Statistical Analysis Plan	
Study Code	D4920C00002
Edition Number	4
Date	01 December 2023

Phase IIB, Randomized, Double-blinded, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of MEDI6570 in Participants with a Prior Myocardial Infarction, Persistent Inflammation, and Elevated N-terminal Prohormone Brain Natriuretic Peptide

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

No table of figures entries found.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AU	Arbitrary Units
BILI	Total Bilirubin
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CI	Confidence Interval
CK	Creatine Kinase
CM	Concomitant Medication
CS	Compound Symmetry Covariance Structures
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTA	(Coronary) Computed Tomography Angiography
CDV	Cardiovascular
CV	Coefficient of Variation
ECG	Electrocardiogram
CCI	[redacted]
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EXP	Exponential
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GeoMean	Geometric Mean
GeoCV	Geometric Coefficient of Variation
GLS	Global Longitudinal Strain
GeoSD	Geometric Standard Deviation

Abbreviation or special term	Explanation
HDL	High Density Lipoprotein
HF	Heart Failure
CCI	CCI [redacted]
hs-CRP	High Sensitivity C Reactive Protein
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
CCI	CCI [redacted]
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intention To Treat
KM	Kaplan Meier
LAPV	Low Attenuation Plaque Volume
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
LN	Normal Logarithm
LOCF	Last Observation Carried Forward
LVEF	Left Ventricular Ejection Fraction
LSmeans	Least-Square Means
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMRM	Mixed Model Repeated Measures
CCI	[redacted]
[redacted]	[redacted]
NC	Not Calculable
NCPV	Non Calcified Plaque Volume (Global)
$NCPV_{MD}$	Non Calcified Plaque Volume in The Most Diseased Coronary Segment
NT-proBNP	N Terminal Prohormone Brain Natriuretic Peptide
NQ	Not Quantifiable
NR	Not Reportable
NS	No Sample
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
PDMP	Protocol Deviation Management Plan
PCI	Percutaneous Coronary Intervention
PK	Pharmacokinetics
PT	Preferred Term

Abbreviation or special term	Explanation
Q4W	Every 4 Weeks
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
CCI	[redacted]
SOC	System Organ Class
SQRT	Square Root
STEMI	ST Segment Elevation Myocardial Infarction
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
Q-Q	Quantile-Quantile
CCI	[redacted]
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
UN	Unstructured Covariance Structures
UNSCH	Unscheduled
WHO	World Health Organization
WHO-DD	World Health Organization- Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
15SEP2020, v1.0	NA
28APR2021, v2.0	Study design and sample size sections updated to be consistent with clinical study protocol (CSP) amendment 1. Details for pre-interim analysis added. Definition of analysis set updated following CSP amendment 1, especially CCI dose switching to CCI Definition details and guidance reference added for computed tomography angiography (CTA) parameters. List of fasting lipid parameters added. Vital sign reference ranges added. Tables and listings related to COVID pandemic added. Sensitivity analysis without subjects having received both CCI added. Some subgroup categories (geographical region, N terminal prohormone brain natriuretic peptide (NT-pro-BNP), CCI low density lipoprotein (LDL), left ventricular ejection fraction (LVEF)) added. Specification of ADA analyses added. Specific analyses for CCI added. AE incidence by SOC and PT for bleeding and injection site reaction added. ALT, AST and BILI elevations summaries added.

Date	Brief description of change
07MAR2022, v3.0	Due to visit 9 removed in CSP amendment 2, visit 9 and following visits do not correspond to the same visit according to when patient was randomized. The visit "Day XX/Visit Y" were replaced by "Day XX" in all the SAP and Shells. Variables removed from CSP amendment 2.0 are kept in the Statistical Analysis Plan (SAP) and will be analysed with descriptive statistics only (no statistical model, no figure, no subgroup analysis). Secondary endpoints removed from CSP amendment 2 are analysed as exploratory endpoints. Since interim CTA at Day 122 was removed, only descriptive statistics will be provided at Day 122 for CTA parameters (no statistical model). Everything that concerns interim analyses was removed especially section 5. Analysis visit windows were added, and it was removed that nominal eCRF visits will be used in statistical analyses. The rule for complete/partially missing start and stop dates of concomitant medication was updated. For geometric mean calculation, an imputation rule was added for variables records with zero value. It was added that the description of primary and secondary efficacy parameters will be studied over the course of the study using baseline value. In case of departure from the a priori distribution, the statistical analysis planned in this SAP will be updated. Definitions of change from baseline (normal distribution), relative change from baseline (log-normal distribution) and percent change (any distribution) were added. It was specified "one sided" before "p-value", also "95% CI" was replaced by "90% CI". A listing on overdose was added. Following sensitivity analyses were removed: LOCF and MMRM (not appropriate since interim CTA is removed). Sensitivity on patients without CTA assessment changed from baseline to Day 253 was added. Some subgroup removed: CCI subgroup defined on tertiles were removed only medians were kept, repetition of subgroups on patients with reduced ejection fraction. LLOQ value was updated to 0.0328 µg/mL. CCI [redacted] CCI [redacted] Addition that the bioanalytical test site will have access to the randomization list.

1 STUDY DETAILS

1.1 Study objectives

The following endpoints in Table 1 will be evaluated in order to meet the objectives of the study.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of MEDI6570 on non-calcified coronary atherosclerotic plaques compared with placebo	Change from baseline to Day 253 in non-calcified plaque volume in the most diseased coronary segment ($NCPV_{MD}$), as measured by CTA imaging
Secondary	
To evaluate the effect of MEDI6570 on a surrogate biomarker of HF compared with placebo	Change from baseline to Day 253 in NT-proBNP
To evaluate the effect of MEDI6570 on left ventricular systolic function compared with placebo	Change from baseline to Day 253 in: • LVEF • GLS as measured by echocardiography
To evaluate the effect of MEDI6570 on left ventricular systolic function among participants with reduced ejection fraction (defined as <50%) compared with placebo	Change from baseline to Day 253 in: • LVEF • GLS as measured by echocardiography
To evaluate the effect of MEDI6570 on other measures of non-calcified coronary atherosclerotic plaque compared with placebo	Change from baseline to Day 253 in: • Global non-calcified plaque volume • Low attenuation plaque volume as measured by CTA imaging
To evaluate the immunogenicity of MEDI6570	• ADA incidence • Titre as measured in serum during the intervention and follow-up periods
To evaluate the PK of MEDI6570	MEDI6570 concentrations as measured in serum during the intervention and follow-up periods

Objectives	Endpoints
Safety	
To assess the safety and tolerability of MEDI6570 compared with placebo	During the treatment and follow-up periods: • AEs • Clinically important changes in: Vital signs ECGs Safety laboratory assessments
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ADA, anti-drug antibody(ies); AE, adverse event; CTA, computed tomography angiography; CDV, cardiovascular; ECG, electrocardiogram; CCI [redacted] (ratio); GLS, global longitudinal strain; HF, heart failure; CCI [redacted]; LVEF, left ventricular ejection fraction; CCI [redacted]; MI, myocardial infarction; $NCPV_{MD}$, non-calcified plaque volume in the most diseased coronary segment, NT-proBNP, N-terminal prohormone brain natriuretic peptide; PK, pharmacokinetic(s); SAE, serious adverse event; CCI [redacted]

Some parameters are no longer listed as objectives and endpoints following CSP amendment 2 CCI [redacted]; but summary statistics are still required for patients enrolled under CSP V1 and CSP amendment 1. Thus, they are not listed in Table 1 but can be found in Sections 3 and 4 as exploratory endpoints.

1.2 Study design

This is a Phase IIB, randomized, double-blinded, placebo-controlled, parallel-group, multicenter, international study to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of MEDI6570 in subjects 30 to 365 days post MI with persistent inflammation defined as high sensitivity C-reactive protein (hs-CRP) ≥ 1 mg/L). Participants will be randomized to receive CCI (in an injection volume of 1.5 mL), or CCI (in an injection volume of 4.0 mL) MEDI6570 subcutaneously (SC), or an injection/volume-matched placebo (1.5 or 4.0 mL) every 4 weeks (Q4W) for 32 weeks (9 doses in total). Approximately 400 participants will be randomized CCI [redacted] Participants who were randomized to a study intervention under Protocol Version 1.0 or Amendment 1 (when there was also a CCI dose group) and were allocated a dosing volume of 0.5 mL will continue on their randomized study intervention (CCI MEDI6570, or its injection/volume-matched placebo) to the end of the study, and the study blind will be maintained with regard to active versus placebo. The randomization will be stratified by geographic region (Asia, North America and Rest of the World) and by statin therapy status (no, low- or moderate-intensity statin therapy vs high-intensity statin therapy) at baseline.
The study will be conducted at approximately 70 to 100 study sites across Europe, Asia, Australia, and North America.

Subjects will be enrolled in the study for up to approximately 12 months, comprising an optional pre-screening period of up to 42 days (6 weeks), a screening and pre-randomization period of up to 42 days (6 weeks), a treatment period of 225 days (31 to 32 weeks), and a follow-up period of 100 days (approximately 14 weeks). Following screening and confirmation of eligibility, subjects will undergo an echocardiogram and (Coronary) computed tomography angiography (CTA) scan before randomization. The first dose of study treatment will be administered on Day 1 (Visit 3), after randomization. During the follow-up period, subjects will undergo an echocardiogram and CTA scan.

An Independent Data Monitoring Committee (IDMC) will review safety data from this study. A separate charter establishes the rules, meeting frequency, and scope of responsibilities of the IDMC. The report that will be received by the IDMC to evaluate safety will contain some of the TFL listed in this Statistical analysis plan (SAP).

No formal interim analysis is planned.

An analysis restricted to PK (serum MEDI6570 concentration) and PD CCI [redacted] data, will be performed after approximately 80 participants have completed the Day 57 (Visit 6), to evaluate the PK data and

the PK-PD relationship. Non-study personnel who have no other involvement in the study will perform this evaluation. These PK and PD data will be reviewed in conjunction with the safety data by the independent IDMC.

1.3 Number of subjects

The 3 injection/volume-matched placebo groups will be pooled for the analyses. CCI

[redacted]

2 ANALYSIS SETS

2.1 Definition of analysis sets

There are 9 populations defined for this study (Table 2).

Table 2 Populations for Analyses

Population	Description
All enrolled subjects	All enrolled subjects include those who have signed the informed consent form (pre-screen ICF or screen ICF).
Intent-to-treat (ITT) Population *	All randomized subjects will be included in the Intent-to-treat (ITT) Population. Subjects will be analysed according to their randomized treatment group. Subjects initially randomized to the CCI group who consented CSP amendment 1 and should switch dose to CCI will be analysed according to the CCI group.

Population	Description
As-treated population*	Randomized subjects who received any study treatment will be included in the As-treated Population. Subjects will be analysed according to the actual treatment they received, regardless of their randomized treatment group. Subjects treated within the CCI group that received at least one CCI dose during the study will be analysed according to the CCI group. If a patient received incorrect study drug for only a part of the treatment duration but also received correct study drug for the remaining time, the associated as-treated group for that patient will be the treatment group the patient was randomized to.
CTA Analysis population	Subjects within the ITT population who have interpretable** CTA scans at baseline and at Day 253 or at Day 122 will be included. (Note that separate analyses will be conducted for Day 253 and Day 122). Subjects will be analysed according to their randomized treatment group.
Per-protocol CTA analysis population	Subjects in the CTA Analysis Population who received at least 3 doses of study treatment will be included in the Per-protocol CTA Analysis Population. Subjects will be analysed according to the actual treatment they received.
Echocardiogram Analysis population	Subjects within the ITT population who have interpretable echocardiograms in the baseline and follow-up periods will be included in the Echocardiogram Analysis Population. Subjects will be analysed according to their randomized treatment group.
CCI	[redacted]
PK population	All subjects who received ≥ 1 dose of MEDI6570 and have ≥ 1 one post-dose evaluable MEDI6570 serum concentration will be included in the PK population. Subjects will be analysed according to the actual treatment they received. Subjects who received both CCI doses during the study will be analysed as a separate CCI group.
Immunogenicity population	Subjects included in the As-treated Population who have ≥ 1 immunogenicity sample will be included in the Immunogenicity Population. Subjects will be analysed according to the actual treatment they received.

* All subjects randomized in initial CSP accepted CSP amendment 1 and took at least one dose under CSP amendment 1. This means that any subject initially randomized in CCI have taken at least one dose of CCI

**An interpretable CTA scan is defined as having 1 or more matching evaluable segment at baseline and at Day 253 or at Day 122. LOCF (Last Observation Carried Forward) method not applied. The baseline scan must have quantifiable plaque present after segment matching to be interpretable. Programming specifics on matching evaluable segments are detailed in a separate CTA imaging guidance document (Version 4.0).

2.2 Violations and deviations

The protocol deviation management plan (PDMP) categorizes the important and non-important protocol deviations and outlines how the deviations are handled.

3 BASELINE, PRIMARY, SECONDARY, EXPLORATORY AND SAFETY VARIABLES

3.1 General principles

3.1.1 Handling of missing data

Except for the below and unless otherwise specified, missing data will not be imputed.

3.1.1.1 Imputation of time of first dose of IP

Completely missing time where only hour is missing will be imputed to 00:00. If the time (hours/minutes: HH:MM) of the first dose of IP is completely missing or the hour HH is missing, imputation will be 00:00. If only the minutes are missing imputation will be HH:00. .

3.1.1.2 Imputation of adverse event / concomitant medication start date

Missing start dates (where in eCRF UN, UNK and 0000 indicate unknown or missing Day, Month and Year respectively for partial missing dates, while completely missing dates would be left empty):

- Completely missing dates will not be imputed.
- If the day is missing and the month and year are different from the month and year of the first dose of study treatment, assume 01-MMM-YYYY. If the month and year are the same as the first dose of IP month and year and the end date (after any imputation) is on or after (including still on-going/ missing at the end of the study) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date (after any imputation) is prior to the first dose of IP, then assume the end date for the start date.
- If the month is missing and the year is different from the year of first dose of IP, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of IP and the end date (after any imputation) is on or after (including still on-going/ missing at the end of the study) the first dose of IP, then assume the date of the first dose of IP. If the year is

the same as the first dose of IP and the end date (after any imputation) is prior to the first dose of IP, then assume the end date for the start date.

After applying these rules, if the imputed AE start date is after a complete AE end date (or date of death or date of end of study), the imputed start date will be the same as the complete AE end date (or date of death or date of end of study); if the end date is missing and the imputed AE start date is after the end of study date then assume the same date as the study end date.

CCI [redacted].

3.1.1.3 Imputation of adverse event / concomitant medication stop date

Missing stop dates (where in eCRF UN, UNK and 0000 indicate unknown or missing Day, Month and Year respectively for partial missing dates, while completely missing dates would be left empty):

- Completely missing dates will not be imputed.

Partial missing AE/CM end dates are imputed as below:

- If the AE/CM is not ongoing and if only the day is missing: Assume the last day of the collected month.
- If the AE/CM is not ongoing and the month is missing: Assume 31-DEC-YYYY (of the collected year).

After applying these rules, if the imputed AE or concomitant medication (CM) stop date is after the date of death (or after the date of the end of the study), the imputed stop date will be the same as the date of death (or the date of the end of the study).

- If the AE/CM is ongoing, the stop date will remain missing. Completely missing dates will not be imputed.

3.1.2 Baseline definition and analysis visit windows

Baseline is defined as the last evaluable non-missing assessment prior to the start of IP and any information taken after first dose of IP will be regarded as post-baseline information. For CTA parameters additional rules apply related to matching evaluable segments, please refer to CTA imaging guidance document (Version 4.0). If two or more assessments are equally eligible to assess subject status at baseline (i.e. on the same date prior to first dose with no time recorded to distinguish the assessments), the average should be taken as the baseline value. For non-numeric assessments where taking an average is not possible then the best category for ordinal data and the last measurement for non-ordinal categorical data would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1/Visit 3,

one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline, assuming it could be determined that it occurred prior to first dose. If the assessment is collected on Day 1 but it cannot be determined if it was done before or after the first dose of IP (due to missing time and/or planned time point), then it will be considered as collected after the first dose of IP except if as per protocol the measurement at day 1 is planned to be done before the first dose of IP. If no value exists before the first dose of IP, then the baseline value will be treated as missing.

For analysis visit post baseline for CTA, if more than one measurement falls in the same visit window but in different days, the latest will be used. If several measurements are collected within the same distance from the scheduled study day, the data of the latest visit after the scheduled study day within that window is used. If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements is taken. If there are several categorical values corresponding to the worst case, then the last measurement registered in CRF will be taken.

The date of first dose of study treatment will be considered relative Day 1/Visit 3, and the day before the first dose of study treatment will be relative Day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the first dose of study treatment: date of assessment - date of first dose of study treatment + 1.

For days before the first dose of study treatment: date of assessment - date of first dose of study treatment.

For the purpose of the statistical analysis, efficacy and safety variables are allocated to the analysis visit as reported in the table below. Analysis visit is defined based on analysis day the visit occurred, visit window reported below, and using scheduled or unscheduled eCRF visits. The allocation to analysis visit windows is performed after the imputation of date of first and last doses of IP as in Section 3.1.1. Measurements with missing or partially missing dates cannot be imputed to any analysis visit.

Table 3 Scheduled analysis visit windows

Analysis visit	CSP visit name		Visit window (days)	
	After amendment 2[d]	Before amendment 2	CTA – ECHO – Biomarkers[a]	Other parameters
Pre-treatment	Visit 2 – Visit 3		<= 1[b]	
Day 10	Visit 4		CCI : 3 -17	3 -17
Day 29	Visit 5		Biomarkers: 21 – 37	21 – 37
Day 57	Visit 6		CCI : 49 – 65	49 – 65
Day 85	Visit 7		Biomarkers: 77 – 93	77 – 93
Day 113	Visit 8		Biomarkers: 105 – 121	105 – 121[c]
Day 122		Visit 9	CTA: 114 – 140 CCI and biomarkers: 118-126	118 – 126
Day 141	Visit 9	Visit 10	CCI 133 - 149	133 - 149
Day 169	Visit 10	Visit 11	CCI 161 - 177	161 - 177
Day 197	Visit 11	Visit 12		188 - 206
Day 225	Visit 12	Visit 13	Biomarkers: 217 - 233	217 - 233
Day 253	Visit 13	Visit 14	CCI : 249-264 Biomarkers except CCI : 249 - 285 CTA, ECHO: 234 - 326	244 - 271
Day 325/405	Visit 14	Visit 16	CCI : 317 - 333/ 394 - 416	317 - 333/ 394 - 416

[a] CCI , NT-proBNP, CCI CCI NT-proBNP, we will include analysis visits of pre-treatment, Day 113 and Day 253. CCI we will include analysis visits of pre-treatment, Day 10, Day 29, Day 57, Day 113, and Day 253.
[b] Includes all measurements collected before or on day 1 prior to first dose of IP. If measurement is done on day 1 but time of collection is missing and per CSP parameter should be collected before first dose of study, analysis phase is "Pre-treatment".
[c] to avoid conflict between analysis visit Day 113 and Day 122, for participants who performed visit 8 before amendment 2 the visit window will be 109 – 117. For participants with missing date of reconsent for amendment 2 or who did Visit 8 before 25Jan2022 (Date of migration in EDC) the visit window will be also 109 – 117.
[d] Some scheduled visits were removed after the protocol amendment 2 but these analysis visits will be included in the analysis because they fall in the analysis windows defined before the protocol amendment 2. Please check the latest version of the protocol for more details.

End of Treatment is defined as the last value in the on-treatment phase as defined in section 3.1.3.

Baseline visit window will be derived for the analysis purpose and includes measurements collected prior day 1 or at day 1 prior to the first dose of study treatment.

An analysis visit is classified as scheduled if it was requested per the Schedule of Activity at the time the patient did the visit (especially if visit done before or after protocol amendment 2). Except otherwise specified, the data being assigned as unscheduled analysis visits will not be summarized in tables or presented in figures but only displayed in listings.

3.1.3 Analysis phase windows

For the purpose of the statistical analysis, the assessments will also be assigned to the analysis phase in which they are collected as reported in Table . In case of partially missing date, the imputed date will be used to assign the analysis phase.

Table 4 Analysis phase

Analysis phase	Phase window for analysis (Days)
Pre-treatment	Before first dose of study treatment (<= 1[a])
On-treatment	From Day 1[b]/Visit 3 up to and included 28 days after the last dose of study treatment
Follow-up	More than 28 days after the last dose of study treatment

[a] Includes measurements collected prior day 1 or at day 1 prior to the first dose of study treatment. If measurement is done on day 1 but time of collection is missing and per CSP parameter should be collected before first dose of study, analysis phase is "Pre-treatment".
[b] Includes measurements collected at day 1, at the time of study treatment intake and after.

3.2 Baseline assessments and other subject-specific characteristics

3.2.1 Demographic and subject characteristics

Demographic and subject characteristics include age (years), age group (>=21-<40; >=40 - <50; >=50 -<65; >=65), sex, race, height (cm), weight (kg), body mass index (BMI) and ethnicity as well as indication [Non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI)], type of coronary procedure (Diagnostic coronary angiography only, Coronary intervention/revascularisation), extent of disease at start of angiography, procedure type [Percutaneous coronary intervention (PCI), Coronary artery bypass grafting (CABG), No procedure], stent (yes, no), type of stent, stent(s) placed for treatment of qualifying MI (yes, no) and vessels treated (left main, left anterior descending and branches, right coronary artery and branches, left circumflex artery and branches, ramus branch).

Age is the age at screening as reported in the eCRF. BMI (kg/m^2) is calculated as: weight (kg)/ [height (cm)/100]^2. Only baseline values are included in the demographic and subject characteristics.

3.2.2 Medical history

Medical history includes medical and cardiac history and risk factor. They are coded by the most up to date version of Medical Dictionary for Regulatory Activities (MedDRA).

3.3 Efficacy and safety variables

The primary objective of the study is the evaluation of the effect of MEDI6570 on non-calcified plaque volume in the most diseased coronary segment ($NCPV_{MD}$) compared with placebo. The effect will be evaluated by using as primary endpoint the change from baseline to Day 253 in $NCPV_{MD}$, as measured by CTA imaging.

Secondary and Exploratory efficacy endpoints are described in sections 3.3.2 and 0.

Additional secondary objectives are the evaluation of pharmacokinetics (PK) and immunogenicity of MEDI6570. Furthermore, the safety of MEDI6570 compared with placebo will be explored in terms of adverse events (AE) including serious adverse events (SAEs), laboratory evaluations, vital signs, and Electrocardiogram (ECG) analyses.

3.3.1 Primary efficacy endpoint

The primary efficacy endpoint is the change from baseline to Day 253 in $NCPV_{MD}$ (mm^3), as measured by CTA imaging. $NCPV_{MD}$ is assigned to the analysis visits as described in section 3.1.2 and will be measured and compared to placebo.

The most diseased coronary segment is defined as the coronary segment with the highest non-calcified plaque volume on the baseline scan that also has a matching evaluable segment on Day 253 scan. Specific algorithms for programming are provided in a separate CTA imaging guidance document (Version 4.0) finalized before database lock.

3.3.2 Secondary efficacy endpoints

Secondary efficacy endpoints include:

- Change from baseline to Day 253 in NT-proBNP
- Change from baseline to Day 253 in Left ventricular function: ejection fraction (LVEF), Global longitudinal strain (GLS) as measured by Echocardiography
- Change from baseline to Day 253 in other related imaging parameters as assessed by CTA (Global non-calcified plaque volume and Low attenuation plaque volume)

3.3.2.1 NT-proBNP

Serum samples will be collected for the Heart failure (HF) biomarker NT-proBNP (pg/mL). The central laboratory result of NT-proBNP is assigned as per timepoint related to analysis visits (Table 3). Log-transformed value of NT-proBNP will be used for the analysis for comparison with placebo. Change from baseline will be defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value. Results will be derived for all subjects and then for a subset of subjects with reduced ejection fraction (defined as <50% at baseline).

3.3.2.2 LVEF and GLS

LVEF (%) and GLS (%) are other secondary endpoints for evaluating the effect of MEDI6570 on HF. The central laboratory result of LVEF and of GLS is assigned as per timepoint related to analysis visits (Table 3). Change from baseline to Day 253 in LVEF and in GLS by echocardiography imaging will be measured and compared with placebo. Results will be derived for all subjects and then for a subset of subjects with reduced ejection fraction (defined as <50% at baseline).

3.3.2.3 Parameters assessed by CTA

Secondary endpoints that are measured by CTA will be analysed based on CTA Analysis Population. CTA imaging results will be assigned as per timepoint related to analysis visits (Table 3). Change from baseline to Day 253 in Global non-calcified plaque volume (NCPV mm^3) and in Low attenuation plaque volume (LAPV, mm^3) will be measured and compared to placebo. The CTA parameters are measured at the level of the coronary segment. Prior to computing change from baseline, global values will be derived programmatically. Specific algorithms for programming are provided in a separate CTA imaging guidance document (Version 4.0) finalized before database lock.

3.3.3 Other secondary endpoints

Other secondary endpoints include:

- Immunogenicity [Anti-drug antibody(ies) (ADA) incidence and Titre]
- Pharmacokinetic concentrations

3.3.3.1 Immunogenicity parameters

Immunogenicity parameters include:

- ADA
- Titre

The Immunogenicity population will be used for the immunogenicity analyses. Descriptive statistics will be provided at baseline, Day 10, Day 29, Day 57, Day 85, Day 113, Day 122, Day 141, Day 169, Day 197, Day 225, Day 253 and Day 325/405. ADA samples may also be tested further for characterization of ADA response. ADA and Titre results will be assigned as per timepoint related to analysis visits (Table 3).

3.3.3.2 PK parameters and PK concentration

Individual serum concentrations (µg/mL) of MEDI6570 and summary of serum concentrations of MEDI6570 will be presented at baseline, Day 10, Day 29, Day 57, Day 85, Day 113, Day 122, Day 141, Day 169, Day197, Day 225, Day 253 and Day 325/405 based on all subjects in the PK population. PK results will be assigned as per timepoint related to analysis visits (Table 3).

3.3.4 CCI

[redacted]

3.3.4.1 Inflammatory and target engagement biomarkers

CCI [redacted]

[redacted]

CCI

3.3.4.2 CCI

3.3.4.3 CCI

3.3.4.4 CCI

[redacted]

3.3.4.5 CCI

[redacted]

3.3.4.6 CCI

[redacted]

3.3.5 Safety endpoints

3.3.5.1 Adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign

(e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse events (SAEs) will be collected from time of signature of informed consent (either the brief, pre-screening ICF or the full, screening ICF), throughout the treatment period and including the follow-up period. All non-serious AEs will be recorded from time of first dose of study treatment, throughout the treatment period and including the follow-up period. Adverse events (AEs) will be coded with the most up to date MedDRA version. For any additional details on AE reporting please refer to the study protocol.

The AEs are assigned to the analysis phases described in section 3.1.3, based on the AE start date as follows:

- If the AE start date is before the first dose of treatment date, then the AE is assigned to the pre-treatment phase,
- If the AE start date is on or after the first dose of treatment date through 28 days after last dose of treatment (inclusive), then the AE is assigned to the on-treatment phase,
- If the AE start date is more than 28 days after last dose of treatment, then the AE is assigned to the follow-up phase.

If the start date of an AE is completely missing, the AE is assigned as follows:

- If the AE end date is known and is before the first dose of treatment date, then the AE is assigned to the pre-treatment phase,
- If the AE end date is completely missing or if the AE end date is on or after the first dose of treatment date no assignation can be done.

The study day of start of the AE is calculated as the start date of the AE - date of the first dose of treatment +1 for AE started on or after day 1 and as the start date of the AE - date of the first dose of treatment for AE started before day 1. Study day of start of AE is calculated for complete dates only. Imputed dates should not be used. If one of the dates is missing or partially missing, the study day of start of the AE is missing.

All the AEs in the on-treatment and follow-up phases are considered treatment emergent adverse events (TEAEs).

The duration of AE is calculated as the end date of the AE – start date of the AE +1. Duration is calculated for complete dates only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

The analysis will be based on as-treated population.

3.3.5.2 Laboratory evaluations

Clinical laboratory safety tests are performed in a central and/or local clinical laboratory. A list of clinical laboratory safety tests is reported below:

Table 5 Clinical Laboratory Safety Test

Serum chemistry	**Haematology**	**Coagulation Parameters (screening only)**
S/P-Creatinine	B-Haemoglobin	International Normalized Ratio
S/P-Bilirubin, total	B-Leukocyte count	Activated Partial Thromboplastin Time
S/P- Alkaline Phosphatase (ALP)	B-Leukocyte differential count (absolute count)	
S/P- Aspartate Transaminase (AST)	B-Platelet count	
S/P- Alanine Transaminase (ALT)		
S/P-Albumin		
S/P-Potassium		
S/P-Calcium, total		
S/P-Sodium		
S/P- Creatine Kinase (CK)		
eGFR		
S/P, serum/plasma		

Additionally, fasting lipid panel will be included in serum chemistry:

- High density-lipoprotein (HDL)-Cholesterol Direct, 4th Generation
- Triglycerides
- Cholesterol
- Low density lipoprotein (LDL)-Cholesterol

Laboratory data are assigned as per timepoint related to analysis visits (Table 3).

The analysis will be based on as-treated population.

Occurrences of AST or ALT ≥ 3 × Upper limit of normal (ULN) together with total bilirubin ≥ 2 × ULN are reported as SAEs (Potential Hy´s law) as described in the study protocol.

3.3.5.3 Vital signs

Vital signs include:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Vital signs parameters are assigned to the analysis visits as described in section 3.1.2. Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges (Table):

Table 6 Vital signs normal reference ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	90 – 130 mmHg
Diastolic blood pressure	50 – 80mmHg
Heart rate	50 – 100 bpm
BMI	18 – 25 kg/m^2

The analysis will be based on as-treated population.

3.3.5.4 ECG

Overall ECG evaluation (normal, abnormal) is collected. If abnormal, also reason and clinically significance is collected.

ECG evaluations are assigned as per timepoint related to analysis visits (Table 3).

ECG last observation on treatment is defined as last available value among those in the on-treatment analysis phase.

The analysis will be based on as-treated population.

3.4 Exposure and treatment compliance

As per study protocol, subjects will receive study treatment directly from the investigator or designee, under medical supervision, at the clinic. They will receive the subcutaneous (SC) injections from Day 1.
Study treatment will be given at the following study visits:

- Day 1
- Day 29
- Day 57
- Day 85
- Day 113
- Day 141
- Day 169
- Day 197
- Day 225

3.4.1 Exposure

Exposure and extended exposure (days) is calculated only for subjects in the as-treated population.

Exposure is calculated as the study treatment last dose date minus study treatment first dose date plus one. If any of the first or last dates are missing or partially missing, then exposure to study treatment is set to missing.

Cumulative exposure is also computed based on exposure, using the following duration (days) categories:

- >=29
- >=57

- >=85
- >=113
- >=141
- >=169
- >=197
- >=225

Extended exposure is calculated as the study treatment last dose date minus study treatment first dose date plus 28. If any of the first or last dates are missing or partially missing, then extended exposure to study treatment is set to missing.

Cumulative extended exposure is also computed based on extended exposure, using the following duration (days) categories:

- >=56
- >=84
- >=112
- >=140
- >=168
- >=196
- >=224
- >=252

3.4.2 Compliance

Considering the way of the treatment administration, compliance to the treatment will not be analysed and not provided in listing.

3.5 Concomitant medications

The most up to date version of WHO Drug Dictionary (WHO-DD) is used to classify medications by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification of ingredients.

The imputation method described in section 3.1.1.2 and 3.1.1.3 is used in case of medication start date or stop date partially missing. Completely missing concomitant medication start dates and stop dates are not imputed.

After the end date imputation, the medications will be classified as either prior or concomitant (but not both) according to its stop date. Concomitant medication is defined as any medication with a stop date on or after the first dose of study drug, or any medication taken prior to study

drug and that is ongoing. Medications with completely missing stop date are classified as concomitant.

4 ANALYSIS METHODS

4.1 General principles

Data will be summarized using descriptive statistics at each visit. For the analyses and listings, placebo will be the 3 injection/volume-matched placebo groups pooled. Treatment groups will be:

- MEDI6570 with dose CCI and placebo for ITT, CTA analysis, Echocardiogram analysis populations. In these analyses, subjects initially randomized to the CCI group who consented to CSP amendment 1 and were switched to CCI dose were analysed according to the CCI group. For the safety and efficacy analyses, the number of subjects randomized to the CCI group who consented to amendment 1 of the CSP and switched to the CCI dose is specified.
- MEDI6570 with dose CCI or CCI and placebo for as treated, Per-protocol CTA analysis and Immunogenicity populations. In these analyses patients treated within CCI group who received at least one CCI dose during the study will be analysed according to the CCI group.
- MEDI6570 with dose CCI or CCI and CCI (listing only) and placebo for PK and CCI analysis populations. Subjects who only received CCI will be analysed according to the CCI group. Subjects who received both CCI and CCI doses during the study will be analyses as a separate CCI group. Due to few subjects in CCI treatment group they will not be included in summary table and figures as well as in modelling outputs. They will be included in listings only.

For continuous variables and unless otherwise specified descriptive statistics will include the number of subjects (n), mean, SD, median, minimum, and maximum. The 1st and 3rd quartiles will be added to exposure and ADA only if not requested otherwise. If the parameter is assumed to be log-normally distributed, the descriptive statistics will additionally include geometric mean (GeoMean) and geometric coefficient of variation (GeoCV). For geometric mean calculation, variables records with zero value will be imputed by half of the minimum of the non-zero records prior to the log-transformation.

Decimal places will always apply the following rules:

- n will be presented as integer.

- Percentage (including CV and GeoCV) will be presented with 1DP except Kaplan Meier (KM) estimate that will be with 2DP.
- For derived variables, the precision of the calculated variable will be one more than the least number of decimal places among the raw data used for calculation with a maximum of 3DP.
- Ratio (including hazard ratio and crude rate) will be presented with 2DP.
- Min and max will be presented as the original value. All other statistics (mean, SD, median, Q1, Q3, GeoMean, LSmeans, LSGeomean, Standard error (SE), geometric LSmeans, CI bounds) will be presented as the original value +1 additional decimal place considering a maximum of 3 DP for raw/derived and 4 DP for the other statistics.
- P-value will be presented with 3DP. If p-value is lower than 0.001, will be displayed "<0.001" and if p-value is higher than 0.999 or equal to 1, will be displayed ">0.999".
- If parameter unit is percentage (such as LVEF or GLS) the original value has 1DP.

Normality will be defined a priori and will be assessed graphically using "quantile–quantile" plots (Q-Q plots) & histogram and by Tests of Normality for primary efficacy endpoint ($NCPV_{MD}$). If $NCPV_{MD}$ shows large departure from distribution assessment, the parameter will be log-transformed and thus reported in the modeling as a log-normally distributed parameter (e.g. LSGeomean, ...). If the assumption of normal distribution of $NCPV_{MD}$ holds, summary statistics will report the values in original scale (e.g. GeoMean, GeoCV, ...). Finally, if primary efficacy endpoint ($NCPV_{MD}$) will not follow the normal distribution, subsequently the distribution of NCPV global and LAPV will be assumed as log-normally distributed because are subset of non-calcified plaque. .

All efficacy, exploratory and safety endpoints will be summarized by treatment group and at each visit as appropriate using descriptive statistics as above. Except otherwise specified, unscheduled visits will only be listed. For continuous variables, descriptive statistics will be provided for the observed values, the changes from baseline and the percent change from baseline (where appropriate).

The definition of the change from baseline will be related on the normal-/log-normal distribution of the evaluated variables, as following:

- for normally distributed variable: change from baseline, is defined as post-baseline visit value minus baseline value.

- for log-normally distributed variable: change from the baseline is defined as the logarithmic transformation of the value of the visit after the baseline value minus the logarithmic transformation of the baseline value.

For the observed variable (log-normally distributed) the descriptive statistics also include the GeoMean and the GeoCV% calculated as follows:

GeoMean = (EXP (AVERAGE (log)))

GeoCV% = SQRT (EXP (SD (logs)^2)–1) *100

Percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value*100.

Changes from baseline in categorical variables will be summarized using shift tables where appropriate. The number and percent of subjects within each treatment group will be generated for each category post-baseline by baseline category.

If not otherwise specified, all the analyses will include the post treatment discontinuation data for those subjects who discontinue from study treatments but are still followed up for their scheduled visits. The following statistical models will be used to compare MEDI6570CCI versus placebo, MEDI6570CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo (only for PK andCCI populations listing) and pooled MEDI6570CCI versus placebo.

Statistical hypothesis tests for all endpoints will be conducted at a one sided 0.05 significance level without multiplicity adjustment, for all analyses. All confidence intervals (CI) will be one-sided 90%.

The following table provides for each endpoint the expected direction of the change:

Table 7 Expected direction of the change with MEDI6570 compared to placebo

Endpoint	Direction
$NCPV_{MD}$	Reduction
NT-proBNP	Reduction
LVEF	Increase
GLS	Increase (in absolute value)
NCPV Global	Reduction
LAPV	Reduction

Table 7 Expected direction of the change with MEDI6570 compared to placebo

Endpoint	Direction
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4.1.1 Analysis of covariance (ANCOVA)

The ANCOVA model will be used to fit change from baseline at each concerning visit. Data used in the model are data from baseline and the scheduled tested visit. The group of treatment will be considered as a fixed effect of the model while the baseline value and the stratification factors (geographic region and statin therapy intensity at screening) as covariates. Comparisons of MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be assessed using the same model. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; one sided difference test with alpha level at 5% and two-sided 90% CI will be used for the comparisons. No data imputation will be used.

In case of singularity between the covariates (i.e. within each treatment group subjects have exactly the same combination of both stratification factors), the second stratification factor (level of statin therapy) will be removed from the model.

ANCOVA model will be run by subgroup see section 4.2.8.1.5, 4.2.8.2.2, 4.2.8.3.2, 4.2.10.1.1 for details. In case of low number of subjects (less than 13 observations) in a subgroup the results will not be provided since there are not estimable or not reliable.

If the parameter is assumed to be normally distributed, the variable fitted in the model will be the change from baseline; the ANCOVA model and the reportable results will be those described below:

- The least-square means (LSmeans) and their standard errors for each group

- The difference between active groups and placebo (LSmean difference) together with its 90% CI
- The one-sided p-value for the difference between active groups and placebo

If the parameter is assumed to be log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

The ANCOVA model will be as described above but the reportable results from the model will be:

- Back transformed LSmeans for each group using exponential (EXP) function, calculated as: EXP (LSmeans of the logarithmic transformation) = Geometric LSMeans and their back transformed Coefficient Variance {SQRT [(EXP (variance for log transformed data))-1]} *100 = SQRT [(EXP ((SD) -1)]*100 ,
- The ratio between active groups and placebo; the ratio is calculated as EXP (LSMean difference) together with its back-transformed 90% CI, calculated as [EXP(Lower)]; [EXP(Upper)].
- the one-sided p-value of the comparison between active groups and placebo

To be noted that a ratio lower than 1 means that the active group shows a higher decrease (or a lower increase) compared to the placebo group. On the other hand, a ratio greater than 1 means that the active group shows a lower decrease (or a higher increase) compared to the placebo group.

The ANCOVA model will be used at final analysis.

4.1.2 The mixed model repeated measures (MMRM)

Fitting a MMRM to change from baseline will be used at final analysis. If the dependent variable is assumed to be log-normally distributed, then the value in logarithmical scale will be used for the model.

The reportable results from the model depending on the distribution of the variable will be as stated below.

If the dependent variable is assumed to be normally distributed:

- The LSmeans and their standard errors for each group

- The difference between active groups and placebo (LSmean difference) together with its CI
- The one-sided p-value for the difference between active groups and placebo

If the dependent variable is assumed to be log-normally distributed:

- Back transformed LSmeans for each group, calculated as: EXP (LSmeans of the logarithmic transformation) = Geometric LSMeans and their back transformed Coefficient Variance {SQRT [(EXP (variance for log transformed data))-1]}*100 = {SQRT [(EXP(variance for ln(Visit X) - LN(Baseline visit)))-1]}*100 ,
- The back transformed difference between active groups and placebo, ratio is calculated as [EXP (LSmeans difference)], together with its back transformed CI, calculated as [EXP(Lower)]; [EXP(Upper)].
- The one-sided p-value of the comparison between active groups and placebo.

Data used in the model come from the scheduled visits as outlined in the footnote of table 3. Fixed effects of the model will be treatment group, visit and treatment*visit interaction. The baseline value and the stratification factors (geographic region and statin therapy intensity at screening) will be used as covariates. Visit within subject will be considered as repeated measurements. Comparisons of MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be assessed using the same model. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; one sided difference test with alpha level at 5% and one-sided 90% CI will be used for the comparisons.

The unstructured covariance structure will be used in the model for the repeated measures. Visit will be expressed as planned days to accomplish the variance-covariance matrix estimation.

In case the model does not converge for any reasons, the compound symmetry (CS) will be used instead of the unstructured (UN). In case the model does not converge with CS or UN, the autoregressive (AR (1)) and Toeplitz will be used.

4.1.3 Cox Proportional Hazards model

Time to event analyses will be performed using Cox Proportional Hazards model. The reportable results from the model will be as stated below:

- Number and percentage of subjects with event
- Hazard ratio for active groups versus placebo and its 90% CI

- The one-sided p-value for the comparison between active groups and placebo

The hazard ratio with corresponding CI and p-value for treatment comparisons will be presented, fitted by a Cox Proportional Hazards model including stratification factors (geographic region and statin therapy intensity at screening). The Kaplan Meier Estimate at Day 326 will also be provided for each group. Comparisons of MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be assessed using the same model.

4.2 Analysis of variables

4.2.1 Disposition of subjects

Subject dispositions (number and percentage of subjects enrolled, subjects randomized, subjects who received at least one dose of study treatment, subjects who completed the treatment and subjects who completed the study) will be presented in a summary table for each treatment group and overall (two different totals will be considered as following: one with placebo and one without placebo subjects). Subject disposition related to the global/country situation will be presented in the same summary table at final analysis only. A listing including all standardized disposition terms will be also provided for all discontinued subjects. Both, the table and the listing will be based on all enrolled subjects population. The table will be performed in IDMC reports and at final analysis. The listing will be provided at final analysis.

The number of subjects belonging to each analysis population will be presented in a separate summary table for each treatment group. The table will be based on all randomized subjects population and will be performed at final analysis. Listings of all subjects excluded from each analysis population will be also provided at final analysis. The listings will include reason for exclusion from respective population and will be based on all enrolled subjects population.

Randomization code and actual kit will also be listed at final analysis.

4.2.2 Important protocol deviations

The number and percentage of subjects with at least one Important protocol deviation (IPD) will be displayed following the Protocol Deviation Management Plan categories for each treatment group and overall (including sub selection related to the global/country situation; additionally two different totals will be considered as following: one with placebo and one without placebo subjects), for all subjects in the as-treated population.

IPDs will be presented in IDMC reports and at final analysis. The listing will be presented for final analysis.

Subjects meeting an IPD category more than once will be counted once for the corresponding IPD category. Any subjects who have more than one IPD category will be counted once in the overall summary.

4.2.3 Baseline assessment and other subject-specific characteristics

4.2.3.1 Demographic and subject-specific characteristics

All demographic and subject-specific characteristics reported in section 3.2.1 will be presented in summary tables for each treatment group and overall (two different totals will be considered as following: one with placebo and one without placebo subjects); Age, height, weight and BMI will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; all the other demographic and subject-specific characteristics will be summarized as categorical variables with the number and percentages of subjects by categories. Age group categories >=21 - <40; >=40 - <50; >=50 -<65; >=65 will be summarized. Only the baseline measurement for height, weight and BMI will be considered.

All demographic and subject-specific characteristics will be also provided in listing on the ITT population for final analysis only.

The tables will be based on the ITT population and will be presented in IDMC reports and at final analysis.

Indication (NSTEMI, STEMI), type of coronary procedure (Diagnostic coronary angiography only, Coronary intervention/revascularisation), extent of disease at start of angiography, procedure type (PCI, CABG, No procedure), stent (yes, no) and type of stent will also be summarized descriptively as categorical variables. The table will be based on the ITT population and will be provided for final analysis. Listings will be provided based on the ITT population for final analysis only.

4.2.3.2 Medical history

Relevant and disease related medical history, cardiac history and risk factor as described in section 3.2.2 will be presented in summary tables as number and percentages of subjects by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall (two different totals will be considered as following: one with placebo and one without placebo subjects). Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Table will be sorted alphabetically by SOC and PT. The table will be based on the ITT population and presented at final analysis only.

4.2.4 Concomitant medications

Concomitant medications are defined in section 3.5. The number and percentage of subjects with at least one concomitant medication and the number and percentage of subjects by ATC level 4 and product name will be provided using the ITT population at final analysis only.

Additionally, the number and percentage of subjects with at least one cardiac medication will be presented using the ITT population at final analysis only. Cardiac medications include the following ATC level 2 classifications: antithrombotic agents, agents acting on the renin-angiotensin system, beta blocking agents, drugs used in diabetes, and lipid modifying agents. Only medications started prior to randomization or ongoing at the end of study will be summarized.
Cardiac concomitant medication started prior to randomization is defined as any medication with a start date prior to randomization date.
Cardiac concomitant medication ongoing at end of study is defined as any medication with a start date prior to or on the date of end of study or ongoing or no end date.

Concomitant medications will be listed for the ITT population at final analysis.

4.2.5 Treatment and compliance

4.2.5.1 Exposure

Exposure and extended exposure are described in section 3.4.1. Exposure, duration and cumulative exposure over time (days) will be presented in a summary table for each treatment group and overall (total will not include placebo subjects). Summary statistics will include n, mean, SD, 1st and 3rd quartile, median, minimum, and maximum. The same summary will be provided for subjects being dosed with at least 6 doses (it can be non-consecutive). The table will be based on the as-treated population and will be provided in IDMC reports and at final analysis.

Exposure and extended exposure will also be summarized as categorical variables in the as-treated population in IDMC reports and final analysis.

Exposure data will also be reported in a listing for all subjects in the as-treated population for final analysis.

4.2.5.2 Compliance

Considering the way of the treatment administration, compliance to the treatment will not be analysed. Administration of investigational product will be listed for the as-treated population for final analysis.

4.2.5.3 Overdose

Any dose of MEDI6570 greater than the intended maximum investigated dose per subject will be considered an overdose. Overdoses will be reported in a listing for all subjects in the as-treated population for final analysis.

4.2.6 Study Recruitment

The number and percentage of recruited subjects per geographic region, country and centre will be provided for each treatment group and overall using the ITT population in IDMC reports and at final analysis.

4.2.7 Stratification factors

The number and percentage of subjects stratified by geographic region and by statin therapy status at randomization, as explained in sections 4.2.8.1.5, 4.2.8.2.2, 4.2.8.3.2, 4.2.10.1.1 will be provided for each treatment group and overall using the ITT population in IDMC reports and at final analysis.

Randomization scheme and codes including the stratification factors will be listed for all randomized subjects at final analysis.

4.2.8 Primary and secondary efficacy endpoints

All the outputs listed below will be presented in final analysis.

4.2.8.1 CTA analysis

An overview of the ANCOVA analysis (section 4.1.1) performed to compare MEDI6570 [redacted] versus placebo, MEDI6570 [redacted] versus placebo MEDI6570 [redacted] versus placebo and pooled MEDI6570 [redacted] doses versus placebo will be presented. This overview will include the difference in LSmeans between treatment groups and placebo from the ANCOVA analysis on change from baseline to Day 253 of each of the following CTA variables (sections 3.3.1 and 3.3.2.3):

- $NCPV_{MD}$
- Global non-calcified plaque volume
- Low attenuation plaque volume

All parameters assessed by CTA are assumed to be normally distributed.

Baseline and post-baseline definitions are detailed in section 3.1.2.
Tables and listings will be based on the CTA analysis population and presented for each treatment group.

CTA variables will be reported in a listing.

Different subgroup analyses will be performed at final analysis: a complete description of these analyses is provided in section 4.2.8.1.5.

4.2.8.1.1 Primary efficacy endpoint $NCPV_{MD}$

$NCPV_{MD}$ is described in section 3.3.1. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the CTA analysis population and presented for each treatment group.

$NCPV_{MD}$ will be summarized descriptively as continuous variable at Baseline, Day 122 and Day 253 for observed value, change and percent change from baseline. Change of $NCPV_{MD}$ will be also presented in figure with mean and SD by visit.

ANCOVA model described in section 4.1.1 will be used for change from baseline to Day 253 of $NCPV_{MD}$.

A forest plot will also be presented in figure for the 4 comparisons between active groups and placebo using the ANCOVA model for change of $NCPV_{MD}$ at Day 253.

Sensitivity analyses for the primary endpoint are described in section 4.2.8.1.2.

4.2.8.1.2 Sensitivity analysis of the primary efficacy endpoint

All the tables and figure for analysis of primary efficacy endpoint presented in section 4.2.8.1.1 will be repeated with the aim to consolidate the results obtained with the previous ANCOVA model and with summary statistics.

The following sensitivity analyses will be performed on the per-protocol CTA analysis population:

- The same ANCOVA model (sensitivity analysis 1);
- The same ANCOVA model restricted to those who completed treatment (no missing treatment at Day 253) (sensitivity analysis 2);

The following sensitivity analyses will be performed on the CTA analysis population:

- The same ANCOVA model but without subjects having received both CCI and CCI (sensitivity analysis 3);
- The same ANCOVA model restricted to subjects with no scanner change between baseline and Day 253 (sensitivity analysis 4).

4.2.8.1.3 Secondary efficacy endpoints NCPV and LAPV

NCPV and LAPV are described in section 3.3.2.3. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the CTA analysis population and presented for each treatment group.

Parameters will be summarized descriptively as continuous variable at Baseline, Day 122 and Day 253 for observed value, change and percent change from baseline. Change from baseline in NCPV and LAPV will be also presented in separate figures with mean and SD by visit.

NCPV and LAPV will follow same distribution of $NCPV_{MD.}$ At this regard, only if $NCPV_{MD}$ after normality checking will be log-normally distributed, both of these parameters will be assumed log-normally distributed.

An ANCOVA model as described in section 4.1.1 for change from baseline in NCPV and LAPV at Day 253 will be also separately presented for each of these CTA variables. Separate forest plots will be also presented in figure for the 4 comparisons between active groups and placebo using the ANCOVA model for change from baseline in NCPV and LAPV at Day 253.

Subgroup analysis as described in section 4.2.8.1.5 will be performed including baseline and Day 253.

Sensitivity analyses for the secondary endpoints NCPV and LAPV are described in section 4.2.8.1.4.

4.2.8.1.4 Sensitivity analysis for NCPV and LAPV

All the tables for analysis of NCPV presented in section 4.2.8.1.3 will be repeated with the aim to consolidate the results obtained with the previous ANCOVA model and with summary statistics.

The following sensitivity analyses will be performed on the per-protocol CTA analysis population:

- The same ANCOVA model (sensitivity analysis 1)
- The same ANCOVA model restricted to those who completed treatment (no missing value at Day 253) (sensitivity analysis 2)

The following sensitivity analysis will be performed on the CTA analysis population:

- The same ANCOVA model restricted to subjects with no scanner change between baseline and Day 253 (sensitivity analysis 3)

4.2.8.1.5 Subgroup Analysis of CTA endpoints

Subgroups planned for analysis include but are not limited to those defined by randomization (by IVRS) stratification factors. Stratification factors include geographic region (Asia, North America, Rest of the World) and statin therapy status (no, low or moderate and high intensity statin therapy).

A complete list of the subgroups (*(subgroup level 1; subgroup level 2; ...; subgroup level x*) analysed at the final analysis for $NCPV_{MD}$ and NCPV is provided below.

- Sex *(Male; Female)*
- Age *(<65; >=65 years)*
- Race *(Caucasian; Non-Caucasian)*
  with *Caucasian* = White and *Non-Caucasian* = American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other.
- Geographic region
  - *Asia, North America; Rest of the World*
  - *Western (North America and Rest of the World); Asia*

  Asia will not be repeated in the second subgroup.
- Diabetes mellitus *(Presence; Absence)*
  with *Presence* = if diabetes mellitus (type 1 or type 2) in Medical History (MH) or Cardiac History and Risk Factor (SPECHIS) forms and *Absence* otherwise.
- Smoking Status *(Smoker; Non-smoker)*
  with *Smoker* = current or former smoker and *Non-smoker* = never smoked.
- Qualifying MI Type *(STEMI; NSTEMI)*
  using Indication field from Coronary Revascularisation - Qualifying Event (PROCCA) form
- Baseline eGFR *(<60 mL/min/1.73 m^2; ≥ 60 mL/min/1.73 m^2)*
- Statins *(None/Low/Moderate intensity; High intensity)*
- Baseline NT-ProBNP
  - *(< Median; >= Median)*
  - *(< 125 pg/mL; >= 125 pg/mL)*
- CCI [redacted]
- Baseline Global NCPV *(< Median; >= Median)* to be performed only for Global NCPV using baseline value computed after segment matching to Day 253
- Baseline $NCPV_{MD}$ *(< Median; >= Median)* to be performed only for $NCPV_{MD}$

using baseline value computed after segment matching to Day 253

- Baseline LDL (*<70 mg/dL; >=70 mg/dL)*
- Coronary intervention/revascularisation (for qualifying event) *(Yes, No)*
  using Type of coronary procedure from Coronary Revascularisation - Qualifying Event (PROCCA) form
- Time from the date of qualifying event to randomization *(<3 months; ≥3 months)*
  in case of multiple qualifying events, the latest event is used.
- Baseline LVEF *(<50%; >=50%)*

Subgroup analysis will present both summary and inferential tables (ANCOVA model described in section 4.1.1) for CTA analysis population. ANCOVA model will be presented for change at Day 253 for $NCPV_{MD}$ and NCPV.

4.2.8.2 Analysis of NT-proBNP

NT-proBNP is described in section 3.3.2.1. NT-proBNP is assumed to be log-normally distributed. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

An overview of the MMRM analysis (section 4.1.2) performed to compare MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be presented. This overview will include the results from the 4 comparisons of the MMRM fit on NT-proBNP variable (section 3.3.2.1).

NT-proBNP will be summarized descriptively as continuous variable at baseline, Days 29, 85, 113, 122, 225 and 253 for observed value and change from baseline. Change of NT-proBNP will be also presented in figure with mean and SD by visit.

A MMRM model as described in section 4.1.2 for change of NT-proBNP, at Day 253 will be also presented. A forest plot will also be presented in figure for the 4 comparisons between active groups and placebo using the MMRM model for change of NT-proBNP at Day 253.

NT-proBNP will be also reported in a listing for the ITT population.

These summaries (tables and figures) will be also repeated for final analysis only among subjects with reduced ejection fraction (defined as <50% at baseline).

4.2.8.2.1 Sensitivity analysis of NT-proBNP

A sensitivity analysis with the same MMRM model will be performed on the ITT population but without subjects having received both CCI and CCI (sensitivity analysis 1).

A second sensitivity analysis may be performed by including all analysis visits regardless of protocol version.

4.2.8.2.2 Subgroup Analysis of NT-proBNP

Subgroup analysis will present the same summary and inferential tables (MMRM model described in section 4.1.2) for the ITT population described in the previous section (excluding sensitivity analysis). A complete list of the subgroup analyses at final analysis is provided below.

The following subgroups at the final analysis will be analysed:

- Sex *(Male; Female)*
- Age *(<65; >=65 years)*
- Race *(Caucasian; Non-Caucasian)*
  with *Caucasian* = White and *Non-Caucasian* = American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other.
- Geographic region
  - *Asia, North America; Rest of the World Western (North America and Rest of the World); Asia*

  Asia will not be repeated in the second subgroup.
- Diabetes mellitus *(Presence; Absence)*
  with *Presence* = if diabetes mellitus (type 1 or type 2) in Medical History (MH) or Cardiac History and Risk Factor (SPECHIS) forms and *Absence* otherwise.
- Smoking Status *(Smoker; Non-smoker)*
  with *Smoker* = current or former smoker and *Non-smoker* = never smoked.
- Qualifying MI Type *(STEMI; NSTEMI)*
  using Indication field from Coronary Revascularisation - Qualifying Event (PROCCA) form
- Baseline eGFR *(<60 mL/min/1.73 m^2; ≥ 60 mL/min/1.73 m^2)*
- Baseline NT-ProBNP
  - *(< Median; >= Median)*
  - *(< 125 pg/mL; >= 125 pg/mL)*
- CCI [redacted]

CCI

- Baseline LVEF *(<50%; >=50%)*

4.2.8.3 Echocardiogram analysis

As described in section 3.3.2.2, the variables assessed by echocardiography include:

- LVEF
- GLS

LVEF and GLS, as part of the echocardiography evaluations, are assumed to be normally distributed.

Baseline and post-baseline definitions are detailed in section 3.1.2. Tables, listings and figures will be based on the Echocardiogram analysis population and presented for each treatment group.
An overview of the ANCOVA analysis (section 4.1.1) performed to compare MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be presented. This overview will include the results from the 4 comparisons of the change from baseline to Day 253 of LVEF and of GLS. The same ANCOVA analysis will be done for this overview to present results for subjects with reduced ejection fraction (<50% at baseline).

LVEF and of GLS will be summarized descriptively as continuous variable at Baseline and Day 253 for observed value, change and percent change from baseline.

An ANCOVA model as described in section 4.1.1 for change from baseline in LVEF and for change from baseline in GLS, respectively at Day 253 will be presented. Forest plots will also be presented in separate figures for the 4 comparisons between active groups and placebo using the ANCOVA model for change of LVEF and change of GLS, at Day 253.

LVEF and GLS will be also reported in a listing for the Echocardiogram analysis population.

These summaries (tables and figures) will be also repeated for both variables among subjects with reduced ejection fraction (defined as <50% at baseline).

4.2.8.3.1 Sensitivity analysis of Echocardiogram variables

A sensitivity analysis will be performed for LVEF with the same ANCOVA model on the Echocardiogram analysis population but without subjects having received both CCI and CCI [redacted] (sensitivity analysis 1).

4.2.8.3.2 Subgroup Analysis of Echocardiogram variables

Subgroup analysis will present both summary and inferential tables (ANCOVA model described in section 4.1.1) described in the previous section for the Echocardiogram analysis population (excluding sensitivity analysis). A complete list of the subgroup analyses at final analysis is provided below.

The following subgroups at the final analysis will be analysed:

- Sex *(Male; Female)*
- Age *(<65; >=65 years)*
- Race *(Caucasian; Non-Caucasian)*
  with *Caucasian* = White and *Non-Caucasian* = American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other.
- Geographic region
  - *Asia, North America; Rest of the World*
  - *Western (North America and Rest of the World); Asia*

  Asia will not be repeated in the second subgroup.
- Diabetes mellitus *(Presence; Absence)*
  with *Presence* = if diabetes mellitus (type 1 or type 2) in Medical History (MH) or Cardiac History and Risk Factor (SPECHIS) forms and *Absence* otherwise.
- *Smoking status (Smoker; Non-Smoker)*
  with *Smoker* = current or former smoker and *Non-smoker* = never smoked.
- Qualifying MI Type *(STEMI; NSTEMI)*
  using Indication field from Coronary Revascularisation - Qualifying Event (PROCCA) form
- Baseline eGFR *(<60 mL/min/1.73 m^2; ≥ 60 mL/min/1.73 m^2)*
- Baseline NT-ProBNP
  - *(< Median; >= Median)*
  - *(< 125 pg/mL; >= 125 pg/mL)*
- CCI [redacted]

- CCI [redacted]
- Baseline LVEF *(<50%; >=50%)*

4.2.9 Other secondary endpoints

Other secondary endpoints include:

- Immunogenicity (ADA incidence and Titre)
- Pharmacokinetic concentrations

4.2.9.1 Immunogenicity analysis

The endpoints to evaluate immunogenicity of MEDI6570 are ADA incidence and Titre. ADA and Titre are described in section 3.3.3.1. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the Immunogenicity population and presented for each treatment group and overall (total will not include placebo subjects).

ADA will be summarised in IDMC reports (if data available prior to the meeting) and at final analysis using the following categories:

- ADA negative at all assessments, including baseline and post-baseline (ADA negative)
- ADA positive at baseline and/or post-baseline (ADA prevalence)
- TE-ADA positive (ADA incidence)
- Treatment-induced ADA positive
- Treatment-boosted ADA positive
- TE-ADA negative
- Both baseline and post-baseline positive
- Only baseline positive
- ADA persistently positive
- ADA transiently positive
- TE-ADA positive with maximum titre > median of maximum titres.

ADA negative is defined as having ADA negative at all assessment, including baseline and post-baseline. TE-ADA positive is defined as the sum of treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) and treatment-boosted ADA positive (ADA positive at baseline and boosted the pre-existing titre during the study period).

TE-ADA negative is defined as ADA positive but not fulfilling the definition of TE-ADA positive. ADA incidence is the proportion of TE-ADA positive subjects in a population.

ADA persistently positive is defined as ADA negative at baseline and ADA positive at >= 2 post-baseline assessments (with >= 16 weeks between first and last positive) or ADA positive at last post-baseline assessment. ADA transiently positive is defined as ADA negative at baseline, having at least one post-baseline ADA positive assessment and not fulfilling the conditions of ADA persistently positive.

The median of maximum titres is calculated based on the maximum titre for each ADA positive subject within each treatment group (including both baseline and post-baseline measurements).

ADA will be also reported in a listing in IDMC reports (if data available prior to the meeting) and at final analysis.

ADA will be summarized by visit at final analysis only as categorical variable with the number and percentages with a positive result at the baseline, Days 10 to 141, Day 225, Day 253 and Day 325/405. Immunogenicity titre will be summarized descriptively as continuous variable, only for ADA positive tests, with median, interquartile range, minimum and maximum, at same analysis visits as ADA.

ADA positive subjects will also be listed at final analysis only.

All ADA analyses above except the summary statistics by visit will include scheduled and unscheduled ADA measurements.

4.2.9.2 PK analysis

Tables and figures will be based on the PK population and presented for each treatment group at final analysis.

Individual serum concentrations (µg/mL) of MEDI6570 will be summarized descriptively as a continuous variable by analysis visit for each treatment group and tabulated. Descriptive statistics include, but not limited to, geometric mean (GeoMean), geometric coefficient of variation (GeoCV), arithmetic mean, SD, geometric SD (GeoSD), minimum, median, maximum, n and n below the lower limit of quantification (LLOQ). The LLOQ for MEDI6570 is 0.03280 µg/mL.

GeoMean and GeoSD of serum concentrations (µg/mL) of MEDI6570 vs analysis visit and treatment group will be presented in graph using log-linear and linear scale.

Individual serum concentrations (µg/mL) of MEDI6570 vs actual time will be plotted by treatment group using log-linear and linear scale.

Individual serum concentrations (µg/mL) of MEDI6570 for each actual time point will be listed.

If data allows, impact of ADA on PK will be evaluated by plotting serum concentrations (µg/mL) time profile of MEDI6570 by ADA category using box plot and by plotting individual serum concentrations (µg/mL) time profile of MEDI6570 by ADA category using spaghetti plot.

4.2.9.2.1 Handling of concentrations below Lower Limit of Quantification (LLOQ)

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as NQ (Not Quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

Concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the GeoMean, the GeoSD, GeoMean ± GeoSD and GeoCV% will be set to Not Calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The GeoMean, minimum, median and maximum will be reported as NQ and the GeoCV%, GeoSD and GeoMean ± GeoSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).
- Three observations > LLOQ are required as a minimum for a serum concentration to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC. One observation > LLOQ is presented as maximum with the other summary statistics as NC.

4.2.10 Exploratory efficacy endpoints

4.2.10.1 CCI

[redacted]

CCI

[redacted]

4.2.10.1.1 CCI

[redacted]

- CCI [redacted]

[redacted]

[redacted]

4.2.10.2 CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2.10.3 CCI [redacted]

[redacted]

[redacted]

CCI

[redacted]

4.2.10.4 CCI

[redacted]

4.2.10.5 CCI

[redacted]

4.2.10.6 CCI

[redacted]

4.2.10.7 Adverse events

After having assigned the AEs to the corresponding analysis phase as described in section 3.3.5.1, the AEs will be summarized for each treatment group and overall (total will not include placebo subjects). The AEs tables will be based on the as-treated population except the AE by ADA tables which will be based on the Immunogenicity population. Summary tables will include AEs in the on-treatment phase and AEs in the follow-up phase.

Summary tables are listed below.

An overview table containing:

- Number and percentage of subjects with any AEs
- Number and percentage of subjects with any AEs with outcome of death
- Number and percentage of subjects with any SAE (including events with outcome = death)
- Number and percentage of subjects with any AEs leading to discontinuation of treatment
- Number and percentage of subjects with any AEs leading to withdrawal from study

Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

An overview table containing:

- Any AE
- Any AEs with outcome of death
- Any SAE (including events with outcome of death)
- Any AE leading to discontinuation of treatment
- Any AE leading to withdrawal from study

Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than 1 category are counted multiple times in each of those categories.

The following summary tables will be presented by SOC and PT:

- The number and percentage of subjects with any AEs
- The number of AEs
- The number and percentage of subjects with AEs with outcome of death
- The number of SAEs
- The number and percentage of subjects with SAEs
- The number and percentage of subjects with SAEs, assessed by investigator as possibly related to investigational product
- The number and percentage of subjects with AEs leading to discontinuation
- The number and percentage of subjects with any bleedings (all events from bleeding event form or from adverse event form with SMQ= “Haemorrhages narrow”)
- The number and percentage of subjects with any injection site reactions (all events from ISR form or from adverse event form with HLT= “Injection site reactions”)
- Overall summary of number and percentage of subjects with any AEs by ADA (anti-drug antibody category)
- The number and percentage of subjects by ADA (anti-drug antibody category)

The following summary tables will be presented by PT:

- The number and percentage of subjects with most common AEs (frequency of >5%). Most common should be defined according to % in any of the treatment groups.
- The number and percentage of subjects with any AEs by maximum reported intensity.
- The number and percentage of subjects with any AEs and investigator's causality assessment. If a subject has multiple events in the same PT, the event with the strongest relationship will be counted.

Where number of subjects with AEs are summarized by system organ class (SOC) and/or preferred term (PT), subjects with multiple events in the same SOC/PT are counted only once in that SOC/PT. Subjects with events in more than one SOC/PT are counted once in each of those SOCs/PTs.

Additionally, the following tables will be presented:

- The number and percentage of subjects with non-serious AEs occurring with a frequency > 5.0% in any treatment group for each SOC and PT.

This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the clinical study report (CSR). It will be delivered at the same time as the CSR outputs.

Key subject information for subjects with:

- AEs with outcome of death
- SAEs
- AEs leading to discontinuation of study treatment

The durations reported in these tables, will be derived only for fully completed dates as below:

- Time from first dose of treatment to AE (in days) will be calculated as the AE start date minus date of first dose +1.
- Time from first dose to death (in days) will be calculated as the date of death minus date of first dose +1.
- The same approach will be used for deriving time from start of treatment to AE becoming serious or discontinuation.
- Time from last dose prior to AE start and last dose prior to death will be calculates as the date of death minus the date of last dose prior to AE/death +1.

A listing will be provided for all the AEs regardless of the analysis phases for all subjects included in the as-treated population.

All analyses will be conducted in IDMC reports and at final analysis.

4.2.10.8 Laboratory evaluation

Laboratory evaluations are described in section 3.3.5.2. Baseline and post-baseline definitions are detailed in section 3.1.2. All tables and listings for laboratory data will be based on the as-treated population and presented for each treatment group in IDMC reports and at final analysis.

Laboratory test results for haematology, coagulation and clinical chemistry quantitative parameters will be summarized, with their units of measure, with n, mean, SD, median, minimum, and maximum at each visit and for change from baseline.

Shifts from baseline to maximum and minimum value during the on-treatment phase will be presented for haematology and clinical chemistry parameters.

All individual laboratory data for haematology, coagulation and clinical chemistry will be also presented in a listing in that order.

In addition to the tables above, as described in the study protocol, also the following will be presented:

- Plots for the maximum on-treatment ALT/maximum on-treatment AST by maximum total bilirubin, expressed as multiples of ULN for assessing Hy's law criteria,
- List of key subject information for subjects with potential Hy's law combined ALT or AST, and bilirubin, and
- Proportion of subjects with elevated liver test based on measured laboratory values

In the 3 tables and figures listed above all measurements including unscheduled visits will be taken into account.

Elevated liver tests are defined as elevations from baseline up to the end of the study as follows:

ALT elevations

- ALT > 3xUpper Limit of Normal (ULN)
- ALT > 5xULN
- ALT > 10xULN
- ALT > 20xULN

AST elevations

- AST > 3xULN
- AST > 5xULN
- AST > 10xULN
- AST > 20xULN

AST or ALT elevations

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN

Total bilirubin (BILI) elevations

- BILI > 1.5xULN
- BILI > 2xULN

(ALT or AST elevations) and BILI elevation

- (ALT > 3xULN or AST > 3xULN) and (BILI > 1.5xULN within 14 days on or after ALT or AST elevation)
- (ALT > 3xULN or AST > 3xULN) and (BILI > 2xULN within 14 days on or after ALT or AST elevation)
- (ALT > 3xULN or AST > 3xULN) and ((BILI > 2xULN and no initial ALP >= 2xULN) within 14 days on or after AST or ALT elevation)

ALP elevations

- ALP > 1.5xULN
- ALP > 3xULN

Occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN are reported as SAE (Potential Hy´s law) as described in the study protocol.

4.2.10.8.1 Handling of results below or above Limit of Quantification (LOQ)

Values lower (or upper) the limit of quantification (LLOQ or ULOQ) will be imputed for summary tables. Original values will be reported in the listings. Imputation will be based on the significant digits reported. The following approach will be taken, with x, y and z representing integers ≥1.

- If the original result is >x or ≥x then the result will be imputed by x+1
- If the original result is >x.y or ≥x.y then the result will be imputed by x.y+0.1
- If the original result is >x.yz or ≥x.yz then the result will be imputed by x.yz+0.01
- Etc

- If the original results is <x or ≤x then the result will be imputed by x-1
- If the original results is <x.y or ≤x.y then the result will be imputed by x.y-0.1
- If the original results is <x.yz or ≤x.yz then the result will be imputed by x.yz-0.01
- Etc

4.2.10.9 Vital signs

Vital signs are described in section 3.3.5.3. Baseline and post-baseline definitions are detailed in section 3.1.2. Vital signs (systolic blood pressure, diastolic blood pressure and heart rate) tables and listings will be based on the as-treated population and presented for each treatment group at final analysis.

Vital signs will be summarized descriptively as continuous variables at each visit and for change from baseline at each post-baseline visit.

All vital signs data will be listed. The listing will include reference ranges and classification of vital signs as normal, low and high.

4.2.10.10 ECG

ECG parameters are described in section 3.3.5.4. Baseline and post-baseline definitions are detailed in section 3.1.2. ECG listing will be based on the as-treated population and presented for each treatment group at final analysis.

Overall evaluation will be listed for subjects with clinically significant abnormalities.

4.2.11 Assessments related to global/country situation

Additional analyses will be performed to explore the impact of global/country situation and COVID-19 in particular. All outputs will be performed for all enrolled subjects at final analysis only. The number and percentage will be provided for the following categories:

- participants discontinued from study or study treatment due global/country situation
- participants with at least one important protocol deviations related to global/country situation (also will be performed in IDMC reports)

In addition, the following listings will be provided for:

- participants affected by the COVID-19 related study disruption
- participants with reported issues in the Risk and Issues Management due to COVID-19 pandemic.

5 INTERIM ANALYSES

No formal interim analysis is planned.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The following analysis set populations were added: All enrolled subjects population and CCI analysis population.

Some parameters are no longer listed as objectives and endpoints following CSP amendment 2 CCI); but summary statistics are still required for patients enrolled under CSP V1 and CSP amendment 1.

The bioanalytical test site will have access to the randomization list. A limited number of bioanalytical personnel, who will not be involved in the treatment or clinical evaluation of subjects, will be unblinded to subject treatment allocation to enable analysis of PK samples. Local SOPs will govern maintenance of the blind and information on treatment allocation will not be communicated outside of these bioanalytical personnel.

Two subjects were randomized by error PPD they will not be included in ITT population. Subjects did not take any dose of IP and are classified as screen failures. In the time to event analyses for CCI the time from randomization to Day 253 was updated by time from randomization to Day 326.

7 REFERENCES

Not applicable.

8 APPENDIX

8.1 Appendix 1 Changes made to the SAP after initial sign-off

8.1.1 Version 1.0

Not applicable.

8.1.2 Version 2.0

Section 1.2
Study design was updated to be consistent CSP amendment 1
The PK pre-interim analysis details were added

Section 1.3
Sample size section was updated to be consistent CSP amendment 1

Section 2.1
For ITT population, added that "Subjects initially randomized to the CCI group who accepted CSP amendment 1 and should switch dose to CCI will be analysed according to the CCI group."
For As-treated population, added that "Subjects treated within the CCI group that received at least one CCI dose during the study will be analysed according to the CCI group. Participants that only received CCI will be analysed as a separate CCI group."
For PK population, added that "Subjects that received both CCI and CCI doses during the study will be analysed as a separate CCI group."
CCI analysis population definition added
Definition of CTA interpretable was added

Section 3.1.2
Added that "Additionally, End of Study visit as the recorded per CRF will be used. End of Treatment is defined as the last value in the on-treatment phase as defined in section 3.1.3"

Section 3.3.1 and 3.3.2.3 and 3.3.4.3
Details were added regarding how to define most diseased coronary segment and other CTA parameters

Section 3.3.2.1
It was added that results will be derived for all subjects and then for a subset of subjects with reduced ejection fraction

Section 3.3.3.1
It was removed that ADA will be follow-up until value returns to baseline

Section 3.3.3.2
It was deleted that PK analysis will not be part of the SAP

Section 3.3.4.1

It was specified that in case of departure from log normal distribution, other analyses will be explored

Section 3.3.4.3
CCI [redacted]

Section 3.3.4.4
CCI [redacted]

Section 3.3.5.1
AE start datetime imputation updated since time of start of AE is not collected

Section 3.3.5.2
Table 4 was update to be consistent with CSP and fasting lipid parameters were added

Section 3.3.5.3
Vital sign normal ranges (low, normal, high) with reference ranges value were added

Section 3.4.1
Extended exposure definition and cumulative extended exposure definition were added

Section 4.1
Presentation of treatment group CCI [redacted] and placebo) and especially patient randomized in CCI [redacted] who switched to CCI [redacted] according to analysis population was added

It was also added "Statistical hypothesis tests for all endpoints will be conducted at a 2-sided 0.05 significance level without multiplicity adjustment, for the final analysis as well as for the interim analyses."

Section 4.2.1

Subject disposition related to covid situation was added

Section 4.2.4
A table providing the number and percentage of subjects with at least one cardiac medication saw added

Section 4.2.5.1
Descriptive statistics table on extended exposure was added. Categorical analysis added for exposure and extended exposure

Section 4.2.8.1.2

Another sensitivity analysis added on the CTA analysis population but without subjects having received both[redacted] (sensitivity 5).

Section 4.2.8.1.6, 4.2.8.2.2, 4.2.8.3.2, 4.2.10.1.1, 5.2.1.2, 5.2.2.1, 5.2.3.1, 5.2.4.1, 5.2.5.1 and 5.3.1.1

Geographical region subgroup updated as follows:

- Asia, North America; Rest of the World
- Western (North America and Rest of the World); Asia

Other classification added for hsCRP (<2 mg/L; >= 2 mg/L), NPproBNP (< 125 pg/mL; >= 125 pg/mL), baseline LDL(<70 mg/dL; >=70 mg/dL), baseline LVEF (<50%; >=50%) subgroups.

Section 4.2.8.2

It was added that “These summaries (tables and figures) will be also repeated for final analysis only among subjects with reduced ejection fraction (defined as <50%)”.

Section 4.2.8.2.1

Sensitivity analysis added for NT-proBNP

Section 4.2.8.3

Descriptive statistics added for LVEF and of GLS. Also listing added

Section 4.2.8.3.1

Sensitivity analysis added for LVEF

Section 4.2.9.1 and 5.2.6

All ADA section was updated to describe analyses

Section 4.2.10.1

Specific analyses were added for [redacted] analysis population

Section 4.2.10.5

[redacted]

Section 4.2.11.1 and 5.4.1

AE table incidence by SOC and PT added for bleeding and Injection site reaction

Section 4.2.11.2

Tables on ALT, AST and BILI elevations were added

Section 4.2.12
Details were added regarding COVID tables and listings

8.1.3 Version 3.0

General
Due to visit 9 removed in CSP amendment2, visit 9 and following visits do not correspond to the same visit according to when patient was randomized. The visit "Day XX/Visit Y" were replaced by "Day XX" in all the SAP and Shells.

Variables removed from CSP amendment 2.0 are kept in the SAP and will be analysed with descriptive statistics only (no statistical model, no figure, no subgroup analysis). Secondary endpoints removed from CSP amendment 2 are analysed as exploratory endpoints.

Since interim CTA at Day 122 was removed, only descriptive statistics will be provided at Day 122 for CTA parameters (no statistical model)

Interim analyses were removed. Abbreviation
Some abbreviations added/removed when needed and within the document full description of abbreviation added at the first occurrence of abbreviation

Amendment history
Complete version 2.0 and version 3.0 history of changes

Section 1.1
Update study objectives as per CSP amendment 2.0.

Section 1.2
Update study design as per CSP amendment 2.0.

Section 3.1.2
Analysis visit windows were added and it was removed that nominal eCRF visits will be used in statistical analyses.

Section 3.1.3
It was added that "In case of partially missing date, the imputed date will be used to assign the analysis phase."

Section 3.3.2.3

CCI

Section 3.3.3.1 and 3.3.3.2
The visits analysed were added

Section 3.3.5.2
Except otherwise specified the laboratory parameters will be presented in international standard units

Section 3.5
The rule for complete/partially missing start and stop dates of concomitant medication was updated

Section 4.1
For geometric mean calculation, an imputation rule was added for variables records with zero value
It was added that the description of primary and secondary efficacy parameters will be studied over the course of the study using baseline value. In case of departure from the a priori distribution, the statistical analysis planned in this SAP will be updated
Definitions of change from baseline (normal distribution), relative change from baseline (log-normal distribution) and percent change (any distribution) were added

Section 4.1.1, 4.1.2, 4.1.3
It was specified that comparisons of MEDI6570CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo, MEDI6570 CCI versus placebo and pooled MEDI6570 CCI versus placebo will be assessed using two separate models

It was specified “one sided” before “p-value”, also “95% CI” were replaced by “90% CI”.

Section 4.1.2
Other variance-covariance matrices were added in case MMRM model does not converge with UN and CS

Section 4.1.3
The results from the Cox model reported in the table were clearly listed

Section 4.1.4
Negative binomial regression model was added

Section 4.2.2

Analyses planned on protocol deviations were clarified

Section 4.2.4
"Medical therapy" was replaced by "concomitant medication"

Section 4.2.5.2
A listing on overdose was added

Section 4.2.8.1.2, 4.2.8.1.4
Following sensitivity analyses were removed LOCF and MMRM (not appropriate since interim CTA is removed) and Sensitivity on patients without CTA device changed from baseline to Day 253 was added

Section 4.2.8.1.4
Section removed since parameter is classified as exploratory

Section 4.2.8.1.5, 4.2.8.2.2, 4.2.8.3.2, 4.2.10.1.1, 5.2.1.2, 5.2.2.1, 5.2.3.1, 5.2.4.1, 5.2.5.1 and 5.3.1.1
Some subgroups were removed: CCI, subgroup defined on tertiles were removed only medians are kept, repetition of subgroups on patients with reduced ejection fraction

Section 4.2.9.2
LLOQ value for MEDI6570 was updated to 0.0328 µg/mL

Section 4.2.10.1.1
CCI [redacted]

Section 4.2.10.5
CCI [redacted]

Section 6
CCI [redacted]
Add analysis set that were not foreseen in CSP in SAP
Add parameters removed in CSP amendment 2
Add that the bioanalytical test site will have access to the randomization list

8.1.4 Version 4.0

List of abbreviations
Add: AU Arbitrary Units, eGRF Estimated Glomerular Filtration Rate, ICF Informed Consent; CDV Cardiovascular; CV Coefficient of Variation; Form, KM Kaplan Meier

'gmean' replaced with 'GeoMean'
'gCV' replaced with 'GeoCV'
'gSD' replaced with 'GeoSD'

1.1 Study objectives
Deleted 'Relative' as per new AZ rules
Deleted CCI as per new AZ request

2.1 definition of analysis sets
'at least one post-baseline' replaced with 'at Day 253
CTA analysis population defined as Subjects within the ITT population who have interpretable** CTA scans at baseline and at Day 253 or at Day 122 will be included. (Note that separate analyses will be conducted for Day 253 and Day 122.)
Modified footnote in Table 2 in "An interpretable CTA scan is defined as having 1 or more matching evaluable segment at baseline and at Day 253 or at Day 122. LOCF (Last Observation Carried Forward) method not applied".
Added 'version 4.0' after CTA imaging guidance document

3.1.2 Baseline definition and analysis visit windows
Added 'version 4.0' after CTA imaging guidance document
In table 3 Modified footnote a (in "CCI , NT-proBNP, CCI . For MMRM of CCI NT-proBNP, we will only include VISITs 3, 8 and 13analysis visits of pre-treatment, Day 113 and Day 253. For MMRM of CCI , we will include analysis visits of pre-treatment, Day 10, Day 29, Day 57, Day 113, and Day 253) and added footnote d ("Some scheduled visits were removed after the protocol amendment 2 but these analysis visits will be included in the analysis because they fall in the analysis windows before the protocol amendment 2. Please check the latest version of the protocol for more details."
In table 3 modified under "CTA – ECHO – Biomarkers": "CTA: 114 – 140 CCI and biomarkers"

3.2.1 Demographic and subject characteristics
Added 'stent(s) placed for treatment of qualifying MI (yes, no) and vessels treated (left main, left anterior descending and branches, right coronary artery and branches, left circumflex artery and branches, ramus branch)'

3.3.1 Primary efficacy endpoint
'programming specifies on matching evaluable segments are detailed in a separate CTA imaging guidance document' replaced with 'Specific algorithms for programming are provided in a separate CTA imaging guidance document (Version 4.0)'

3.3.2 Secondary efficacy endpoint
Deleted ‘Relative’ as per new AZ rules

3.3.2.1 NT-proBNP
Deleted ‘relative change from baseline is defined ad ratio of post-baseline visit value over the baseline value’ as per new AZ rules
‘change will be defined as log (post-baseline visit value) minus log (baseline value)’ replaced with ‘Change from baseline will be defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value’

3.3.2.3 Parameters assessed by CTA
‘programming specifies on matching evaluable segments are detailed in a separate CTA imaging guidance document’ replaced with ‘Specific algorithms for programming are provided in a separate CTA imaging guidance document (Version 4.0)’

3.3.3.1 Immunogenicity parameters
Added ‘Day 169, Day 197’ to be consistent with analysis visit plan

3.3.3.2 PK parameters and PK concentration
Added ‘Day 169’ to be consistent with analysis visit plan
Added ‘PK results will be assigned visits as described in Table 3’

3.3.4 Exploratory endpoints
CCI [redacted]

3.3.4.1 Inflammatory and target engagement biomarkers
‘ng/L’ replaced with ‘pg/mL’
‘ug/L’ replaced with ‘ng/mL’
‘ng/L’ replaced with ‘ng/mL’
‘ng/L’ replace with ‘pg/mL’
Added CCI [redacted]
‘change will be defined as log (post-baseline visit value) minus log (baseline value)’ replaced with ‘Change from baseline will be defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value’

3.3.4.4 CCI [redacted]

Added in title and paragraph 'score'

CCI [redacted]

[redacted] CCI [redacted]

3.3.5.2 Laboratory evaluations
Deleted 'except otherwise specified laboratory will be provided in international standard (SI) unit'
Added in Table 5 eGFR, according to AZ comment will be reported in new shift chemistry table only

3.3.5.2 Vital Signs
Updated ranges in Table 6Vital signs normal reference ranges

4.1 General principles
Added CCI [redacted]
Added 'subjects initially randomized to the CCI group who consented to CSP amendment 1 and were switched to CCI dose were analysed according to the CCI group. For the safety and efficacy analyses, the number of subjects randomized to the CCI group who consented to amendment 1 of the CSP and switched to the CCI dose is specified.'
Added 'and if p-value is higher than 0.999 or equal to 1, will be displayed ">0.999".'
Added new rules about 'Relative change' parameters
Added Normality checking for primary endpoint only
Added 'listing' after CCI populations

4.1.1 Analysis of covariance (ANCOVA) and 4.1.2 the mixed model repeated measures (MMRM)
Deleted 'relative change'

4.1.3 Cox Proportional Hazards model
Replaced with 'using the same model'

4.2.4 Concomitant medications
Deleted '(or the highest level available i.e. if ATC level 4 is missing)'

4.2.5.1 Exposure
Added 'SD'

4.2.8.1.2 Sensitivity analysis of the primary efficacy endpoint, 4.2.8.1.4 Sensitivity analysis for NCPV and LAPV, 4.2.8.2.1 Sensitivity analysis for NT-proBNP and 4.2.8.3.1 Sensitivity analysis for Echocardiogram variables
Added 'analysis' after sensitivity

4.2.8.2 Analysis of NT-proBNP
Deleted 'the corresponding values will be cack transformed from logarithmical to original scale'
Deleted 'relative'

4.2.8.2.1 Sensitivity analysis of NT-proBNP
Sentence modified in "A second sensitivity analysis may be performed by including all analysis visits regardless of protocol version".

4.2.8.2.2 Subgroup analysis of NT-proBNP, 4.2.8.3.2 Subgroup analysis of Echocardiogram variables, CCI
Added specific information for each subgroup as section 4.2.8.1.5

4.2.9.1 Immunogenicity Analysis
Added category ADA negative at all assessments, including baseline and post-baseline (ADA negative)

4.2.9.2 PK analysis
Added 'using box plot and by plotting individual serum concentrations (µg/mL) time profile of MEDI6570 by ADA category using spaghetti plot.'

4.2.10.1 Inflammatory and target engagement biomarkers
Deleted 'relative' and 'back transformed'
Added Day 169 in this sentence "CCI will be summarized descriptively as continuous variables at baseline, Days 10, 29, 57, 85, 113, 122, 141, 169, 225, 253 and 325/405 for observed value and change from baseline".

CCI

CCI

4.2.10.6 CCI

Deleted ‘relative’ and ‘back transformed’ as per new AZ rules and updated formula applying new unit of measurement

4.2.10.7 Adverse events
Added ‘(total will not include placebo subjects).’
Added ‘except the AE by ADA tables which will be based on the Immunogenicity population’
Added Overall summary of number and percentage of subjects with any AEs by ADA (anti-drug antibody category)
Added The number and percentage of subjects by ADA (anti-drug antibody category)

4.2.10.8 Laboratory evaluation
‘SI units’ Replaced with ‘with their units of measure’
Added ‘Shifts from baseline to maximum and minimum value during the on-treatment phase will be presented for haematology and clinical chemistry parameters.’

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d4920c00002-sap-ed-4		
Document Title:	Statistical Analysis Plan Edition 4	
Document ID:	Doc ID-004425642	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
04-Dec-2023 12:53 UTC	PPD	Author Approval
06-Dec-2023 10:41 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.