Clinical Study Protocol	
Study Intervention	MEDI6570
Study Code	D4920C00002
Amendment Number	2
Date	09 November 2021

A 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

Sponsor Names:

Global Sponsor: AstraZeneca, AB, 151 85 *Södertälje, Sweden*

Local Sponsor: AstraZeneca, KK, 3-1*, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan*

Regulatory Agency Identifier Numbers: IND 139103; EudraCT 2020-000840-75

This CSP has been subject to a peer review according to AstraZeneca standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D4920C00002

Amendment Number: 2

Study Intervention: MEDI6570

Study Phase: IIB

Short Title: A Phase IIB Parallel-group Study to Evaluate the Efficacy and Safety of MEDI6570 in Participants with a Prior Myocardial Infarction

Acronym: GOLDILOX-TIMI 69 *Miti***G***ating* **O***x*-**LD***L induced coronary* **I***nflammation, Atheroma and Heart Failure via* **LOX**-*1 receptor inhibition — Thrombolysis in Myocardial Infarction 69*

Medical Monitor name and contact information will be provided separately.

TERMS AND CONVENTIONS USED IN THIS DOCUMENT

The list of abbreviations is given in Appendix H.

In addition, the following terms are used interchangeably in this document:

- 'Intervention' and 'treatment'
  'Intervention' is used generically in clinical studies to describe the intervention under evaluation (eg, medical device, pharmaceutical product, physical or behavioral adjustment etc). 'Intervention' is used in most sections of this document for MEDI6570 or its injection/volume-matched placebo; however, 'treatment' is used in the statistical sections for consistency with standard statistical terminology.

- 'Participant' and 'subject'
  'Participant' is used generically to describe healthy volunteers or patients taking part in a clinical study. 'Participant' is used in most sections of this document; however, 'subject' is used in the statistical sections for consistency with standard statistical terminology.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	09Nov2021
Amendment 1	10Mar2021
Original Protocol	22May2020

Amendment 2 (09Nov2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the amendment, given the complexity and burden of the current trial configuration and the corresponding impact on recruitment, is to simplify the protocol to reduce the patient burden and be more patient-centric. The protocol has a reduced total sample size while maintaining the assessment of the primary endpoint at a slightly reduced power and increased type 1 error.

Substantial changes to the protocol are listed in Table 1 and non-substantial changes are listed in Table 2.

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Visit 9 and all of its evaluations including the interim CTA were removed. The following secondary endpoint and exploratory endpoint were also removed:	To reduce the patient burden in the study and reduce operational complexity	Section 1.1 Synopsis; Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period; Section 4.1 Overall Design; Section 8.1.1.2 Criteria for CTA Imaging; Section 8.1.1.3 Radiation Exposure from CTA Imaging, Including Rules for Repeating CTA Scans ~~and Conducting the Interim CTA~~
• CCI		Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 4.2.2.2 Secondary Endpoints; Section 8.1.1.4 CTA Image Analysis
• CCI		Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 8.1.1.4 CTA Image Analysis

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
CCI	CCI	Section 1.1 Synopsis; Section 1.3 Schedule of Activities, Table 4 Schedule of Activities: Intervention Period; Section 3 Objectives and Endpoints; CCI (section deleted)
CCI	CCI	Section 1.1 Synopsis; Section 3 Objectives and Endpoints
Randomization to the CCI dose group was removed.	• To reduce the overall sample size of the study • The current number of participants in the CCI mg dose group is expected to provide sufficient dose-response information on the PK-PD relationship and endpoints, and is unlikely to be the dose with the optimal clinical risk-benefit balance.	Section 1.1 Synopsis; Section 1.2 Schema; Section 4.1 Overall Design; Section 4.3 Justification for Dose; Section 6.1 Study Interventions Administered, Table 8 Investigational Products; Section 6.2.3 Dose Preparation Steps, Table 9 Dose Preparation for Fixed SC Doses of CCI and CCI mg MEDI6570 and Placebo; Section 6.3.1 Randomization Procedure; Section 6.3.2 Blinding Procedure; Section 6.3.3 Unblinding for Interim Analysis Purposes (section deleted); Section 9.2 Sample Size Determination; Section 9.5 Interim Analyses

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
The number of participants was reduced from 792 to 400. CCI [redacted]	To reduce the overall sample size and improve feasibility of completion while maintaining acceptable power to inform development program decisions	Section 1.1 Synopsis; Section 1.2 Schema; Section 4.1 Overall Design; Section 9.2 Sample Size Determination
The 2 formal interim analyses were removed.	The interim analyses were administrative in nature. The full study results will be used for decision making on future development options. The study was designed to continue to completion regardless of the results of the interim analyses.	Section 1.1 Synopsis; Section 1.2 Schema; Section 4.1 Overall Design; Section 6.3.3 Unblinding for Interim Analysis Purposes (section deleted); Section 9.4.1 General Considerations; Section 9.5 Interim Analyses
The Day 405 visit (formerly Visit 16) was removed and the Day 325 visit (Visit 14) (formerly Day 334 [Visit 15]) is the new End of Study Visit	The safety follow-up visit will be performed approximately 3 months after the last dose (shortened from 6 months). CCI [redacted]	Section 1.1 Synopsis; Section 1.3 Schedules of Activities, Table 5 Schedule of Activities: Follow-up Period; Section 4.1 Overall Design

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
• CCI [redacted]	[redacted]	[redacted]
• Selected blood sample collections were removed for the following variables (for the time point[s] indicated): ° CCI [redacted]	To reduce the patient burden in the study	Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities and Table 4 Schedule of Activities: Intervention Period
° PK (Day 85 [Visit 7], Day 141 [Visit 9, formerly Visit 10], and Day 225 [Visit 12, formerly Visit 13])		Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
° CCI [redacted]		Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities and Table 4 Schedule of Activities: Intervention Period
° CCI and NT-proBNP (Day 29 [Visit 5], Day 85 [Visit 7], Day 225 [Visit 12, formerly Visit 13])		Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
° Circulating biomarkers of inflammation and CV disease (Screening, Day 29 [Visit 5], Day 225 [Visit 12, formerly Visit 13])		Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities and Table 4 Schedule of Activities: Intervention Period

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
° Samples for diagnostic assay development (Screening, Day 29 [Visit 5], Day 85 [Visit 7])		Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities and Table 4 Schedule of Activities: Intervention Period
° Immunogenicity (Day 10 [Visit 4], Day 85 [Visit 7], Day 141 [Visit 9, formerly Visit 10], Day 225 [Visit 12, formerly Visit 13])		Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
° Hematology and clinical chemistry (Day 85 [Visit 7], Day 141 [Visit 9, formerly Visit 10]), Day 197 [Visit 11, formerly Visit 12], and Day 225 [Visit 12, formerly Visit 13])		Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
• The following blood sample collections removed from Day 141 [Visit 9, formerly Visit 10], were added to Day 169 (Visit 10): ° PK ° ADA ° CCI		
ECG collections were removed for the following time points: Day 85 [Visit 7], Day 141 [Visit 9, formerly Visit 10]), Day 197 [Visit 11, formerly Visit 12], and Day 225 [Visit 12, formerly Visit 13])	To reduce the patient burden in the study	Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
All urine sample collections for the evaluation of albumin-to-creatinine ratio were removed	To reduce the patient burden in the study	Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period and Table 5 Schedule of Activities: Follow-up Period; Section 6.3.2 Blinding Procedure

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Inclusion criterion 2 was amended to state that female participants need to be aged ≥ 40 years, but male participants need to be aged ≥ 21 years.	To broaden the inclusion criteria to include younger male patients post myocardial infarction given effect modification by age is not anticipated	Section 4.2.1 Rationale for Study Population; Section 5.1 Inclusion Criteria
Exclusion criterion 2 was amended as follows: 'Percutaneous coronary intervention ~~[PCI]~~ **or diagnostic angiogram** planned after screening Visit 1. Eligible participants who have a ~~PCI~~ **diagnostic angiogram performed** ~~after screening Visit 1~~ **in the absence of undergoing a new PCI may continue screening after the diagnostic angiogram has been performed or** may be rescreened ~~after the PCI has been performed~~ (Section 5.4).' and	To reduce the likelihood of recruiting patients who need further investigation that may confound study results	Section 5.2 Exclusion Criteria

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
'• Eligible participants who exceed the 42-day pre-randomization window may be rescreened to determine eligibility before randomization **and the Medical Monitor will decide whether screening laboratory evaluations should be repeated**. If the screening assessments are not considered to be representative of the usual status of the health of the participant by the investigator, or if ≥ 1 exclusion criteria are considered temporary (eg, ~~planned PCI~~ **diagnostic angiogram**) or from a reversible condition, repeat screening assessments to establish eligibility will generally be permitted once, at the discretion of the investigator.' and 'Eligible participants who have a ~~PCI~~ **diagnostic angiogram performed** ~~planned~~ after screening Visit 1 **in the absence of undergoing a new PCI** may ~~be rescreened~~ **continue screening** after the ~~PCI~~ **diagnostic angiogram** has been performed (Exclusion Criterion 2). **If they exceed the 42-day pre-randomization window, the Medical Monitor will decide whether the participant is required to be rescreened and whether screening laboratory evaluations should be repeated. Participants who have a PCI performed between screening Visit 1 and Randomization Visit 3 may not be rescreened.**'		Section 5.4 Screen Failures

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Exclusion criterion 6(b) was amended as follows: (b) ~~Active bleeding or high risk for major bleeding (eg, gastrointestinal pathology, malignancy with high risk of bleeding, active peptic ulcer).~~ **Signs of ongoing bleeding at screening (eg, identified macroscopic bleeding, low hemoglobin presumed to be caused by bleeding) or high risk for major bleeding in accordance with the Investigator's assessment.**	Exclusion criteria updated for clarity and with the aim to avoid unnecessary exclusion of participants due to the theoretical risk of bleeding, by introducing some flexibility for medical assessment by the Investigator	Section 5.2 Exclusion Criteria
Exclusion criterion 6(c) was amended as follows: (c) Need for chronic **therapeutic** anticoagulation therapy **anticipated to be required throughout the course of the study** (**short-term treatment with** prophylactic doses of heparin/**low molecular weight heparin** are allowed).	Exclusion criteria updated for clarity	Section 5.2 Exclusion Criteria
Exclusion criterion 12 was amended as follows: 'Planned participation in an additional **investigational** study of an intervention or biologic before the end of the follow-up period. **Participation in observational studies or studies without investigational drugs or devices is allowed.**'	To allow patients who are participating in observational studies of devices to participate in this study	Section 5.2 Exclusion Criteria

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Text was amended as follows: 'Participants with a need for chronic **therapeutic** anticoagulation therapy are excluded from study participation; however, ~~prophylactic doses of heparin are allowed~~ **short-term treatment with prophylactic doses of heparin/low molecular weight heparin are allowed**'	Text updated for clarity and to align with updated wording in exclusion criterion 6(c). with the aim to avoid unnecessary discontinuation of participants due to the theoretical risk of bleeding, by introducing some flexibility for medical assessment by the Investigator	Section 6.5.1 Permitted Concomitant Medications
Text on discontinuation of study intervention was amended as follows: '(a) Providers should consider temporary or permanent discontinuation of study intervention in **participants who**: (i) ~~In participants~~ **D**evelop a condition that requires the use of **chronic therapeutic** anticoagulation therapy. (ii) **Experience** severe bleeding that is not readily explained by a reversible alternate etiology. All bleeding events should be treated and followed up according to local clinical practice. Study intervention may be resumed when the risk of bleeding is deemed low in the judgment of the investigator.'	Text updated for clarity and to align with updated wording in exclusion criterion 6(c). with the aim to avoid unnecessary discontinuation of participants due to the theoretical risk of bleeding, by introducing some flexibility for medical assessment by the Investigator	Section 7.1 Discontinuation of Study Intervention

Table 1 Substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
The following new text was added to the Pregnancy section: 'Nonsterilized male study participants should be advised to use a condom for all sexual intercourse with a female partner of childbearing potential from Day 1 through the end of the study follow-up period. All male participants should refrain from fathering a child or donating sperm during the study and for 190 days following the last dose. If the partner becomes pregnant, the partner will be asked (under a separate consent) to provide information about the pregnancy and newborn baby.' In addition, the order of paragraphs in the section was re-arranged to match the template.	AstraZeneca has reassessed the theoretical risk to women of childbearing potential of exposure to semen from male participants receiving MEDI6570. The reassessment confirms that semen from male participants exposed to MEDI6570 poses low to no risk to the fetus of pregnant sexual partners or the potential fetus of sexual partners who may become pregnant. However, as a conservative and cautionary approach, following the AstraZeneca and Clinical Trial Facilitation Group guidelines, AstraZeneca has decided to update the clinical study protocol accordingly.	Section 8.3.8 Pregnancy; Section 8.3.8.1 Maternal Exposure (new section created with existing text); Section 8.3.8.2 Paternal Exposure (new text added to new section)
The following text was removed: 'For the biomarker samples collected at Day 1 (Visit 3), Day 29 (Visit 5) and Day 85 (Visit 7) for CCI NT-proBNP, CCI part of each sample will be reserved for exploratory subgroup analysis for predicting response to therapy in primary, secondary, and exploratory endpoints'	Analyses will not be performed	Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis
The wording of the alternative hypothesis was amended as follows: 'The alternative hypothesis is that ~~there is a difference in this endpoint in participants given MEDI6570 compared with placebo~~ **the change from baseline in $NCPV_{MD}$ reduction is larger in the MEDI6570 CCI mg group compared with the pooled placebo group**.'	To reflect the change from 2-sided analyses to 1-sided analyses	Section 9.1 Statistical Hypotheses

ADA, anti-drug antibody(ies); CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; CCI [redacted] hs-CRP, high sensitivity C-reactive protein; CCI [redacted] MVPA, moderate-to-vigorous physical activity; $NCPV_{MD}$, Non-calcified plaque volume in the most diseased coronary segment; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PCI, percutaneous coronary intervention; PK, pharmacokinetic; CCI [redacted]; ULN upper limit of normal

Table 2 Non-substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Rationale text was amended as follows: 'The results of the Phase IIB study ~~will~~ **may** inform future clinical development options and precision medicine strategy for future clinical studies.'	For clarification	Section 1.1 Synopsis
The time window for the Baseline Imaging visit was extended from **21** - 1 day before randomization to **30** - 1 day before randomization	To align with Section 8.1.1.3 language and to provide sites with more flexibility to obtain baseline image without affecting study endpoint	Section 1.2 Schema; Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities; Section 8.1.1.3 Radiation Exposure from CTA Imaging, Including Rules for Repeating CTA Scans and Conducting the Interim CTA
The rows for weeks were removed from the schedules of activities	To add clarity because the weeks did not always correspond directly with visit days	Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities, Table 4 Schedule of Activities: Intervention Period, and Table 5 Schedule of Activities: Follow-up Period
Text was added to indicate that a local laboratory sample for coagulation may be used to assess eligibility	To allow flexibility if the central laboratory sample does not provide a valid result; the result from a central sample would be required to establish the baseline value before dosing	Section 1.3 Schedules of Activities, Table 3 Schedule of Activities: Pre-randomization Activities

Table 2 Non-substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Text was added to clarify that the visit window is ± 7 days for dosing visits and ± 3 days for non-dosing visits (ie, Day 10 [Visit 4]), and that if a participant is dosed outside of the visit window, he or she should return to the initial planned schedule for subsequent visits.	For clarification	Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
Text was modified to reflect that blood and urine samples will be drawn before dosing, not before randomization.	For clarification	Section 1.3 Schedules of Activities, Table 4 Schedule of Activities: Intervention Period
The terms 'alanine transaminase' and 'aspartate transaminase' were amended to 'alanine aminotransferase' and 'aspartate aminotransferase', respectively	For consistency with other study documents	Section 5.2 Exclusion Criteria; Section 8.2.4 Clinical Safety Laboratory Assessments; Table 10 Laboratory Safety Variables; Appendix H Abbreviations
Text requiring permission from the Medical Monitor for additional repeat screening was removed.	To reduce participant burden, participants will not be asked to rescreen more than once	Section 5.4 Screen Failures
Superscript 'a' was corrected	Incorrect original footnote 'a' was deleted and newly required footnote 'a' was added	Section 6.1 Study Interventions Administered, Table 8 Investigational Products
Text relating to re-allocation of dosing volumes was amended to past tense	To clarify that the re-allocation applied under Protocol Amendment 1 only	Section 6.3.1 Randomization Procedure
The following text was added: 'A full coronary CTA interpretation will not be performed locally.'	For clarification	Section 8.1.1.4 CTA Image Analysis

Table 2 Non-substantial Changes to the Protocol

Description of Change	Brief Rationale	Sections Affected
Text was amended as follows: '…The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples **and images (CTA and echocardiogram)** and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or **have their unused samples and images (CTA and echocardiogram)** used in future use research and may withdraw their consent at any time and for any reason during the retention period. …'	For clarification	Appendix A 3 Informed Consent Process
Minor formatting and capitalization changes	For consistency	Throughout

CTA, computed tomography angiography

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A 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

Short Title: A Phase IIB Parallel-group Study to Evaluate the Efficacy and Safety of MEDI6570 in Participants with a Prior Myocardial Infarction

Rationale: This Phase IIB, proof-of-concept, dose-range finding clinical study is being conducted to evaluate the anti-inflammatory potential of MEDI6570 and its effect on surrogates for atherosclerotic and heart failure (HF) events in patients with a history of myocardial infarction (MI). The results of the Phase IIB study may inform future clinical development options and precision medicine strategy for future clinical studies.

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	Relative 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 • Titer as measured in serum during the intervention and follow-up periods

Objectives	Endpoints
To evaluate the PK of MEDI6570	MEDI6570 concentrations as measured in serum during the intervention and follow-up periods
Safety	
To assess the safety and tolerability of MEDI6570 compared with placebo	During the intervention and follow-up periods: • AEs • Clinically important changes in: Vital signs ECGs Safety laboratory assessments
Exploratory	
CCI	
CCI	

The Day 253 endpoint includes the visit window around Visit 13 of - 4 to + 11 days.

ADA, anti-drug antibody(ies); AE, adverse event; CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; CCI (ratio); GLS, global longitudinal strain; HF, heart failure; CCI ; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; 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

Overall Design:

This is a randomized, double-blinded, placebo-controlled, parallel-group, multicenter (approximately 70 to 100), international study in participants who have recently (within the previous 30 to 365 days) had an MI (either ST segment elevation MI or non-ST segment elevation MI), with persistent inflammation (high sensitivity C-reactive protein [hs-CRP] ≥ 1 mg/L). Participants will be randomized in a 2:2:1:1 ratio to receive CCI in an injection volume of 1.5 mL) or CCI (in an injection volume of 4.0 mL) MEDI6570, or an injection/volume-matched placebo, subcutaneously (SC), every 4 weeks (Q4W) for 32 weeks (9 doses in total). 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 World) and by statin therapy intensity at screening (no, low- or moderate-intensity statin therapy vs high-intensity statin therapy).

Participants will undergo an echocardiogram and computed tomography angiography (CTA) scan before randomization and administration of study intervention. During the follow-up period, participants will also undergo an echocardiogram and CTA scan.

Disclosure Statement: This is a parallel-group, treatment study with 6 intervention groups (including the legacy CCI mg dose group and matched placebo) that is participant- and investigator-blinded.

Number of Participants: Approximately 400 participants will be randomly assigned to a study intervention, with an anticipated 369 participants being randomized to receive active study intervention (123 participants in each of the 2 MEDI6570 groups), and 123 participants being randomized across the 3 placebo groups (ie, including participants already randomized to the legacy dose/volume-matched placebo group for the CCI mg dose). It is estimated that approximately 360 evaluable participants (111 evaluable participants in each of the 2 MEDI6570 groups [CCI and CCI mg], plus 27 evaluable participants in the legacy CCI mg MEDI6570 group, plus 111 participants across the 3 placebo groups) will complete the study. Evaluable participants are defined as those with an evaluable CTA at baseline and follow-up (Day 253; Visit 13).

Intervention Groups and Duration: The study intervention is MEDI6570, a human Immunoglobulin G1 lambda (IgG1λ) triple mutation antibody that binds to CCI Going forward from Amendment 2, the study will include 4 intervention groups: CCI and CCI mg MEDI6570, and 2

injection/volume-matched placebo groups, while the participants previously randomized to CCI mg MEDI6570 or its injection/volume-matched placebo will continue their assigned treatment to the end of the study. Participants 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), an intervention period of 225 days (31 to 32 weeks), and a follow-up period of 100 days (approximately 14 weeks). Doses of MEDI6570 or placebo will be administered in the clinic SC Q4W for 32 weeks (9 doses in total).

Data Monitoring Committee: Yes

Statistical Methods:

Sample size estimate and justification: The 3 injection/volume-matched placebo groups will be pooled for the analyses. The planned 111 evaluable participants in each of the 2 MEDI6570 intervention groups and across the 3 injection/volume-matched placebo groups combined will provide CCI power to detect an 11 mm^3 change from baseline in the non-calcified plaque volume in the most diseased coronary segment ($NCPV_{MD}$), comparing the CCI mg MEDI6570 intervention group with the pooled placebo group, assuming a standard deviation of CCI [redacted]

Populations for analysis: Seven populations are defined for analysis of study data:

- Intent-to-treat (ITT): all randomized participants; participants will be analyzed according to their randomized intervention group. Patients randomized to the CCI mg group that switch dose to CCI mg during the study will be analyzed according to the CCI mg group.
- As-treated: randomized participants who receive any study intervention; participants will be analyzed according to the actual intervention they receive, regardless of their randomized intervention group. Participants randomized to the CCI mg group that receive at least one CCI mg dose during the study will be analyzed according to the CCI mg group. Participants that only receive CCI mg will be analyzed as a separate CCI mg group.
- CTA analysis: Participants within the ITT population who have interpretable CTA scans at baseline and at least one post-baseline time point
- Per-protocol CTA analysis: Participants in the CTA Analysis Population who receive at least 3 doses of study intervention will be included in the Per-protocol CTA Analysis Population. Participants will be analyzed according to the actual intervention they receive.
- Echocardiogram analysis: Participants within the ITT population who have interpretable echocardiograms in the baseline and follow-up periods
- Pharmacokinetic (PK): participants who receive ≥ 1 dose of MEDI6570 per protocol and have at least one post-dose, evaluable, MEDI6570 serum concentration determination
- Immunogenicity: participants in the As-treated Population who have ≥ 1 immunogenicity sample

Statistical methods for primary endpoint: The primary endpoint is change from baseline in $NCPV_{MD}$. An analysis of covariance (ANCOVA) model on change from baseline adjusted for treatment group, baseline, and randomization strata will be used for the primary analysis.

Statistical methods for secondary efficacy endpoints: Secondary endpoint of relative change from baseline in NT-proBNP will be analyzed with a mixed model with repeated measures analysis on change from baseline for the log-transformed value of NT-proBNP. The results will be back-transformed to the original scale. The model will include fixed effects of treatment group, visit, treatment group-by-visit interaction, and randomization strata, with baseline NT-proBNP as a covariate. Repeated measures for the model will be visit within subjects; an unstructured covariance structure will be used for the repeated measures. In case the model does not converge, back-up covariance structures and other analysis solutions will be detailed in the statistical analysis plan.

Secondary endpoints that are measured by echocardiogram or CTA will be analyzed based on the Echocardiogram or CTA Analysis Population, respectively. ANCOVA analyses similar to the primary endpoint will be performed; the model will adjust for treatment group, respective baseline value, and randomization strata.

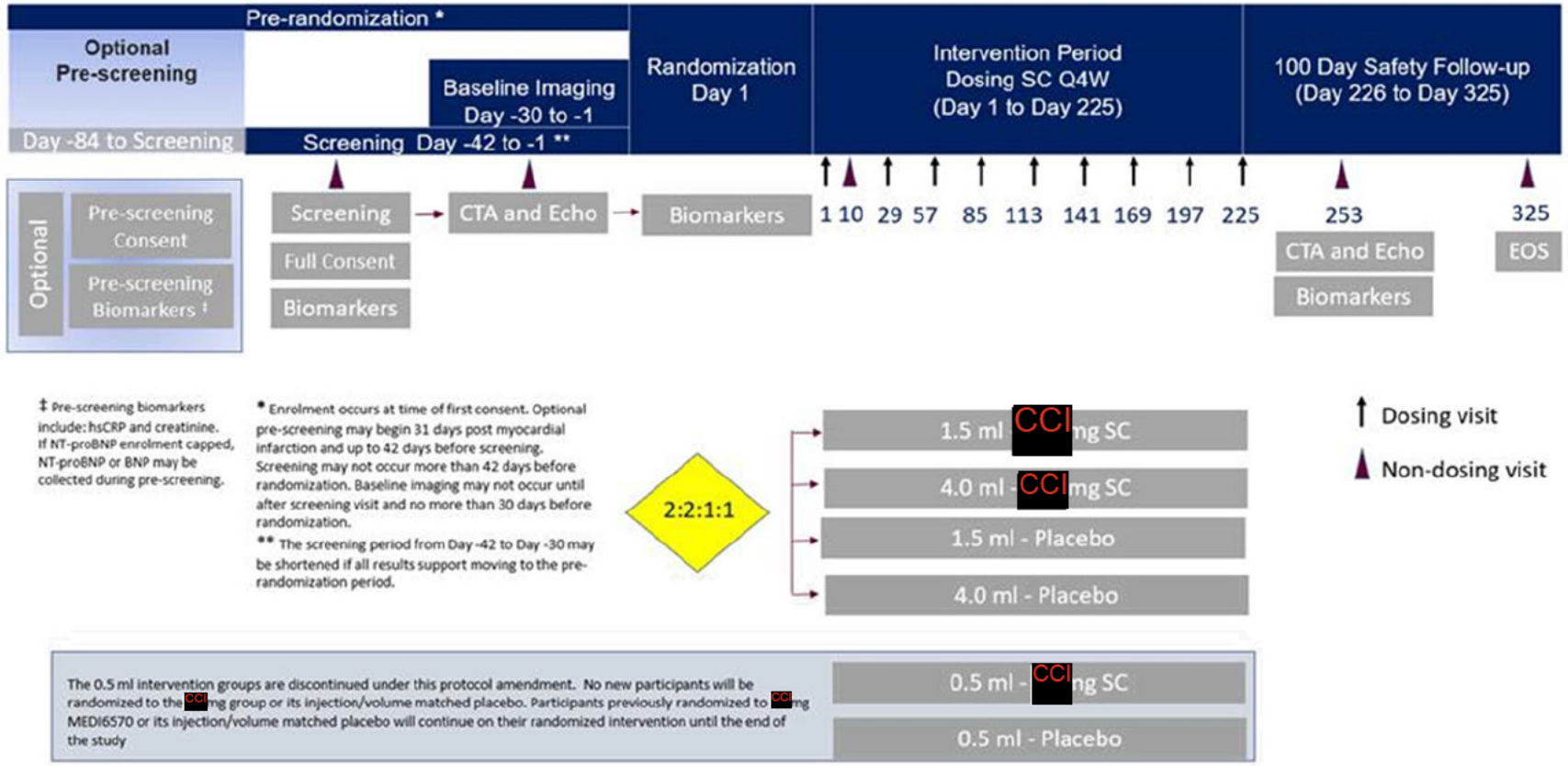
Statistical methods for safety variables: Type, incidence, severity, and relationship of adverse events (AEs) and serious adverse events to study intervention will be summarized by MedDRA System Organ Class and Preferred Term and by study intervention. Specific AEs will be counted once for each participant for calculating percentages. If the same AE occurs multiple times within a participant, the highest severity and level of relationship to study intervention observed will be reported. Vital signs and safety laboratory data will be summarized descriptively at each time point by study intervention.

Interim analysis: No formal interim analysis is planned.

An analysis restricted to PK (serum MEDI6570 concentration) CCI [redacted] 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 DMC.

1.2 Schema

Figure 1 Study Design



BNP, brain natriuretic peptide; CTA, computed tomography angiography; Echo, echocardiogram; EOS, end of study; hs-CRP, high sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone brain natriuretic peptide; Q4W, every 4 weeks; SC, subcutaneous(ly).

1.3 Schedules of Activities

Activities for the pre-randomization, intervention, and follow-up periods are given in Table 3, Table 4, and Table 5, respectively.

Table 3 Schedule of Activities: Pre-randomization Activities

Procedure	Pre-screening (Optional)	Screening	Baseline Imaging	Notes	Details in CSP section or appendix
	Optional visit	Visit 1	Visit 2	○ Enrollment occurs at time of first consent (ie, pre-screening or full consent). Optional pre-screening may begin 31 days post myocardial infarction and up to 42 days before screening. Screening may not occur more than 42 days before randomization. Baseline imaging may not occur until after screening visit and no more than 30 days before randomization. ○ The screening period from Day -42 to Day -30 may be shortened if all results support moving to the pre-randomization period.	
	Day -84 to Screening	Day -42 to -1	Day -30 to -1		
Informed consent(s)	X [a]	X		○ Brief informed consent for local laboratory sample collection at pre-screening only - optional [a] ○ Informed consent for main protocol at screening - required ○ Informed consent for future use at screening - optional ○ Informed consent for Genomics Initiative at screening - optional	Appendix A 3 Appendix D 2
Med. history; Con. meds.		X			Section 5.2
Full physical examination		X		Including height and weight	Section 8.2.1

Table 3 Schedule of Activities: Pre-randomization Activities

Procedure	Pre-screening (Optional)	Screening	Baseline Imaging	Notes	Details in CSP section or appendix
	Optional visit	Visit 1	Visit 2	○ Enrollment occurs at time of first consent (ie, pre-screening or full consent). Optional pre-screening may begin 31 days post myocardial infarction and up to 42 days before screening. Screening may not occur more than 42 days before randomization. Baseline imaging may not occur until after screening visit and no more than 30 days before randomization. ○ The screening period from Day -42 to Day -30 may be shortened if all results support moving to the pre-randomization period.	
	Day -84 to Screening	Day -42 to -1	Day -30 to -1		
Vital signs and ECGs		X		When vital signs and blood draws are scheduled for the same nominal time, blood draws should occur last. The timing of vital signs and ECGs should allow the blood draw (eg, PK blood sample) to occur at the assigned nominal time. ECGs can occur at any time relative to dosing and will be interpreted locally.	Sections 8.2.2 and 8.2.3
Assessment of SAEs	X	X	X	SAE collection will start from enrollment (ie, when the participant signs the first informed consent form, at either pre-screening or screening) [a]	Section 8.3
Collect blood for:					
Clinical safety		X		Samples for clinical chemistry, hematology, coagulation panel (a local sample may be used to assess eligibility; if central laboratory screening sample is not resulted because of a technical issue, a central laboratory sample would be redrawn before dosing), LH and FSH (female participants only), Hepatitis B and C, HIV	Sections 5.1, 8.2.4

Table 3 Schedule of Activities: Pre-randomization Activities

Procedure	Pre-screening (Optional)	Screening	Baseline Imaging	Notes	Details in CSP section or appendix
	Optional visit	Visit 1	Visit 2	○ Enrollment occurs at time of first consent (ie, pre-screening or full consent). Optional pre-screening may begin 31 days post myocardial infarction and up to 42 days before screening. Screening may not occur more than 42 days before randomization. Baseline imaging may not occur until after screening visit and no more than 30 days before randomization. ○ The screening period from Day -42 to Day -30 may be shortened if all results support moving to the pre-randomization period.	
	Day -84 to Screening	Day -42 to -1	Day -30 to -1		
hs-CRP	X [a]	X		A sample for hs-CRP may be collected at pre-screening. The sample must be collected again at screening and processed at the central laboratory to determine eligibility.	Section 8.6.1
NT-proBNP	X [a]	X		If randomization of participants with NT-proBNP < 125 pg/mL is capped, a sample for NT-proBNP (or BNP if NT-proBNP is not available) may be collected at pre-screening.	Sections 5.1 and 8.6.1
Creatinine for calculating eGFR	X [a]	X		○ A sample for creatinine may be collected at pre-screening using the local laboratory. The sample must be collected again at screening and processed at the central laboratory to determine eligibility.[a] ○ CTA: sample is required within 30 days before CTA scan (if the CTA sample is not the same sample that was used to determine eligibility, then the central laboratory or local laboratory or point of care testing may be used (according to local standard of care [plasma or serum]).	Sections 5.2, 8.1.1.2 and 8.2.4
Verify eligibility		X	X	Participants must meet the study eligibility criteria before undergoing the echocardiogram and CTA scan.	Sections 5.1 and 5.2

Table 3 Schedule of Activities: Pre-randomization Activities

Procedure	Pre-screening (Optional)	Screening	Baseline Imaging	Notes	Details in CSP section or appendix
	Optional visit	**Visit 1**	**Visit 2**	○ Enrollment occurs at time of first consent (ie, pre-screening or full consent). Optional pre-screening may begin 31 days post myocardial infarction and up to 42 days before screening. Screening may not occur more than 42 days before randomization. Baseline imaging may not occur until after screening visit and no more than 30 days before randomization. ○ The screening period from Day -42 to Day -30 may be shortened if all results support moving to the pre-randomization period.	
	Day -84 to Screening	**Day -42 to -1**	**Day -30 to -1**		
Echocardiogram and CTA scan			X	Participants must meet the study eligibility criteria before undergoing the echocardiogram and CTA scan. In addition, participants must meet CTA scan eligibility criteria before CTA scan imaging. If the echocardiogram and CTA scan are performed on the same day, the echocardiogram must always occur before the CTA scan and before any additional beta-blocker is given for the CTA scan.	Sections 8.1.1 and 8.1.2 (including instructions for repeating uninterpretable echocardiograms and CTA scans)

[a] An optional, pre-screening visit may occur before screening Visit 1 to collect blood for evaluating (using the local laboratory) hs-CRP and creatinine (for calculating e[GFR]), and, if randomization of participants with NT-proBNP < 125 pg/mL is capped, NT-proBNP (or BNP) (Section 5.1). Participants must sign a brief ICF for pre-screening before any pre-screen evaluations may be performed. If pre-screen evaluations are performed, written, informed consent for the full screening evaluations must still be given, and the full screening assessments (including hs-CRP and creatinine, and NT-proBNP if applicable) must still be performed for the participant to progress in the study. The pre-screening ICF must be signed not more than 42 days before the full ICF is signed. Participants who undergo pre-screening will be considered to have enrolled in the study.

BNP, brain natriuretic peptide; CSP, Clinical Study Protocol; CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FSH, follicle stimulating hormone; hs-CRP, high sensitivity C-reactive protein; LH, luteinizing hormone; NT-proBNP, N-terminal prohormone brain natriuretic peptide; SAE, serious adverse event.

Table 4 Schedule of Activities: Intervention Period

Procedure	Visit:	3	4	5	6	7	8	9	10	11	12	Notes	Details in CSP section or appendix
	Day (± 7): [a]	1	10[a]	29	57	85	113	141	169	197	225		
Physical examination		X										Abbreviated; includes weight	Section 8.2.1
Vital signs		X	X	X	X	X	X	X	X	X	X	When vital signs and blood draws are scheduled for the same nominal time, blood draws should occur last. The timing of vital signs should allow the blood draw (eg, PK blood sample) to occur at the assigned nominal time.	Section 8.2.2
ECG		X	X	X	X		X		X			The timing of ECGs should allow the blood draw (eg, PK blood sample) to occur at the assigned nominal time. ECGs can occur at any time relative to dosing and will be interpreted locally.	Section 8.2.3

Table 4 Schedule of Activities: Intervention Period

Procedure	Visit:	3	4	5	6	7	8	9	10	11	12	Notes	Details in CSP section or appendix
	Day (± 7): [a]	1	10[a]	29	57	85	113	141	169	197	225		
Collect blood for:													
Clinical safety (hematology and clinical chemistry)		X	X	X	X		X		X			Must be collected before dosing study intervention.	Section 8.2.4
PK		X	X	X	X		X		X			Must be collected before dosing study intervention.	Section 8.5.1
CCI		X	X	X	X		X		X			Must be collected before dosing study intervention.	Section 8.6.1
CCI NT-proBNP		X					X						Section 8.6.1
Circulating biomarkers of inflammation and CV disease		X					X						Section 8.6.1
Genomics Initiative		X										• Optional; collect sample if participant signed informed consent • Samples will be collected before dosing, and stored. • If for any reason the sample is not drawn at Visit 3, it may be	Section 8.7

Table 4 Schedule of Activities: Intervention Period

Procedure	Visit:	3	4	5	6	7	8	9	10	11	12	Notes	Details in CSP section or appendix
	Day (± 7): [a]	1	10[a]	29	57	85	113	141	169	197	225		
												taken at any visit until the last study visit	
Samples for diagnostic assay development		X					X					Must be collected before study intervention. Samples will be collected and stored.	Section 8.6.1
Immunogenicity		X		X	X		X		X			On dosing visits, must be collected before dosing study intervention.	Section 8.5.2
Collect urine for:													
Future use (optional)		X										Sample will be collected and stored	Section 8.6.2
Randomization		X										To be randomized, baseline CTA must be interpretable.	Section 6.3.1
Study intervention administration		X		X	X	X	X	X	X	X	X	Dosing will occur after blood and optional urine samples have been collected	Sections 6.2.3 and 6.2.4

Table 4 Schedule of Activities: Intervention Period

Procedure	Visit:	3	4	5	6	7	8	9	10	11	12	Notes	Details in CSP section or appendix
	Day (± 7): [a]	1	10[a]	29	57	85	113	141	169	197	225		
Observational period		X		X								Participant must be in clinic for 2 hours after dosing.	Section 8.2.5.2
Assessment of AEs/SAEs		X	X	X	X	X	X	X	X	X	X		Section 8.3
Concomitant medications		X	X	X	X	X	X	X	X	X	X		Section 6.5
Assess for injection site reactions		X		X	X	X	X	X	X	X	X		Section 8.2.5.3

[a] The visit window is ± 7 days for dosing visits and ± 3 days for non-dosing visits (ie, Day 10 [Visit 4]). If a participant is dosed outside of the visit window, he or she should return to the initial planned schedule for subsequent visits.

AE, adverse event; CSP, Clinical Study Protocol; CV, cardiovascular; ECG, electrocardiogram; HIV, human immunodeficiency virus; CCI [redacted] NT-proBNP, N-terminal prohormone brain natriuretic peptide; PK, pharmacokinetic(s); SAE serious adverse event; CCI [redacted]

Table 5 Schedule of Activities: Follow-up Period

Procedure	Visit:	13	14	Notes	Details in CSP section or appendix
	Day:	253 (- 4 to + 11 days)	325 (± 7 days)		
End of study visit			X		Section 4.3
Full physical examination			X		Section 8.2.1
Weight			X		Section 8.2.1
Vital signs		X	X	Whenever vital signs and blood draws are scheduled for the same nominal time, the blood draws should occur last.	Section 8.2.2

Table 5 Schedule of Activities: Follow-up Period

Procedure	Visit:	13	14	Notes	Details in CSP section or appendix
	Day:	253 (- 4 to + 11 days)	325 (± 7 days)		
ECGs		X	X		Section 8.2.3
Assessment of AEs/SAEs		X	X		Section 8.3
Concomitant medications		X	X		Section 6.5
Collect blood for:					
Clinical safety (clinical chemistry and hematology)		X	X		Section 8.2.4
PK		X	X		Section 8.5.1
CCI		X	X	Sample collected on Day 325 will be stored.	Section 8.6.1
CCI NT-proBNP		X			Section 8.6.1
Circulating biomarkers of inflammation CV disease		X			Section 8.6.1
Immunogenicity		X	X		Section 8.5.2
Creatinine for calculating eGFR		X		should occur within 30 days before the CTA; either local laboratory or point of care testing can be used.	Section 8.2.4
Collect urine for:					
Future use (optional)		X		Sample will be collected and stored.	Section 8.6.2
Echocardiogram		X			Section 8.1.1 and 8.1.2 (including instructions for repeating uninterpretable

Table 5 Schedule of Activities: Follow-up Period

Procedure	Visit:	13	14	Notes	Details in CSP section or appendix
	Day:	253 (- 4 to + 11 days)	325 (± 7 days)		
					echocardiograms scans)
Verify criteria for CTA scan imaging		X		Participants must meet CTA scan eligibility criteria before CTA scan imaging.	Section 8.1.1
CTA scan		X		If the echocardiogram and CTA scan are performed on the same day, the echocardiogram must always occur before the CTA scan and before any additional beta-blocker is given for the CTA scan. If the end of study CTA is determined to be of inadequate image quality by the CTA core laboratory, the participant may return for a repeat CTA up to 274 days after Dose 1.	Section 8.1.1 (including instructions for repeating uninterpretable CTA scans)

AE, adverse event; CSP, Clinical Study Protocol; CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; CCI [redacted]; NT-proBNP, N-terminal prohormone brain natriuretic peptide; eGFR, estimated glomerular filtration rate; SAE, serious adverse event; CCI [redacted]

2 INTRODUCTION

MEDI6570 is an IgG1λ triple mutation antibody that is being developed as an adjunct therapy to standard of care to reduce the rate of CV outcomes in patients with a history of MI.

2.1 Study Rationale

This Phase IIB, proof-of-concept, dose-range finding clinical study will evaluate the anti-inflammatory potential of MEDI6570 and its effect on surrogates for atherosclerotic and HF events in patients with a history of MI. The results of the Phase IIB study will inform the future clinical development options and precision medicine strategy for future clinical studies.

2.2 Background

Despite marked improved adherence to medical and lifestyle changes for secondary prevention, CHD remains the leading cause of mortality worldwide with a recorded 8930369 deaths attributed to it in 2018. Of those deaths 2110562 occurred in Europe (87019 in the United Kingdom and 18317 in Sweden), 581645 occurred in North America (533166 in the United States and 48381 in Canada), 4929141 in Asia, 728511 in Africa, 33667 in Australia and 477308 in Latin America and the Caribbean (BHF-CVD-Statistics 2019). The economic burden is also substantial with an estimated cost of $218.7 billion for the year 2014 to 2015 in the United States alone.

CHD is a product of CAD, the latter being defined as the presence of atherosclerosis in the coronary arteries. CAD can lead to CHD in the form of stable angina, ACS, a syndrome of unstable angina, NSTEMI, and STEMI.

Atherosclerosis develops as a result of 2 interrelated primary mechanisms: lipid deposition and coronary inflammation (Ross 1999, Linton et al 2000). Patients with a prior MI are at increased risk of MACE from atherosclerosis, including CV death, MI, and stroke. Treatment with statins, which decrease low-density lipoprotein concentration, forms part of the current standard of care for patients with a prior MI. While statins decrease the residual lipid risk and partially decrease the inflammatory risk in patients with a prior MI, a clinically significant risk of MACE remains, indicating a possible need to reconsider whether background statin use should be mandated. CANTOS demonstrated that targeting the inflammatory risk with canakinumab, a monoclonal antibody against interleukin-1 β, reduces MACE compared with placebo (Ridker et al 2017). Natriuretic peptides were not evaluated in this study; therefore, it is not known whether canakinumab affected natriuretic peptide levels. To the sponsor's knowledge, there are no plans to develop canakinumab for the CHD indication.

Furthermore, ischemic CHD is the most common cause of HF (Crespo-Leiro et al 2016), a global epidemic affecting > 37.7 million people worldwide (Ziaeian and Fonarow 2016), with a projected 46% increase in the prevalence by the year 2030 (Savarese and Lund 2017). In

addition to its considerable impact on mortality and morbidity (Crespo-Leiro et al 2016), HF accounts for 1% to 2% of the total healthcare expenditure in Europe and North America (Cowie et al 2014). Despite the increasing availability of therapies for HF, there is a need for additional therapies as the prevalence and costs of HF increase.

CCI

MEDI6570 is anticipated to reduce the following in patients with a prior MI, residual inflammation, and elevated NT-proBNP:

- Reduce the lipid and inflammatory risks that cause atherosclerosis, and thus reduce the incidence of MACE
- Reduce the inflammatory risk and endothelial dysfunction that contribute to HF, and thus reduce the incidence of HF hospitalization

A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI6570 is provided in the IB.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Table 6 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data and/or Rationale for Risk	Mitigation Strategy
Study intervention		
Bleeding	• CCI [redacted] • Activated platelets express CCI [redacted] and the IgG Fc receptor FcγRIIa. There is a hypothetical risk that crosslinking of platelets via Fc receptors could trigger platelet destruction leading to thrombocytopenia (Arman and Krauel 2015), which is a risk factor for bleeding. • There have been no indications of abnormal bleeding in monkeys during toxicity studies with MEDI6570. CCI [redacted]	• Exclusion of participants with a history or presence of known bleeding disorder, active bleeding, or high risk of bleeding, need for chronic anticoagulant therapy or platelet count < 100000 platelets/μL. (Arman and Krauel 2015). Please refer to exclusion criteria (Section 5.2). • Standard hematological safety monitoring, including platelet count (Section 8.2.4), and monitoring participants for bleeding events (Section 8.2.5.1) • Encourage the use of PPIs if the concomitant use of NSAID therapy is required. • All bleeding events will be reported as AEs and characterized further.

Table 6 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data and/or Rationale for Risk	Mitigation Strategy
Hypersensitivity reactions including anaphylactic reactions and immune complex disease	• Pharmacological administration of any peptide or protein may lead to hypersensitivity reactions including anaphylactic reactions, and of most concern clinically, immune complex disease. • CCI	• Exclusion of participants with a known history of hypersensitivity reactions to other biologics, to human IgG preparations, or to any component of MEDI6570 (Section 5.2). • Participants will be monitored closely during and after administration of study intervention for hypersensitivity reactions, including monitoring for signs and symptoms of immune complex disease. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be available at all sites (Section 8.2.5.2). If a hypersensitivity reaction occurs, dosing of the participant will be stopped (Section 7.1).
ADA	• Treatment of participants with mAbs carries the theoretical risk of induction of ADA.	• Participants will be assessed for the development of ADA (Section 8.5.2).
Study procedures		
Injection site reactions	• As with any exogenous protein substance, injection site reactions may be seen as a response to SC injection of MEDI6570. • No instances of injection site reactions were reported in monkeys during toxicity studies with MEDI6570. • CCI	• Participants receiving SC injections of study intervention will be monitored closely for the development of injection site reactions (Section 8.2.5.3)

Table 6 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data and/or Rationale for Risk	Mitigation Strategy
CTA scan	Potential clinical consequences of undergoing a CTA scan include, as follows: • Radiation exposure • Reactions to iodinated contrast • Renal impairment due to contrast administration • Detection of incidental findings that may require assessment	• Radiation reduction technologies, including prospective ECG-triggering and iterative reconstruction, allow CTA scans to be performed at low radiation doses (Chen et al 2013, Hou et al 2014, Meyersohn et al 2017, Schmermund et al 2017). Radiation reducing image acquisition techniques will be used (Section 8.1.1) and the anticipated median (range) radiation exposure per CTA imaging time point is 6 (3-10) mSv. • Risks of renal impairment will be minimized by excluding participants with clinically significant renal disease from CTA scanning (Section 8.1.1). • For each CTA scan, critical alert findings of clinical importance will be interpreted locally at the site to permit appropriate assessment and treatment (Section 8.1.1).

ADA, anti-drug antibody(ies); AE, adverse event; CTA, computed tomography angiography; ECG, electrocardiogram; Ig, immunoglobulin; CCI [redacted]; mAb, monoclonal antibody; mSv, millisievert; NSAID, Non-steroidal anti-inflammatory drug; PPI, Proton Pump Inhibitors; SC, subcutaneous(ly)

More detailed information about the potential risks of MEDI6570 can be found in the IB.

This study is being conducted during the COVID-19 global pandemic. As a result, a risk assessment evaluation for COVID-19 has been prepared to protect study participants and site staff, including COVID-19 vaccination guidance and recommendations (Appendix G).

2.3.2 Benefit Assessment

Despite improvements made over the last decades in the prevention of secondary MIs, a clinically significant risk of mortality and morbidity remains for up to 5 years post-MI, with the highest risk in the first months post-MI (Fox et al 2010). Plaque progression has also been shown to predict ACS independently (Ridker et al 2017, Tardif et al 2019). Furthermore,

treating the inflammatory pathways associated with MIs results in improved outcomes (Ridker et al 2017, Tardif et al 2019). In preclinical models of atherosclerosis and HF, deletion of the CCI has demonstrated decreased atherosclerosis, reductions in myocardial fibrosis, improvements in left ventricular function, and improvements in adverse remodeling of the heart following MI (Lu et al 2012, Hu et al 2008, Mehta et al 2007, Yokoyama et al 2016). CCI More extreme inflammatory phenotypes, such as patients with psoriasis, who have an increased risk of CHD also have elevated CCI levels. A recent study demonstrated that treatment with anti-inflammatory therapies in psoriasis decreased CCI levels and non-calcified plaque burden. Moreover, CCI levels during treatment predicted regression of non-calcified plaque burden (Dey et al 2020). CCI Given the preclinical and clinical data, MEDI6570 may decrease the severity of atherosclerosis and HF and is a potential future therapy for the secondary prevention of CV death, MI, stroke, HF, and revascularization.

However, as the efficacy of MEDI6570 in patients with a prior MI is yet to be determined, participants might receive limited or no efficacy benefits from participating in this study.

Participants might also benefit from receiving close monitoring and follow-up of their disease status post-MI.

2.3.3 Overall Benefit: Risk Conclusion

Given the measures taken to minimize risk to participants enrolled in this study, the potential risks identified in association with MEDI6570 are justified by the potential benefits of reduced severity of atherosclerosis and HF that are anticipated for participants with a prior MI.

3 OBJECTIVES AND ENDPOINTS

In participants with a prior MI, persistent inflammation and elevated NT-proBNP, the following endpoints in Table 7 will be evaluated in order to meet the objectives of the study.

Table 7 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	Relative 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 • Titer 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
Safety	
To assess the safety and tolerability of MEDI6570 compared with placebo	During the intervention and follow-up periods: • AEs • Clinically important changes in: Vital signs ECGs Safety laboratory assessments

Table 7 Objectives and Endpoints

Objectives	Endpoints
Exploratory	
CCI	
CCI	

The Day 253 endpoint includes the visit window around Visit 13 of - 4 to + 11 days.

ADA, anti-drug antibody(ies); AE, adverse event; CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; CCI ; GLS, global longitudinal strain; HF, heart failure; CCI MI, myocardial infarction; $NCPV_{MD}$, non-calcified plaque volume in the most diseased coronary segment, CCI PK, pharmacokinetic(s); SAE, serious adverse event; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a Phase IIB, randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI6570 in participants 30 to 365 days post-MI with persistent inflammation defined as hs-CRP ≥ 1 mg/L. Participants will be randomized to receive CCI mg (in an injection volume of 1.5 mL), or CCI mg (in an

injection volume of 4.0 mL) MEDI6570, or injection/volume-matched placebo (1.5 or 4.0 mL), subcutaneously (SC), every 4 weeks (Q4W) for 32 weeks (9 doses in total). Approximately 400 participants will be randomly assigned to a study intervention, with an anticipated 369 participants being randomized to receive active study intervention (123 participants in each of the 2 MEDI6570 groups), and 123 participants being randomized across the 3 placebo groups (ie, including participants already randomized to the legacy dose/volume-matched placebo group for the CCI mg dose). It is estimated that approximately 360 evaluable participants (111 evaluable participants in each of the 2 MEDI6570 groups [CCI and CCI mg], plus 27 evaluable participants in the legacy CCI mg MEDI6570 group, plus 111 participants across the 3 placebo groups) will complete the study. The randomization will be stratified by geographic region (Asia, North America and Rest of World) and by statin therapy status (no, low- or moderate-intensity statin therapy vs high-intensity statin therapy; refer to Appendix F) at baseline.

Participants who were randomized to a study intervention under Protocol Version 1.0 or Amendment 1 (when there was also a CCI mg dose group) and were allocated a dosing volume of 0.5 mL will continue on their randomized study intervention (CCI mg 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.

In accordance with the ESC/EAS and ACC/AHA guidelines regarding lipid modification and the reduction of residual CV risk, the use of high-dose statins in secondary prevention is a Class I recommendation with Level A evidence to support it (Mach et al 2020, Grundy et al 2019). As such, and in keeping with the expected standard of care, the implementation and maintenance of the highest tolerated dose of statins (although not mandated) is strongly encouraged in this study population.

The study will be conducted at approximately 70 to 100 study sites globally. The COVID-19 pandemic may continue to affect different geographic regions differently, having an unpredictable impact on study enrollment; therefore, a more accurate estimation of the number of countries and study sites that may be included globally is challenging.

Participants 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 baseline imaging period of up to 42 days (6 weeks), an intervention period of 225 days (31 to 32 weeks), and a follow-up period of 100 days (approximately 14 weeks; Figure 1). Following screening and confirmation of eligibility, participants will undergo an echocardiogram and CTA scan before randomization. The first dose of study intervention will be administered on Day 1 (Visit 3), after randomization. During the follow-up period, participants will undergo an echocardiogram and CTA scan.

An independent DMC will review safety data from this study (Section 9.6 and Appendix A 5).

No formal interim analysis is planned. An analysis restricted to PK (serum MEDI6570 concentration) and CCI data will be performed after approximately 80 participants have completed the Day 57 visit (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 DMC.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Population

A study population comprising participants with a prior MI and persistent inflammation was chosen because it reflects the population proposed for subsequent clinical development. A majority of participants will also have elevated NT-proBNP.

Patients surviving an MI remain at high risk of mortality and morbidity with the greatest risk occurring within the first 30 days post event (Abu-Assi et al 2016, Jernberg et al 2015, Johansson et al 2017). This increased risk is partially driven by the presence of significant atherosclerosis in the non-infarct related vessels (Momiyama et al 2012, Park 2014, Kato et al 2012), which may become more susceptible to rupture due to the intense inflammatory response, a prerequisite for healing and scar formation triggered by the MI (Frangogiannis et al 2002). This post-infarction inflammatory process peaks within the first and second weeks post-ischemic event and resolves by the third or fourth week (Sun et al 2009). Moreover, evidence from clinical studies suggests that patients with persistent elevation of serum inflammatory biomarkers 4 weeks after an ACS have worse outcomes (de Lemos et al 2007).

NCPV and total plaque volume have been shown to be significant predictors of cardiac events in ACS, with NCPV being a better predictor of a MACE than total plaque volume or calcium score (Kristensen et al 2011). These different components of coronary atherosclerosis during CTA have been shown to be of incremental value for prognostication (Radosavljevic-Radovanovic et al 2016).

In addition, NT-proBNP has been shown to be a strong predictor of future AEs in the post-MI population (Lindahl et al 2005), being more reliable when measured in the relatively stable phase (Kurtul et al 2016). Furthermore, the levels of NT-proBNP were associated with the severity and complexity of the underlying CAD (Kurtul et al 2016).

The lower limit of 30 days post-MI was selected both to refrain from suppressing the necessary inflammatory response and because the expected elevated levels in hs-CRP, cytokines and NT-proBNP during this window may not persist long-term. In addition, this period would allow patients' standard of care medical therapy to be optimized and stabilized before being enrolled in the study. An upper limit of 365 days after the MI was selected to include patients who have a high residual risk of MACE and may derive benefit from

treatment with MEDI6570 in addition to the standard of care (Fox et al 2006, Fox et al 2010, Fox 2006, Goldberg et al 2004, Miao et al, 2020, Tangri et al 2017).

4.2.2 Rationale for Endpoints

4.2.2.1 Primary Endpoint

The primary endpoint is change in NCPV in most diseased coronary segment ($NCPV_{MD}$) as measured by CTA from baseline to Day 253. The most diseased coronary segment is defined as that coronary segment with the highest non-calcified plaque volume on the baseline scan. This primary endpoint was chosen because it assesses modifiable plaque formation in a coronary segment that may represent the coronary segment at most imminent risk to cause future events. Furthermore, the most diseased segment and atherosclerotic plaque extent, severity, and characteristics affect the downstream myocardial perfusion (Lindahl et al 2005) and future risk of CV events (Wallentin et al 2009). In post-MI patients, NCPV is a better predictor of MACE when compared with Agatston calcium score and total plaque volume (Kristensen et al 2011). In patients with psoriasis, anti-inflammatory biologic therapies have been shown to decrease CCI levels, and reductions in CCI are associated with regression of NCPV (Dey et al 2020). In studies evaluating plaque regression with statin use, regression of NCPV and other plaque components have been observed.

Computed tomography angiography was selected as the imaging modality for the primary endpoint based on its non-invasive nature, broad accessibility, and participant acceptance. A CTA can assess the plaque associated with the greatest clinical risk in addition to the plaque burden within the entire coronary tree. A CTA has been shown to predict future ACS events in subjects with high-risk plaque (Kristensen et al 2011, Thomsen and Abdulla 2016).

4.2.2.2 Secondary Endpoints

NT-proBNP

The secondary endpoint is relative change from baseline to Day 253 in HF biomarker NT-proBNP. NT-proBNP is released in response to myocardial strain. Increases in NT-proBNP have been correlated with an increase in CV events in participants with a prior MI (Lindahl et al 2005). Recent HF therapies such as valsartan/sacubitril and dapagliflozin have demonstrated decreases in NT-proBNP. In the PLATelet inhibition and patient Outcomes (PLATO; Wallentin et al 2009) clinical study in a post-ACS population, decreases in NT-proBNP were strongly associated with a reduction in the hazard ratio for the composite endpoint of CV death, MI, and stroke (unpublished data from sponsor). In addition, a 25% reduction in NT-proBNP was associated with a 20% to 25% reduction in the composite endpoint of CV death, MI, and stroke.

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Left Ventricular Function: Ejection Fraction and Global Longitudinal Strain

Complimenting NT-proBNP for the evaluation of MEDI6570 in HF, LVEF and GLS will be secondary endpoints in the study. Change in LVEF and change in GLS by echocardiography imaging from baseline to Day 253 will be measured and compared with placebo.

LVEF is a well-established measurement of the systolic function of the left ventricle that predicts prognosis in post-MI patients (Multicenter Postinfarction Research Group 1983). In addition, changes in LVEF following MI are predictive of sudden cardiac arrest and death (Chew et al 2018). Furthermore, pharmacologic improvements in LVEF have been linked to decreases in mortality and HF hospitalizations (Breathett et al 2016, Kramer et al 2010). Improvements in LVEF can occur with anti-inflammatory therapies. The CANTOS study demonstrated an improvement in the exercise capacity (measured by peak oxygen consumption) and LVEF in a subgroup analysis (Trankle et al 2018). LVEF will be calculated as the ratio of stroke volume divided by end-diastolic volume.

Although LVEF is the most extensively used and investigated assessment of left ventricular function, GLS is a new, emerging technique that may have a more significant predictive value pertaining to outcomes in the HF population when compared with LVEF (Kalam et al 2014). In a study of 4172 patients with acute HF and varying degrees of LVEF, 1% improvement in GLS was associated with a 5% reduction in mortality risk irrespective of the ejection fraction (Park et al 2018). Furthermore, it has been shown that the reproducibility of GLS as a measurement of left ventricular function surpasses that of LVEF, regardless of the level of echocardiographic training (Karlsen et al 2019).

Global Non-calcified Plaque Volume and Low Attenuation Plaque Volume

Two further measurements of plaque burden will be used in this study as a secondary endpoint. NCPV is the total volume of plaque in the coronary arteries that lacks calcification. A subset of NCPV is LAPV.

Previous studies have shown increased NCPV and LAPV in patients with ACS when compared with patients with stable angina (Motoyama et al 2015, Dey et al 2014). This

finding is consistent with low attenuation plaque being a lipid-rich plaque, laden with lipid-rich foam cells, at the core of an atheroma. These lipid-rich foam cells are the target of MEDI6570. Due to the spatial resolution of CTA, it is important to measure NCPV and LAPV to evaluate the effect of MEDI6570 on modifiable plaque volume in the coronary arteries comprehensively. Computed tomography angiography measurements of NCPV and LAPV are highly reproducible (Andelius et al 2018). Change in NCPV and LAPV in the coronary arteries will be measured from baseline to Day 253 and compared with placebo. NCPV and LAPV were selected as secondary endpoints over calcified and total plaque volume for several reasons. First, when studied in ACS, specifically non-STEMI, NCPV is a better predictor of MACE when compared with Agatston calcium score and total plaque volume (Kristensen et al 2011). CCI [redacted] In studies evaluating plaque regression with statin use, regression of both NCPV and LAPV have been observed. LAPV reduction has been associated with decrease in CV events (Andelius et al 2018). NCPV and LAPV will be measured in all vessels ≥ 2 mm in diameter and expressed in mm^3. Coronary segments with stents or otherwise deemed uninterpretable on the baseline or follow-up scan will be excluded from analysis.

4.2.2.3 CCI [redacted]

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4.3 Justification for Dose

Doses for this study have been selected based on analysis of final PK-PD data for single and multiple ascending doses of MEDI6570 in Phase I clinical study, D4920C00001. In that study, single doses of CCI mg to CCI mg SC and multiple doses of CCI mg to CCI mg Q4W SC were administered to participants with Type 2 Diabetes Mellitus. CCI

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As MEDI6570 is a monoclonal antibody that is being developed as a chronic therapy, only SC dosing will be used. Injection/volume-matched placebo groups are included for detecting an efficacy response.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all periods of the study through to the final protocol-specified visit/assessment (including telephone contact) or death, regardless of the number of doses of study intervention that was received.

The end of the study is defined as the date of the last visit/assessment (including telephone contact) of the last participant in the study globally.

5 STUDY POPULATION

Prospective approvals of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Participants may undergo an optional pre-screening visit upon providing written, informed consent for pre-screening. The optional pre-screening visit is for the purpose of collecting blood samples to assess qualifying biomarker values (Table 3). The local laboratory may be used for analyzing pre-screening samples. The optional pre-screening visit will not replace the screening visit; all screening visit laboratory samples must be collected and will be used to determine eligibility.

Participants are considered to have enrolled in the study from the time they (or their legally acceptable representatives) sign the first ICF (either the ICF for the optional pre-screening evaluations, or the ICF for the full screening evaluations).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1 Participant must provide informed consent before any study-specific activities are performed (Appendix A 3), must be able and willing to meet all requirements for randomization within 42 days after signing the full ICF, and must adhere to the schedules of activities.

2 Women must be ≥ 40 years of age at the time of signing the ICF. Men must be ≥ 21 years of age at the time of signing the ICF.

3 Participant must:

   (a) be 30 to 365 days after presumed type-1 (ie, due to plaque rupture or erosion) MI (either STEMI or NSTEMI) at the time of enrollment.

   (b) have persistent inflammation, defined as hs-CRP ≥ 1 mg/L, as measured centrally at screening Visit 1.

4 Participant must have body mass index within the range 18 to 40 kg/m^2 inclusive.

5 For female participants, the participant must not be pregnant or lactating and must be of non-childbearing potential, confirmed at screening Visit 1 by one of the following:
   (a) Postmenopausal, defined as amenorrhea for ≥ 12 months following cessation of all exogenous hormonal treatments, and with luteinizing hormone and follicle stimulating hormone levels in the postmenopausal range.
   (b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. Tubal ligation is not considered as irreversible surgical sterilization.
6 Participant must have an evaluable, pre-randomization CTA with quantifiable, non-calcified plaque, as confirmed by the core laboratory.

Participants will be reassessed for study eligibility before study intervention is administered on Day 1 (Visit 3). Participants should be considered for a high-intensity statin based on existing guidelines for long-term management of patients after an MI. Participants should ideally be on a stable dose of lipid-lowering therapy throughout the treatment period of the study; therefore, efforts should be made to maximize statin intensity before randomization.

The proportion of participants with an NT-proBNP value < 125 pg/mL at screening who can be randomized to a study intervention may be capped. If this proportion is capped, a baseline NT-proBNP value of ≥ 125 pg/mL will be required for inclusion in the study. During the study, randomization to an intervention group may also be capped within other specific participant subgroups.

In addition to the inclusion criteria specified above, study participants may elect to take part in the Genomics Initiative; participants who chose to do this must provide written informed consent before samples are collected for the optional genetic research that supports the Genomics Initiative (Appendix D 2).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1 History of any clinically important disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or influence the results or the participant's ability to participate in the study.
2 Percutaneous coronary intervention or diagnostic angiogram planned after screening Visit 1. Eligible participants who have a diagnostic angiogram performed in the absence of undergoing a new PCI may continue screening after the diagnostic angiogram has been performed or may be rescreened (Section 5.4).
3 History of or planned coronary artery bypass grafting.

4 Documented episode of post-MI pericarditis (eg, Dressler's Syndrome) in the 3 months before enrollment.

5 Ongoing New York Heart Association Class IV (severe) HF.

6 Increased risk of bleeding
   (a) Patients with history or presence of any bleeding disorder.
   (b) Signs of ongoing bleeding at screening (eg, identified macroscopic bleeding, low hemoglobin presumed to be caused by bleeding) or high risk for major bleeding in accordance with the Investigator's assessment.
   (c) Need for chronic therapeutic anticoagulation therapy anticipated to be required throughout the course of the study (short-term treatment with prophylactic doses of heparin/low molecular weight heparin are allowed).
   (d) Known severe liver disease (eg, ascites and/or clinical signs of coagulopathy).

7 History or presence of any of the following:
   (a) Ongoing infection or febrile illness that in the opinion of the investigator may be the cause of elevated hs-CRP on screening (Visit 1).
   (b) Ongoing atrial fibrillation or flutter.
   (c) Cancer within 5 years before randomization (Day 1; Visit 3), with the exception of non-melanoma skin cancer.
   (d) Alcohol or substance abuse within 6 months before randomization (Day 1; Visit 3), as judged by the investigator.
   (e) Known history of hypersensitivity reactions to other biologics, to human IgG preparations, or to any component of MEDI6570, or ongoing severe allergy as judged by the investigator.
   (f) Patients with active positive results on screening for serum hepatitis B surface antigen, hepatitis C antibody, or HIV.

8 Any clinically important abnormalities in clinical chemistry, hematology, coagulation parameters, as judged by the investigator, including but not limited to:
   (a) AST > 2.0 × ULN.
   (b) ALT > 2.0 × ULN.
   (c) TBL > 1.5 x ULN (unless due to Gilbert's syndrome).
   (d) Platelet count < 100000 platelets/µl.

9 BP values at screening Visit 1:
   (a) Systolic BP < 90 mmHg or > 180 mmHg.
   (b) Diastolic BP > 100 mmHg.
   (c) Participants who are excluded based on elevated BP may be rescreened following adequate treatment.

The eligibility assessment is based on measurements taken starting from after 5 minutes of rest; if the result is outside these limits, additional BP measurements can be taken over the following 5 minutes, ie, up to a total of 10 minutes of rest (repeated a maximum of 3 times). If the result is outside these limits during this period, the participant is considered a screen fail.

10 Participants with any of the following contraindications to CTA:
   (a) eGFR < 50 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation, or end stage renal disease treated with kidney transplant or renal replacement therapy.
   (b) Allergy to iodinated contrast.
   (c) History of contrast-induced nephropathy.
   (d) Contraindication to nitroglycerin.
   (e) Rapid heart rate that is uncontrolled by medical therapy.
   (f) Inability to hold breath for at least 6 seconds.
11 Receipt of any investigational device or therapy within 6 months or 5 half-lives before screening (whichever is longer).
   This criterion does NOT apply for inactive, non-replicating COVID-19 vaccines approved by Health Authorities or under emergency use authorization.
12 Planned participation in an additional investigational study of an intervention or biologic before the end of the follow-up period. Participation in observational studies or studies without investigational drugs or devices is allowed.
13 Participants who are legally institutionalized.
14 An employee or close relative of an employee of the sponsor, the CRO, or the study site, regardless of the employee or close relative's role.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Potential participants who are pre-screened and/or screened for the purpose of determining eligibility for the study, but are not randomly assigned in the study, are considered screen failures.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Rescreening

Participants who fail screening may be rescreened under the following circumstances:

- Eligible participants who exceed the 42-day pre-randomization window may be rescreened to determine eligibility before randomization and the Medical Monitor will decide whether screening laboratory evaluations should be repeated. If the screening assessments are not considered to be representative of the usual status of the health of the participant by the investigator, or if ≥ 1 exclusion criteria are considered temporary (eg, diagnostic angiogram) or from a reversible condition, repeat screening assessments to establish eligibility will generally be permitted once, at the discretion of the investigator.
- Eligible participants who have a diagnostic angiogram performed after screening Visit 1 in the absence of undergoing a new PCI may continue screening after the diagnostic angiogram has been performed (Exclusion Criterion 2). If they exceed the 42-day pre-randomization window, the Medical Monitor will decide whether the participant is required to be rescreened and whether screening laboratory evaluations should be repeated. Participants who have a PCI performed between Screening Visit 1 and Randomization Visit 3 may not be rescreened.
- Participants who are excluded based on elevated BP may be rescreened following adequate treatment (Exclusion Criterion 9(c)).

For eligible participants who are rescreened, the rescreen date must also be within the MI window of not more than 365 days since MI.

Rescreened participants should be assigned the same enrollment code as for the initial screening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

In this study, the study intervention is an IMP, and the IMP is a biologic or its matching placebo (Table 8). The study intervention/IMP is MEDI6570, a human IgG1λ triple mutation antibody that binds to human[redacted]

MEDI6570 is supplied as a lyophilized powder that needs to be reconstituted; whereas, the placebo is supplied in liquid form.

Table 8 Investigational Products

Group name	MEDI6570			Placebo
Intervention name	MEDI6570			Placebo
Type	Biologic			Placebo
Supplied as	A sterile, white to off-white, lyophilized product in a 6R glass vial stoppered with a 20 mm rubber stopper, and sealed with a flip-off cap overseal			A sterile, clear to slightly opalescent, colorless to slightly yellow liquid, free from visible particles in a 6R glass vial at a nominal volume of 5.3 mL, stoppered with a 20 mm rubber stopper, and sealed with a flip-off cap overseal.
Dose formulation (after reconstitution)	After reconstitution, the vial contains a nominal volume of 1.0 mL, at concentrations of CCI mg/mL MEDI6570, 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, 0.04% (w/v) polysorbate 80, and at pH 6.0.			The supplied vial contains 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, 0.02% (w/v) polysorbate 80, at pH 6.0.
Unit dose strength	CCI mg MEDI6570 per vial			NA
Dosage levels	CCI mg Q4W for 32 weeks (9 doses in total) [a]	CCI mg Q4W for 32 weeks (9 doses in total)	CCI mg Q4W for 32 weeks (9 doses in total)	Q4W for 32 weeks (9 doses in total) dependent on intervention group
Route of administration	SC injection			SC injection
Use	Experimental			Placebo comparator
IMP or NIMP	IMP			IMP
Sourcing	Provided centrally by the sponsor.			Provided centrally by the sponsor.
Packaging and labeling	Study intervention will be provided in 6R vials packaged into single vial kits. Each 6R vial and outer carton will be labeled as required per country requirement.			Study intervention will be provided in 6R vials packaged into single vial kits. Each 6R vial and outer carton will be labeled as required per country requirement.

[a] Under Protocol Amendment 2, no new participants will be randomized to the CCI mg dose group or its injection/volumed matched placebo (0.5 mL); participants who were randomized to CCI mg MEDI6570 or its injection/volume-matched placebo will continue on their randomized intervention until the end of the study. For participants enrolled under Amendment 2, there will be 2 placebo groups to match the dosing volumes of the 2 active groups: 1.5 and 4.0 mL.

IMP, investigational medicinal product; NA, not applicable; NIMP, non-investigational medicinal product; Q4W, every 4 weeks; SC, subcutaneous; w/v, weight per volume.

6.2 Preparation/Handling/Storage/Accountability of Interventions

6.2.1 Study Intervention Inspection

MEDI6570 is supplied in 6R vials as a sterile white to off-white lyophilized product. Placebo is supplied in 6R vials as a sterile liquid.

If there are any defects noted with the study intervention, the investigator and site monitor should be notified immediately.

6.2.2 Storage

The study intervention should be stored at 2°C to 8°C (36°F to 46°F). The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before the study intervention is used.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions and with access limited to authorized, unblinded site staff.

6.2.3 Dose Preparation Steps

The MEDI6570 and placebo doses must be prepared by the site's designated unblinded study intervention manager using aseptic technique.

The total time from needle puncture of the MEDI6570 vial or placebo vial to SC administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the preparation time exceeds the time limits, a new dose must be prepared from new vials. MEDI6570 and placebo do not contain preservatives and any unused portion must be discarded.

Reconstitution Procedure

Each vial of MEDI6570 must be reconstituted with 1.3 mL of sterile water for injection to achieve CCI mg/mL MEDI6570. Slowly add 1.3 mL of sterile water for injection by tilting the vial to one side such that the liquid stream is directed along the vial wall and not directly onto the lyophilized product. Gently swirl the solution until all solids are dissolved. Do not shake or vigorously agitate the vial. Visually inspect the solution to ensure that the entire content of the lyophilized product is completely reconstituted. The reconstituted solution should appear clear to opalescent. A thin layer of bubbles on the surface of the liquid is normal.

Subcutaneous Dose Preparation

SC doses should be prepared by withdrawing the required volume of CCI mg/mL MEDI6570 or equivalent volume of sterile placebo accurately into a 1, 2, or 3 mL syringe. The syringes used to prepare doses by the unblinded staff will be provided to the blinded staff for administration. Syringes containing MEDI6570 look identical to those containing placebo; therefore, syringe covers are not necessary. Further details on volumes required for different dose levels are given in Table 9. Vials should only be used once to prepare a single dose. No incompatibilities have been observed between MEDI6570 and polycarbonate or polypropylene syringes, or between placebo and polycarbonate or polypropylene syringes. If syringes have been stored at 2°C to 8°C (36°F to 46°F), they must equilibrate to room temperature before administration.

CCI

[redacted]

CCI

[redacted]

6.2.4 Treatment Administration

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention.

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3). The first day of dosing is considered Day 1.

The study intervention administrator should be experienced in performing SC injections. The skin surface of the anterolateral thigh, upper outer tricep area, upper buttocks, or abdomen (avoid a 2-inch [5 cm]) radius around the umbilicus) should be prepared with an alcohol wipe and allowed to air dry. The skin will be pinched to isolate SC tissue from the muscle. The needle will be inserted at a 90-degree angle to the skin surface approximately halfway into the SC tissue. The study intervention will be injected slowly (at an appropriate speed in accordance with local procedures) into the SC tissue using gentle pressure. The area should not be massaged after injection.

Study intervention should NOT be administered if it is not fully reconstituted, if it has been at room temperature for more than 4 hours, or if it has been at 2°C to 8°C (36°F to 46°F) for more than 24 hours.

6.2.5 Accountability

The site's designated unblinded study intervention manager is required to maintain accurate study intervention accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the sponsor. All unused study intervention will be destroyed locally, in accordance with local standard operating procedures, after full accountability by the site has been performed. Destruction can be outsourced to a third party. Certificates of destruction must be collected.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization Procedure

Participants will be randomized to an intervention group to minimize bias.

Randomization will be performed after the blood and urine samples are collected on Day 1 (Visit 3).

A 3-stage randomization procedure will be implemented:

1 Participants will first be grouped into strata according to geographic region (Asia, North America and Rest of World).
2 Then, within each geographic region, participants will be grouped into strata according to the status of their statin therapy intensity at baseline (no, low- or moderate-intensity statin therapy, vs high-intensity statin therapy; refer to Appendix F).
3 Then, within each stratum, participants will be assigned randomly to an intervention group according to randomization schedules using an RTSM system.

Before the study starts, the instructions for the RTSM will be provided to each site.

Re-allocation of participants to a dosing volume (Protocol Amendment 1): As a result of removing the CCI mg dose and introducing the CCI mg dose in Amendment 1, all participants enrolled under Protocol Version 1.0 were re-allocated to the appropriate dosing volume for their randomized intervention group under Amendment 1. Participants originally randomized to the CCI mg MEDI6570 group under Protocol Version 1.0 who had not completed treatment were switched to the CCI mg MEDI6570 group under Amendment 1. Participants originally randomized to the placebo group and who had not completed study treatment were re-randomized to one of the 3 injection/volume-matched placebo groups under Amendment 1.

6.3.2 Blinding Procedure

The participant, the investigator, and the site staff performing study-related procedures will all be blinded to the participant's intervention group, with respect to active treatment versus placebo, to minimize bias.

The RTSM will provide to the investigators or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the RTSM user manual provided to each study site.

The sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the study intervention and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining whether unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator must document and report the action to the sponsor, without revealing the participant's treatment to the sponsor's staff.

Participants enrolled under Protocol Amendment 2 will be randomly assigned to one of 4 possible intervention groups in a 2:2:1:1 ratio: CCI mg (with an injection volume of 1.5 mL) or CCI mg (with an injection volume of 4.0 mL) MEDI6570, or an injection/volume-matched placebo (1.5 or 4.0 mL). Investigators will remain blinded to each participant's assigned study intervention, with respect to active treatment versus placebo, throughout the course of the study.

Participants who were randomized to a study intervention under Protocol Version 1.0 or Amendment 1 and were allocated a dosing volume of 0.5 mL will continue on their randomized study intervention ([redacted] mg 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.

To maintain the study blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in the times taken to dispense the study interventions following randomization.

Areas of the pharmacy where the study intervention is being stored and prepared must be accessed only by unblinded team members.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization and/or dispensing has been done accurately.

Laboratory results

The participant, investigator and study site staff will remain blinded to the following post-randomization laboratory results:

- [redacted]
- NT-proBNP
- [redacted]
- [redacted]
- Concentrations of MEDI6570 in serum
- ADAs

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision, at the clinic. The date, and time if applicable, of dose administration will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines and/or vitamins) that the participant is receiving at the time of enrollment, or receives during the study, must be recorded along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care. Specifically, participants should receive standard of care during the study in accordance with their institutional guidelines. Participants should be considered for a high-intensity statin and for anti-platelet therapies based on existing guidelines for long-term management of patients after a myocardial infarction. Participants with a need for chronic therapeutic anticoagulation therapy are excluded from study participation; however, short-term treatment with prophylactic doses of heparin/low molecular weight heparin are allowed (Section 6.5.2 and Section 7.1).

In view of the use of anti-platelet therapy in this population, the use of PPIs is encouraged, to confer gastric protection in the event that the concomitant use of NSAIDs is required. This is of special consideration in this study population because of a theoretical risk of bleeding highlighted in Table 6.

If the participant requires concomitant NSAID therapy, Investigators are encouraged to prescribe PPIs in order to minimize the theoretical risk of bleeding events.

Guidance for participants undergoing COVID-19 vaccination during the study is provided in Appendix G 4.

6.5.2 Prohibited Concomitant Medications

The need for chronic therapeutic anticoagulation therapy is an exclusion criterion. If the participant develops a condition that requires the use of chronic therapeutic anticoagulation therapy during dosing, temporary or permanent discontinuation of study intervention should be considered by the investigator, based on assessment of bleeding risk.

6.6 Dose Modification

Not applicable.

6.7 Intervention after the End of the Study

No study intervention will be provided to participants following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to discontinue study intervention temporarily or permanently. An individual participant will discontinue study intervention (either temporarily or permanently) if any of the following occurs in the participant in question:

1 An AE that in the opinion of the investigator or the sponsor contraindicates dosing.
2 Clinical symptoms of spontaneous bleeding so that the PI judges further administration of study intervention should be paused or stopped.
   (a) Providers should consider temporary or permanent discontinuation of study intervention in participants who:
      (i) Develop a condition that requires the use of chronic therapeutic anticoagulation therapy.
      (ii) Experience severe bleeding that is not readily explained by a reversible alternate etiology. All bleeding events should be treated and followed up according to local clinical practice. Study intervention may be resumed when the risk of bleeding is deemed low in the judgment of the investigator.
   (b) Study intervention must be stopped in the event of severe thrombocytopenia (platelet count < 50000 platelets/μL) which does not resolve, or if after resolution the investigator thinks it is not appropriate to restart study intervention because it may put the participant at undue risk.
3 A generalized hypersensitivity reaction occurring which, in the opinion of the PI and/or the Medical Monitor, would warrant discontinuation.
4 After initial dosing, there exists a clinically significant safety issue based on information not known or not disclosed before randomization.
5 Participant non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal or inability to adhere to scheduled visits).
6 Withdrawal of consent.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 7.2) or the participant is lost to follow-up (Section 7.3).

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request (withdrawal of consent).
- A participant who considers withdrawing consent from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). If the participant agrees to any of these methods of follow-up, then he/she will not be considered to have withdrawn consent.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed whether he/she still agrees that existing samples may be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulations. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site by the end of the study.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- If the participant's final health status can be determined by contact with a relative or personal doctor, then the participant will not be deemed to be lost to follow-up.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not receive study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

- Patients will only be designated as "Lost to Follow-up" at the time of database lock when all attempts to contact or gain vital status for the participant have failed.

Discontinuation of specific sites or of the study as a whole is described in Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- An optional pre-screening visit to collect local laboratory values for hs-CRP and creatinine (for eGFR calculation) may occur upon completing the pre-screening informed consent within 42 days before signing the screening ICF (screening Visit 1). If randomization of participants with NT-proBNP < 125 pg/mL is capped, NT-proBNP (or BNP if NT-proBNP is not available) may also be collected during pre-screening.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 630 mL. Repeat or unscheduled samples may be taken for safety reasons or if there are technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 CTA Imaging

8.1.1.1 Timing of CTA Imaging Relative to Echocardiogram

If echocardiogram (Section 8.1.2) and CTA imaging are performed on the same day, echocardiogram imaging must always occur before CTA imaging, and before any additional beta-blocker administration above the daily dose used by the participant, to avoid large doses of a beta-blocker affecting echocardiogram measurements. This only applies to a beta-blocker given for the purposes of heart rate control for coronary CTA. Participants should continue taking their clinically prescribed dose of beta-blocker as scheduled.

8.1.1.2 Criteria for CTA Imaging

For the pre-randomization period, CTA imaging requirements are included in the inclusion criteria (Section 5.1).

For the follow-up period, participants must meet the following criteria before CTA imaging:

1 Using creatinine samples for the calculations, eGFR must be ≥ 45 mL/min/1.73m^2 (within 30 days before the CTA scan). Sites are permitted to test for an additional creatinine (local or central), if needed for the purposes of CTA imaging.

2 No known allergy to iodinated contrast or known history of contrast-induced nephropathy.

3 No history of coronary bypass surgery.

4 No active arrhythmia including atrial fibrillation or atrial flutter on the day of CTA imaging that would likely interfere with quality of CTA imaging. Participants can return for CTA imaging on another day, if necessary.

5 No contraindication to nitroglycerin.

6 Not have rapid heart rate that is uncontrolled by medical therapy.

7 Participants who have any condition that, in the opinion of the investigator, would increase the risk associated with having CTA imaging (eg, clinically significant renal disease) will not undergo CTA imaging.

8.1.1.3 Radiation Exposure from CTA Imaging, Including Rules for Repeating CTA Scans

The overarching principle for CTA imaging will be to maximize high-quality CTA imaging for endpoint ascertainment while minimizing radiation exposure to participants.

The anticipated median (range) radiation exposure per CTA imaging time point is 6 (3-10) mSv. A maximum cumulative radiation exposure of 30 mSv is anticipated in this study and will be monitored by the CTA core laboratory through a radiation monitoring escalation plan. Radiation dose will be estimated based on dose length product using a K (conversion) factor of 0.014. Dose-saving image acquisition techniques will be used where applicable.

The baseline and follow-up CTA scans may be repeated under certain circumstances.

In order to ensure that the overall radiation exposure remains within the specified limit, rules for CTA scans are detailed by time point below:

1 Baseline CTA (Day -30 to -1; Visit 2):

   (a) If the baseline CTA scan is obtained but randomization does not occur within the prespecified screening window, there is a 30-day window to repeat screening and proceed with randomization using the initial baseline CTA. If repeat screening

extends beyond 30 days from date of initial baseline CTA scan, discussion with the Medical Monitor is required to determine whether the initial baseline CTA needs to be repeated before randomization.

(b) If the baseline CTA scan is deemed uninterpretable by the core laboratory, it may only be repeated if corrective action can be taken to result in an anticipated total cumulative research radiation exposure of < 30 mSv for all CTAs.

2 End of study CTA (Day 253; Visit 13)

(a) End of study CTA scan should not be performed in participants whose anticipated cumulative research radiation exposure would exceed 30 mSv.

(b) If the end of study CTA scan is deemed uninterpretable by the core laboratory, it may only be repeated if corrective action can be taken to result in an anticipated total cumulative research radiation exposure of < 30 mSv.

For all repeat CTA scans:

- The eGFR must be re-measured before the CTA scan is repeated.
- The repeat CTA scan must be taken ≥ 48 hours after the original CTA scan, and within the relevant study visit window.

8.1.1.4 CTA Image Analysis

Imaging personnel and equipment will undergo certification by a separate, independent, core laboratory that is blinded to study treatment. CTA imaging will be performed at time points as specified in the SoA. CTA coverage will extend from the right pulmonary artery to the diaphragm, to cover the full extent of the heart and coronary arteries.

Planned measurements include:

- $NCPV_{MD}$
- NCPV (global)
- LAPV
- CCI
- Any additional measurements as described in the CTA imaging manual/protocol

Critical alert findings of clinical importance will be interpreted locally and provided to the investigator to permit appropriate assessment and treatment. A full coronary CTA interpretation will not be performed locally.

The CTA images will be analyzed in the core laboratory. The CTA imaging manual describes the CTA imaging protocol, which will accommodate differences in imaging platforms across sites.

8.1.2 Echocardiography

Participants must meet the study eligibility criteria (Sections 5.1 and 5.2) before undergoing echocardiogram imaging. If echocardiogram and CTA imaging are performed on the same day, echocardiogram imaging must always occur before CTA imaging, and before any additional beta-blocker is administered above the daily dose used by the participant.

Imaging personnel and equipment will undergo certification by a separate, blinded, independent core laboratory. Echocardiography will be performed at time points specified in the SoA (Section 1.3).

Planned measurements include, as follows:

- Left Ventricular Ejection Fraction
- Left Ventricular GLS
- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- Any additional measurements as described in the echo imaging manual/protocol

The echocardiogram images will be analyzed in the core laboratory. The echocardiography imaging manual describes the imaging protocol, which will accommodate differences in imaging platforms across sites.

If for any reason an echocardiogram image is deemed uninterpretable for any planned measurements by the core laboratory, then echocardiography may be repeated at the discretion of the investigator, participant, and Medical Monitor. The repeat echocardiogram must be obtained within the time specified for the visit window in the SoA (Section 1.3).

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will be performed and will include assessments of the following: general appearance; the respiratory, CV, thyroid, muscular-skeletal (including spine and extremities) and neurological systems; the abdomen, skin, head and neck (including ears, eyes, nose and throat), and lymph nodes; weight and height.

An abbreviated physical examination will include, at a minimum, assessments of the skin, the respiratory and CV systems, the abdomen (liver and spleen), and any type of bleeding.

Physical examination will be performed at timelines as specified in the SoA (Section 1.3).

8.2.2 Vital Signs

Vital signs (BP and heart rate) will be measured at the time points specified in the SoA (Section 1.3). Measurements will be taken after the patient has rested for at least 5 minutes in a sitting position. If multiple vital signs measurements are taken, the last measurement is the one that should be recorded.

8.2.3 Electrocardiogram

Electrocardiogram will be performed at the time points specified in the SoA (Section 1.3).

Participants will have 12-lead ECG recordings taken as specified in SoA, recorded after a 5-minute rest with the participant in the supine position. Analysis of the ECG results will be performed locally and results recorded using electronic data capture.

8.2.4 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry, hematology, and coagulation variables will be collected at the visits indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and type of sample will be recorded on the appropriate eCRF.

The clinical chemistry and hematology safety laboratory samples will be analyzed at a central core laboratory. Laboratory safety variables are listed in Table 10.

Table 10 Laboratory Safety Variables

Hematology (whole blood)	Clinical chemistry (serum)	Eligibility
B-Hemoglobin	S/P-Creatinine	Luteinizing Hormone
B-Leukocyte count	S/P-Bilirubin, total	Follicle Stimulating Hormone
B-Leukocyte differential count (absolute count)	S/P-ALP	HIV
B-Platelet count	S/P-AST	Hepatitis B
Coagulation panel including INR, and aPTT (screening only)	S/P-ALT	Hepatitis C
	S/P-Albumin	

	S/P-Potassium	
	S/P-Calcium, total	
	S/P-Sodium	
	S/P-CK	

If a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN refer to Appendix E.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; HIV, human immunodeficiency virus; INR, international normalized ratio; S/P, serum/plasma; TBL, total bilirubin; ULN, upper limit of normal

8.2.5 Other Safety Assessments

8.2.5.1 Bleeding

Study participants will be monitored for AEs related to bleeding by reviewing AEs and SAEs assessed at time points specified in the SoA (Section 1.3). All bleeding events will be reported as AEs and characterized further, allowing for their classification according to bleeding type.

8.2.5.2 Monitoring for Hypersensitivity Reactions

Participants will be closely monitored during and after administration of study intervention during the observation period as specified in the SoA (Section 1.3) for hypersensitivity reactions, including monitoring for signs and symptoms of immune complex disease. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be available at all sites. If a hypersensitivity reaction occurs, dosing of the participant will be stopped.

Hypersensitivity reactions will be recorded as AEs or SAEs, as appropriate.

8.2.5.3 Injection Site Reactions

Study participants will be monitored for injection site reactions. All injection site reactions will be recorded as AEs and further characterized.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE are given in Appendix B.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Non-serious AEs will be collected from the time of randomization throughout the treatment period and including the follow-up period.

Serious adverse events will be recorded from the time of signing of the first ICF (either the brief, pre-screening ICF or the full, screening ICF) throughout the treatment period and including the follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

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

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Whether the AE is an injection site reaction
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused participant's discontinuation of IP administration (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider, reported in response to an open question from the study site staff (ie, Have you had any health problems since the previous visit/you were previously asked?), or revealed by observation, will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

In addition, the recording of CV events (in this study to include CV death, MI, stroke, coronary revascularization, and heart failure hospitalization) are important efficacy measures in CV clinical trials. All CV events will be recorded as AEs to allow for further characterization. Although this study will not be powered for these endpoints, the study will explore the effect of MEDI6570 on these important parameters.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration from baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment [eg, dose adjustment or drug interruption]).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3x ULN together with TBL ≥ 2x ULN may need to be reported as SAEs. Further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law is given in Appendix E.

8.3.7 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the sponsor's appropriate representatives within 1 day, ie, immediately but **no later than 24 hours** after he or she becomes aware of it.

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

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

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture system, an automated email alert is sent to the sponsor's designated representative.

If the electronic data capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate sponsor representative by telephone.

The sponsor's representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the study intervention.

8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except if the pregnancy is discovered before the study participant has received any study intervention.

8.3.8.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after he or she becomes aware of it.

The sponsor's designated representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within 1 or 5 calendar days for SAEs (Section 8.3.7) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.8.2 Paternal Exposure

Nonsterilized male study participants should be advised to use a condom for all sexual intercourse with a female partner of childbearing potential from Day 1 through the end of the study follow-up period. All male participants should refrain from fathering a child or donating sperm during the study and for 190 days following the last dose. If the partner becomes pregnant, the partner will be asked (under a separate consent) to provide information about the pregnancy and newborn baby.

8.3.9 Study Intervention Error

If a study intervention error occurs during the study, then the investigator or other site personnel informs the sponsor's appropriate representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The sponsor's designated representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the study intervention error (Section 8.3.7) and within 30 days for all other study intervention errors.

The definition of a study intervention error can be found in Appendix B.

8.4 Overdose

For this study, any dose of MEDI6570 greater than the intended maximum investigated dose per participant will be considered an overdose.

In cases of known or suspected overdose:

- Symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose of a study intervention occurs during the study, the investigator or other site personnel inform the appropriate sponsor representatives immediately, but **no later than 24 hours** after he or she becomes aware of it.

The sponsor's designated representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days for overdoses associated with an SAE (Section 8.3.7) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples (Appendix C).

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report is finalized, unless participants provided consent for their use in future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the PK samples to evaluate and validate the analytical method further. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained by the sponsor or its designee for up to 2 years after registration. If the program is terminated, samples may be disposed of sooner. Additional use includes but is not limited to further characterization of any ADAs, and confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of MEDI6570 as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- PK samples from participants receiving placebo will be analyzed at minimum to demonstrate lack of dosing.
- Serum samples will be used to analyze the PK of MEDI6570. Samples collected for analyses of MEDI6570 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by a bioanalytical test site operated by or on behalf of the sponsor, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis may be performed. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of the sponsor, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be tested further for characterization of the ADA response.

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual.

8.5.3 Pharmacodynamics

CCI [redacted]

8.6 Human Biological Sample Biomarkers

Blood will be collected to evaluate:

- CCI [redacted]
- Known inflammatory markers in atherogenesis (CCI [redacted] and HF biomarker (NT-proBNP) in serum, using validated clinical assays.

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to take part in the study, the participant consents to the mandatory research components of the study.

The following blood sample collections are mandatory; the time points for their collection are given in the SoA (Section 1.3), and instructions for collecting, handling, labeling, storing, and shipping samples are given in the laboratory manual:

- Samples for circulating biomarkers, including:
  - CCI [redacted]
  - NT-proBNP (HF biomarker)
  - CCI [redacted]
  - [redacted]

- Samples for additional evaluation of circulating biomarkers of inflammation and biomarkers of CV disease pathogenesis and related disease states.
- Samples for diagnostic assay development; these will be stored and may be used for commercial diagnostic assay development.

8.6.2 Collection of Optional Samples for Biomarker Analysis

Collection of urine samples and unused plasma and serum samples for future use is also part of this study and is subject to the participant's optional consent.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the ICF addendum.

For storage and destruction of genetic samples see Appendix D.

8.8 Medical Resource Utilization and Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy variable is $NCPV_{MD}$, which is defined as the coronary segment with the largest NCPV on the baseline scan. The null hypothesis is that there is no difference in change from baseline in $NCPV_{MD}$ between a MEDI6570 dose group and the placebo group. The alternative hypothesis is that the change from baseline in $NCPV_{MD}$ reduction is larger in the MEDI6570 CCI mg group compared with the pooled placebo group.

9.2 Sample Size Determination

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

CCI

[redacted]

9.3 Populations for Analyses

There are 7 populations defined for this study (Table 11).

Table 11 Populations for Analyses

Population	Description
ITT	All randomized participants will be included in the ITT Population. Participants will be analyzed according to their randomized intervention group. Participants randomized to the CCI mg group that switch dose to CCI mg during the trial will be analyzed according to the CCI mg group.
As-treated	Randomized participants who receive any study intervention will be included in the As-treated Population. Participants will be analyzed according to the actual intervention they receive, regardless of their randomized intervention group. Participants randomized to the CCI mg group that receive at least one CCI mg dose during the study will be analyzed according to the CCI mg group. Participants that only receive CCI mg will be analyzed as a separate CCI mg group.
CTA Analysis	Participants within the ITT population who have interpretable CTA scans at baseline and at least one post-baseline time point will be included in the CTA Analysis Population.
Per-protocol CTA analysis	Participants in the CTA Analysis Population who receive at least 3 doses of study intervention will be included in the Per-protocol CTA Analysis Population. Participants will be analyzed according to the actual intervention they receive.
Echocardiogram Analysis	Participants within the ITT population who have interpretable echocardiograms in the baseline and follow-up periods will be included in the Echocardiogram Analysis Population.
PK	All participants who receive ≥ 1 dose of MEDI6570 per protocol and have ≥ one post-dose, evaluable, MEDI6570 serum concentration determination will be included in the PK analysis set.
Immunogenicity	Participants included in the As-treated Population who have ≥ 1 immunogenicity sample will be included in the Immunogenicity Population.

CTA, computed tomography angiography; ITT, Intent-to-treat; PK, pharmacokinetic.

9.4 Statistical Analyses

This section summarizes the planned statistical analyses of the endpoints, including primary and secondary endpoints.

A comprehensive SAP will be finalized within one month of the first participant being dosed. The SAP will include a more technical and detailed description of the statistical analyses described in this section. Any subsequent amendments to the SAP will be documented, with final amendments completed before unblinding of the data for the analysis. Details of all analyses will be documented fully in the SAP.

9.4.1 General Considerations

All primary, secondary, and exploratory efficacy endpoints will be summarized descriptively. Categorical data will be summarized by the number and percentage of participants in each category. Continuous variables will be summarized by descriptive statistics, eg, n, mean, geometric mean, SD, coefficient of variation, median, interquartile range, minimum, and maximum. Baseline values will be defined as the last assessment before the first administration of study intervention.

P-values will be presented as 1-sided without multiplicity adjustments. Confidence intervals will be presented as 90%, 2-sided, without multiplicity adjustments.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The primary endpoint is change from baseline in $NCPV_{MD}$. An ANCOVA model on change from baseline adjusted for treatment group, baseline, and randomization strata will be used for the primary analysis. The CTA analysis population will be used for the primary analysis.

Per-protocol analysis for the primary endpoint will be performed on the per-protocol CTA analysis population. Additional sensitivity analysis may also be done for the primary endpoint, and baseline-by-treatment interaction effect will be evaluated; further details will be provided in the SAP.

9.4.2.2 Secondary Endpoints

NT-proBNP

Secondary endpoint of relative change from baseline in NT-proBNP will be analyzed based on the ITT population. Relative change from baseline is defined as the ratio of the post-baseline visit value over the baseline value, expressed as a percentage. A MMRM analysis will be performed. The dependent variable is change from baseline for the log-transformed value of NT-proBNP, ie log(post-baseline visit value) minus log(baseline value). The results will be back-transformed to the original scale. The model will include fixed effects of treatment group, visit, treatment group-by-visit interaction, and randomization strata, with baseline

NT-proBNP as a covariate. Repeated measures for the model will be visit within subjects. An unstructured covariance structure will be used for the repeated measures. In case the model does not converge, back-up covariance structures and other analysis solutions will be detailed in the SAP.

Secondary Endpoints Derived from Echocardiogram and CTA

Secondary endpoints that are measured by echocardiogram or CTA will be analyzed based on the Echocardiogram or CTA Analysis Population, respectively. ANCOVA analyses similar to the primary endpoint will be performed; the model will adjust for treatment group, respective baseline value, and randomization strata.

Immunogenicity Analyses

The Immunogenicity Population will be used for the immunogenicity analyses.

The number and percentage of participants with confirmed positive serum ADA to MEDI6570 will be reported by dose level. Titer data will be summarized descriptively.

The potential impact of ADA on MEDI6570 PK, efficacy, and safety will be evaluated as data allow.

PK Analyses

The PK Population will be used for the PK analyses.

MEDI6570 serum concentration data will be summarized descriptively, tabulated and plotted.

9.4.2.3 CCI

[redacted]

9.4.2.4 Subgroup Analyses

Subgroups planned for analysis include but are not limited to those defined by randomization stratification factors. Further details will be provided in the SAP.

9.4.3 Safety

The As-treated Population will be used for the safety analyses.

AEs and SAEs will be coded using the most up-to-date version of MedDRA. Type, incidence, severity, and relationship to study intervention will be summarized by MedDRA System Organ Class and Preferred Term and by study intervention. Specific AEs will be counted once for each participant for calculating percentages. If the same AE occurs multiple times within a participant, the highest severity and level of relationship to study intervention observed will be reported.

Vital signs and safety laboratory data will be summarized descriptively at each time point by study intervention.

9.5 Interim Analyses

No formal interim analysis is planned.

An analysis restricted to PK and PD data will be performed after approximately 80 participants have completed the Day 57 visit (Visit 6). The purpose of this evaluation will be to confirm the predicted PK and exposure-response relationship, based on data in participants with Type 2 Diabetes Mellitus in the post-MI study population. Non-study personnel who have no other involvement in the study will perform this evaluation. This analysis will be based on serum MEDI6570 concentration and CCI data. These PK and PD data will be reviewed in conjunction with safety data by the independent DMC; full details are provided in the independent DMC charter.

9.6 Data Monitoring Committee

For details on the independent DMC, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the sponsor.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies, except those using medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it, and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The ICF may be an electronic form or a paper consent form.

In this study, participants may take part in optional, pre-screening evaluations, and a separate, brief ICF will be used to obtain informed consent for any pre-screening evaluations. Participants who are pre-screened and then progress to the full screening phase of the study must sign the full ICF before any of the full screening evaluations can occur.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and images (CTA and echocardiogram) and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or have their unused samples and images (CTA and echocardiogram) used in future use research and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor, or its delegate, will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

An independent DMC will be appointed. The DMC will be responsible for safeguarding the interests of the participants, by assessing the safety of the intervention during the study and for reviewing the overall conduct of the study. The DMC will have access to the individual treatment codes and allocated doses and will be able to merge these with the collected study data while the study is ongoing. The DMC will review prespecified data (including the effects of the increased dose from CCI mg MEDI6570) periodically to ensure participant safety and make recommendations to the sponsor regarding further conduct of the study. This recommendation will be relayed to the sponsor's safety review committee and appropriate action will be taken. The DMC will have scheduled meetings at study initiation and at predefined study milestones with greater frequency during the initial part of the study. A separate charter will establish the rules, meeting frequency, and scope of responsibilities of the DMC.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on an eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or contracts.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the periods of time specified by the sponsor's policies, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension promptly, as specified by the applicable regulatory requirements. The investigator shall inform the participant promptly and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites may have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study will be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. The coordinating investigator will lead the multicenter publication.
- Authorship will be in accordance with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, 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 intervention has been administered.

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an Important Medical Event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

AEs for **malignant tumors** reported during a study should generally be assessed as **serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an Important Medical Event; medical judgment must be used.

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

Intensity Rating Scale

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding whether there is a 'reasonable possibility' that an AE may have been caused by the study intervention.

- Time Course. Exposure to study intervention. Has the participant actually received the study intervention? Did the AE occur in a reasonable temporal relationship to the administration of the study intervention?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the study intervention (pharmacology and toxicology) or interventions of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE re-occur if the study intervention was reintroduced after having been stopped? The sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the study intervention?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Study Intervention Error

For the purposes of this clinical study, a study intervention error is an unintended failure or mistake in the process for administering a study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A study intervention error is not lack of efficacy of the study intervention, but rather a human or process related failure while the study intervention is in the control of the study site staff or participant.

Study intervention error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as study intervention errors:

- Study intervention name confusion
- Dispensing error, eg, study intervention prepared incorrectly, even if it was not actually given to the participant
- Study intervention not administered as indicated, for example, wrong route or wrong site of administration
- Study intervention not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Study intervention not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the study intervention (excluding RTSM errors)
- Wrong study intervention administered to participant (excluding RTSM errors)

Examples of events that **do not** require reporting as study intervention errors in clinical studies:

- Errors related to or resulting from RTSM - including those which lead to one of the events listed above that would otherwise have been a study intervention error
- Participant accidentally missed study intervention dose(s) eg, forgot to take study intervention
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused study intervention or empty packaging

Study intervention errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

The sponsor or delegated representatives will keep oversight of the entire lifecycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the sponsor's assigned biobanks or other sample archive facilities and will be tracked by the appropriate staff during for the remainder of the sample lifecycle.

If required, the sponsor will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples have already been analyzed, the sponsor is not obliged to destroy the results of the research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's-withdrawal of informed consent to the use of donated samples is highlighted immediately to the sponsor or delegate
- Ensures that relevant human biological samples from that participant, if stored at the study site, are identified immediately, disposed of appropriately, and that the action is documented
- Ensures that the participant and the sponsor are informed about the sample disposal

The sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately, and that samples are disposed of or repatriated as appropriate, and that the action is documented and study site is notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name.

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- The sponsor intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in healthcare and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained for up to 15 years after the end of the study.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in Section 5.1 and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2.

Collection of Samples for Genetic Research

The blood sample for this genetic research will be obtained from the participants at Day 1, Visit 3 (before dosing). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Day 1, Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the sponsor's genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (sponsor employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at sponsor or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- The sponsor will not provide individual genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, a sponsor physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system by the sponsor and/or designated organizations to analyze the samples.
- The sponsor and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

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

Specific guidance on managing liver abnormalities can be found in Section 8.3.6.

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

All sources of laboratory data are appropriate for the determination of Potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, Potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible Potential Hy's Law events.

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

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

E 2 Definitions

Potential Hy's Law
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2x ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

Central Laboratories Being Used:

When a participant meets any of the Potential Hy's Law identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to the sponsor's representative).

The investigator will also remain vigilant for any local laboratory reports where the Potential Hy's Law identification criteria are met; where this is the case, the investigator will:

- Notify the sponsor's representative.
- Request a repeat of the test (new blood draw) by the central laboratory without delay.
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result.

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

- Determine whether the participant meets Potential Hy's Law criteria (refer to Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor's representative.
- Determine whether the participant meets Potential Hy's Law criteria (refer to Appendix E 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet Potential Hy's Law criteria the investigator will:

- Inform the sponsor's representative that the participant has not met Potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet Potential Hy's Law criteria the investigator will:

- Determine whether Potential Hy's Law criteria were met at any study visit before starting study treatment (refer to Section 8.3.6).
- Notify the sponsor's representative who will then inform the central Study Team
- Within 1 day of Potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important Medical Event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met Potential Hy's Law criteria before starting the study intervention, the investigator is not required to submit a Potential Hy's Law SAE unless there is a significant change[1] in the participant's condition.
- The Study Physician contacts the investigator to provide guidance, discuss, and agree on an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- After this contact, the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which of the tests available in the Hy's Law lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

[1] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator to review available data and agree on whether there is an alternative explanation for meeting Potential Hy's Law criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities within 15 calendar days from date Potential Hy's Law criteria was met. The sponsor's Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the sponsor's standard processes.

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

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

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to investigational product and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted Potential Hy's Law SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law lab kit for central laboratories	
Additional standard chemistry and coagulation tests	GGT
	LDH
	Prothrombin time
	INR
Viral hepatitis	IgM anti-HAV
	IgM and IgG anti-HBc
	HBsAg
	HBV DNA [a]
	IgG anti-HCV
	HCV RNA [a]
	IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV
	IgM & IgG anti-HSV
	IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin
Autoimmune hepatitis	Antinuclear antibody
	Anti-Liver/Kidney Microsomal Ab
	Anti-Smooth Muscle Ab
Metabolic diseases	alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin
	Transferrin saturation

[a] HCV RNA; HBV DNA are only tested when IgG anti-HCV is positive or inconclusive

Ab, antibody; anti-CMV, antibody to the cytomegalovirus; anti-EBV, antibody to the Epstein-Barr virus; anti-HAV, antibody to the hepatitis A virus; anti-HBc, antibody to the hepatitis B core antigen; anti-HCV, antibody to the hepatitis C virus; anti-HEV, antibody to the hepatitis E virus; anti-HSV, antibody to the herpes simplex virus; GGT, Gamma-glutamyltransferase; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HCV RNA, hepatitis C virus ribonucleic acid; HEV RNA, hepatitis E virus ribonucleic acid; INR, international normalized ratio; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactic acid dehydrogenase

E 7 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15.

FDA Guidance for Industry 2009
FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation. [cited 28Oct2021]. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Appendix F Intensity Categories for Statin Therapy

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease.

High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel) [a]		
High-Intensity Statin Therapy	**Moderate-Intensity Statin Therapy**	**Low-Intensity Statin Therapy**
Daily dose lowers LDL-C, on average, by approximately ≥ 50%	Daily dose lowers LDL-C, on average, by approximately 30% to < 50%	Daily dose lowers LDL-C, on average, by < 30%
Atorvastatin (40 [b])–80 mg	**Atorvastatin 10 (20) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (40) mg	**Rosuvastatin (5) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg [c]	**Lovastatin 20 mg**
	Pravastatin 40 (80) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

[a] Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

[b] Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.

[c] Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Boldface type indicates specific statins and doses that were evaluated in RCTs included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3. All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

BID, twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials.

Appendix G Risk Assessment for COVID-19 Pandemic

G 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus spread across the globe rapidly, and caused the WHO to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have affected current and new clinical studies. As the threat of the pandemic burden, including new outbreaks, locally or globally, will affect the conduct of clinical studies, appropriate risk assessments and mitigation measures need to be considered in all clinical studies to protect participants, site staff, and society as a whole.

Both EMA and FDA, as well as national health authorities in Europe, have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during the COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at a high pace. Given the circumstances of a potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in the future, special attention will be paid to protect study participants and site staff against infection with COVID-19 as requested by the EMA guideline.

G 2 Risk Assessment for COVID-19 Pandemic

G 2.1 Risk versus Benefit Assessment for MEDI6570

CCI [redacted]

Furthermore, in a recent study conducted in severe and critical COVID-19-infected patients, researchers reported that the expression of CCI [redacted] by immature neutrophils positively correlated with clinical severity and with the cytokine storm (IL-1b, IL-6, IL-8, TNFα), (Combadiere et al 2020). Moreover, it was associated with intravascular coagulation and higher risks of severe thrombosis (Combadiere et al 2020). These data suggest that treatment with MEDI6570, CCI [redacted], may offer benefit for those infected with COVID-19.

G 2.2 Measures to Mitigate Risks of Infection with COVID-19

Participation in the study might increase the likelihood of COVID-19 infection among study participants and staff as a result of increased travel (to and from study sites) and interaction between participants and study site staff to conduct protocol-specified procedures.

Measures to mitigate the additional risks caused by COVID-19 are as follows:

- Enrollment to the study will only start when the sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.
- The sponsor and CRO will perform continual risk assessments throughout the study, paying attention to evolving local infection rates and adapting as required, for example, by temporarily pausing screening at a site if required. Current national laws and local recommendations for prevention of pandemic will be adhered to strictly.
- Participants will be monitored closely throughout the study during the pandemic for any of the signs and symptoms currently recognized by the WHO and local guidelines to indicate possible COVID-19 infection. If clinical signs of COVID-19 infection are reported by participants, the investigator will determine whether protocol-specified study samples can be collected, and whether safety data can be recorded on site. If not, adverse events and concomitant medications will be obtained via phone calls. If a participant shows symptoms of COVID-19 infection, the investigator will have discretion (with support and guidance from the Medical Monitor if required) to determine whether the participant should continue with dosing.
- The probability of virus transmission will be controlled as much as possible by:
  - Advising the participant to adhere to local requirements for reducing the public exposure while ambulatory.
  - Study site staff will monitor themselves for COVID-19 symptoms, and in the event of developing symptoms or having a positive COVID-19 test result, should not attend the site or come into person-to-person contact with any participants; this may also extend to other scenarios of potential infection risk as defined by local guidance and laws.
  - Participants may be contacted by telephone before a visit to enquire whether COVID-19 symptoms and signs are present, and they should be asked not to attend the site if they are suspected to be infected with COVID-19. In addition, participants may be asked whether they have been in contact with a person who has tested positive for COVID-19. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will apply during site visits and in-house confinement.

- Where physical distancing is not possible, personal protective equipment will be used by study participants (face masks, gloves) and staff (for example but not limited to: face masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to improve physical distancing further.

G 2.3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public COVID-19 exposure while ambulatory. If applicable, before Screening Visit 1, potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study participants will be asked to use face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

G 3 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to the minimum required as deemed appropriate during the COVID-19 pandemic in accordance with local regulations.

In addition, where possible, other measures for carrying out protocol-related activities, such as but not limited to home-nursing, may be employed as required.

G 4 COVID-19 Vaccination Guidance and Recommendations

The COVID-19 pandemic continues to have a profound impact on society as a whole, and global mass vaccination to prevent infection, disease, and transmission is underway and expected to persist beyond 2021. For AstraZeneca, the safety and well-being of study participants is of primary importance and this includes vaccination in the current pandemic situation.

Currently, inactive/non-replicating COVID-19 vaccines are being approved across the globe as emergency use products. AstraZeneca has no data on the co-administration of MEDI6570 and respective COVID-19 vaccines. Potential MEDI6570/vaccine interactions affecting patient safety or IP and vaccine efficacy are therefore unclear. In addition, vaccine-related AEs may confound the AE profile of the MEDI6570 investigational drug.

Current local guidelines, vaccine availability, and a benefit-risk assessment should all be considered when determining whether a participant should be vaccinated. Ultimately, the decision to vaccinate will be based on the judgment of the treating physician taking into account the participant's best interest.

Patients enrolled in studies with MEDI6570 can be vaccinated against Covid-19 particularly since many patients are likely to belong to one of the risk groups targeted for vaccination).

G 4.1 Considerations to Facilitate COVID-19 Vaccination

Covid-19 vaccination may be administered before, during or after enrollment in the study. If administered during the study it should be recorded as a concomitant medication. .

G 4.1.1 COVID-19 Vaccination before Entering Clinical Study/Randomization

For study participants with flexibility as to when to start in the study and if COVID-19 vaccination is planned, complete vaccination (both doses of vaccine, where applicable) before the first dose may be advisable. If possible, the first dose of MEDI6570 should be given at least 14 days after the last dose of vaccine.

G 4.1.2 COVID-19 Vaccination during the Ongoing Study (Dosing Period)

For study participants already receiving treatment with MEDI6570, Covid-19 vaccination is acceptable if the benefit/risk assessment does not indicate otherwise.

In order to understand whether a potential reaction is caused by administration of a vaccine or by MEDI6570 consider administering IP and vaccine 7 days apart.

G 4.1.3 End of Study

For participants approaching the end of study, Covid-19 vaccination could be delayed, if possible, until after the last dose of study drug is given.

G 4.2 CRF

To better assess the overall impact of COVID-19 vaccination on a particular study and study population, COVID-19 vaccines should be recorded in the CRF as concomitant medications (including date and type of vaccine).

G 4.3 AE Monitoring

Vaccinated study participants should be monitored according to local guidelines and the guidance within this study protocol.

For AEs with an onset date near the time of administration of a COVID-19 vaccination, the investigator should adhere to the standard practice in judging whether there is a reasonable possibility that an AE is considered related to MEDI6570.

Appendix H Abbreviations

Abbreviation or special term	Explanation
ACS	acute coronary syndrome
ACC	American College of Cardiology
ADA	Anti-drug antibody(ies)
AE	Adverse event
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
$AUC_{0\text{-}tau}$	Area under the curve from time 0 over the dosing interval
BNP	Brain natriuretic peptide
BP	Blood pressure
CAD	Coronary artery disease
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcome Study
CHD	Coronary heart disease
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CRO	Contract research organization
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTA	(Coronary) computed tomography angiography
CV	Cardiovascular
DILI	Drug Induced Liver Injury
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology

Abbreviation or special term	Explanation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLS	Global longitudinal strain
HED	Human equivalent dose
HF	Heart failure
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ICF	Informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IgG1λ	Immunoglobulin G1 lambda
CCI	[redacted]
IRB	Institutional Review Board
IMP	Investigational medicinal product
ITT	Intent-to-treat (population)
LAPV	low attenuation plaque volume
CCI	[redacted]
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed model with repeated measures
mRNA	Messenger RNA
mSv	millisievert
NCPV	Non-calcified plaque volume
$NCPV_{MD}$	Non-calcified plaque volume in the most diseased coronary segment
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST segment elevation myocardial infarction
NT-proBNP	N-terminal prohormone brain natriuretic peptide
CCI	[redacted]
PBMC	Peripheral blood mononuclear cell

Abbreviation or special term	Explanation
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetics
PPI	Proton pump inhibitor
Q1W	Every week
Q4W	Every 4 weeks
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard deviation
CCI	[redacted]
SoA	Schedule(s) of Activities
STEMI	ST segment elevation myocardial infarction
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
ULN	Upper limit of normal
WHO	World Health Organization

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (10Mar2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

- to change the dose strength in the high dose group from CCI to CCI mg MEDI6570 to achieve full CCI suppression in a majority of participants
- to modify the participant population to widen eligibility to the study by increasing the post-infarction eligibility window, reducing the threshold for hs-CRP, and not requiring all participants to have elevated NT-proBNP at baseline

In addition, the following other substantial changes were made: to minimize the theoretical risk of bleeding events; to minimize the number of injections required; to introduce an optional pre-screening visit; to provide guidance on conducting the study during the COVID-19 pandemic; to clarify permitted and prohibited concomitant medications; to clarify that participants who discontinue investigational product because of an AE may remain in the study; and to remove the requirement that a participant who develops ADAs should be followed up until the value returns to baseline. All of the changes and their rationale are summarized below.

Substantial changes:

Description of Change	Brief Rationale	Sections Affected
Upper limit of allowable time after MI before enrollment in the study was extended from 180 to 365 days	To allow a pragmatic approach for identifying suitable candidates who may still be at risk of MACE and may derive benefit from treatment with MEDI6570 when added to standard of care	Section 1.1 Synopsis; Section 4.1 Overall Design; Section 4.2.1 Rationale for Study Population; Section 5.1 Inclusion Criteria; Section 5.4 Screen Failures
Definition of persistent inflammation was changed from hs-CRP ≥ 2 to hs-CRP ≥ 1 mg/L	The study has witnessed a high screen fail rate secondary, in part, to the hs-CRP requirement. Furthermore, emerging data have demonstrated that an hs-CRP of ≥2 mg/L is not required for anti-inflammatory studies (Tardif et al 2019 and Nidorf et al 2020), inflammatory risk rises linearly between 1 and 2 mg/L, and there are	Section 1.1 Synopsis; Section 4.1 Overall Design; Section 5.1 Inclusion Criteria

Description of Change	Brief Rationale	Sections Affected
	racial differences in the optimal threshold of hs-CRP to identify residual inflammatory risk (ie, lower threshold in Asian populations).	
The highest MEDI6570 dose group CCI mg) has been discontinued and replaced with a CCI mg dose group. Participants already randomized to receive the CCI mg dose, who have not completed treatment, will switch to the CCI mg dose. Consequential changes are outlined below:	CCI [redacted] This dose is supported by safety and exposure data from the Phase 1 study D4920C00001and the 6-month toxicology study.	Throughout Section 1.1 Synopsis and the text, as specified for each item below.
• Pertinent final results from 6-month non-clinical toxicology study SBL446-001 and Phase I study D4920C00001 have been included.	• Inclusion of these data explains the rationale for increasing the dose, and demonstrates that positive safety margins are maintained with the CCI mg dose.	• Section 4.3 Justification for Dose
• For the ITT population, text was added to explain that participants randomized to the CCI mg group that switch dose to CCI mg during the study will be analyzed for the ITT population according to the CCI mg group.	• To maintain the ITT principle	• Section 1.1 Synopsis; Section 9.3 Populations for Analysis (Table 11)
• For the As-treated Population, text was added to explain that participants randomized to the CCI mg group that receive at least one CCI mg dose during the study will be analyzed according to the CCI mg group, and participants that only received CCI mg will be analyzed as a separate CCI mg group.	• To reflect the highest dose level a participant actually received	• Section 1.1 Synopsis; Section 9.3 Populations for Analysis (Table 11)
• Text was added to explain that the independent DMC will have access to participants' allocated doses and will review early PK-PD data in conjunction with safety data to evaluate the effects of the dose increases from CCI to CCI mg MEDI6570.	• To maintain independent evaluation of the effects of changing the CCI mg dose level to CCI mg on PK-PD in conjunction with safety data	• Section 1.1 Synopsis; Appendix A 5 Committees Structure
The dosing volumes and numbers of injections to be administered for each	The dosing volumes were reduced to minimize the number of injections	Section 6.1 Study Interventions Administered;

Description of Change	Brief Rationale	Sections Affected
intervention were changed, from 3 injections (totalling 2.5 mL, for all interventions), to 1 injection (of 0.5 mL for the CCI mg group and 1.5 mL for the CCI mg group) or 2 injections (totalling 4 mL for the CCI mg group). Consequential changes are outlined below:	required and to make the study more patient-centric.	Section 1.1 Synopsis; Section 6.2.3 Dose Preparation Steps, text and Table 9; Section 6.2.4 Treatment Administration
• The placebo intervention now comprises 3 injection/volume-matched placebo groups, and the randomization ratio has changed (from 1:1:1:1 for 3 MEDI6570 dose groups and 1 placebo group to 3:3:3:1:1:1 for 3 MEDI6570 dose groups and 3 injection/volume-matched placebo groups.	• To maintain the study blind between active treatment and placebo	• Terms and Conventions Used in this Document; Section 4.1 Overall Design; Section 4.3 Justification for Dose; Section 6.2.3 Dose Preparation Steps, text and Table 9; Section 6.2.4 Treatment Administration; Section 6.3.1 Randomization Procedure; Section 6.3.2 Blinding Procedure
• Text was amended to clarify that the study is blinded with respect to active treatment versus placebo.	• In minimizing the numbers of injections required at each dose level to make the study more patient-centric, is no longer blinded with regard to dose level, but it remains blinded to active versus placebo.	• Section 6.3.2 Blinding Procedure
• Text was added to explain that participants enrolled under Protocol Version 1.0 will be re-allocated to the appropriate dosing volume for their randomized intervention group, and that participants originally randomized to receive placebo will be re-randomized to a placebo group that is injection/volume-matched to a MEDI6570 treatment group.	• To transition participants from Protocol Version 1.0 to Amendment 1 while maintaining the integrity of the randomization schedule and the study blind (with regard to active versus placebo)	• Section 6.3.1 Randomization Procedure; Section 6.3.2 Blinding Procedure
• Text was added to explain that the 3 injection/volume-matched placebo groups would be pooled for the analyses.	• For clarification	• Section 1.1 Synopsis; Section 9.2 Sample Size Determination
An optional pre-screening visit and associated brief ICF have been introduced to allow local laboratory assessment of hs-CRP and creatinine	To allow a pragmatic approach to identifying suitable candidates for screening.	Section 1.2 Schema; Section 1.3 Schedule of Activities, Table 3; Section 5 Study Population;

Description of Change	Brief Rationale	Sections Affected
(and NT-proBNP [or BNP] if randomization of participants with NT-proBNP < 125 pg/mL is capped). The pre-screening visit does not replace the full screening visit. Participants who sign the brief, pre-screen, ICF are considered to have enrolled in the study.		Section 5.1 Inclusion Criteria; Section 5.4 Screen Failures; Section 8 Study Assessments and Procedures; Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; Appendix A 3 Informed Consent Process
Changes to participant population with regard to NT-proBNP profile: • A screening NT-proBNP value ≥125 pg/mL was removed as an inclusion criterion and replaced with an option to cap the proportion of participants with an NT-proBNP value of < 125 pg/mL who are randomized. • Removal of statement 'The proposed sample size in this Phase IIB clinical study is powered to detect a 25% reduction in NT-proBNP.'	• To widen eligibility for participation in the study • No longer applicable	• Section 4.1 Overall Design; Section 4.2.2.2 Secondary Endpoints; Section 5.1 Inclusion Criteria • Section 4.2.2.2
Instruction to encourage the use of PPIs if concomitant NSAID therapy is required	To minimize the theoretical risk of bleeding events	Section 2.3.1 Risk Assessment, Table 6
Changes caused by COVID-19 global pandemic: • Change to eligibility criteria to include participants who have had inactive, non-replicating COVID-19 vaccines approved by Health Authorities or under emergency use authorization • Addition of new appendix	• To allow inclusion of participants who have been vaccinated against COVID-19 • To provide details on the additional risk and risk-mitigating measures for study participants related to COVID-19 and COVID-19 vaccination	• Section 2.3.1 Risk Assessment; Section 5.2 Exclusion Criteria; Section 6.5.1 Permitted Concomitant Medications • Appendix G Risk Assessment for COVID-19 Pandemic
Addition of Subsections 6.5.1 and 6.5.2 for permitted and prohibited concomitant medications; reiteration of the encouragement to use PPI if concomitant NSAID therapy is required.	To provide clarity on permitted and prohibited concomitant medications; to minimize the theoretical risk of bleeding events	Section 6.5 Concomitant Therapy

Description of Change	Brief Rationale	Sections Affected
Addition of guidance text on spontaneous severe bleeding events including development of conditions requiring anticoagulation therapy as a reason for considering temporary or permanent discontinuation of study intervention	To minimize the theoretical risk of exacerbating bleeding events	Section 7.1 Discontinuation of Study Intervention
Text updated to capture whether an AE caused the participant to discontinue investigational product administration, rather than whether an AE caused the participant to withdraw from the study	To clarify that a participant may wish to discontinue investigational product administration and still remain in the study	Section 8.3.2 Follow-up of Adverse Events and Serious Adverse Events
Changes related to collecting ADA samples: • Removal of the statement, 'Any participants who develop ADAs will be followed until the value returns to baseline' • The statement 'Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring' was added.	• Removed because of the Phase 1 safety profile and because participants are already followed for 6 months after their last dose in current study design. • This situation may apply if samples were required during an AE and outside the pre-specified sampling visit.	• Section 8.5.2 Immunogenicity Assessments • Section 8.5.2 Immunogenicity Assessments

ADA(s), anti-drug antibody(ies); AE, adverse event; BNP, brain natriuretic peptide; COVID-19, coronavirus disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); DMC, data monitoring committee; hs-CRP, high sensitivity C-reactive protein; ICF, informed consent form; ITT, intent-to-treat; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug; PD, pharmacodynamic; PK, pharmacokinetic; PPI, proton pump inhibitor; CCI [redacted]

Non-substantial changes:

Description of Change	Brief Rationale	Sections Affected
Minor PK changes: • The PK endpoints were changed from C_{max} and terminal $t_{1/2}$ in serum to MEDI6570 concentrations in	• To align the PK endpoint and analyses sections with the sparse PK sampling schedule, which does not allow for accurate estimation of C_{max} and terminal $t_{1/2}$.	• Section 1.1 Synopsis; Section 3 Objectives and Endpoints; Section 9.4.2.2 Secondary Endpoints

Description of Change	Brief Rationale	Sections Affected
serum; the planned PK analyses were amended from PK parameter determinations to descriptive summaries, tabulations and plots of MEDI6570 serum concentration data • The PK Population definition was changed from 'participants who receive ≥ 1 dose of MEDI6570 per protocol and have at least one post-dose, evaluable, MEDI6570 PK determination' to '… at least one post-dose, evaluable, MEDI6570 serum concentration determination'	• To reflect the changes in the PK endpoints	• Section 1.1 Synopsis; Section 9.3 (Table 11) Populations for Analysis
Clarification footnotes added to Objectives and Endpoints table: • to explain that physical activity monitor results will be reported separately from the clinical study report • to include the Day 253 study visit window	For clarification	Section 1.1 Synopsis; Section 3 Objectives and Endpoints
The number of participants undergoing the interim CTA between the fifth and sixth doses was amended from 50 participants/intervention group to 200 participants overall.	To simplify the presentation	Section 1.1 Synopsis
Notes were added the Schedule of Activities for vital signs and ECG.	To clarify the timing of vital signs relative to blood draws	Section 1.3 Schedule of Activities, Table 3
The table notes and text for creatinine for calculating eGFR were all amended to clarify that the collection should occur within 30 days before the CTA, and that a local laboratory or point of care could be used	For clarification	Section 1.3 Schedule of Activities, Table 3, Table 4 and Table 5; Section 8.1.1.2 Criteria for CTA Imaging
Changes in sample collection timepoints in the Schedules of Activities: • Urine collections for albumin-to-creatinine ratio analyses at Visits 2, 5, 7, 10 and 12 were removed.	• The number of collections was reduced to correct an error; the change from baseline will only be evaluated at one time point	• Section 1.3 Schedule of Activities, Table 3 and Table 4

Description of Change	Brief Rationale	Sections Affected
	and this will reduce the patient burden	
• Day 85 (Visit 7) sample collections for CCI , NT-proBNP; gene expression biomarkers; and circulatory (exploratory) biomarkers; and samples for diagnostic assay development were moved to Day 113 (Visit 8) • (For CCI and NT-proBNP; and for diagnostic assay development, a sample is still collected at Day 85 [Visit 7] for storage.) • The sample collections for CCI NT-proBNP; and circulating biomarkers of inflammation CV disease were removed for Day 405 (Visit 16)	• Sample collections moved to gain information on gene expression biomarkers and circulatory (exploratory) biomarkers concentrations at predose and postdose for the dosing interval • To minimize the number of blood sample collections and thus reduce the patient burden	• Section 1.3 Schedule of Activities, Table 4 and Table 5
CCI [redacted]	[redacted]	Section 1.3, Schedule of Activities, Table 4; Section 8.1.3 CCI
Text was added for gene expression biomarkers stating that samples will only be collected for the first approximately 290 participants randomized.	Approximately 290 participants are expected to provide sufficient data to explore gene expression profiling across the intervention groups at the different time points.	Section 1.3, Schedule of Activities, Table 4, Table 5, Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis
Text was inserted as follows: CCI [redacted]	For clarification	Section 2.3.1 Risk Assessment Table 6
Text was amended as follows: CCI [redacted]	For clarification	Section 2.3.1 Risk Assessment Table 6
Number of study sites and geographic regions		

Description of Change	Brief Rationale	Sections Affected
• The planned number of study sites was amended from 60 to 85 to approximately 70 to 100, and the following text was added: 'The COVID-19 pandemic may continue to affect different geographic regions differently, having an unpredictable impact on study enrollment; therefore, a more accurate estimation of the number of countries and study sites that may be included globally is challenging.'	• To allow more flexibility in the number of sites and countries participating in the study	• Section 1.1 Synopsis; Section 4.1 Overall Design
• The 3 geographic regions used for the randomization strata were amended from 'North America, Europe and Japan' to 'Asia, North America and Rest of World'	• To better reflect the likely global distribution of study sites	• Section 1.1 Synopsis; Section 4.1 Overall Design; Section 6.3.1 Randomization Procedure
Changes caused by change in definition of persistent inflammation:		
• Deletion of 'with ongoing inflammation reflected by a hs-CRP > 2 mg/L present in > 60% of patients post-MI being a strong predictor of ongoing risk of MACE (Carrero et al 2019)'	• Discussion of CRP > 2 mg/L no longer required	• Section 4.2.1 Rational for Study Population;
• Deletion of 'Multiple studies have suggested various cut-off points for the upper limit of a clinically meaningful value of NT-proBNP (McCullough and Kluger 2018). Both the FDA and the European Society of Cardiology have proposed an exclusion cut-off of < 125 pg/mL (McCullough and Kluger 2018); as such, this was the threshold that was selected. This allows for the investigation of the efficacy of MEDI6570 in a population with a wide range of NT-proBNP and corresponding degrees of HF.'		• Section 11 References

Description of Change	Brief Rationale	Sections Affected
• Deletion of Carrero et al 2019 and McCullough and Kluger 2018 references		
The type of myocardial infarction participants must have had to take part in the study was added (presumed Type-I)	For clarification	Section 5.1 Inclusion Criterion 3(a)
The wording of Exclusion Criterion 7a was amended from: 'History or presence of any of the following: Ongoing infection or febrile illness within 30 days before randomization (Day 1; Visit 3),' to: '…Ongoing infection or febrile illness that in the opinion of the investigator may be the cause of elevated hs-CRP on screening (Visit 1)'	For clarification	Section 5.2 Exclusion Criterion 7(a)
The time window for measuring BP, and the number of measurements allowed, at Screening was added	For clarification	Section 5.2 Exclusion Criterion 9
The equation used to calculate eGFR was changed from the Modification in Diet in Renal Disease to the Chronic Kidney Disease Epidemiology Collaboration equation	For calculating eGFR, the Chronic Kidney Disease Epidemiology Collaboration equation has an improved performance over the Modification in Diet in Renal Disease calculation	Section 5.2 Exclusion Criterion 10(a)
A new subsection was added ('Rescreening')	To consolidate the different circumstances that could warrant rescreening	Section 5.4 Screen Failures
Additional information was included on the study intervention supplied	To describe the appearance, packaging and formulation in greater detail.	Section 6.1 Study Interventions Administered, text and Table 8
Serum concentrations of MEDI6570, albumin-to-creatinine ratios in urine and ADAs were added to the list of variables that will remain blinded to the participant, investigator and site staff	For clarification	Section 6.3.2 Blinding Procedure

Description of Change	Brief Rationale	Sections Affected
The following text was added: 'unable to be contacted by the study site by the end of the study.'	For clarification	Section 7.3 Lost to Follow-up
Text was amended from: 'Imaging personnel and equipment will undergo certification by a separate, blinded, independent, core laboratory.' To: Imaging personnel and equipment will undergo certification by a separate, ~~blinded~~, independent, core laboratory that is blinded to study treatment.	For clarification	Section 8.1.1.4 CTA Image Analysis
Updated to state that if multiple vital signs measurements are taken, the last measurement is the one that should be recorded	For clarification	Section 8.2.2 Vital Signs
Updated to state that ECGs will be recorded after the participant has rested for 5 minutes	For clarification	Section 8.2.3 Electrocardiogram
Updated to state that all CV events will be recorded as AEs to allow further characterization.	For clarification	Section 8.3.4 Adverse Events based on signs and symptoms
CCI [redacted]	[redacted]	Section 8.5.3 Pharmacodynamics
Text amended to state that the number of participants providing samples for gene expression biomarkers will be monitored by the study team.	For clarification	Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis
Changes to the interim analyses: • Text deleted: '~~Other endpoints may also be analyzed at the interim.~~' and replaced with: CCI [redacted] Data for this analysis will be based on serum MEDI6570	• For clarification	• Section 9.5 Interim Analyses

Description of Change	Brief Rationale	Sections Affected
concentration and CCI data.'		
• Text was added explaining that the exposure-response relationship will be evaluated before the first interim analysis.	• For clarification	• Section 1.1 Synopsis; Section 9.5 Interim Analyses
Paragraph removed: • 'In the event of positive outcome at the interim analyses, an evaluation of exposure-response relationship may be performed. This analysis has the intention to guide the dose selection for the next study. This will be performed by non-study personnel with no other involvement in the study. Data for this analysis will be based on PK and primary, secondary, and exploratory efficacy and biomarker endpoints.'	• Text was consolidated for brevity.	• Section 1.1 Synopsis; Section 9.5 Interim Analyses
Paragraph removed: • 'A separate analysis plan will also be prepared for the evaluation of exposure-response relationship and it should be finalized before the first interim analysis.' were removed. And replaced with:	• An exposure-response analysis plan may not be prepared.	• Section 1.1 Synopsis; Section 9.5 Interim Analyses
• 'In addition, an analysis restricted to PK and PD data, will be performed before the first formal interim analysis, after approximately 80 participants have completed the Day 57 visit (Visit 6). The purpose of this evaluation will be to confirm the predicted PK and exposure-response relationship, based on data in participants with Type 2 Diabetes Mellitus in the post-MI study population. Non-study personnel who have no other involvement in the study will perform this evaluation. This analysis will	• For clarification	

Description of Change	Brief Rationale	Sections Affected
be based on serum MEDI6570 concentration and CCI data. These PK and PD data will be reviewed in conjunction with safety data by the independent DMC; full details are provided in the independent DMC charter.'		
• Details of the PK-PD interim analysis were added	• For completeness	• Section 4.1 Overall Design
Corrections of minor errors and typos:		
• The approximate number of participants in second interim analysis was changed from 400 to 355	• Correction of typo for number of participants	• Section 1.1 Synopsis; Section 4.1 Overall design; Section 9.5 Interim Analyses
• Collection of the optional genomics blood sample was moved from Screening Visit 1 to Day 1, Visit 3, and a note was added to clarify that if for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit.	• To correct an error in the Schedules of Activities and to reduce the sampling burden on participants who may fail screening	• Section 1.3 Schedule of Activities, Table 3 and Table 4; Appendix D, Optional Genomics Initiative Sample
• CCI	• Correction of typo	• Section 1.3, Schedule of Activities, Table 4
• The cross-references for albumin-to-creatinine ratio were updated to Section 8.6.1	• To correct error and guide reader to the appropriate location	• Section 1.3 Schedules of Activities, Table 4 and Table 5
• The note '(after the 9th dose)' was removed for the Day 253 Echocardiogram	• Correction of typo	• Section 1.3 Schedules of Activities, Table 5
• The requirement of syringes to have appropriate covers and/or shields was replaced with a statement clarifying that syringes containing MEDI6570 look identical to those containing placebo.	• Correction of error; there are no visual differences between the IMP and placebo.	• Section 6.2.3 Dose Preparation Steps (Subcutaneous Dose Preparation)
• Text was amended as follows: 'It may be necessary for a participant to discontinue ~~(definitive discontinuation)~~ study intervention temporarily or permanently.'	• To remove unnecessary text	• Section 7.1 Discontinuation of Study Intervention

Description of Change	Brief Rationale	Sections Affected
• 'neutrophils' was replaced with 'buffy coat'	• To correct the terminology	• Section 8.6 Human Biological Sample Biomarkers
• Updated footer text table for abbreviation for HCV DNA to HBV DNA	• Corrected typo in footer text	• Appendix E 6 Laboratory Tests
• Added italic font to table	• Italic type was missing from the table. Updated to align with table footer.	• Appendix F Intensity Categories for Statin Therapy
• The year of the Zhang et al reference was corrected from 2008 to 2009 in the hyperlink	• Correction of typo	• Section 11 Reference List
• In-text definitions of abbreviations at first use were removed	• For consistency with style conventions	• Throughout

ADA(s), anti-drug antibody(ies); AE, adverse event; BP, blood pressure; C_{max}, maximum observed concentration; COVID-19, Coronavirus disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); CTA, computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; DMC, data monitoring committee; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; HBV DNA, hepatitis B virus deoxyribonucleic acid; HF, heart failure; CCI [redacted] IMP, investigational medicinal product; MACE, major adverse cardiovascular events; MI, myocardial infarction; CCI [redacted] No, number; NT-proBNP: N-terminal prohormone brain natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; PPI, proton pump inhibitor; CCI [redacted] $t_{1/2}$, half-life

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