Tabular summaries will be presented by treatment group with placebo group combined when appropriate. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product on Day 1. Confidence intervals will be one-sided and nominal p-values will be reported when appropriate. Additional details of statistical analyses will be described in the statistical analysis plan.

4.8.1.1 Analysis Populations

Intent-to-Treat (ITT) Population: all subjects that are randomized, analyzed according to randomized treatment assignment.

As-treated Population: all randomized subjects who receive any investigational product. Subjects who receive any dose of MEDI6012 will be assigned to MEDI6012 group. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive any dose of MEDI6012 will be analyzed with the MEDI6012 group. Safety analyses will be performed on the As-treated Population.

Primary Efficacy Analysis Population: all randomized subjects who receive at [redacted] doses of investigational product with [redacted]. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive 2 or more doses of MEDI6012 will be analyzed with the MEDI6012 group.

Efficacy Analysis Population [redacted]: all randomized subjects who receive at least two doses of investigational product with [redacted]. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive 2 or more doses of MEDI6012 will be analyzed with the MEDI6012 group.

Efficacy Analysis Population [redacted]: all randomized subjects who receive at least two doses of investigational product with [redacted]. Subjects who receive only placebo doses will be analyzed with the placebo group; conversely, subjects who receive 2 or more doses of MEDI6012 will be analyzed with the MEDI6012 group.

CTA Analysis Population: randomized subjects in [redacted] who receive a full treatment course of investigational product and are eligible for coronary CTA and have 1 or more CTA performed. The subjects who receive [redacted] placebo doses will be analyzed with the placebo group; conversely, subjects who receive [redacted] doses of MEDI6012 will be analyzed with the MEDI6012 group.

Immunogenicity Population: all subjects in the As-treated Population who have at least one serum sample for immunogenicity testing.

PK Population: all subjects in the As-treated Population who have at least one detectable serum concentration measurement for LCAT mass or activity.

4.8.2 Sample Size

A total of 90 subjects per arm will provide 80% power to detect a [redacted] reduction in infarct size between MEDI6012 [redacted] group and combined placebo group ([redacted] placebo groups), and between MEDI6012 [redacted] group and combined placebo group with one-sided alpha 0.05 assuming a coefficient of variation of [redacted]. A total of 180 subjects per arm is

required as a [redacted]% rate of exclusion from the primary efficacy analysis population is expected due to [redacted] in the infarct-related artery on initial angiography and other reasons for subsequent exclusion or drop-out (Botker et al, 2010; Hausenloy et al, 2013). A [redacted] reduction in infarct size is thought to be clinically significant, assuming it would equate to an approximate [redacted]% absolute reduction in infarct size in a future trial that enrolls subjects with large infarcts. A [redacted]% absolute reduction in infarct size is associated with a [redacted]% relative risk reduction in heart failure and mortality. With this same sample size, the power to detect a [redacted]% absolute difference in EF between each MEDI6012 group and combined placebo group with [redacted] alpha [redacted] is >[redacted]% assuming standard deviation [redacted]%. For the secondary endpoint of non-calcified coronary plaque regression/progression, there will be >[redacted]% power to detect a [redacted] mm^3 change in NCPV from index CTA to the 10-12 week CTA between MEDI6012 group and placebo group with [redacted] assuming a common standard deviation of [redacted] mm^3 and [redacted]% drop-out. It is estimated that the study will involve approximately 43 sites in approximately 10 countries.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The primary objective of this study is to evaluate the effect of MEDI6012 on the reduction of infarct size compared with placebo. The primary efficacy endpoint is infarct size as a percentage of LV mass measured on delayed-enhanced CMR imaging 10-12 weeks post- MI.

The primary efficacy endpoint of infarct size will be analyzed using t-test with log-transformation of the data based on the primary efficacy analysis population.

4.8.3.2 Additional Analyses of the Primary Endpoint

The primary endpoint of infarct size will also be analyzed based on the Efficacy Analysis Population - TIMI 2-3, the Efficacy Analysis Population - TIMI 0-3, and the ITT Population.

4.8.3.3 Secondary Efficacy Analyses

Secondary efficacy endpoints include EF measured by cine MRI at 10-12 weeks post-MI, Change in NCPV in the coronary arteries from index CTA to 10-12 weeks post-MI, and Myocardial mass and left ventricular volumes at end-systole and end-diastole.

EF, myocardial mass, and left ventricular volumes will be analyzed similarly to infarct size without the log-transformation of the data.

Change from index CTA in NCPV will be analyzed using t-test based on CTA analysis population.

4.8.3.4 Exploratory Analyses

The exploratory objectives are to determine whether MEDI6012 [redacted]

[redacted]

Incidence of CV death or heart failure and incidence of CV death, MI, unstable angina or urgent coronary revascularization from randomization to final study visit (10-12 weeks post-randomization) will be calculated. Time to first major adverse CV event will be analyzed using log-rank test.

The proportion of TFG at baseline (on initial angiography, pre-PCI) and the proportion of subjects with decline in renal functions at 48 hours will be compared between MEDI6012 and placebo using chi-square test.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

Safety analysis will be based on the As-treated Population. AE collection begins after randomization and lasts until the end of the study. SAE collection begins after the subject signs the informed consent document and lasts until the end of the study. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by SOC and PT. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All TEAEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Clinical laboratory safety tests including serum chemistry and hematology parameters will be summarized using descriptive statistics at each time point by treatment group with placebo group combined when appropriate. Change from baseline to each post baseline time point in these data will also be summarized, where appropriate. A shift table will be provided for these clinical laboratory parameters as well where possible.

4.8.4.3 Other Safety Analyses

Vital sign results will be summarized using descriptive statistics at each time point by treatment group.

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

ADA incidence rate and titer will be tabulated for each treatment group. Samples confirmed positive for ADA will be tested and analyzed for nAb and summarized similarly.

Serum MEDI6012 mass concentration-time profiles will be summarized for MEDI6012 treated subjects by dose cohort by visit.

Additional PK analyses may be conducted as appropriate. Data obtained in this study may be pooled with other MEDI6012 studies to perform population PK analysis and/or PK/PD analysis.

4.8.6 Analysis of Pharmacodynamic Parameters

The following PD markers will be collected: [redacted].

The PD markers measured at each time point and change from baseline each post baseline time point will be summarized using descriptive statistics by treatment group with placebo group combined when appropriate.

4.8.7 Data Monitoring Committee

An independent DMC will be appointed. The DMC will be responsible for safeguarding the interests of the patients, by assessing the safety of the intervention during the study and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. DMC will review prespecified data periodically to ensure subject safety and make recommendations to the sponsor regarding further conduct of the study. This recommendation will be relayed to the MedImmune safety review committee and appropriate action will be taken. The DMC will have scheduled meetings at study initiation and at the following enrollment milestones – 15%, 30%, and 60% enrollment achieved. In addition, the DMC chairman will receive data once every two months and may schedule *ad hoc* meetings at his/her discretion. A separate charter will establish the rules, meeting frequency and scope of responsibilities of the DMC.

4.8.8 Interim Analysis

[redacted] interim analyses are planned. The objective of the [redacted] interim analysis will be for futility and potentially dropping a dose regimen. It will be conducted after 30% of the initially planned Primary Efficacy Analysis Population (N = 74) is enrolled and will require that > 50% of subjects (N > 37) have acute anterior STEMI and have completed their final study visit. The [redacted] interim analysis will be conducted through Data Monitoring Committee with details in the DMC charter. The [redacted] interim analysis is planned to accelerate decision on future development options for MEDI6012 and will be performed once 60% of the revised Primary Efficacy Analysis Population (N = 162) is enrolled and will require that > 50% of subjects (N > 81) have acute anterior STEMI and have completed their final study visit. Details of the second interim analyses will be specified in the interim analysis plan. The

sponsor and Principal Investigator will monitor the statistical assumptions in a blinded fashion and decide the exact time for interim analyses.

5 ASSESSMENT OF SAFETY

5.1 Safety Monitoring

The details of safety monitoring will be detailed in the safety monitoring plan. Safety monitoring will be performed by the principal investigator, sponsor medical monitor in consultation with the global safety physician, TIMI safety desk and the DMC.

The principal investigator is responsible for monitoring enrolled subjects for safety findings, including the recording in the eCRF (RAVE) of AEs, SAEs, and appropriate reporting, communication, and follow-up of laboratory abnormalities. The TIMI hotline is staffed by TIMI study physicians and will be available 24 hours per day, 7 days per week for protocol and safety related questions and concerns. When an SAE is entered into the eCRF, the TIMI safety desk, medical monitor, and global safety physician will be notified. The TIMI hotline and TIMI safety desk will be responsible for documenting protocol and safety related issue communications with PIs and communicating significant findings to Medimmune and the sponsor medical monitor. When an SAE is documented in the clinical database (RAVE), the TIMI safety desk will submit queries within 24 hours confirming seriousness, causality, and further details regarding the SAE to facilitate whether further information is needed. These assessments will be made urgently in order to comply with the timeframes for reporting to regulatory authorities. The investigator is required to respond to these queries within 24 hours.

SAEs will be reviewed by the sponsor medical monitor, in consultation and with the global safety physician, and further queries issued, if necessary. If there is no evidence for the designation of an event as serious (in line with the appropriate protocol definition) or there is no apparent evidence for the positive investigator causality assessment, TIMI and the sponsor medical monitor may query or discuss with the investigator. However, if agreement is not reached, the investigator assessment will be respected and not changed by TIMI or Medimmune. The same is true if there is evidence to suggest a positive causality assessment for an SAE that has been assessed as unrelated by the investigator.

SAE reconciliation between the safety database (Sapphire) and the clinical study database will be performed on a monthly basis by TIMI and reviewed by the global study physician and medical monitor via monthly meetings.

The details of safety monitoring will be detailed in the Safety Monitoring Plan.

5.2 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). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A non-TEAE 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.

5.3 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.

5.4 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 5.3 for the definition of SAEs and Section 10.2 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.

Infusion of biological products is commonly associated with infusion related reactions. Anaphylaxis and infusion related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions are commonly observed during or shortly after the first time of exposure to therapeutic monoclonal antibodies delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic, skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI6012, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Section 10.4.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of randomization throughout the treatment period until the end of the follow-up period(s).

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

Non-TEAEs (ie, AEs that occur during the period from the time informed consent is signed but prior to the subject receiving investigational product) should not be reported. However,

nontreatment SAEs 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 have to 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 in the course of 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 electronic data capture (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. The AE/SAE should be reported in the EDC as soon as it becomes available.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in this 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 course of 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

Patients with acute STEMI are very likely to show aminotransferase elevations at inclusion, either originating from cardiomyocytes, or, if released from hepatocytes, related to hepatic ischemia or congestion. Definition of potential signals for Drug-Induced Liver Injury and requirements for expedited reporting need to be adapted accordingly. Please refer to Section 10.5 for details.

5.6.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor.

5.6.3.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study.

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 Day 1 through the end of the study follow-up period.

Male subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose.

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 the date of the first investigational product administration until 12 weeks after the last investigational product administration 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 also 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 of these 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 each/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), or death regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.6 and 4.1.7).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment, which may be the date of the last Day 70 to 84 visit (including telephone contact), or the Extended Follow-up if required at Week 25, 39, or 52, or death for the last subject in the study, whichever occurs last.

6.4 Data Management

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

An EDC 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 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 using the TIMI Hotline number (+1-617-278-0900). 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 (ICF) 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.

7.2 Ethics and Regulatory Review

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

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

MedImmune should approve any substantive modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC 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/IEC, and principal investigators.

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 ICF as well as alternate short-form consent for use by all investigators in the clinical study (according to local regulations). MedImmune must approve any modifications to the ICF 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 written or verbal informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF 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 ICF that is approved by an IRB/IEC

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 principle investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and according to local requirements, the national regulatory authority approval. The IRB/IEC must also approve revisions to the ICF, 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/IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC 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, Good Clinical Practice (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 6, 04May2020

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 6. All changes made to the body of the protocol have been reflected in the Protocol Synopsis and minor copyediting issues were addressed.

Changes to the protocol considered substantial are summarized below:

- The List of Abbreviations was updated to include and define COVID-19.
- Section 4.2.1 (Enrollment, Treatment, and Follow-up Periods): It was clarified to include "Follow-up" period, and cross-references to the Schedule of Study Procedures tables, Table 8 and Table 9, were added.
- Section 4.2.1.1 (Study Procedure Modifications in Response to the COVID-19 Pandemic):

  To enable safety monitoring of subjects enrolled in the trial through an extended blood sampling window, the following was added:

  – If the Visit 6 (Day 70-84) follow-up visit cannot be conducted in person due to the COVID-19 pandemic, where possible, a subject should return to the clinic as soon as possible after the planned Visit 6 (Day 70-84) visit but no more than 150 days post dose 1 for blood sample collection. Assessment of AEs/SAEs and concomitant medications should be done via telephone contact within the originally specified window for Visit 6 (ie, Day 70-84). If a subject returns to the clinic for blood sample collection within the extended window, any AEs/SAEs that occur between the telephone contact and the date of this visit should also be recorded.

  To maintain trial integrity for the primary and secondary endpoints by enrolling all remaining patients in Cohort B (to obtain both the CMR and CTA as well as extended dosing data), which has had a greater dropout rate further impacted by COVID-19, the following was added:

  – All subjects will be randomized into Cohort B [redacted]); subjects will be randomized in a 1:1 ratio to receive MEDI6012 or placebo.
- Table 8 (Treatment Period and Follow-up Procedures: Cohort A [redacted]) and Table 9 (Treatment Period and Follow-up Procedures: Cohort B [redacted]): The tables were updated to include a footnote cross-referencing Section 4.2.1.1 (Study Procedure Modifications in Response to the COVID-19 Pandemic). Subsequent footnotes were renumbered.
- Sections 4.2.2 (Extended Follow-up period for Subjects Testing Positive for Anti-Drug Antibodies Plus > 30% Decrease from Baseline in HDL-C at Day 70 to 84 or Presence of a Neutralizing Antibody on Day 70 to 84), 4.3.7 (Immunogenicity Evaluation and Methods), and 4.3.9 (Estimate of Volume of Blood to be Collected): It was clarified that during the Extended Follow-up period if the ADA test result becomes negative or the HDL-C is no longer > 30% decreased compared with baseline, the subject does not need

to return for additional Extended Follow-up visit(s) and will be considered as having completed the Extended Follow-up period.

- Section 4.5.1.6 (Reporting Product Complaints): Deleted an obsolete phone number and fax number.
- Section 4.8.1 (General Considerations): It was clarified that 2 independent database locks may be conducted. The initial database lock for the purpose of clinical study analysis and reporting will occur after all randomized subjects in the study either complete the Day 70 to 84 visit or are discontinued prior to the visit. If no subjects are ongoing in the Extended Follow-up period, then this database lock will be considered the final database lock for the study. If subjects are ongoing in the Extended Follow-up period, a second database lock will occur after all subjects who entered the Extended Follow-up period have completed their Week 25, 39, or 52 visits (as described in Section 4.2.2) or are discontinued prior to these visits and this will be considered the final database lock. If the last Extended Follow-up visit occurs before the last Day 70 to 84 visit on the study, the second database lock will not be needed. The site, subjects, and local CRO personnel will remain blinded to treatment assignment until the final database lock is declared. Safety data will be generated for the Extended Follow-up period and summarized as an addendum to the clinical study report.
- Section 6.3 (Study Timetable and End of Study): It was clarified that the end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment, which may be the date of the last Day 70 to 84 visit (including telephone contact), or the Extended Follow-up if required at Week 25, 39, or 52, or death for the last subject in the study, whichever occurs last.
- Appendix 10.1 (Appendix 1 – Signatures): The sponsor signature page in Appendix 10.1 was deleted in lieu of an attached electronic signature page.
- Throughout the protocol where "> 30% decrease in HDL-C" is cited, it has been clarified that this refers to "> 30% decrease **from baseline** in HDL-C".

9.2 Protocol Amendment 5, 26Jul2019

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 5. All changes made to the body of the protocol have been reflected in the Protocol Synopsis and minor copyediting issues were addressed.

Changes to the protocol considered substantial are summarized below:

1 Section 3.1.1 (Overview), Figure 3 (Overall Study Schema), 3.1.2 (Treatment Regimen), 4.1.1 (Number of Subjects), 4.6.1 (Methods for Assigning Treatment Groups), 4.8.1 (General Considerations), 4.8.2 (Sample Size), and 4.8.8 (Interim Analysis): the approximate number of subjects was changed from at least 414 to approximately 540; total numbers per cohort, sample size calculation and second interim analysis were updated to reflect this. Sample size change was implemented to reflect the observed coefficient of variation of blinded data relative to the expected in the statistical assumption. The alpha threshold was amended to be a one-sided alpha of 0.05 to reflect

the one-sided hypothesis testing (superiority of MEDI6012) for this Phase 2b program designed to inform future drug development.

Changes to the protocol considered non-substantial are summarized below:

2 Title Page: medical monitor changed to

3 Section 3.1.1 (Overview) and 4.8.2 (Sample Size): number of study sites updated from 40 to 43.

4 Table 5 (Exploratory Objectives and Associated Endpoints), and Section 3.2.3.4 (Rationale for Exploratory Endpoints):

5 Section 4.1.4 (Additional Study Procedure Requirements): under Coronary CTA, the fifth requirement was revised to read, "No contraindication to heart rate lowering using betablockers to allow for high quality, low-radiation dose CTA (per-protocol). Please note, if heart rate is well-controlled allowing for a high quality, low radiation CTA without betablocker, then a contraindication to betablocker does not exclude the subject from coronary CTA". The text was revised to clarify that if betablockers are contraindicated, subject could still undergo CTA if their heart rate is low enough to assure a low radiation dose can be achieved. Nitroglycerin contraindication was removed from the list of requirements since subjects could undergo CTA without nitroglycerin administration.

6 Section 4.8.1.1 (Analysis Populations): descriptions of analysis populations updated to reflect the statistical analysis plan.

9.3 Protocol Amendment 4, 18Apr2019

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 4. Minor copyediting was addressed; "coronary vessel volume" was corrected to "lumen volume" and "myocardial area at risk" was changed to "resting perfusion deficit".

1 Protocol Synopsis: Update made to the exploratory objectives (bullet point 3) and endpoints (third bullet) for in line with the updates to Table 5 in the main body of the protocol.

2 Table 5 (Exploratory Objectives and Associated Endpoints): Clarification to wording of the safety objective and endpoints related .

3 Section 3.1.1 (Overview): Index CTA window altered from "no earlier than 48 hours" to "no earlier than 40 hours" post Dose 1 as previous language was inconsistent within the protocol between the time periods stated in the heading of Table 9, and the time periods stated in footnote o of Table 9 and the overview section. CMR window for repeat scans increased from 1 week to 4 weeks following the end of study visit (up to 112 days post

Dose 1) to accommodate scheduling of a repeat scan if needed due to inadequate image quality.

4 Section 3.2.3.4 (Rationale for Exploratory Endpoints) and Section 4.8.3.4 (Exploratory Analyses): [redacted] included in this study in line with the updates to the exploratory objectives and endpoints in Table 5.

5 Table 8 (Treatment Period and Follow-up Procedures: Cohort A [[redacted]]) and Table 9 (Treatment Period and Follow-up Procedures: Cohort B [redacted]]): Footnote c was added in Tables 8 and 9, to clarify that screening vital signs taken as part of standard of care can be used as long as they are taken within 30 minutes pre-dose (must be repeated if more than 30 minutes pre-dose), to avoid unnecessary repeating of vital signs assessments in the acute setting of this study where there is a very short screening period, and to clarify that screening vitals and pre-dose vitals do not need to be duplicated if one set has been taken within 30 minutes pre-dose, to reduce patient burden and avoid interfering with standard of care procedures. Footnote j updated in both tables to clarify the timeframe for creatinine measurement and review prior to MRI and CTA. Footnote n updated in both tables to reflect change in MRI window for repeat scans from 1 week to 4 weeks following the end of study visit (up to 112 days post Dose 1) as MRI results are still clinically relevant in this time period. Footnote g in both tables adjusted to state that missed doses or visits outside the specified window may be adjusted with approval from TIMI Hotline to clarify when the sites should contact TIMI Hotline in this instance. Footnote o in Table 9 updated to correct discrepancy with table contents stating that index CTA may be performed no earlier than 40 hours post Dose 1. Footnotes o and p in Table 9 adjusted to specify CTA procedure in cases of CABG surgery as the comparison of pre- and post-CABG surgery CTAs would be difficult. All footnote labels in Tables 8 and 9 readjusted to accommodate additional footnotes.

6 Section 4.2.2 (Extended Follow-up Period for Subjects with Anti-Drug Antibodies Plus > 30% Decrease in HDL-C and/or Presence of a Neutralizing Antibody on Day 70 to 84) and Table 10 (Extended Follow-up Period for Subjects with Anti-Drug Antibodies Plus > 30% Decrease in HDL-C and/or Presence of a Neutralizing Antibody on Day 70 to 84): The time frame of Day 70 to 84 was added in line with protocol main text to clarify that this extended follow-up period would apply only for subjects with ADA in addition to > 30% decrease in HDL-C and/or presence of nAb on Day 70 to 84.

7 Section 4.3 (Description of Study Procedures): Added exception to order of vital signs and blood draw to be exclusive of Visit 1 (Day 1) as due to compressed timeframes at this point in clinical procedures, it is not always possible to take vital signs and blood draws in this same order.

8 Section 4.3.5 (Pharmacokinetic Evaluation and Methods): Added text to clarify that PK samples taken from subjects on Visits 3, 5, and 6 (Days 17, 31, and 70-84, respectively) from Cohort A, and Visit 6 (Day 70-84) from Cohort B will be collected but not measured unless deemed useful by the study team based on emerging data (ie, assessment of

immunogenicity) as the results from these time points may not be required for all subjects since the level of investigational product will be below the limit of quantification for MEDI6012. The samples are still useful as they can be used to determine if ADAs have an impact on LCAT levels to assess immunogenicity.

9 Section 4.3.8 (Imaging Biomarker Evaluation and Methods): [redacted]

9.4 Protocol Amendment 3, 14Jun2018

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 3. Text under the heading "Additional Study Procedure Requirements" and "Coronary CTA" was revised to clarify the requirement as "no" contraindications to betablockers and nitroglycerin. Text was also revised to add clarification to the length of time subjects will be under medical supervision following administration of investigational product. Minor copyediting was also addressed, in particular, "baseline" CTA was changed to "index" CTA. Major changes to the protocol are summarized below.

1 Section 3.1.1 (Overview), Cohorts A and B: For Inpatient Phase – Cohorts A and B, text was added that following Doses [redacted] for Cohort A, or [redacted] Cohort B, subjects will be monitored for 2 hours in a location with personnel trained in Adult Advanced Life Support with resuscitation equipment available. For Outpatient Phase – Cohort B, text was added that "subjects who did not undergo index CTA for any reason will not undergo the CTA at the end of the study."

2 Section 4.1.4 (Additional Study Procedure Requirements): The title of the Cardiovascular MRI subsection was revised to read, "Administration of Gadolinium Contrast for Cardiovascular MRI." Additionally, the word "gadolinium" was added to clarify the contrast agent. Under Coronary CTA, the fifth requirement was revised to read, "No" contraindications to betablockers and nitroglycerin. The text was revised to clarify that betablockers and nitroglycerin are to be used. Betablockers enable a lower radiation dose and lack of betablocker use can result in some study sites exceeding the radiation dose limitation; also, betablockers and nitroglycerin improve the quality of the images. A sixth requirement was added that for follow-up CTA, subjects would need to have undergone an index CTA.

3 Section 4.1.7 (Discontinuation of Investigational Product): Text was added to clarify that in cases where a subject is incorrectly randomized, upon review by the TIMI Hotline or

medical monitor, subjects found after randomization to have met an exclusion criterion that is unrelated to safety may continue treatment. Additional text was added that for subjects who never receive investigational product, follow up will consist of a minimum of a single phone call at the end of the study; however, visits are allowed at the discretion of the subject and investigator.

4 Table 8 (Treatment Period and Follow-up Procedures: Cohort A [ ]) and Table 9 (Treatment Period and Follow-Up Procedures: Cohort B [ ]): Procedure and footnotes were added to both tables for post-dose subject observation and monitoring to clarify the period of time that subjects will be monitored following administration of investigational product. Footnote "m" was added to Table 8 for Investigational product administration under Day 3 (48 ± 8 hours) and footnote "o" was added under Days 3-31 to Table 9 to clarify and instruct that "Planned dosing times that will potentially fall outside of the window specified in this table must be discussed with the TIMI Hotline and sponsor," and "visit intervals will need to be adjusted accordingly." Footnote "n" in Table 9 was revised for clarification that follow-up CTA will be done only for subjects with an index CTA.

5 Section 4.3.1 (Medical History and Physical Examination, Weight, and Vital Signs): The word "oral" was removed from body temperature measurements to clarify that other methods for taking body temperature will be permitted.

6 Section 4.3.4 (Clinical Laboratory Tests): The word "automated" was added to white blood cell count and "by central laboratory" to clarify that blood smears should not be done. A footnote added to "Other Laboratory Tests" to indicate that luteinizing hormone and follicle stimulating hormone will be conducted only for female subjects.

7 Section 4.3.8 (Imaging Biomarker Evaluation and Methods):

8 Section 4.5.1.5 (Monitoring of Dose Administration): Text added to clarify that subjects will be monitored for 2 hours following Doses for Cohorts A or Doses for Cohort B.

9 Section 4.6.2 (Methods to Ensure Blinding): Text was added for further clarification that due to the acute nature of the study, members of the research team, and possibly the investigator, may be unblinded.

9.5 Protocol Amendment 2, 28Mar2018

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 2. Estimated GFR criteria were removed and changed to CrCl throughout. Copyediting and formatting errors were corrected throughout; notably, the term "glutamine" dehydrogenase was corrected to "glutamate" dehydrogenase throughout the document. Breastfeeding exclusion criterion was added. Additionally, table numbering was changed to sequential numbering to align with new in-house authoring style. Major changes to the protocol are summarized below.

1 Section 1.7.2 (Secondary Hypotheses): The word "prevent" was replaced with "reduce" to align with the Protocol Synopsis.

2 Section 3.1.1 (Overview – Inpatient Phase – Cohorts A and B): Text was revised for Cohort B to remove eGFR ≥ 60 and replace with subjects with *CrCl ≥ 60 mL/min (Cockcroft Gault equation)* within 6 hours will undergo an index coronary CTA no earlier than 48 hours following the first dose. Changes were made to eGFR to correctly change to CrCl throughout as the Cockcroft Gault equation applies to CrCl.

3 Section 4.1.3 (Exclusion Criteria): Criterion 8 was revised to remove known eGFR < 30 mL/min/1.7.3 m^2 and replace with known *CrCl < 30 mL/min (Cockcroft Gault equation)* as a contraindication to MR imaging. Criterion 9 was revised to exclude women who are breastfeeding. Criterion 10 was added to exclude subjects who are currently or had previously participated in a study using an investigational therapy or devices within the last 30 days.

4 Section 4.1.4 (Additional Study Procedure Requirements – Cardiovascular MRI and Coronary CTA): Text in Cardiovascular MRI subsection was revised to remove eGFR ≥ 30 mL/min/1.73 m^2 and replace with CrCl to read that MRI would be allowed if there were no contraindications to MR imagining (eg, metallic implant, claustrophobia, ICD, pacemaker), but for subjects to receive contrast they must meet the requirements of *CrCl ≥ 30 mL/min (Cockcroft Gault equation)* within 7 days prior to the procedure, and no known allergy to gadolinium contrast agents. This was revised for clarification and to provide a breakdown of MRI criteria to allow MRI (without using contrast) in subjects with no MRI contraindications who cannot receive contrast. The Coronary CTA subsection was revised to remove eGFR ≥ 60 mL/min/1.73 m^2 and replace with *CrCl ≥ 60 mL/min (Cockcroft Gault equation)* within no more than 6 hours prior to index CTA and no more than 7 days prior to follow up.

5 Section 4.1.5 (Subject Enrollment and Randomization): Text was revised to clarify that randomization will be stratified by infarct location, ensuring balanced randomization to active treatment vs placebo within the anterior and the non-interior MI groups.

6 Table 8 (Treatment Period and Follow-up Period Procedures: Cohort A [redacted]) and Table 9 (Treatment Period and Follow-up Period Procedures: Cohort B

[A PK blood sample was added to Table 8 (Cohort A) for Day 31 to align with Cohort B. Record vital signs at Screening was added to Table 9 (Cohort B) to align with Cohort A.

7 Section 4.3.1 (Medical History and Physical Examination, Weight, and Vital Signs): Text was revised to correct that full physical examination will be conducted anytime between Day 1 and 3 prior to administration of Dose . Additionally, "on all days" was deleted from text for measurement of vital signs to align with Schedule of Study Procedures.

8 Section 4.3.8 (Imaging Biomarker Evaluation and Methods –

9 Section 4.5.1.4 (Treatment Administration): Text was revised to add that subjects should be instructed on whether their regular medication can be taken while fasting. This was added for clarification and as a reminder to the investigator to review specific concomitant medication instructions with subjects.

10 Section 4.5.1.5 (Monitoring of Dose Administration): Text was revised to remove "before and after dose administration" to align with Schedule of Study Procedures.

11 Section 4.8.8 (Interim Analysis) and Synopsis: Text was added to clarify that the sponsor and Principal Investigator will monitor the statistical assumptions in a blinded fashion and decide the exact time for interim analyses.

9.6 Protocol Amendment 1, 09Jan2018

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Copyediting and formatting errors were corrected throughout. Major changes to the protocol are summarized below.

1 Section 4.2.1 (Enrollment and Treatment Period), Table 8 (Treatment Period and Follow-up Procedures: Cohort A]): Footnotes a and b were added due to previous omission; footnote h was replaced by footnote g for PK blood sample on Day 1 due to previous error; footnote i was replaced by footnote h for PD blood sample on Day 1, 1-1.5 hour post-dose due to previous error.

2 Section 4.5.1.1 (Investigational Product Handling):

3 Section 4.3.8 (Imaging Biomarker Evaluation and Methods),

10 APPENDICES

10.1 Appendix 1 - Signatures

Signature of Principal Investigator

A Randomized, Placebo-controlled Phase 2b Study to Evaluate the Safety and Efficacy of MEDI6012 in Acute ST Elevation Myocardial Infarction

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

10.2 Appendix 2 – Contraception Guidance

For females:

Females without childbearing potential will be included in this study. Females without childbearing potential are defined as those who are surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are postmenopausal (defined as 12 months with no menses without an alternative medical cause).

For males:

Nonsterilized males who are sexually active with a female partner of childbearing potential must use condom and spermicide from Day 1 through the end of their participation in the study. Because male condom and spermicide is not a highly effective contraception method it is strongly recommended that female partners of a male study subjects also use a highly effective method of contraception throughout this period. 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 13.

Table 13 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] ° Injectable ° Implantable ° Intravaginal

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

10.3 Appendix 3 - Additional Safety Guidance

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

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).

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.

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

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
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 5.3. 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.

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 treatment-emergent SAEs. 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 Disease 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 Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Disease (NAID) and Food Allergy and Anaphylaxis Network (FAAN) 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 potential serious liver injury corresponding to Hy's Law

10.5.1 Introduction

This appendix describes the process to be followed to identify and appropriately report cases of potential serious liver injury corresponding to 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 criteria for potential serious liver injury corresponding to Hy's Law at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting criteria for potential serious liver injury corresponding to Hy's Law to agree whether these criteria are met. This is the case 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 cases of potential serious liver injury corresponding to Hy's Law, 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 serious liver injury corresponding to Hy's Law

- ALT and total bilirubin (TBL) normal at baseline:
  ALT > 3 x upper limit of normal (ULN), with associated elevation in glutamate dehydrogenase (GLDH), without corresponding CK and/or troponin elevation, **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).

- ALT or TBIL abnormal at baseline:
  ALT > 3 x baseline or > 300 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and/or troponin elevation, **together with** TBL ≥ 2 × ULN, or, if abnormal at baseline, > 2 x bsl, at any point during the study following the start of study medication, irrespective of an increase in alkaline phosphatase (ALP).

  If ALT is decreasing from baseline, nadir will be new baseline

10.5.2.2 Serious liver injury corresponding to Hy's Law

- ALT and TBIL normal at baseline:

ALT > 3 x ULN, with associated elevation in GLDH, without corresponding CK and/or troponin elevation, **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.

- ALT or TBIL abnormal at baseline:
  ALT > 3 x baseline or > 300 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and/or troponin elevation, **together with** TBL ≥ 2 × ULN, or, if abnormal at baseline, > 2 x bsl, 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.

If ALT is decreasing from baseline, nadir will be new baseline

For (potential) serious liver injury corresponding to Hy's law, the elevation in ALT 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 ALT and TBL must occur.

10.5.3 Identification of cases of (potential) serious liver injury corresponding to Hy's law

In order to identify cases of (potential) serious liver injury corresponding to 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 and TBIL normal at baseline:

- ALT > 3 x ULN, with associated elevation in GLDH
- TBL ≥ 2 × ULN

ALT or TBIL abnormal at baseline:

- ALT > 3 x ULN, with associated elevation in GLDH, or, if abnormal at baseline, ALT > 3 x baseline or > 300 U/L (whichever occurs first), with associated elevation in GLDH,
- TBL ≥ 2 × ULN, or, if abnormal at baseline, > 2 x bsl

If ALT is decreasing from baseline, nadir will be new baseline

When a subject meets any of the 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 criteria for (potential) serious liver injury corresponding to Hy's law (see Section 10.5.4.2) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

10.5.4 Follow-up

10.5.4.1 Criteria for (potential) serious liver injury corresponding to Hy's law Not Met

If the subject does not meet criteria for (potential) serious liver injury corresponding to Hy's law, the investigator will:

- Inform the study representative that the subject has not met criteria for (potential) serious liver injury corresponding to Hy's law.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

10.5.4.2 Criteria for (potential) serious liver injury corresponding to Hy's law Met

If the subject does meet criteria for (potential) serious liver injury corresponding to Hy's law, the investigator will:

- Determine whether criteria for (potential) serious liver injury corresponding to Hy's law were met at any study visit prior to starting study treatment
- 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 lab kit should be used.
- Complete the Liver CRF Modules as information becomes available
- If at any time (in consultation with the medical monitor) the criteria for potential serious liver injury corresponding to Hy's law are met, report it as an SAE using standard reporting procedures

10.5.5 Review and Assessment of cases of (potential) serious liver injury corresponding to Hy's law

The instructions in this section should be followed for all cases where criteria for (potential) serious liver injury corresponding to Hy's law are met.

No later than 12 days 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 criteria for (potential) serious liver injury corresponding to Hy's law 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. It is recommended to also consult with the hepatic SKG for review of these cases.

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 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 and TBL elevations other than the investigational product:

- Report an SAE (report term 'Drug-induced liver injury') 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 case of (potential) serious liver injury corresponding to Hy's law, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of over 12 days in obtaining the information necessary to assess whether or not the case meets the criteria for (potential) serious liver injury corresponding to 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 'Drug-induced liver injury') 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 criteria for (potential) serious liver injury corresponding to Hy's law are met. Update the SAE report according to the outcome of the review

10.6 Appendix 6 - Management of Liver Toxicity

In the setting of acute MI, transaminases used to monitor for liver toxicity (ALT and AST) can be elevated and of cardiac origin. Table 14 describes actions to be taken according to ALT; GLDH; total bilirubin; and subject symptoms.

Table 14 Actions to be Taken According to ALT, Glutamate Dehydrogenase, Total Bilirubin

Treatment-emergent ALT		Treatment-emergent TBL	Liver Symptoms	Action
1	**If normal at baseline:** ALT > 3 x ULN, with associated elevation in GLDH, without corresponding CK and troponin elevation	Normal	None	Repeat ALT, AST, ALP, TBL, in 24-48 hours Follow-up for symptoms.
	If abnormal at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and troponin elevation *If ALT is decreasing from baseline, nadir will be new baseline.*	For patients with abnormal bsl, No change in baseline TBL		

Table 14 Actions to be Taken According to ALT, Glutamate Dehydrogenase, Total Bilirubin

Treatment-emergent ALT		Treatment-emergent TBL	Liver Symptoms	Action
2	**If normal at baseline:** ALT > 5 x ULN, with associated elevation in GLDH, without corresponding CK and troponin elevation	Normal	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If abnormal at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and troponin elevation *If ALT is decreasing from baseline, nadir will be new baseline*	For patients with abnormal bsl, No change in baseline TBL		
3	**If normal at baseline:** ALT > 3 x ULN, with associated elevation in GLDH, without corresponding CK and troponin elevation	TBL > 2 x ULN	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If abnormal at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and troponin elevation *If ALT is decreasing from baseline, nadir will be new baseline.*	For patients with abnormal bsl, > 2 x bsl		
4	**If normal at baseline:** ALT > 3 x ULN, with associated elevation in GLDH, without corresponding CK and troponin elevation	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and
	If abnormal at baseline:			

Table 14 Actions to be Taken According to ALT, Glutamate Dehydrogenase, Total Bilirubin

Treatment-emergent ALT		Treatment-emergent TBL	Liver Symptoms	Action
	ALT > 2 x baseline or > 200 U/L (whichever occurs first), with associated elevation in GLDH, without corresponding CK and troponin elevation *If ALT is decreasing from baseline, nadir will be new baseline*			liver enzymes return to baseline.

ALT = alanine transaminase; AST = aspartate transaminase; bsl = baseline; CK = creatine kinase; GLDH = glutamate dehydrogenase; TBL = total bilirubin; ULN = upper limit of normal.

10.6.1 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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