MedImmune

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Statistical Analysis Plan Approval

Date: *04Dec2020*
To: Study File
From: *Statistician*
Re: Statistical Analysis Plan Approval for Study *D5780C00007*

The Statistical Analysis Plan, **version 3.0**, for Study *D5780C00007* has been reviewed and approved.

Name:		Signatur	
Role:	Statistician	Date:	December 4, 2020
Name:		Signature	
Role:	Statistical Programmer	Date:	December 8, 2020
Name:		Signature	
Role:	Clinical Development Lead	Date:	December 4, 2020
Name:		Signature	
Role:	Early CVRM Biometrics Team Leader	Date:	December 4, 2020

Statistical Analysis Plan

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

Protocol Number: D5780C00007

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Abbreviation or Specialized Term	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibody
AE	adverse event
ALT	alanine transaminase
apoA1	apolipoprotein A1
apoB	apolipoprotein B
AST	aspartate aminotransferase
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
CAD	coronary artery disease
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
C_{max}	maximum plasma concentration
CMR	cardiovascular magnetic resonance
CTA	computed tomography angiography
CV	cardiovascular disease
ECG	electrocardiogram
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
HF	heart failure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	Interactive response system

Abbreviation or Specialized Term	Definition
LAD	left anterior descending artery
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LV	left ventricle
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
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
TFG	TIMI flow grade
TIMI	Thrombolysis in Myocardial Infarction
ULN	upper limit of normal
USA	United States of America

1 INTRODUCTION

This document describes the statistical analysis for protocol D5780C00007, A Randomized, Placebo controlled Phase 2b Study to Evaluate the Safety and Efficacy of MEDI6012 in Acute ST Elevation Myocardial Infarction. An overview of the study design and objectives are provided in Section 2 (pg. 6). Details for statistical methods and general conventions are provided in Section 3 (pg. 11). In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

The primary objective and associated endpoint is presented in Table 2.1.

Table 2.1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To evaluate the effect of MEDI6012 [redacted]	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 Study Objectives

Secondary objectives and associated endpoints are presented in Table 2.2.

Table 2.2 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 TEAEs and TESAEs.

Table 2.2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint(s)
PK, and Immunogenicity	To describe the PK and immunogenicity of MEDI6012.	LCAT mass and presence of ADAs.

ADAs = anti-drug antibodies; CTA = computed tomography angiography; 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 Study Objectives

Exploratory objectives and associated endpoints are presented in Table 2.3.

Table 2.3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint(s)
Biomarker	To determine whether MEDI6012	
Biomarker	To evaluate the effect of MEDI6012	
Safety	To evaluate the effect of MEDI6012	
Efficacy	To evaluate the effect of MEDI6012	
Efficacy	To evaluate the effect of MEDI6012 on	in serum creatinine of ≥0.5 mg/dL (≥44 μ

CTA = computed tomography angiography; CV = cardiovascular; MI = myocardial infarction; pPCI = primary percutaneous coronary intervention; TFG= TIMI flow grade; TIMI = thrombolysis in myocardial infarction.

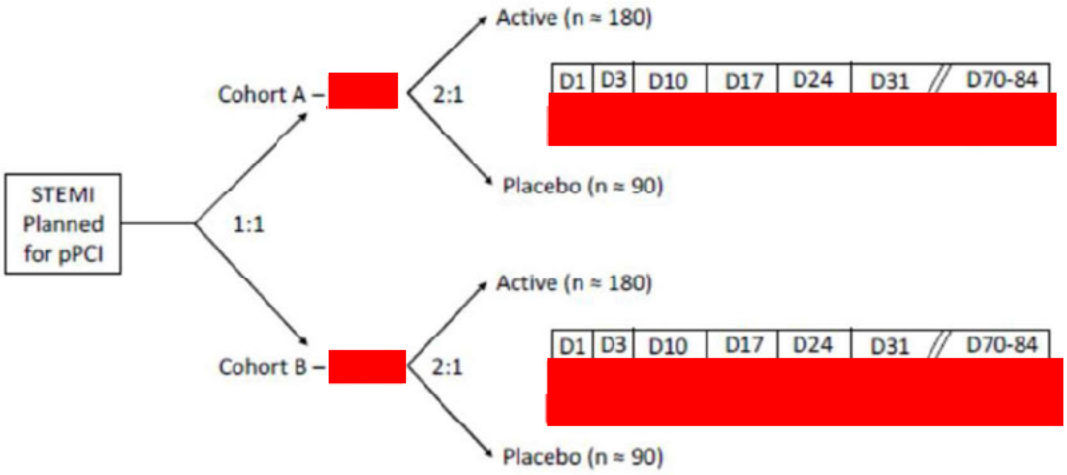
2.2 Study Design

This is a Phase 2b, randomized, placebo controlled- study to evaluate the efficacy, safety, pharmacokinetics/pharmacodynamics (PK/PD), and immunogenicity of repeat doses of MEDI6012 in adult subjects with acute ST segment elevation myocardial infarction (STEMI). The subject and MedImmune staff will be blinded; study sites will be trained to keep the investigator blinded. However, due to the acute nature of the study, members of the study team, and possibly the investigator, may be unblinded.

At least 540 subjects are planned to be randomized across approximately 43 study sites in approximately 10 countries to evaluate a [redacted] and a [redacted] 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 primary percutaneous coronary intervention (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]). 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.

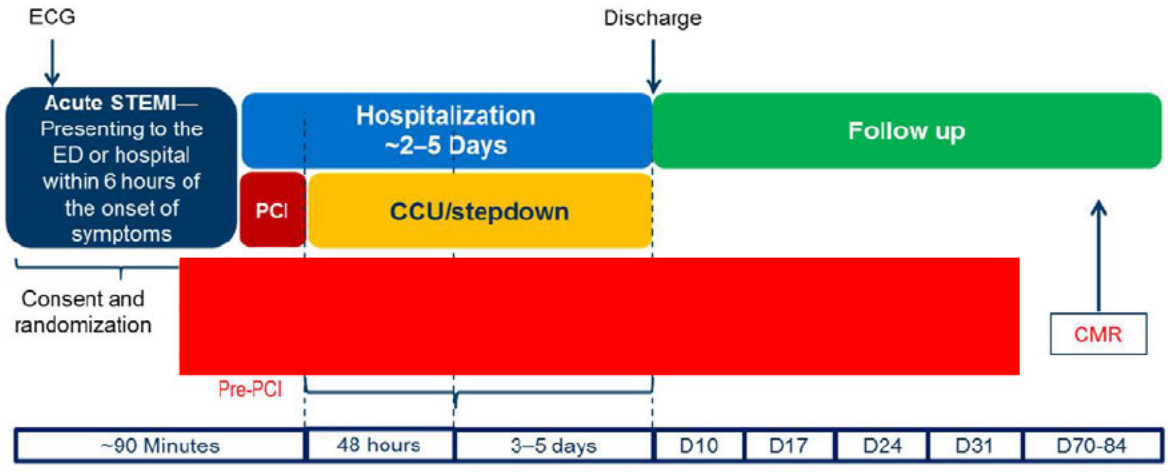
Figure 2.1 Overall Study Schema



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.

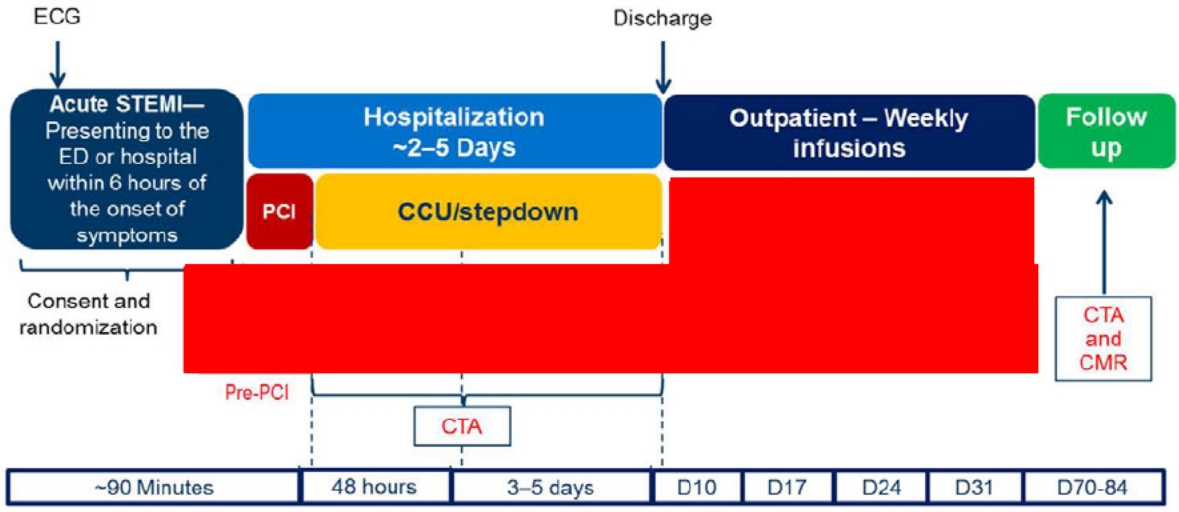
The study flow diagrams for Cohort A and Cohort B are presented in Figure 2.2 and Figure 2.3, respectively.

Figure 2.2 Study Flow Diagram for Cohort A:



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

Figure 2.3 Study Flow Diagram for Cohort B: [redacted]



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

2.3 Treatment Assignment and Blinding

An IXRS will be used for randomization to a treatment regimen. A subject will be considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria. Randomization will be stratified by infarct location. Subjects will be randomized in a 1:1 ratio to one of 2 cohorts, Cohort A ([redacted]) and Cohort B ([redacted]). Within each dose regimen, subjects will be randomized in a 2:1 ratio to receive MEDI6012 or placebo, see Figure 2.1.

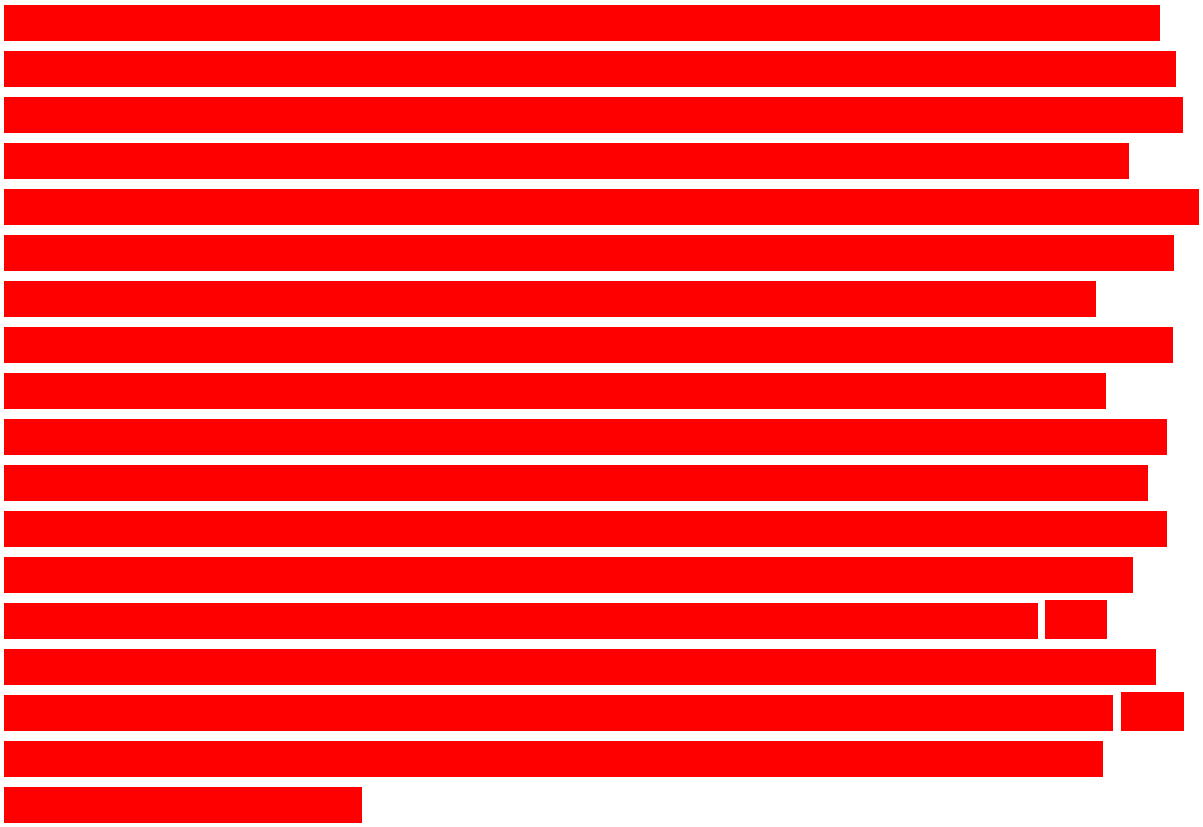
In the event that a dose regimen is dropped at the interim analysis, subjects will be randomized in a 1:1 ratio to receive MEDI6012 or placebo for the remaining dose regimen.

The randomization will be stratified by infarct location, 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.

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). 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. 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 Day 1 blinded to randomization group.

2.4 Sample Size



3 STATISTICAL METHODS

3.1 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 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 unless data are missing, in which case, baseline will be defined as the last value prior to dosing. All statistical tests will be one-sided (based on protocol amendment) at an alpha = 0.05 significance level unless stated otherwise. Confidence intervals will be one-sided (based on protocol amendment) and nominal p-values will be reported when appropriate.

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

3.2 Analysis Populations

The analysis populations are defined in Table 3.1.

Table 3.1 Analysis Populations

Population	Description
ITT Population	The ITT Population consists of subjects who are randomized, and will be analyzed according to their randomized treatment group.
As-treated Population	The As-treated Population consists of randomized subjects who receive any study investigational product. 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.
Primary Efficacy Analysis Population	Randomized subjects who receive at least [redacted] doses of investigational product with TFG 0 or 1 on initial angiography. Subjects who receive all placebo doses will be analyzed with the placebo group; conversely, subjects who receive [redacted] doses of MEDI6012 will be analyzed with the MEDI6012 group.

Table 3.1 Analysis Populations

Population	Description
Efficacy Analysis Population –TIMI 2-3	Randomized subjects who receive at [redacted] doses of investigational product with TFG 2 or 3 on initial angiography. Subjects who receive all placebo doses will be analyzed with the placebo group; conversely, subjects who receive [redacted] of MEDI6012 will be analyzed with the MEDI6012 group.
Efficacy Analysis Population TIMI – 0-3	Randomized subjects who receive at [redacted] of investigational product with TFG 0 to 3 on initial angiography. Subjects who receive all placebo doses will be analyzed with the placebo group; conversely, subjects who receive [redacted] doses of MEDI6012 will be analyzed with the MEDI6012 group.
CTA Analysis Population	Randomized subjects in the [redacted] regimen who receive a full treatment course of investigation product. The subjects who receive [redacted] placebo doses will be analyzed with the placebo group; conversely, subjects who receive [redacted] dose 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.

CTA = computed tomography angiography; ITT = Intent-to-treat; LCAT = lecithin-cholesterol acyltransferase; PK = pharmacokinetic; TFG = TIMI flow grade; TIMI = Thrombolysis in Myocardial Infarction.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

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

3.3.2 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, ethnicity, weight, height, and body mass index will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics may include, but not be limited to medical history and acute cardiovascular disease history.

3.3.3 Study Drug Exposure

The number of subjects for the exposure to investigational product will be summarized descriptively by the total number of dose received.

The entire dose administered (ie, Yes vs No), the reason(s) why the subject was not administered entire dose and the reason(s) why the subject did not receive any investigational product (ie, adverse events [AEs] vs other) will be provided in the listing.

3.3.4 Concomitant Medications

Concomitant medications will be coded using the latest available version of the World Health Organization Drug Dictionary and summarized by preferred term with frequency and percentage by treatment group. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical Classification System.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the infarct size, expressed as a percentage of LV mass measured on delayed-enhanced CMR imaging, in 10–12 weeks post- MI.

3.4.1.2 Handling of Dropouts and Missing Data

Missing data will not be imputed.

3.4.1.3 Primary Efficacy Analysis

The primary efficacy endpoint is the infarct size in 10-12 weeks post MI. The endpoint will be log-transformed due to its skewed distribution and be analyzed by means of 2-sample t-test. The treatment effect is estimated by the geometric mean ratio of MEDI6012 to placebo as well as its 95% CI. Infarct size records with zero value, will be imputed by half of the minimum of the non-zero records prior to the log transformation.

3.4.1.4 Additional Analyses of the Primary Efficacy Endpoint(s)

The primary population is the primary efficacy analysis population (TIMI 0-1). Similar analysis will also be performed for the Efficacy Analysis Population with TIMI 0-3, the efficacy analysis population with TIMI 2-3, and the ITT Population.

Non-parametric (distribution-free) methods will be applied to primary endpoint data if applicable.

3.4.1.5 Subgroup Analyses

The primary endpoint of infarct size will be analyzed for the following subgroups. The first set of subgroups are based on baseline characteristics and time of treatment administration.

- Sex: male vs female

- Diabetic vs non-diabetic
- Smoker vs non-smoker
- Infarct location: anterior vs non-anterior
- TIMI Flow Grade 0 vs 1 vs 2 vs 3 pre-pPCI
- TIMI Flow Grade 0 or 1 vs 2 or 3 pre-pPCI
- Above vs below the median door-to-device time
- Above vs below the median symptom onset-to-device time
- Above vs below the median symptom onset-to-door time

The second set of subgroups, outlined in Table 3.2, are based on post-randomization outcomes and will not be used to make comparisons between treatment and placebo.

Table 3.2 Post-randomization Analysis Subgroups

Endpoint	Comparison Groups
Infarct size by culprit vessel location determined by baseline invasive coronary angiography	LAD vs Non-LAD LAD vs Left Circumflex Artery vs Right Coronary Artery
Infarct size by timing of drug administration	Investigational product administration before vs after pPCI Above vs below the median time between Dose 1 and pPCI
Infarct size by post-pPCI TIMI Flow Grade	TIMI Flow Grade 0 vs 1 vs 2 vs 3 post-pPCI TIMI Flow Grade 0 or 1 vs 2 or 3 post-pPCI

Infarct size by lipid and apolipoprotein levels	Above vs. below the median HDL at baseline Above vs. below the median HDL change from baseline Above vs. below the median apoA1 at baseline Above vs. below the median apoA1 change from baseline
Infarct size by cardiovascular event status	Any CV event vs no CV event HF Hospitalization vs No HF

LAD = left anterior descending artery; pPCI = primary percutaneous coronary intervention; CV = cardiovascular; HF = heart failure

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

3.4.2.1 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include ejection fraction (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.

3.4.2.2 Handling of Dropouts and Missing Data

Missing data will not be imputed.

3.4.2.3 Secondary Efficacy Analyses

EF, myocardial mass, and left ventricular volumes will be analyzed using t-test, if appropriate, based on the Primary Efficacy Analysis Population, the Efficacy Analysis Population – TIMI 2-3; Efficacy Analysis Population – TIMI 0-3; as treated, and the ITT Population.

Change from index CTA in NCPV will be analyzed using t-test, if appropriate, based on CTA Analysis, As-treated, and ITT Populations.

Parameters will first be evaluated for normality which will be evaluated using Q-Q plots.

If the distribution appears to be normal, the endpoint will be analyzed by a 2-sample t-test. The treatment effect is estimated by difference in means of MEDI6012 to placebo as well as its 95% CI.

If the distribution appears to be log-normal, the endpoint will be log-transformed due to its skewed distribution and be analyzed by a 2-sample t-test. The treatment effect is estimated by the geometric mean ratio of MEDI6012 to placebo as well as its 95% CI.

Non-parametric (distribution-free) methods will be applied to the endpoint data if applicable.

3.4.2.4 Subgroup Analyses

The secondary endpoints will be analyzed for the subgroups listed below, which includes a mixture of subgroups defined before and after randomization. As for the primary efficacy endpoint, subgroups defined after randomization will not be used to make comparisons between active and placebo arms.

- Sex: male vs female
- Diabetic vs non-diabetic
- Infarct location: anterior vs non-anterior
- Infarct location: LAD vs non-LAD
- Infarct Location: LAD vs LCX vs. RCA
- TIMI Flow Grade 0 vs 1 vs 2 vs 3 pre-pPCI
- TIMI Flow Grade 0 or 1 vs 2 or 3 pre-pPCI
- TIMI Flow Grade 0 vs 1 vs 2 vs 3 post-pPCI
- TIMI Flow Grade 0 or 1 vs 2 or 3 post-pPCI
- Above vs below the median door-to-device time

- Above vs below the median symptom onset-to-device time
- Above vs below the median symptom onset-to-door time
- Drug administration before vs after pPCI
- Above vs below the median time between dose 1 and pPCI
- Above vs below the median HDL at baseline
- Above vs below the median HDL change from baseline
- Above vs below the median apoA1 at baseline
- Above vs below the median apoA1 change from baseline
- Cardiovascular Event vs No Cardiovascular Event
- HF Hospitalization vs No HF Hospitalization
- Prior statin vs statin naïve
- Baseline LDL-C ≤ 100 vs > 100 mg/dL
- Baseline LDL-C ≤ 70 vs > 70 mg/dL

3.4.3 Other Efficacy Analyses

[redacted]

3.5 Pharmacodynamic Endpoint(s) and Analyses

3.5.1.1 Pharmacodynamic Endpoint(s)

The following pharmacodynamic (PD) markers will be collected: [redacted]

3.5.1.2 Analysis of Pharmacodynamic Endpoint

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

3.6 Safety Analyses

3.6.1 Adverse Events and Serious 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 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. If the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All treatment-emergent adverse events will be summarized overall and by

MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, serious adverse events, and treatment discontinuations due to AEs will be provided.

3.6.2 Adverse Events of Special Interest

Not applicable.

3.6.3 Deaths and Treatment Discontinuations due to Adverse Events

Deaths, and AEs leading to discontinuation of investigational product will be summarized.

3.6.4 Clinical Laboratory Evaluation

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 where possible.

3.6.4.1 Vital Signs

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

3.6.4.2 Electrocardiogram

Not applicable.

3.7 Immunogenicity

Anti-drug antibody (ADA) incidence rate and titer will be tabulated for each treatment group. Samples confirmed positive for ADA will be tested and analyzed for neutralizing antibodies and summarized similarly.

3.8 Pharmacokinetics

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.

3.9 COVID-19 Analyses

COVID-19 study disruptions may be summarized if applicable.

Additional analyses may be performed to explore the impact of COVID-19 and implemented contingency measures (eg, subjects discontinued from study treatment and/or study, protocol deviations related to COVID-19) on the safety and efficacy results reported for the study.

In addition, listings may be provided for

- subjects affected by the COVID-19 pandemic
- subjects with reported issues in the clinical trial management system due to COVID-19 pandemic

4 INTERIM ANALYSIS

Two interim analyses are planned. The objectives of the first interim analysis will be to assess futility and potentially to drop a dose regimen. The analysis, which will be conducted after 30% of the Primary Efficacy Analysis Population (assumed 40% rate of exclusion from the primary efficacy analysis population is expected due to TFG 2 or 3 flow in the infarct-related artery on initial angiography and other reasons for subsequent exclusion or drop-out) based on the original sample size (N = 74) is enrolled, will require that > 50% of subjects (N > 37) have acute anterior STEMI and have completed their final study visit. The first interim analysis will be conducted through the Independent Data Monitoring Committee (IDMC). The second interim analysis is planned to accelerate decision on future development options for MEDI6012 and will be performed once 60% of the Primary Efficacy Analysis Population (assumed 50% rate of exclusion from the primary efficacy analysis population is expected due to TFG 2 or 3 flow in the infarct-related artery on initial angiography and other reasons for subsequent exclusion or drop-out) based on the revised sample size (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 unblinding plan. The sponsor and Principal Investigator will monitor the statistical assumptions in a blinded fashion and schedule the interim analyses accordingly.

The assessment of futility will be based on predictive power, which is conditional power averaged over the distribution of the observed treatment effect at the time of interim analysis. The futility analysis will include all available data at the time of the interim data cut.

The predictive power based on the empirical trend observed at the interim analysis will be calculated by

$$\text{predictive power } pp = \Phi\left(\frac{z_\tau - z_{1-\alpha/2}\sqrt{\tau}}{\sqrt{1-\tau}}\right)$$

τ is the information fraction at the interim analysis, z_τ is the observed value of the test statistic at the interim, α is the two-sided significance level at the final analysis based on the original protocol, and Φ is the standardized normal density function.

Each MEDI6012 dose regimen will be compared to the combined placebo group (pooled over dose regimens).

The study may be declared as "futile" if for both the 2-dose and the [redacted] regimens the calculated predictive power is < 20% for

- infarct size in the Primary Efficacy Analysis Population; AND
- ejection fraction in the Primary Efficacy Analysis Population; AND
- infarct size in the Efficacy Analysis Population - TIMI 0-3; AND
- ejection fraction in the Efficacy Analysis Population - TIMI 0-3.

The [redacted] regimen may be dropped if the calculated predictive power is < 20% for

- infarct size in Primary Efficacy Analysis Population; AND
- ejection fraction in Primary Efficacy Analysis Population; AND
- infarct size in Efficacy Analysis Population – TIMI 0-3; AND
- ejection fraction in Efficacy Analysis Population – TIMI 0-3.

For illustration purposes, Figure 4.1 provides the estimated predictive power when the observed infarct size reduction varies from -20 to 50% in the Primary Efficacy Analysis Population. The 20% predictive power translates into an infarct size reduction of approximately 7%. A value of 50% will result in 18% infarct size reduction, which is the minimally detectable treatment effect for this study. Figure 4.2 provides the estimated predictive power when the observed ejection fraction increase varies from a -5 to 10% in the

Primary Efficacy Analysis Population. Calculated predictive power will be based on observed data.

Figure 4.1 **Predictive power against observed interim relative infarct size reduction when 30% of the Primary Efficacy Analysis Population is enrolled and complete their final study visit**

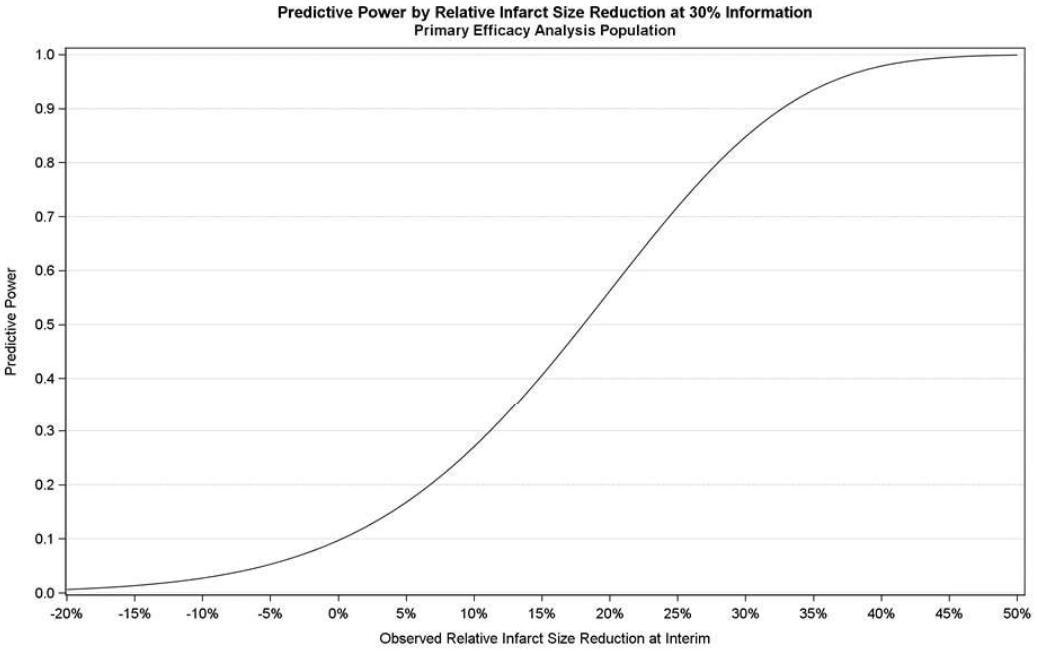
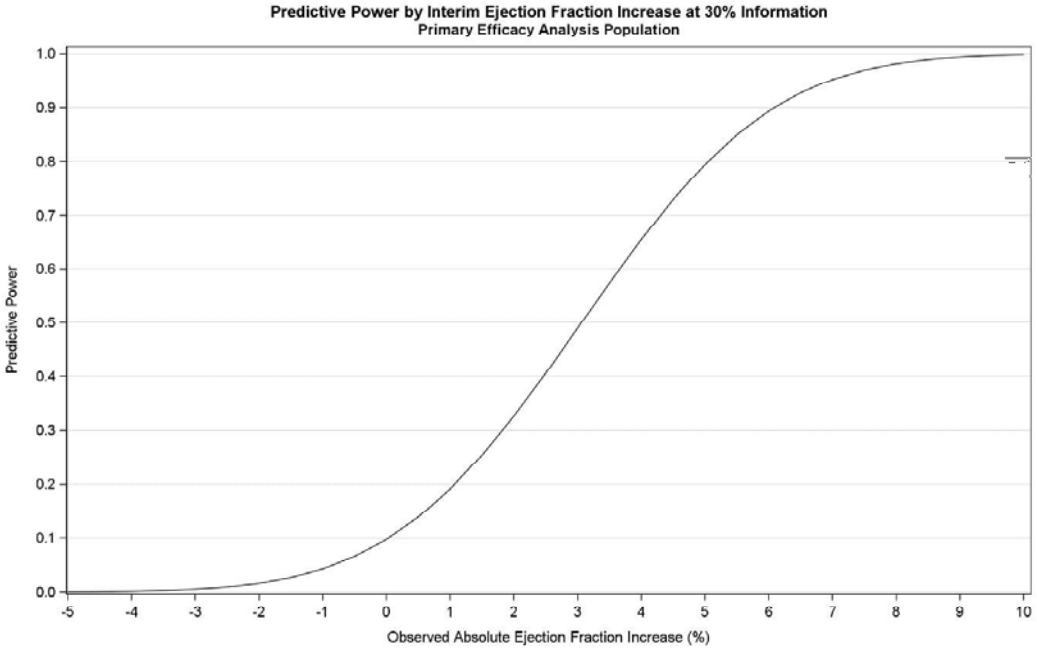


Figure 4.2 **Predictive power against observed interim ejection fraction increase when 30% of the Primary Efficacy Analysis Population is enrolled and complete their final study visit**



Before declaring futility, the IDMC will evaluate data from CTA measurements for plaque regression as well as clinical efficacy endpoints (cardiovascular death, heart failure, myocardial infarction and stroke) and consider these findings in their recommendations regarding futility. If significant benefits for plaque regression and/or clinical outcomes are observed, the IDMC may recommend the data be reviewed by the sponsor's unblinded review committee (URC) for consideration to continue the trial even if the futility criteria for infarct size and ejection fraction are met. Clinical efficacy outcomes will be presented as best-available data [i.e., Clinical Events Committee (CEC) adjudicated + unadjudicated events] as well as CEC adjudicated-only data.

5 REFERENCES

<< Reference: Lan, Gordon K. K., Hu, Peter and Proschan, Michael A. A Conditional Power Approach to the Evaluation of Predictive Power: Statistics In Biopharmaceutical Research May 2009, Vol 1, No. 2.>>

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	04Jun2018	Initial document	Initial document
2.0 First Approved Version in e-TMF/Veeva Vault	01Jul2018	Revised the section 3.2 Analysis Populations. -Primary Efficacy Analysis population: Subjects who receive "2" or more doses of MEDI6012 will be placed to MEDI6012 group. [redacted] Subjects who receive "6" doses of [redacted] Revised the section 3.4.1.5 Subgroup Analyses. - Above vs below the median symptom onset-to-"device" time Added section 3.6.4.2 Electrocardiogram - Electrocardiogram will be summarized using descriptive statistics at end of the study by treatment group.	Incorporated team comments. If Patient gets [redacted] of placebo and then 1 dose of MEDI6012 at end, we won't put in the MEDI arm when assessing efficacy. We modified the language for the clarification. Primary efficacy analysis population: Randomized subjects who receive at least [redacted] doses of investigational product with TFG 0 or 1 or initial angiography. Subjects who receive all placebo doses will be included in the placebo group; conversely, subjects who receive [redacted] doses of MEDI6012 will be placed to MEDI6012 group. If Patient gets [redacted] doses of placebo and then 1 dose of MEDI6012 at end, we won't put in MEDI arm when assessing CTA analysis. We modified the language for the clarification. CTA Analysis

			Population: Randomization subjects in [redacted] regimen who receive a full treatment course of investigation product. Subjects who receive all placebo doses will be included in the placebo group; conversely, subjects who receive [redacted] of MEDI6012 will be placed to MEDI6012 group. Currently the eCRF database captures symptom onset time and device time. We changed balloon to device for subgroup analysis. We added section 3.6.4.2 for Electrocardiogram.
3.0	03Dec2020		Add more details of interim analysis (e.g., predictive power). Add reference of formula of predictive power. Add data handling approach of zero infarct size. Align with protocol amendment with updated numbers related to sample size inflation and changes from two-sided to one-sided significance/alpha. Align with protocol amendment for potential 2 DBLs and extended follow-up period data report. Add statistical checking for the data distribution and applicable statistical testing based on distribution assumption to ensure the statistical appropriateness Add COVID-19 subsection and analysis Remove subgroup of statin therapy intensity Remove ECG language which is not applicable Align with protocol amendment with updated CV endpoints

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