Clinical Study Protocol	
Study Intervention	AZD8233
Study Code	D7990C00006
Version	5.0
Date	16Jun2022

A Phase 1 and 2 study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of AZD8233 following a multiple subcutaneous dose administration in Japanese participants with dyslipidemia (HAYATE)

Sponsor Name: AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifier Number(s): Not applicable

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol 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: D7990C00006

Amendment Number: N/A

Study Intervention: AZD8233Study Phase: Ph 1/Ph 2

Short Title: A Phase 1/2 Study of AZD8233 in Participants with Dyslipidemia

Study Physician Name and Contact Information will be provided separately.

Document History	
Document	**Date**
Version1.0	20-Oct-2020
Amendment 1	13-Nov-2020
Amendment 2	10-May-2021
Amendment 3	02-Nov-2021
Amendment 4	16-Jun-2022

Amendment 1 (13-Nov-2020)

Overall Rationale for the Amendment:

The original CSP, Version 1.0, dated 20 Oct 2020, was updated following the PMDA's review (dated 30 Oct 2020), and updates were made to correct errors and further clarify the contents in this Version 2.0.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria: Criterion 4 (Part A)	Added patients on anti-coagulation therapy as an exclusion criterion for Part A.	To exclude the patients with high risks in bleeding.
Section 5.2 Exclusion Criteria: Criterion 6 (Part A)	Specified the relevant risk classification (subjects in high risk class) based on the Suita Score.	To specify the risk classification.
Section 5.2 Exclusion Criteria: Criterion 7 (Part B)	Added "patients on anti-coagulation therapy" as an exclusion criterion for Part B.	To exclude the patients with high risks in bleeding.
Section 5.3.4 Reproductive Restrictions	Added the contraceptives approved/certified and those not approved/certified in Japan.	To explain the concrete conditions of contraception. in Japan
Section 8.5.3.1 Collection of Samples	Specified the other lipid assessments, in addition to PCSK9 and LDL-C, to be masked.	Clarification
Table 1 Schedule of Activities (Part A)	Corrected the date for the pregnancy test from Day -1 to Day 1.	To correct the erroneous description.
Table 1 Schedule of Activities (Part A)	Pregnancy and reproductive status will not assessed at Visit 2; therefore the assessment at Visit 2 was deleted.	To correct the erroneous description.

Section # and Name	Description of Change	Brief Rationale
Table 1Schedule of Activities (Part A)	Added the concrete date and timing for the pregnancy test in Footnote p	To update the description.
Table 1 Schedule of Activities (Part A)	Added footnote q	Clarification
Table 2 Schedule of Activities (Part B)	Added footnote m	Clarification

Amendment 2 (10-May-2021)

Overall Rationale for the Amendment: The highest dose CCI and a loading dose have been removed from Part B based on the emerging pharmacodynamic data after repeated (Days 1, 8, 29, and 57) dosing of AZD8233 up to CCI in other AZD8233 studies (Study D7990C00002 and Study D7990C00003). Safety descriptions has been updated based on the emerging safety data. Changes to Clinical Study Protocol version 2.0 [13- Nov-2020] are summarised

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Part B)	Overall Design: Intervention Groups and Duration: Corrected the date for the end of screening period / Removed the dosing on Day8 / Removed the highest dose CCI / Revised number of randomized participants / Added the explanation of SRC	To correct the erroneous description / Not applicable to this study. / Revised number of randomized participants due to removal the highest dose. / SRC wording has been updated.
Section 1.2 Schema (Part B)	Removed the CCI arm / Added the footnote	Not applicable to this study/ Added the information in case of a change of the planned dose
Table 1 Schedule of Activities (Part A)	Corrected the participants of the pregnancy tests	All the women participants should have pregnancy tests ,irrespective of childbearing potential.
Table 1 Schedule of Activities (Part A)	Deleted measurement position of BP and pulse rate, and added the description of measurement position of BP and pulse rate in Footnote f	Clarification
Table 1 Schedule of Activities (Part A)	Footnote h: Added the allowance of blood samples.	Clarification
Table 1 Schedule of Activities (Part A)	Footnote o, p: Corrected the participants of the pregnancy tests	All the women participants should have pregnancy tests ,irrespective of childbearing potential.

Section # and Name	Description of Change	Brief Rationale
Table 2 Schedule of Activities (Part B)	Corrected the Screening period	To correct the erroneous description.
Table 2 Schedule of Activities (Part B)	Corrected the participants of the pregnancy tests	All the women participants should have pregnancy tests ,irrespective of childbearing potential.
Table 2 Schedule of Activities (Part B)	Removed the dosing on Day8	Not applicable to this study
Table 2 Schedule of Activities (Part B)	Added description about PK sample	Clarification
Table 2 Schedule of Activities (Part B)	Revised required the fasting hours	Adapted the standard of care treatment in Japan in accordance with the guideline for clinical evaluation of Dyslipidemia
Table 2 Schedule of Activities (Part B)	Footnote d: Specified the allowance of blood samples	Clarification
Table 2 Schedule pf Activities (Part B)	Footnote f: Removed description of “Visit 4(Day8)” and “Visit 4(Day8 ; Loading dose):pre-dose” from the schedule of sampling due to no administration on Day8/Removed description of Dose3 and Final Dose	Improvement of description/Improvement of description
Table 2 Schedule of Activities (Part B)	Footnote k , l: Corrected the participants of the pregnancy tests.	All the women participants should have pregnancy tests ,irrespective of childbearing potential.
Table 2 Schedule of Activities (Part B)	Added Footnote n	Clarification
Section 2.2 Background	Added the safety information from ongoing studies	Updated information

Section # and Name	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment (Table 3)	Liver Toxicity - Transaminase Elevation: Updated the result of toxicology study / added the safety data from ongoing studies Injection Site Reactions: Updated information Complement Activation: Added finding from the 9-month monkey study / Corrected as C3a (Part A only) Inhibition of Intrinsic Coagulation Pathway: Title of potential risk changed from 'Impaired Coagulation' to 'Inhibition of Intrinsic Coagulation Pathway' / Updated information Hypersensitivity and Anaphylactic Reaction: Newly added Flu-like Reactions: Title of potential risk changed from 'Systemic Inflammatory Effects' to 'Flu-like Reactions'/ Improvement of description	Updated information / Improvement of description / C3a assessment will be conducted in Part A only / Newly added
Section 2.3.2 Benefit Assessment	Removed the description of D7990C00002 andD7990C00003 studies	Removed
Section 3 Objectives and Endpoints Table 4 (Part A)	Exploratory: Removed 'serum'	Not applicable to this study
Section 4.1 Overall Design (Part B)	Removed the loading dose on Day8 and AZD8233 CCI SC	Not applicable to this study
Section 4.2 Scientific Rationale for Study Ddesign	Clarified the dosing schedule on Day8	Dosing on Day8 will be conducted in Part A only
Section4.3 Justification for Dose	Part A:Added the explanation of SRC Part B: Added the information of ongoing studies / Removed the loading dose on Day8	Part A: SRC wording has been updated. Part B: Updated information / Not applicable to this study
Section 5.1 Inclusion Criteria: Criterion 5 (Part A)	Improvement description	Unified description with Part B

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria: Criterion 13 (Part A)	Deleted the description of dECG parameters	Not applicable to this study
Section 5.2 Exclusion Criteria: Criterion 12, 13 (Part B)	Modified the measurement position of BP and pulse	Modified in accordance with procedure
Section 5.3.1 Meals and Dietary Restriction (Part B)	Revised required the fasting hours	Adapted the standard of care treatment in Japan in accordance with the guideline for clinical evaluation of Dyslipidemia
Section 6.1.1 Investigational Products	Added the description in case of a change of the planned dose	Added
Section 6.1.1 Investigational Products Table 5 (Part B)	Removed Day8 from Regimen / Removed CCI dose cohort and added footnote in cohort 1	Not applicable to this study / Added the information in case of a change of the planned dose
Section 6.5 Concomitant Therapy (Part A / Part B)	Added a note of administration of COVID-19 vaccines	Added guideline for participants on administrating COVID-19 vaccines
Section 7.1 Discontinuation of Study Intervention (Part A)	Added the explanation of SRC	SRC wording has been updated.
Section 8 Study Assessments and Procedures (Part B)	Corrected the screening period/Removed SC injection at Visit 4/Revised required the fasting hours/ Change the amount of blood	To correct the screening period/This is not applicable to Part B/Adapted the standard of care treatment in Japan in accordance with the guideline for clinical evaluation of Dyslipidemia/To update the latest information
Section 8 Study Assessments and Procedures (Part A)	General description of visits: Change the amount of blood	To update the latest information
Section 8.2.2 Vital Sings	Modified the description of measurement position of BP and pulse Added the description of procedure for pulse Added the description of resting conditions for measurement of BP and pulse	Clarification
Section 8.2.3 Electrocardiograms (Part A)	Corrected procedures for measurement when the 12-lead safety ECG time points coincide with the telemetry time points	Improvement of description

Section # and Name	Description of Change	Brief Rationale
Section 8.2.4 Clinical Safety Laboratory Assessments (Part A)	Added indirect bilirubin to Clinical Chemistry / Corrected the participants of the pregnancy tests (β-hCG and hCG)	Newly added / All the women participants should have pregnancy tests ,irrespective of childbearing potential
Section 8.2.4 Safety Laboratory Assessments (Part B)	Added indirect bilirubin LDH to Clinical Chemistry	Unified laboratory variable with Part A
Section 8.2.4 Clinical Safety Laboratory Assessments (Part B)	Corrected the participants of the pregnancy tests (β-hCG and hCG)	All the women participants should have pregnancy tests ,irrespective of childbearing potential.
Section 8.2.4 Clinical Safety Laboratory Assessments (Part B)	Other laboratory assessments Deleted C3a	Not applicable to Part B
Section 8.3.2 Follow-up of AEs and SAEs	SAEs: Added 'Description of AE'	Added
Section 8.5.1.1 Determination of Drug Concentration (Part B)	Urine sample for determination of AZD8233 of total full length ASOs concentrations is deleted	Correction
Section 8.5.2 Immunogenicity Assessments	Improvement of description	Improvement of description
Section9.2 Sample Size Determination (Part B)	Revised number of randomized participants	Revised number of randomized participants due to removal the highest dose
9.4.2.1 Primary Endpoint (s) (Part B)	Regarding pair-wise comparisons, revised the description from 'high' to 'mid'	Not applicable to Part B
Appendix A 3 Informed Consent Process	Clearly stated the timing of requirement to sign a new ICF for Part B study	Clarification
Appendix I Abbreviations	Added ' ISR '	Newly added
Section11 References	Improvement of description / Added 'Jacqmin P et al 2007'	Updated information / Newly added

Amendment 3 (02-Nov-2021)

Overall Rationale for the Amendment: Part C is planned to investigate the safety and tolerability of AZD8233CCI , following SC administration of multiple dose in a limited number of Japanese patients with dyslipiddemia before progressing to Ph3. Changes to Clinical Study Protocol version 3.0 [10- May-2021] are summarized.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial changes	To ensure consistency with the latest protocol template
1.1 Synopsis	Added "Part C" and "Part B" Short Title / Rationale / Objectives and Endpoints / Overall Design / Disclosure Statement / Number of Participants / Study Period / Intervention Groups and Duration /Data Monitoring Committee/ Safety Review Committee / Statistical Methods	Newly added "Part C study" / Added Data Monitoring Committee in Part B study
1.2 Schema	Figure 1 Study Design : Added "Part C"	Newly added "Part C study"
1.3 Schedule of Activities (Part B)	Pre-dose assessments time changed from within 30 minutes to 60 minutes.	Adapted the turnaround time
Table 2 Schedule pf Activities (Part B)	Complement activation panel: Removed Day8	Not applicable to Part B
1.3Schedule of Activities	Added "Part C"	Newly added "Part C study"
2.1 Study Rationale	Added "Part C"	Newly added "Part C study"
3 Objectives and Endpoints (Table 5)	Added "Part C"	Newly added "Part C study"
4.1 Overall Design	Added "Part C"	Newly added "Part C study"
4.2 Scientific Rationale for Study Design	Added "Part C"	Newly added "Part C study"
4.3 Justification for Dose	Added "Part C"	Newly added "Part C study"
4.4 End of Study Definition	Added "Part C"	Newly added "Part C study"
5 Study Population	Added description of procedure for handling incorrectly randomized participants	Clarification
5.1 Inclusion Criteria	Added "Part C"	Newly added "Part C study"
5.2 Exclusion Criteria	Added "Part C"	Newly added "Part C study"
5.3.1 Meals and Dietary Restrictions	Added "Part C"	Newly added "Part C study"

Section # and Name	Description of Change	Brief Rationale
5.3.2 Caffeine, Alcohol, and Tobacco	Added “Part C”	Newly added “Part C study”
6.1.1 Investigational Products（Table 6）	Added “Part C”	Newly added “Part C study”
6.3 Measures to Minimise Bias: Randomization and Blinding	Added “Part C”	Newly added “Part C study”
6.5Concomitant Therapy	Added “Part C”	Newly added “Part C study”
7.1 Discontinuation of Study Intervention	Added “Part C” / Added the explanation of iSMC for Part B	Newly added “Part C study” / Added iSMC in Part B study
8 Study Assessments and Procedures	Added “Part C” / Pre-dose assessments time changed from within 30 minutes to 60 minutes for Part B.	Newly added “Part C study” / Adapted the turnaround time
8.2.3 Electrocardiograms	Added “Part C”	Newly added “Part C study”
8.2.4 Clinical Safety Laboratory Assessments	Added “Part C”	Newly added “Part C study”
8.2.5 Other Screening Assessments	Added “Part C”	Newly added “Part C study”
8.5.1 Pharmacokinetics	Added “Part C”	Newly added “Part C study”
8.5.1.1 Determination of Drug Concentration	Added “Part C”	Newly added “Part C study”
8.5.2 Immunogenicity Assessments	Added “Part C”	Newly added “Part C study”
8.5.3.1 Collection of Samples （Table 7）	Added “Part C”	Newly added “Part C study”
8.7 Optional Genomics Initiative Sample	Added “Part C”	Newly added “Part C study”
9.1 Statistical Hypotheses	Added “Part C”	Newly added “Part C study”
9.2 Sample Size Determination	Added “Part C”	Newly added “Part C study”
9.4.2.2 Secondary Endpoint(s)	Added “Part C”	Newly added “Part C study”
9.4.3 Safety	Added “Part C”	Newly added “Part C study”
9.5 Interim Analyses	Deleted: CSR for Part B-IA	Not applicable to Part B-IA
9.6Data Monitoring Committee	Added “iSMC”	Newly added in Part B study

Section # and Name	Description of Change	Brief Rationale
Appendix A 3 Informed Consent Process	Added “Part C”	Newly added “Part C study”
Appendix A 5 Committees Structure	Added "Part B" and “Part C”	Added iSMC in Part B study and newly added “Part C study”

Amendment 4 (16-Jun-2022)

Overall Rationale for the Amendment: Deleted all mentions of SRC (Safety Review Committee) for Part C. Changes to Clinical Study Protocol version 4.0 [02- Nov-2021] are summarized.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Study Period: Estimated date of last patient completed was extended.	To consider the period of ADA positive participants follow-up
1.1 Synopsis	Safety Review Committee (SRC): Removed SRC from Part C.	Not applicable to Part C
Table 1 Schedule of Activities (Part A)	Corrected the corresponding section number of Medical History.	Correction
Table 3 Schedule of Activities (Part C)	Corrected a duplicate visit number (English version only) / Corrected the corresponding section number of Medical History.	Correction
6.1.1 Investigational Products Table 6 (Part B)	Footnote *: Corrected a unit of the strength (Japanese version only)	Correction
6.3 Measures to Minimise Bias: Randomization and Blinding	[Part A/Part B] Corrected as the SRC(Part A only)	Not applicable to Part C
7.1 Discontinuation of Study Intervention	Removed Part C from SRC	Not applicable to Part C
8.2.4 Clinical Safety Laboratory Assessments	Central Laboratory name changed from COVANCE to Labcorp	To keep consistency as vendor legal name changed during course of the study
8.5.1.1 Determination of Drug Concentration	Central Laboratory name changed from COVANCE to Labcorp	To keep consistency as vendor legal name changed during course of the study

Section # and Name	Description of Change	Brief Rationale
9.6 Data Monitoring Committee	Appendix reference letter that was missing has been included (English version only)	Typo correction
Appendix A 5 Committees Structure	Removed Part C from SRC	Not applicable to Part C

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 1 and 2 study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of AZD8233 following a multiple subcutaneous dose administration in Japanese participants with dyslipidemia

Short Title:

A Phase 1/2 Study of AZD8233 in Participants with Dyslipidemia

This study consists of Part A ,Part B and Part C.

[Part A]

Part A is designed as a randomized, single-blind (blinding of participants and sites), placebo-controlled, multiple dose, phase 1 study.

Approximately 11 Japanese participants will be randomized in an 8:3 ratio into 1 of the 2 single-blinded treatment arms; AZD8233 CCI or placebo.

[Part B]

Part B is designed as a randomized, double-blind, placebo-controlled, dose-ranging, phase 2 study.

Approximately 60 Japanese participants will be randomized in a 1:1:1 ratio into 1 of the 3 double-blinded treatment arms; AZD8233 CCI , AZD8233 CCI , or placebo.

[Part C]

Part C is designed as a randomized, single-blind (blinding of participants and sites), placebo-controlled, multiple dose, phase 1 study.

Approximately 11 Japanese participants will be randomized in an 8:3 ratio into 1 of the 2 single-blinded treatment arms; AZD8233 CCI or placebo.

Rationale:

[Part A]

In the Phase 1, a single ascending dose (SAD) study that has been conducted in the US, single subcutaneous (SC) doses of up to CCI AZD8233 have been well tolerated in healthy male participants with moderately elevated Low-density Lipoprotein Cholesterol (LDL-C). A

single SC dose of CCI AZD8233 has been administered to healthy subjects of Japanese origin, and no clinically important safety findings have been reported.

In the US, the Phase 1, a multiple ascending dose (MAD) study, is being conducted to assess the safety and tolerability of AZD8233 and to characterize the pharmacokinetic (PK) profile of AZD8233, following SC administration of multiple ascending doses of AZD8233 in 33 participants with dyslipidemia. The study is also assessing the pharmacodynamics (PD) of AZD8233 by investigating the effect of AZD8233 on levels of LDL-C and proprotein convertase subtilisin/kexin type 9 (PCSK9) following SC administration of ascending doses of AZD8233.

The dose to be evaluated in Part A is CCI This is the highest dose that has been evaluated in the MAD study conducted in the US. A dose of CCI monthly is expected to result in close to the maximum achievable reduction in PCSK9 as well as LDL-C levels over the dose interval with AZD8233.

According to the Japanese Guideline for General Considerations for Clinical Trials (International Council for Harmonisation [ICH]-E8, June 1995), patients who have mild hyperlipidaemia alone are permitted to be included in phase I studies of investigational products for hyperlipidaemia.

Therefore, dyslipidaemic patients with a moderately increased LDL-C will be selected for Part A of the study.

The objective of the study is to investigate the safety and tolerability of AZD8233, following SC administration of multiple doses in a limited number of Japanese participants with dyslipidemia before progressing to Part B, where a larger number of participants will be exposed. The study will also investigate the PK and the PD of AZD8233.

[Part B]

Part B is planned to evaluate LDL-C reduction at steady state at different doses of AZD8233.

[Part C]

The objective of the study is to investigate the safety and tolerability of AZD8233 with dosing regimen to be used in phase 3 study, following SC administration of multiple doses in a limited number of Japanese participants with dyslipidemia before progressing to Ph3. The study will also investigate the PK and the PD of AZD8233.

Objectives and Endpoints

[Part A/Part C]

Objectives	Estimands descriptions/Endpoints
Primary	
To assess the safety and tolerability of AZD8233 following SC administration of multiple doses.	Adverse events; vital signs, ECG, cardiac telemetry, injection site reaction examinations and clinical laboratory evaluations including platelet count
Secondary	
To characterize the PK of AZD8233 following SC administration of multiple doses.	Plasma parameters (t_{lag}, t_{max}, Cmax, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}48)}$, AUC, AUCτ, C_{trough}, CL/F, Vz/F, $t_{1/2}$, MRT); urine parameters (Ae, Fe, CLR)
To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.	Absolute change from baseline in log-transformed PCSK9 in plasma Percent change from baseline in PCSK9 in plasma
To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.	Percent change from baseline in levels of LDL-C in serum
To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.	Levels of other lipid parameters, including: • Total cholesterol (TC) • High-density lipoprotein cholesterol (HDL-C) • Non-HDL-C • Very-low-density lipoprotein cholesterol (VLDL-C) • Apolipoproteins (Apo) A1 • ApoB • Lp(a) • Triglycerides

Ae = amount excreted in urine; apoB = apolipoprotein B; AUC = area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}last)}$ = area under the plasma concentration-curve from time zero to time last value above the limit of quantification; $AUC_{(0\text{-}48)}$ = area under the plasma concentration-time curve from time zero to 48 hours after dosing; AUCτ = area under the plasma concentration-time curve from time during the dosing interval; CL_R = renal clearance; CL/F = apparent total body clearance of drug from plasma after extravascular administration; Cmax = Observed maximum plasma concentration; C_{trough} = observed trough plasma drug concentration; Fe = fraction excreted unchanged in urine; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MRT = mean residence time of the unchanged drug in the systemic circulation; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; SC = subcutaneous; t_{max} = time to reach peak or maximum observed concentration or response following drug administration; t_{lag} = time delay between drug administration and the first observed concentration in plasma; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration

[Part B]

Objectives	Estimands descriptions/Endpoints
Primary	
To assess the effect of different doses of AZD8233 on LDL-C versus placebo	Absolute change from baseline in log-transformed LDL-C in serum
Secondary	
To assess the effect of different doses of AZD8233 on PCSK9 versus placebo.	Absolute change from baseline in log-transformed PCSK9 in plasma Percent change from baseline in PCSK9 in plasma
To assess the effect of different doses of AZD8233 on LDL-C versus placebo.	Percent change from baseline in levels of LDL-C in serum
To assess the effect of AZD8233 on other lipid parameters versus placebo	Levels of other lipid parameters including: • TC • HDL-C • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Triglycerides • Remnants cholesterol
To evaluate PK of AZD8233.	Population PK parameters
To evaluate the immunogenicity of AZD8233.	Development of antidrug antibodies (ADA) and ADA titer (if subjects are ADA positive) during treatment and follow-up.
Safety	
To assess the safety and tolerability of AZD8233.	Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, injection site reactions, and clinical laboratory evaluations, including platelet count.

AE = adverse event; ApoA1= apolipoprotein A1; ApoB = apolipoprotein B; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); PK = pharmacokinetics; TC = Total cholesterol; VLDL-C = Very-low-density lipoprotein cholesterol

For Exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol.

Overall Design

This study is composed of three parts, two for the preliminary safety assessment (Part A/Part C) and the other for the main randomized dose ranging study (Part B).

[Part A/Part C]

These are each randomized, single-blind, placebo-controlled, multiple dose Phase 1 study parts, including approximately 11 participants with dyslipidemia in each part. The primary objective of the study is to assess the safety and tolerability of AZD8233 following a multiple SC administration in Japanese patients with dyslipidemia. The study will be conducted at up to 2 sites in Japan.

The Screening Period starts within 28 days before the randomization visit and ends on Day −4. Eligible participants will make 8 visits during the treatment period and 8 additional visits during the follow-up period. They are randomized across 2 different treatment arms in an 8:3 ratio for a 58-day (up to Visit 9) treatment period. The planned treatment arms are AZD8233 CCI (Part A) / AZD8233 CCI (Part C) and placebo. Participants will be dosed subcutaneously on Days 1, 8 (Part A only) , 29, and 57.

[Part B]

This is a randomized parallel, double-blind, placebo-controlled, dose-ranging Phase 2 study part in approximately 60 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD8233 on LDL-C across different dose levels. The study will be conducted at approximately 6 sites in Japan.

The screening period starts within 28 days before the randomization visit and ends on Day −4. Eligible participants will make 7 visits during the treatment period and 7 additional visits during the follow-up period. They are randomized across 3 different treatment arms in a 1:1:1 ratio for a 12-week treatment period. The planned treatment arms are AZD8233 CCI AZD8233 CCI , and placebo. Participants will be dosed subcutaneously on Days 1, 29, and 57.

Disclosure Statement:

[Part A/Part C]

This study is single-blind with regards to treatment (AZD8233 or placebo), and blinded to the participants, site investigators, and site staff. The Sponsor will be unblinded to treatment allocation.

[Part B]

This is a parallel group treatment study in 3 arms with participants, investigators and the sponsor blinded.

Number of Participants:

[Part A/Part C]

Approximately 11 participants will be randomly assigned to the 2 study arms in each part.

[Part B]

Approximately 60 participants will be randomly assigned to the 3 study arms.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Study Period:

[Part A/Part B/Part C]

Estimated date of first patient enrolled: Q4 2020

Estimated date of last patient completed: Q4 2023

Intervention Groups and Duration:

[Part A/Part C]

The screening period starts up to 28 days before the randomization visit and ends on Day −4. Eligible participants will make 8 visits during the treatment period and 8 additional visits during the follow-up period. They are randomized across 2 different treatment arms at an 8:3 ratio for a 58-day (up to Visit 9) treatment period. The planned treatment arms are AZD8233 CCI (Part A) / AZD8233 CCI (Part C) and placebo. Participants will be dosed subcutaneously on Days 1, 8 (Part A only), 29, and 57.

[Part B]

The screening period starts up to 28 days before the randomization visit and ends on Day −4. Eligible participants will make 7 visits during the treatment period and 7 additional visits during the follow-up period. They are randomized across 3 different treatment arms at a 1:1:1 ratio for a 12-week treatment period. The planned treatment arms are: AZD8233 CCI AZD8233 CCI, and placebo. Participants will be dosed subcutaneously on Days 1, 29, and 57.

Data Monitoring Committee:

An internal Safety Monitoring Committee will be used for monitoring of unblinded safety data in Part B.

Safety Review Committee (SRC):

After data are collected from all the participants in Part A until Day 64 (7 days after the last dose), the Safety Review Committee (SRC) will be held to make a decision to initiate the Part B. The data from all participants must be reviewed before that. Data later than Day 64 (if available) may be reviewed by the SRC as needed. Depending on the results, the SRC may decide not to proceed with the Part B.

The SRC meetings will be prepared and conducted in a blinded manner to keep all attendees blinded prior to and during the meetings. Required personnel involved in PD and PK evaluations of data (if available) may be unblinded for the evaluation of these data. Alternatively, PK and PD data will be provided in a blinded manner for the SRC review. Separate unblinded SRC meetings may also be held as needed.

The Part B will be put on temporary hold if any of the following criteria occurs in participants receiving AZD8233:

- At least one serious adverse event (SAE) considered at least possibly related to the Investigational Medicinal Product (IMP) administration.
- At least one severe non-serious AEs considered as, at least, possibly related to the IMP administration) in ≥ 2 participants, independent of within or not within the same system organ class.

The SRC will carefully review the totality of data, taking into account moderate non-serious AEs at least possibly related to the IMP administration and their relations to PD effects (if available), the number of subjects in whom the non-serious AEs occur, concurrency of more than 1 AE within the same subject and potential safety signals identified with the other IMPs in the same class (mechanistic and/or chemical). The SRC will also consider differences between Part A and Part B, including but not limited to dosing regimen, as well as available overall safety and PK/PD conclusions from other AZD8233 studies (including Study D7990C00002 and Study D7990C00003).

Further information on blinding, SRC data review requirements, and SRC process will be included in a separate SRC Charter document.

Statistical Methods

[Part A/Part C]

The primary objective of Parts A and C is to assess safety in Japanese dyslipidaemic participants after multiple dosing of AZD8233. Safety data will be descriptively summarized with regard to AEs (including SAEs), laboratory parameters, vital signs and ECGs, cardiac telemetry, and injection site reactions.

[Part B]

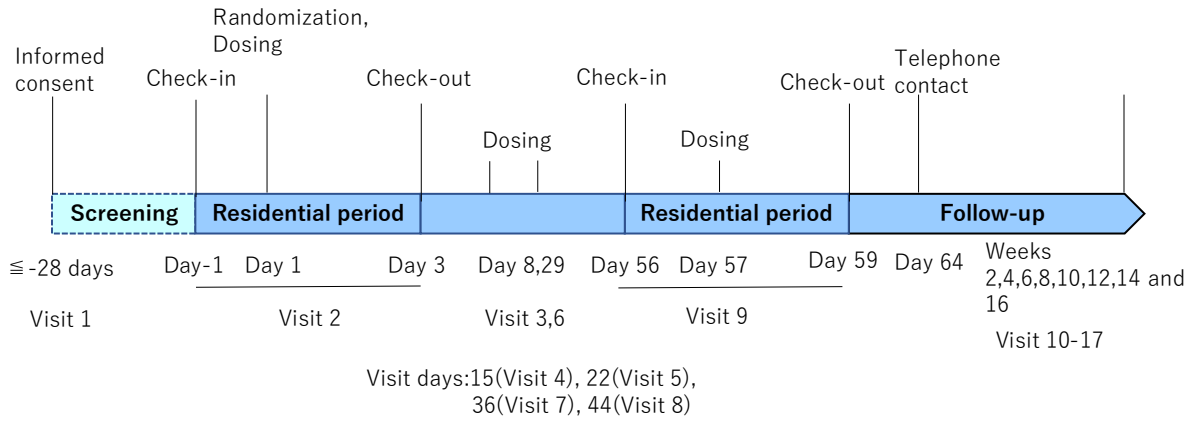
The primary objective of Part B is to compare absolute changes from baseline in log-transformed LDL-C across different dose levels of AZD8233. The key secondary objective of this study is to compare absolute changes from baseline in log-transformed PCSK9 across different dose levels of AZD8233. Both log-transformed LDL-C and log-transformed PCSK9 will be analysed by fitting a mixed model for repeated measures to the data with baseline as covariate and treatment, time (visit number), and interaction between treatment and time as factors. The participants will be analysed according to the treatment to which the participants were randomised. Participants will be analysed with respect to the intention to treat principle using the full analysis set which contains data from each participant who receives at least one dose of placebo or AZD8233.

Key safety objective is overall tolerability, which will be presented with descriptive statistics.

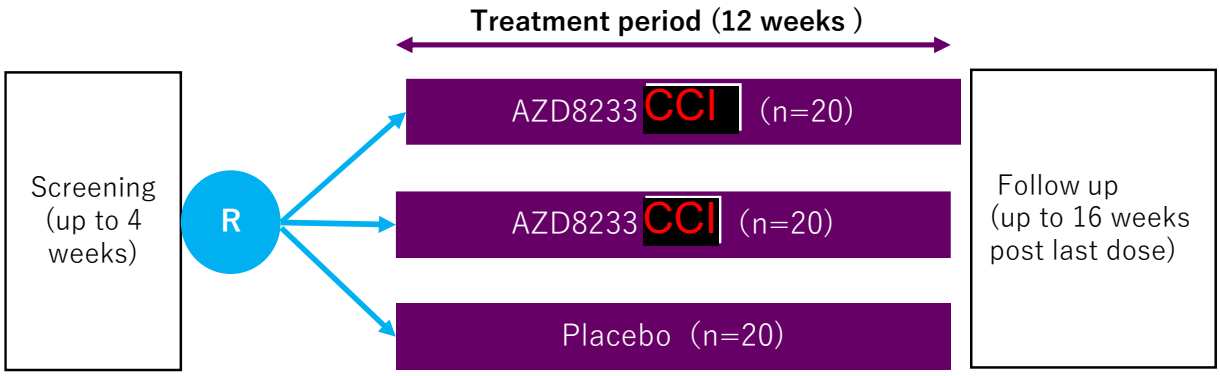
1.2 Schema

Figure 1 Study Design

[Part A]



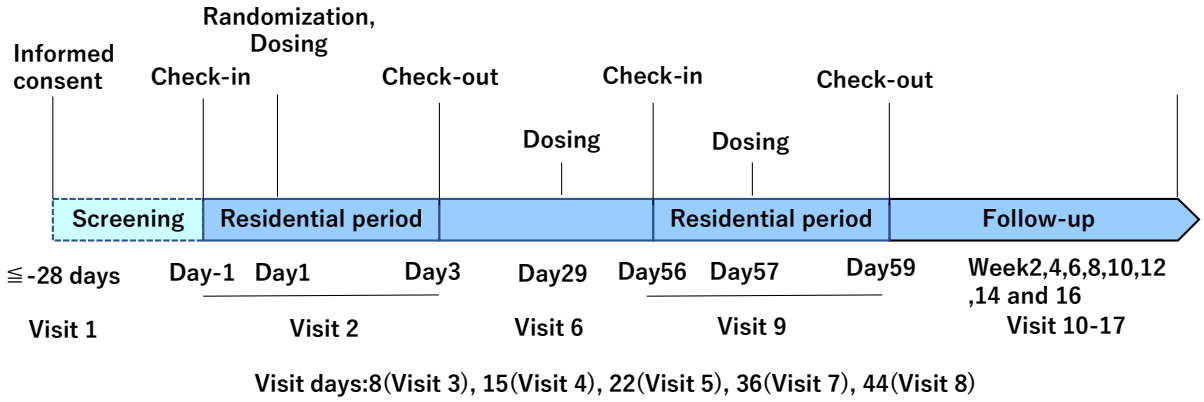
[Part B]



R = randomisation

*In case of a change of the planned dose, the investigational product dose may be used CCI (not exceeding CCI)

[Part C]



1.3 Schedule of Activities

[Part A]

Randomization should only proceed if all required assessments have been performed and all inclusion/exclusion criteria as well as other protocol restrictions have been evaluated; see Sections 5 and 6.5.

Dosing should only be carried out for participants if all required assessments have been performed and evaluated. Dosing is not allowed to proceed until the Investigator has determined that the results are within acceptable range according to the defined stopping criteria. Laboratory assessment results should also be reviewed at every visit to ensure that stopping criteria have not been met.

Assessments scheduled to be done at the same time may be initiated based on the sequence below:

1 ECGs
2 Vital signs (Systolic Blood Pressure [SBP] and Diastolic Blood Pressure [DBP]), pulse rate, and temperature, if appropriate
3 Blood sampling
4 Dose administration

Pre-dose assessments may be performed within 30 minutes prior to dosing.

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact** [k]	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8**[a]**, 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Informed consent	X										Appendix A 3
Inclusion/exclusion criteria[b]	X	X									Sections 5.1, 5.2
Demographic data	X										Section 9.4.1
Weight and height (BMI) [c]	X	X					X (Day 57)			X	Section 8.2.1
Medical history	X										Section 8
Concomitant medication	X	X	X	X	X	X	X	X	X	X	Section 6.5
Drug abuse and alcohol screen [d]	X					X					Section 5.3.2, 5.2
Smoking history	X										Section 5.3.2

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Viral serology [e]	X										Section 8.2.5
Pregnancy test (females only)	X [o]		X [p]								Section 8.2.4
Pregnancy and reproductive status (females only[q])	X										Section 8.2.4
Randomisation			X (Day 1)								Section 6.3
Study residency											
Check-in		X				X					Figure 1
Check-out			X (Day 3 [l])				X (Day 59)				Figure 1

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
IMP administration			X (Day 1)	X			X (Day 57)				Figure 1, Section 6.1.1
Safety and tolerability											
Adverse event questioning (including collection of data for injection site reactions)	X (only SAEs)	X (only SAEs)	X	X	X	X	X	X	X	X	Section 8.3
Physical examination	X (complete)	X (abbre−viated)	X (abbreviated; pre-dose and then 24 and 48 h post-dose)	X (abbre-viated; pre-dose)			X (abbreviated; 24 h post-dose)		X (abbreviated)	X (complete)	Section 8.2.1

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Blood pressure and pulse rate [f]	X	X	X (pre-dose and then 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)		X	X	Section 8.2.2
Body temperature		X	X (pre-dose)	X (pre-dose)			X (pre-dose)		X	X	Section 8.2.2
12-lead safety ECG [g]	X		X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)		X	X	Section 8.2.3

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Cardiac telemetry		X (for at least 4 h)	X (pre-dose to 24 h post-dose)				X (pre-dose to 24 h post-dose)				Section 8.2.3
Hematology, Chemistry and Coagulation including hs-CRP)	X	X	X (24 h post-dose)	X (pre-dose)			X (pre-dose)		X (Week 2, 4, 8 and 12 after last dose)	X	Section 8.2.4
Sampling for renal safety biomarkers	X		X (pre-dose and then 24 and 48 h post-dose)	X (pre-dose)			X (pre-dose)				Section 8.2.4

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact** [k]	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8**[a]**, 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Sampling for dipstick urinalysis for hematuria	X		X (pre-dose and then 24 and 48 h post-dose)	X (pre-dose)			X (pre-dose)				Section 8.2.4
Sampling for platelet count	X	X	X (24 and 48 h post-dose)	X (pre-dose)	X (Days 22, 44)	X			X	X	Section 8.2.4
Complement activation panel [h]			X (pre-dose and then 1, 2 and 4 h post-dose)				X (pre-dose and then 1, 2 and 4 h post-dose)				Section 8.2.4

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Immunogenicity											
Samples for anti-AZD8233 antibodies			X (pre-dose)	X (Day 29 pre-dose)			X (pre-dose)		X (Week 2 after last dose)	X	Section 8.5.2
Pharmacodynamics											
Blood sampling for LDL-C and PCSK9	X [m,]	X [m]	X [m] (pre-dose and then 48 h post-dose)	X [m, n] (pre-dose)	X [m, n]		X [m] (pre-dose and then 24 h post-dose)		X [m]	X [n]	Section 8.5.3.1
Blood sampling for other lipid parameters	X [m]	X [m]	X [m] (pre-dose and then 48 h post-dose)	X [m, n] (pre-dose)	X [m, n]		X [m] (pre-dose and then 24 h post-dose)		X [m]	X [m]	Section 8.5.3.1

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact [k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Exploratory biomarker sampling											
Plasma and urine samples to be stored in the Biobank until further analysis [i]			X (pre-dose)	X (pre-dose)			X (pre-dose)		X (Weeks 2 and 4 after last dose)	X	Section 8.6.1
Pharmacokinetics											
Plasma for AZD8233 and total full length ASOs of AZD8233 [j]			X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post dose)	X (pre-dose)	X		X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post dose)		X	X	Section 8.5.1

Table 1 Schedule of Activities (Part A)

	Screening	Treatment Period						Follow-up Period			Corresponding Section in Protocol
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact** [k]	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8**[a]**, 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**	
Urine for total full length ASOs of AZD8233			X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)				X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)				Section 8.5.1

ASO: Antisense oligonucleotides; BMI = body mass index; ET = early termination; FSH = follicle-stimulating hormone; hs-CRP = high sensitive C-reactive protein; IMP: Investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; PCSK9 = proprotein convertase subtilisin/kexin type-9; SAE: Serious adverse event

Participants are required to be fasted for at least 10 hours overnight prior to all study visits except for Visit 1 (only for the purpose of signing his/her informed consent); subjects are permitted to drink water during this period of fasting until 1 hour before blood sampling. On days when subjects attend the clinic in a fasting state, blood and urine samples should be obtained prior to administration of IMP.

[a] Day 8: no allowances.

[b] The eligibility check should be based on all clinical measurements and blood tests taken during the screening visit (Visit1).

[c] At Visit 1 and on Day −1, BMI be calculated. For Day −1, the height measured on Visit 1 will be utilised. At all other time points, only weight will be measured.

[d] Drugs of abuse and alcohol screen: Investigator will interview participants regarding their use of drugs and alcohol.

[e] Samples for HIV should be tested at a local laboratory.

[f] Allowances: pre-dose (up to 30 minutes prior to dosing) and then 0.25 h (± 2 minutes), 0.5 h (± 10 minutes), 1 h (± 10 minutes), 1.5 h (± 10 minutes), 2 h (± 15 minutes), 2.5 h (±15 minutes), 3 h (±15 minutes), 4 h (± 15 minutes), 6 h (± 15 minutes) , 8 h (± 15 minutes), 12 h (± 30 minutes), 24 h (± 1 hour), 36 h (± 1 hour) and 48 h (±1 hour) post-dose. Screening and Day-1: Sitting position, Day1 to Follow-up Period (Final Follow-up Visit / EDV); Supine position.

[g] Allowances: pre-dose (up to 30 minutes prior to dosing) and then 0.5 h (±10 minutes), 1 h (± 10 minutes), 2 h (±15 minutes), 3 h (±15 minutes), 4 h (±15 minutes), 6h (±15 minutes), 8 h (±15 minutes), 12 h (±30 minutes), 24 h (± 1 hour), 36 h (±1 hour) and 48 h (±1 hour) post-dose

[h] Blood samples for complement activation panel will be collected pre-dose(up to 30 minutes prior to dosing), and 1(±5 minutes), 2(±5 minutes) and 4 h (±10 minutes) post-dose so that the samples can be taken around C_{max}.

[i] Plasma and urine samples for biobanking must be collected at the same hour every morning after an overnight (10-hour) fast.

[j] allowance; pre-dose (up to 30 minutes prior to dosing) and then 0.5 h (±2 minutes), 1 h (±5 minutes), 1.5 h (±5 minutes), 2 h (±5 minutes), 2.5 h (±5 minutes), 3 h (±10 minutes), 4 h (±10 minutes), 5 h (±10 minutes), 6 h (± 10 minutes), 8 h (±10 minutes), 10 h (± 30 minutes), 12 h (± 30 minutes), 24 h (± 1 hour), 36 h (± 1hour) and 48 h (± 1 hour) post dose

[k] Telephone contact: A site or investigator will call participants to assess AEs.

[l] Participants will be discharged after the results from the 48 h post-dose assessments have been reviewed by the Investigator.

[m] The sample should be taken in a fasting state in the morning (after a 10 hour fasting) at approximately the same time point as the pre-dose sample on Day 1

[n] Sampling to be done at approximately the same time points on the days of dosing (pre-dose) as on the non-dosing days (in the morning).

[o] Pregnancy test: Serum β-human chorionic gonadotropin (β-hCG) will be performed on all the women participants , irrespective of childbearing potential.

[p] Pregnancy test (Day1): Urine pregnancy test using dipstick will be performed before randomization on all the women participants , irrespective of childbearing potential at a local laboratory

[q] All the women participants should have FSH and LH levels determined, irrespective of childbearing potential.

[Part B]

Randomization should only proceed if all required assessments have been performed and all inclusion/exclusion criteria as well as other protocol restrictions have been evaluated; see Sections 5 and 6.5.

Dosing should only be carried out for participants if all required assessments have been performed and evaluated. Dosing is not allowed to proceed until the Investigator has determined that the results are within acceptable range according to the defined stopping criteria. Laboratory assessment results should also be reviewed at every visit to ensure that stopping criteria have not been met.

Assessments scheduled to be done at the same time may be initiated based on the sequence below:

1 Electrocardiogram (ECG)
2 Vital signs (SBP and DBP), pulse rate, and temperature, if appropriate
3 Blood sampling
4 Dose administration

Pre-dose assessments may be performed within 60 minutes prior to dosing.

Table 2 Schedule of Activities (Part B)

	Screening		Treatment Period							EDV	Follow-up period[n]	Final Follow-up Visit[n]	Corre-sponding Section in Protocol
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10, 11, 12, 13, 14, 15**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**Days −28 to −10**	**Days −7 to −4**	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**		**Days 85, 99, 113, 127, 141, 155**	**Day 169**	
Visit Window				**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Informed consent	X												Appendix A 3
Optional informed consent for future genetic research sample	X												Appendix D
Verify eligibility criteria	X		X[i]										Sections 5.1, 5.2
Enrolment	X												Sections 6.3, 8
Randomisation			X										Sections 6.3, 8
Medical history	X												Section 8
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Demographics	X												Section 9.4.1
Height	X												
Body weight[a]	X		X		X		X			X	X	X	Section 8.2.1
BMI	X									X		X	Section 8.2.1

Table 2 Schedule of Activities (Part B)

	Screening		Treatment Period							EDV	Follow-up period[n]	Final Follow-up Visit[n]	Corre-sponding Section in Protocol
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10, 11, 12, 13, 14, 15**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**Days −28 to −10**	**Days −7 to −4**	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**		**Days 85, 99, 113, 127, 141, 155**	**Day 169**	
Visit Window				**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
HbA1c	X												Section 8.2.5
Alcohol and smoking history	X	X											
Viral serology	X												Section 8.2.5
Pregnancy test (females only)	X[k]		X[l]										Section 8.2.4
Pregnancy and reproductive status (females only[m])	X												Section 8.2.4
IMP administration (AZD8233/Placebo)			X			X		X					Section 6.1.1
Safety Assessments													
Adverse event review	X (SAEs Only)	X (SAEs Only)	X	X	X	X	X	X	X	X	X	X	Section 8.3
Injection site reactions [b]			X	X	X	X	X	X	X	X	X	X	Section 8.2.6
Physical examination (complete)	X		X							X		X	Section 8.2.1
Physical examination (abbreviated)				X	X	X	X	X	X		X		Section 8.2.1

Table 2 Schedule of Activities (Part B)

	Screening		Treatment Period							EDV	Follow-up period[n]	Final Follow-up Visit[n]	Corresponding Section in Protocol
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10, 11, 12, 13, 14, 15**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**Days −28 to −10**	**Days −7 to −4**	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**		**Days 85, 99, 113, 127, 141, 155**	**Day 169**	
Visit Window				**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Vital signs (blood pressure, pulse and temperature) [c]	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.2
12-lead ECG [c]	X		X	X		X		X		X	X[j]	X	Section 8.2.3
Serum chemistry	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Hematology	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Coagulation parameters	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
hs-CRP	X		X					X		X	X	X	Section 8.2.4
Complement activation panel [d]			X			X		X					Section 8.2.4
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Urine renal safety biomarkers	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Pharmacodynamics													
LDL-C [e]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
PCSK9 [e]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1

Table 2 Schedule of Activities (Part B)

	Screening		Treatment Period							EDV	Follow-up period[n]	Final Follow-up Visit[n]	Corre-sponding Section in Protocol
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10, 11, 12, 13, 14, 15**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**Days −28 to −10**	**Days −7 to −4**	**Day 1**	**Day 8**	**Day 22**	**Day 29**	**Day 43**	**Day 57**	**Day 71**		**Days 85, 99, 113, 127, 141, 155**	**Day 169**	
Visit Window				**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Triglycerides [e]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
Other lipid parameters [e]			X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
Pharmacokinetics													
Plasma sample for total full length ASOs of AZD8233 [f]				X		X	X	X	X	X	X [f]	X	Section 8.5.1
Immunogenicity													
Samples for anti-AZD8233 antibodies [g]			X	X		X		X		X	X [g]	X	Section 8.5.2
Exploratory biomarker analysis													
Biomarker analyses (plasma) [e]	X		X	X	X	X	X	X	X	X	X	X	Section 8.6.1
Biomarker analyses (urine) [e]			X	X	X	X	X	X	X	X	X	X	Section 8.6.1
Genomics Initiative optional, exploratory genetic sample [h]			X										Section 8.7

ADA = antidrug antibody; BMI = body mass index; D = day; ECG = electrocardiogram; EDV = early discontinuation visit; FSH = follicle-stimulating hormone; HbA1c = haemoglobin A1c; hs-CRP = high sensitive C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; PCSK9 = proprotein convertase subtilisin/kexin type-9; PK = pharmacokinetic; IMP = Investigational medicinal product

Subjects are required to be fasted for at least 10 hours overnight prior to all study visits except for Visit 1; subjects are permitted to drink water during this period of fasting until 1 hour before blood sampling. On days when subjects attend the clinic in a fasting state, blood and urine samples should be obtained prior to administration of the IMP.

Samples to be obtained from all treatment arms unless specified in the table.

[a] Weight should be measured in light indoor clothes, without shoes, after using the bathroom. Otherwise, follow the local standard procedure.

[b] Injection Site Reaction assessments to be collected based on adverse event collection criteria.

[c] Vital signs and ECG to be measured pre-dose on dosing days.

[d] Blood samples for complement activation panel will be taken around C_{max} and are to be collected pre-dose and 2 hours (±5 minutes) post-dose.

[e] Samples to be obtained pre-dose on dosing days.

[f] PK sampling to be performed at Visits 4 (Day 8), 6 (Day 29), 7 (Day 43), 8 (Day 57), 9 (Day 71), 10 (Day 85), 12 (Day 113), 14 (Day 141), and final follow-up visit/EDV. Schedule of sampling for Visit 6 (Day 29), 8 (Day 57) is shown below.
Visit 6 (Day 29): pre-dose, Visit 8 (Day 57): pre-dose.

[g] ADA sampling to be performed at Visits 3 (D 1), 4 (D 8), 6 (D 29), 8 (D 57), 10 (D 85), 12 (D 113), 14 (D 141), and final follow-up visit/EDV. ADA samples to be collected pre-dose on all dosing days.

[h] If, for any reason, the sample is not drawn pre-dose on Visit 3 (Day 1), it may be taken at any visit until the final follow-up/EDV visit.

[i] Check screening labs and inclusion/exclusion criteria.

[j] ECG to be performed during the follow-up period at Visits 10 (Day 85), 11 (Day 99), 13 (Day 127), and 15 (Day 155).

[k] Pregnancy test: Serum β-human chorionic gonadotropin (β-hCG) will be performed on all the women participants , irrespective of childbearing potential.

[l] Pregnancy test (Day1): Urine pregnancy test using dipstick will be performed before randomization on all the women participants , irrespective of childbearing potential. at a local laboratory.

[m] All the women participants should have FSH and LH levels determined, irrespective of childbearing potential.

[n] In the case of early discontinuation, follow-up visit will be performed every 2 weeks after last dose.

[Part C]

Randomization should only proceed if all required assessments have been performed and all inclusion/exclusion criteria as well as other protocol restrictions have been evaluated; see Sections 5 and 6.5.

Dosing should only be carried out for participants if all required assessments have been performed and evaluated. Dosing is not allowed to proceed until the Investigator has determined that the results are within acceptable range according to the defined stopping criteria. Laboratory assessment results should also be reviewed at every visit to ensure that stopping criteria have not been met.

Assessments scheduled to be done at the same time may be initiated based on the sequence below:

1 ECGs
2 Vital signs (Systolic Blood Pressure [SBP] and Diastolic Blood Pressure [DBP]), pulse rate, and temperature, if appropriate
3 Blood sampling
4 Dose administration

Pre-dose assessments may be performed within 30 minutes prior to dosing.

Table 3 Schedule of Activities (Part C)

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Informed consent	X										Appendix A 3
Inclusion/exclusion criteria[b]	X	X									Sections 5.1, 5.2
Demographic data	X										Section 9.4.1
Weight and height (BMI) [c]	X	X						X (Day 57)		X	Section 8.2.1
Medical history	X										Section 8
Concomitant medication	X	X	X	X	X	X	X	X	X	X	Section 6.5
Drug abuse and alcohol screen [d]	X						X				Section 5.3.2, 5.2
Smoking history	X										Section 5.3.2

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Viral serology [e]	X										Section 8.2.5
Pregnancy test (females only)	X [n]		X [o]								Section 8.2.4
Pregnancy and reproductive status (females only[p])	X										Section 8.2.4
Randomisation			X (Day 1)								Section 6.3
Study residency											
Check-in		X					X				Figure 1
Check-out			X (Day 3 [k])					X (Day 59)			Figure 1
IMP administration			X (Day 1)		X			X (Day 57)			Figure 1, Section 6.1.1

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Safety and tolerability											
Adverse event questioning (including collection of data for injection site reactions)	X (only SAEs)	X (only SAEs)	X	X	X	X	X	X	X	X	Section 8.3
Physical examination	X (complete)	X (abbre – viated)	X (abbreviated; pre-dose and then 24 and 48 h post-dose)	X (abbre-viated)	X (abbre-viated; pre-dose)			X (abbreviated; 24 h post-dose)	X (abbreviated)	X (complete)	Section 8.2.1

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Blood pressure and pulse rate [f]	X	X	X (pre-dose and then 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X	X	Section 8.2.2
Body temperature		X	X (pre-dose)	X	X (pre-dose)			X (pre-dose)	X	X	Section 8.2.2
12-lead safety ECG [g]	X		X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose)	X	X	Section 8.2.3

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Cardiac telemetry		X (for at least 4 h)	X (pre-dose to 24 h post-dose)					X (pre-dose to 24 h post-dose)			Section 8.2.3
Hematology, Chemistry and Coagulation including hs-CRP)	X	X	X (24 h post-dose)	X	X (pre-dose)			X (pre-dose)	X (Week 2, 4, 8 and 12 after last dose)	X	Section 8.2.4
Sampling for renal safety biomarkers	X		X (pre-dose and then 24 and 48 h post-dose)	X	X (pre-dose)			X (pre-dose)			Section 8.2.4

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Sampling for dipstick urinalysis for hematuria	X		X (pre-dose and then 24 and 48 h post-dose)	X	X (pre-dose)			X (pre-dose)			Section 8.2.4
Sampling for platelet count	X	X	X (24 and 48 h post-dose)	X	X (pre-dose)	X (Days 22, 44)	X		X	X	Section 8.2.4
Complement activation panel [h]			X (pre-dose and then 1, 2 and 4 h post-dose)					X (pre-dose and then 1, 2 and 4 h post-dose)			Section 8.2.4
Immunogenicity											
Samples for anti-AZD8233 antibodies			X (pre-dose)		X (pre-dose)			X (pre-dose)	X (Week 2 after last dose)	X	Section 8.5.2

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Pharmacodynamics											
Blood sampling for LDL-C and PCSK9	X[l]	X[l]	X[l] (pre-dose and then 48 h post-dose)	X[l,m]	X[l, m] (pre-dose)	X[l, m]		X[l] (pre-dose and then 24 h post-dose)	X[l]	X[m]	Section 8.5.3.1
Blood sampling for other lipid parameters	X[l]	X[l]	X[l] (pre-dose and then 48 h post-dose)	X[l,m]	X[l, m] (pre-dose)	X[l, m]		X[l] (pre-dose and then 24 h post-dose)	X[l]	X[l]	Section 8.5.3.1

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Exploratory biomarker sampling											
Plasma and urine samples to be stored in the Biobank until further analysis [i]			X (pre-dose)	X	X (pre-dose)			X (pre-dose)	X (Weeks 2 and 4 after last dose)	X	Section 8.6.1
Pharmacokinetics											

	Screening	Treatment Period							Follow-up Period		Corre-sponding Section in Protocol
Visit Number	**1**	**2**		**3**	**6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**	
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Day 8[a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**	
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	
Plasma for AZD8233 and total full length ASOs of AZD8233 [j]			X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post dose)	X	X (pre-dose)	X		X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post dose)	X	X	Section 8.5.1
Urine for total full length ASOs of AZD8233			X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)					X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)			Section 8.5.1

ASO: Antisense oligonucleotides; BMI = body mass index; ET = early termination; FSH = follicle-stimulating hormone; hs-CRP = high sensitive C-reactive protein; IMP: Investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; PCSK9 = proprotein convertase subtilisin/kexin type-9; SAE: Serious adverse event
Participants are required to be fasted for at least 10 hours overnight prior to all study visits except for Visit 1 (only for the purpose of signing his/her informed consent); subjects are permitted to drink water during this period of fasting until 1 hour before blood sampling. On days when subjects attend the clinic in a fasting state, blood and urine samples should be obtained prior to administration of IMP.

[a] Day 8: no allowances.
[b] The eligibility check should be based on all clinical measurements and blood tests taken during the screening visit (Visit1).
[c] At Visit 1 and on Day −1, BMI be calculated. For Day −1, the height measured on Visit 1 will be utilised. At all other time points, only weight will be measured.
[d] Drugs of abuse and alcohol screen: Investigator will interview participants regarding their use of drugs and alcohol.
[e] Samples for HIV should be tested at a local laboratory.
[f] Allowances: pre-dose and then 0.25 h (± 2 minutes), 0.5 h (± 10 minutes), 1 h (± 10 minutes), 1.5 h (± 10 minutes), 2 h (± 15 minutes), 2.5 h (±15 minutes), 3 h (±15 minutes), 4 h (± 15 minutes), 6 h (± 15 minutes) , 8 h (± 15 minutes), 12 h (± 30 minutes), 24 h (± 1 hour), 36 h (± 1 hour) and 48 h (±1 hour) post-dose. Screening and Day-1: Sitting position, Day1 to Follow-up Period (Final Follow-up Visit / EDV); Supine position
[g] Allowances: pre-dose and then 0.5 h (±10 minutes), 1 h (± 10 minutes), 2 h (±15 minutes), 3 h (±15 minutes), 4 h (±15 minutes), 6h (±15 minutes), 8 h (±15 minutes), 12 h (±30 minutes), 24 h (± 1 hour), 36 h (±1 hour) and 48 h (±1 hour) post-dose
[h] Blood samples for complement activation panel will be collected pre-dose and 1(±5 minutes), 2(±5 minutes) and 4 h (±10 minutes) post-dose so that the samples can be taken around C_{max}.
[i] Plasma and urine samples for biobanking must be collected at the same hour every morning after an overnight (10-hour) fast.
[j] allowance; pre-dose and then 0.5 h (±2 minutes), 1 h (±5 minutes), 1.5 h (±5 minutes), 2 h (±5 minutes), 2.5 h (±5 minutes), 3 h (±10 minutes), 4 h (±10 minutes), 5 h (±10 minutes), 6 h (± 10 minutes), 8 h (±10 minutes), 10 h (± 30 minutes), 12 h (± 30 minutes), 24 h (± 1 hour), 36 h (± 1hour) and 48 h (± 1 hour) post dose
[k] Participants will be discharged after the results from the 48 h post-dose assessments have been reviewed by the Investigator.
[l] The sample should be taken in a fasting state in the morning (after a 10 hour fasting) at approximately the same time point as the pre-dose sample on Day 1
[m] Sampling to be done at approximately the same time points on the days of dosing (pre-dose) as on the non-dosing days (in the morning).
[n] Pregnancy test: Serum β-human chorionic gonadotropin (β-hCG) will be performed on all the women participants , irrespective of childbearing potential.
[o] Pregnancy test (Day1): Urine pregnancy test using dipstick will be performed before randomization on all the women participants , irrespective of childbearing potential at a local laboratory.
[p] All the women participants should have FSH and LH levels determined, irrespective of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

[Part A]

AstraZeneca is developing AZD8233, a PCSK9 targeted antisense oligonucleotide (ASO) for the reduction of circulating levels of LDLs, a major cardiovascular disease (CVD) risk factor. Patients with dyslipidemia have increased risks of CVD events compared with the general population. Low levels of LDL-C are associated with a monotonically lower risk of incident atherosclerotic CVD events. The blood level of LDL-C is decreased by inhibiting PCSK9 from binding to LDL receptors (LDLRs) and by promoting the uptake of LDL-C into hepatocytes.

In the US, the Phase 1, MAD study, is being conducted to assess the safety and tolerability of AZD8233 and to characterize its PK following SC administration of multiple ascending doses. The study is also assessing the PD of AZD8233 by investigating its effect on levels of LDL-C and PCSK9 following SC administration of ascending doses.

According to the Japanese Guideline for General Considerations for Clinical Trials (ICH-E8, June 1995), patients who have mild hyperlipidaemia alone are permitted to be included in the phase I studies of investigational products for hyperlipidaemia.

Therefore, dyslipidaemic patients with a moderately increased LDL-C will be selected for the study.

The objective of Part A of the study is to investigate the safety and tolerability of AZD8233, following SC administration of multiple doses in a limited number of Japanese patients with dyslipidemia before progressing to part B of the study. Part A of the study will also investigate the PK and the PD of AZD8233.

CCI is the highest repeated administered dose that has been evaluated in a multiple dosing study conducted in the US (Study D7990C00002) and is also the highest planned dose to be evaluated in dose finding studies in Western populations. A dose of CCI per month is expected to result in close to the maximum achievable reduction in PCSK9 as well as LDL-C levels over the dose interval with AZD8233.

[Part B]

AZD8233 is a PCSK9-targeted ASO for the reduction of circulating levels of LDL-C. This study part aims to evaluate the dose-dependent reduction in LDL-C after SC administration of multiple doses of AZD8233 as well as the associated adverse effects profile. The data

generated will be used to guide choice of doses, dosing regimens, and sample sizes, as well as safety and PD monitoring in the further clinical development program.

[Part C]

The objective of Part C of the study is to investigate the safety and tolerability of AZD8233 CCI [redacted], following SC administration of multiple doses (QM dosing) in a limited number of Japanese patients with dyslipidemia before progressing to Ph3. Part C of the study will also investigate the PK and the PD of AZD8233. This dose has been evaluated in the ongoing D7990C00004 study (SOLANO) , and is also the planned dose to be evaluated in Ph3.

2.2 Background

Dyslipidemia, particularly elevated levels of plasma LDL-C, is a main risk factor for CVD. Hypercholesterolemia is typically caused by a combination of environmental and genetic factors. Statin therapy is the standard lipid lowering medication for both secondary and primary preventions of CVD, as an adjunct to diet. Reduction of LDL-C by statins leads to a significant reduction in cardiovascular events (Collins R et al 2016). Statins reduce LDL-C by inhibiting 3 hydroxy 3 methyl glutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme of hepatic cholesterol synthesis. However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C targets and some continue to be at residual risk despite maximum doses; for others, side effects such as myalgia and myositis may preclude statin use.

Genetic studies have identified PCSK9 as an important, HMG-CoA-independent circulating regulator of LDL-C (Cohen J et al 2005, Cohen J et al 2006). Gain of function mutations in PCSK9 causes familiar dominant hypercholesterolemia; loss of function is associated with low circulating levels of LDL-C and a reduced risk of major vascular events. Circulating PCSK9 is derived mainly from the liver and increases LDL-C by promoting degradation of hepatic LDL receptors.

Two monoclonal antibodies (evolocumab [Amgen] and alirocumab [Sanofi/Regeneron]) have been successfully developed to pharmacologically inhibit circulating PCSK9. Injection of these compounds lowers LDL-C levels by approximately 60%, even in subjects already receiving maximum dose statin therapy (Sabatine MS et al 2017, Ray KK et al 2017).

Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a PCSK9 targeted-N acetylgalactosamine-conjugated ASO specifically inhibiting intracellular PCSK9 expression in the liver (Prakash TP et al 2014). The potential risks identified for AZD8233 based on ASO class are presented in Table 4. AZD8233 may provide novel treatment options to patients with dyslipidemia.

In the ongoing SAD (Study D7990C00001), global MAD (Study D7990C00002), this study

(Study D7990C00006), and global dose ranging (Study D7990C00003 [ETESIAN]) studies, > 120 participants have been exposed to multiple doses of subcutaneous administration of AZD8233.

The majority of the AEs reported have been mild or moderate. Injection site reactions (ISRs) have been reported in some participants, of which one was discontinued from treatment.

A total of six participants presented treatment-emergent ALT increases between 3 × ULN and < 6 × ULN (max = 268 U/L). No increase in total bilirubin has been observed in any of these participants, and no clinical signs or symptoms have been associated. In all 6 participants, the elevation in ALT was transient, and all participants recovered while still in the study (3 on continued treatment, and 3 that had discontinued).

Except for these findings, there have been no indications of ASO-related platform risks, including thrombocytopenia (platelet counts have remained stable in all participants), renal injury, impaired blood coagulation, complement activation, hypersensitivity/anaphylactic reaction, and flu-like reactions. Results on ADA from ongoing studies are not yet available. Overall, AZD8233 has been generally well tolerated at all doses studied with no significant safety findings on vital signs, ECG, body temperature, haematological, or clinical chemistry safety lab parameters.

Preliminary data from Study D7990C00001 showed that AZD8233 doses of ≥CCI reduced PCSK9 by ≥ 90% and LDL-C by as much as 70%.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the Investigator's Brochure (Investigator's Brochure 2021).

2.3 Benefit/Risk Assessment

Potential risks of AZD8233 and mitigation strategy are shown in Table 4. More detailed information about the known and expected benefits and potential risks of AZD8233 may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Table 4 Risk Assessment

Potential risk of clinical significance	Rationale for risk	Mitigation Strategy
Study intervention		
Thrombocytopenia	Severe thrombocytopenia has been observed in some ASO programs and it is not known whether other members of the class may be affected (Crooke ST et al 2017). One case of severe thrombocytopenia was observed in a non-human primate toxicology study with AZD8233.	Monitoring of platelet count. In case of severe thrombocytopenia, the action plan detailed in Appendix F will be followed.
Kidney injury	The kidney is an oligonucleotide high-uptake tissue. Tubular necrosis has been observed with ASOs including an ASO inhibiting PCSK9. This was not observed in toxicology studies with AZD8233 (Van Poelgeest EP et al 2013, Van Poelgeest EP et al 2015, Van Meer L et al 2017).	Monitoring of S-creatinine, BUN, urine albumin, and urine total protein as well as calculation of eGFR.
Liver Toxicity - Transaminase Elevation	The liver is an oligonucleotide high-uptake tissue (Hung G et al 2013). Oligonucleotide treatment may cause transient transaminase elevations in mice, monkeys, and humans at therapeutic exposures (Burdick AD et al 2014, Hagedorn PH et al 2013, Hildebrandt Eriksen ES et al 2012). AZD8233 is a GalNAc conjugated oligonucleotide, utilizing the ASGP-R to enhance the uptake by hepatocytes. In the 6-month mouse chronic toxicology study, higher levels in liver enzymes (AST and ALT) in males and/or in females was observed and minimal to mild histopathological changes in few animals at high doses, however deemed not to be adverse.	Monitoring a panel of liver safety biomarkers including transaminases

Potential risk of clinical significance	Rationale for risk	Mitigation Strategy
	In ongoing clinical studies with AZD8233, transient increases in transaminases have been seen in 6 participants (see Section 2.2 for details).	
Antidrug Antibodies	There is a potential risk for antibody formation. Emergence of ADA has been observed in a proportion of clinical study participants after repeated oligonucleotide treatment, leading to change in the PK profile. To date, no apparent association of ADA with loss of efficacy or safety findings has been observed.	Assessment of ADAs and monitoring for immunogenicity effects (including hypersensitivity reactions and ADA effect on PK/PD). Guidance on the definition of an anaphylactic reaction and the action plan that needs to be followed with regards to ADA sampling are presented in Appendix G.
Injection Site Reactions	As with any exogenous substance, injection site reactions may occur as a response to the SC injection of AZD8233. Possible risks associated with SC administration are redness, swelling, pain, induration, and sometimes infection at the administration site. There have been reports in some ASO programs of a few cases of severe ISRs with a high incidence of discomfort to the patient that have led to withdrawal from treatment. In the ongoing clinical programme for AZD8233, mild ISRs have been observed in a few participants (see Section2.2for details).	Monitoring for injection site reactions
Complement Activation	This is a known class effect of oligonucleotides and appears to be directly plasma concentration (C_{max}) driven. Monkeys are considered more sensitive to complement activation than humans (Crooke ST et al 2016). In the 9-month monkey study, minimal to mild higher complement Bb was observed at ≥ 6 mg/kg/occasion at the end of the	Assessment of complement activation around C_{max} (C3a [Part A only], C5a, Bb)

Potential risk of clinical significance	Rationale for risk	Mitigation Strategy
	study and correlated microscopically with mononuclear cell (predominantly lymphocytic) infiltration/inflammation observed in multiple tissues, including the administration site.	
Inhibition of Intrinsic Coagulation Pathway	Increases in aPTT, in the absence of clinical or pathological sequelae, have been observed with ASOs (Burel S et al 2013, Henry SP et al 1997). Mechanistically, interaction of ASOs with the intrinsic tenase complex and thrombin results in a selective inhibition of the intrinsic clotting cascade and hence aPTT was prolonged. (Henry SP et al 2017, Sheehan JP, Lan HC 1998, Sheehan JP, Thao PM 2001). Changes in activity of the intrinsic clotting pathway reverse when ASOs are cleared from plasma. Transient prolongation of aPTT has been described in man and was observed to correlate in a linear manner with the C_{max} at the end of infusion (Sewell KL et al 2002). There were no treatment related changes in any coagulation parameters in the nonclinical toxicology studies	Assessment of aPTT and PT
Hypersensitivity and Anaphylactic Reaction	Similar to any foreign biological agent, administration of AZD8233 may induce hypersensitivity reactions. These acute reactions are important because they may be severe but are considered rare.	Monitoring for immunogenicity effects (severe allergy and hypersensitivity reactions and ADA), see Appendix G
Flu-like Reactions	Flu-like symptoms (chills, myalgia, arthralgia, feeling hot, and body temperature increase) are rather common for some ASOs No indications of systemic inflammatory effects induced by	Monitoring for any flu-like symptoms and assessment of hs-CRP

Potential risk of clinical significance	Rationale for risk	Mitigation Strategy
	AZD8233 have been seen in the toxicology studies.	
Study procedures		
Subcutaneous Injection	Pain near the injection site (for 1 or 2 days) is the most common complication of subcutaneous injections.	Slow injection of AZD8233 using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites.

ADA = antidrug antibody; aPTT = activated partial thromboplastin time; ASGP-R = asialoglycoprotein receptor; ASO = antisense oligonucleotide; BUN = blood urea nitrogen; C_{max} = maximum plasma concentration; eGFR = estimated glomerular filtration rate; hsCRP high sensitive C reactive protein; IB = Investigator's Brochure; ISR = injection site reaction; PCSK9 = proprotein convertase subtilisin/kexin type-9; PT = prothrombin time; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous

2.3.2 Benefit Assessment

In a previous single ascending dose study, SC administrations of up to CCI of AZD8233 have been well-tolerated with no particular safety findings. Doses of ≥ CCI were efficacious in lowering PCSK9 by ≥ 90% and LDL by up to approximately 70% (Study D7990C00001).

Consequently, AZD8233 is expected to lower circulating PCSK9 in Study D7990C00006 in all participants (see Section 4.3). Pharmacologic inhibition of PCSK9 is known to increase the catabolism of LDL-C and reduce circulating LDL-C significantly. Low levels of LDL-C are associated with a monotonically lower risk of incident atherosclerotic CVD events, providing an important clinical benefit to patients with dyslipidemia.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the Investigator's Brochure.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to the participants in this study, the potential risks identified in association with AZD8233 are justified by the anticipated benefits that may be afforded to participants with dyslipidemia.

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

[Part A/Part C]

Objectives	Estimands descriptions/Endpoints
Primary	
To assess the safety and tolerability of AZD8233 following SC administration of multiple doses.	Adverse events; vital signs, ECG, cardiac telemetry, injection site reaction examinations and clinical laboratory evaluations including platelet count
Secondary	
To characterize the PK of AZD8233 following SC administration of multiple doses.	Plasma parameters (t_{lag}, t_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}48)}$, AUC, AUCτ, C_{trough}, CL/F, Vz/F, $t_{1/2}$, MRT); urine parameters (Ae, Fe, CLR).
To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.	Absolute change from baseline in log-transformed PCSK9 in plasma Percent change from baseline in PCSK9 in plasma
To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.	Percent change in levels of LDL-C in serum
To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.	Levels of other lipid parameters, including: • TC • HDL-C • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Triglycerides
Exploratory	
To collect and store plasma and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies), and tolerability related to AZD8233 treatment or cardiometabolic diseases.	The biomarkers to be analyzed may include but not limited to Apo CIII (3), ANGPTL3, ANGPTL4, ANGPTL8, and ProC3. The result will not form part of the CSR for this study.
To collect and analyse samples for exploration of antidrug immunogenicity	ADAs

Ae = amount excreted in urine; ANGPLT3 = angiopoietin-like protein 3; ANGPLT4 = angiopoietin-like protein 4; ANGPLT8 = angiopoietin-like protein 8; apoB = apolipoprotein B; apoCIII (3) = apolipoprotein CIII (3); AUC = area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}last)}$ = area under the plasma concentration-curve from time zero to time last value above the limit of quantification; $AUC_{(0\text{-}48)}$ = area under the plasma concentration-time curve from time zero to 48 hours after dosing; AUCτ = area under the plasma concentration-time curve from time during the dosing interval; CL_R = renal clearance; C_{max} = Observed maximum plasma concentration; CL/F = apparent total body clearance of drug from plasma after extravascular administration; CSR = clinical study report; C_{trough} = observed trough plasma drug concentration; Fe = fraction excreted unchanged in urine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MRT = mean residence time of the unchanged drug in the systemic circulation; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamics; PK = pharmacokinetics; ProC3 = propeptide of type III collagen; SC = subcutaneous; t_{max} = time to reach peak or maximum observed concentration or response following drug administration; t_{lag} = time delay between drug administration and the first observed concentration in plasma; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration

[Part B]

Objectives	Estimands descriptions/Endpoints
Primary	
To assess the effect of different doses of AZD8233 on LDL-C versus placebo	Absolute change from baseline in log-transformed LDL-C in serum
Secondary	
To assess the effect of different doses of AZD8233 on PCSK9 versus placebo.	Absolute change from baseline in log-transformed PCSK9 in plasma Percent change from baseline in PCSK9 in plasma
To assess the effect of different doses of AZD8233 on LDL-C versus placebo.	Percent change in levels of LDL-C in serum
To assess the effect of AZD8233 on other lipid parameters versus placebo	Levels of other lipid parameters including: • TC • HDL-C • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Triglycerides • Remnants cholesterol
To evaluate the pharmacokinetics (PK) of AZD8233.	Population PK parameters
To evaluate the immunogenicity of AZD8233.	Development of ADA and ADA titer (if subjects are ADA positive) during treatment and follow-up.
Safety	

Objectives	Estimands descriptions/Endpoints
To assess the safety and tolerability of AZD8233.	Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, injection site reactions, and clinical laboratory evaluations, including platelet count.
Exploratory	
To collect and store blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies) and tolerability related to AZD8233 treatment or cardiometabolic diseases.	Evaluation of changes in biomarkers. Results of potential future exploratory biomarker research may be reported outside this study's CSR.
Optional: To collect and store DNA from blood samples according to local and ethical procedures for future exploratory research into genes/genetic variation that may influence response to treatment.	Results of possible future genetic research may be reported outside this study's CSR.

AE = adverse event; ApoA1= Apolipoproteins A1; ApoB = apolipoprotein B; CSR = clinical study report; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); PK = pharmacokinetics; TC = Total cholesterol; VLDL-C = Very-low-density lipoprotein cholesterol

4 STUDY DESIGN

4.1 Overall Design

For an overview of the study design, see Figure 1. For details on treatment given during the study, see Section 6.1.

[Part A/Part C]

These are each randomized, single-blind, placebo-controlled, multiple dose Phase 1 study parts, including approximately 11 participants with dyslipidemia in each part. The primary objective of the study is to assess the safety and tolerability of AZD8233 following a multiple subcutaneous dose administration in Japanese patients with dyslipidemia. The study will be conducted at up to 2 sites in Japan.

The Screening Period starts within 28 days before the randomization visit and ends on Day −4. Eligible participants will make 8 visits during the treatment period, 1 telephone contact and 8 additional visits during the follow-up period. They are randomized across 2 different treatment arms in an 8:3 ratio for a 58-day (up to Visit 9) treatment period. The planned treatment arms are AZD8233 CCI (Part A) / AZD8233 CCI (Part C) and placebo. Participants will be dosed subcutaneously on Days 1, 8(Part A only), 29, and 57.

These studies are each single-blind with regards to treatment (AZD8233 or placebo). AZD8233 and placebo should be matched in appearance. Participants randomized to placebo

will receive the same volume of injection as that of AZD8233.

After the treatment period, participants will continue in a follow-up period of 14 weeks (up to 16 weeks after the last dose).

For detailed information, please refer to the Schedule of Activities (SoA) (Table 1:Part A, Table 3: Part C).

[Part B]

This is a randomized, parallel, double-blind, placebo-controlled, dose-ranging phase 2 study in approximately 60 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD8233 on LDL-C across different dose levels. The study will be conducted at approximately 6 sites in Japan.

Eligible participants will make 7 visits during the treatment period and 7 additional visits during the follow-up period. They are randomized across 3 different treatment arms in a 1:1:1 ratio for a 12-week treatment period. The planned treatment arms are AZD8233 CCI SC, AZD8233 CCI SC, and placebo SC to be dosed on Days 1, 29, and 57.

This is a double-blind study with regards to treatment (AZD8233 or placebo) at each dose level. AZD8233 and placebo should be matched in appearance. Participants randomized to placebo will receive a volume of injection that does not differ visually from the active drug.

After the treatment period, participants will continue in a follow-up period of 12 weeks (up to 16 weeks after the last dose).

For detailed information, please refer to the SoA (Table 2).

4.2 Scientific Rationale for Study Design

AstraZeneca is developing AZD8233 for the treatment of dyslipidemia. This study consists of Part A, Part B and Part C. The objective of Part A is to investigate the safety and tolerability of AZD8233 following SC administration of multiple doses in a limited number of Japanese participants with dyslipidemia before progressing to Part B where a larger number of participants will be exposed. The study will also investigate the PK and the PD of AZD8233. Part B aims to evaluate the effect of different doses of AZD8233 on LDL-C at steady state to select a therapeutic dose for further clinical development. The objective of Part C is to investigate the safety and tolerability of CCI AZD8233 following SC administration of multiple dose (QM dosing) in a limited number of Japanese participants with dyslipidemia before progressing to Ph3. The study will also investigate the PK and the PD of AZD8233.

The dosing schedule (dosing on Days 1, 8 [Part A only], 29, and 57) should be sufficient to closely reach steady state conditions in the tissues at the end of the dosing period (the

estimated terminal half-life of the full length ASO in plasma is 2 to 3 weeks). Based on these data and the expected time course for PCSK9 and LDL-C reduction, the dosing schedule is predicted to allow for a robust assessment of safety, tolerability, PK, as well as PCSK9 and LDL-C reduction to guide dose selection for further clinical development of AZD8233.

The dosing and follow-up schedule are selected based on the long estimated terminal half-life of the full length AZD8233 ASO in plasma as well as the observed time course for PCSK9 levels to return to baseline after single dose administration in humans. Monthly dosing is predicted to result in a low level of fluctuation of PCSK9 levels and tissue exposure during a dose interval.

4.3 Justification for Dose

[Part A]

In the Phase 1 SAD study (Study D7990C00001), which has been conducted in the US, single SC doses of AZD8233 up to CCI have been well tolerated in participants with elevated LDL-C.

The dose to be evaluated in Part A is CCI.

This is the highest dose that has been evaluated in the MAD study (Study D7990C00002) conducted in the US, and is also the highest planned dose to be evaluated in Part B. A dose of CCI monthly is expected to result in close to the maximum achievable reduction in PCSK9 and hence LDL-C levels over the dose interval with AZD8233.

One extra dose (loading dose) is planned to be administered one week after the first dose with the purpose to reach steady state conditions more quickly in trough concentrations (assumed to reflect tissue concentrations). As the loading dose is administered after the initial large decline in plasma concentrations of the first dose, the loading dose is predicted to result in minimally higher C_{max} or AUC_{0-48} as compared to the first single dose. Thus, a total of 4 doses are planned to be administered to each subject, i.e., dosing on Days 1, 8, 29, and 57.

A dose of CCI monthly is expected to result in a mean C_{max} and AUC_{0-48} at steady state at approximately half the exposure limits defined from the NOAEL dose in a 3-month toxicity study in cynomolgus monkeys. From a safety perspective, risks observed in other ASO development programs can be divided into acute and chronic risks. Acute risks, as those related to C_{max}, including transient increase in activated partial thromboplastin time (aPTT), are expected to occur very soon after dosing. Chronic risks, like reduction of platelet count and development of ADAs have, if at all, most often appeared after more than 3 months of dosing.

Taken together, the benign safety profile observed for single doses of AZD8233 up to CCI

support initiation of Part B after the SRC will review safety data up to 7 days after last dose administration in Part A. Data later than Day 64 (if available) may be reviewed by the SRC as needed.

The SRC will review safety and tolerability data (AEs, vital signs [SBP], pulse rate and body temperature, cardiac telemetry, physical examination, laboratory assessments [hematology, clinical chemistry, coagulation, renal safety biomarkers, and dipstick urinalysis for hematuria]) collected up to 7 days after last dose. The SRC will also consider differences between Part A and Part B, including but not limited to dosing regimen, as well as available overall safety and PK/PD conclusions from other AZD8233 studies (including Study D7990C00002 and Study D7990C00003).

[Part B]

The doses of Part B are selected based on observed PCSK9 and LDL-C reduction in the SAD study (Study D7990C00001) and MAD study (Study D7990C00002). The original plan was to include three doses, mid and high doses planned to be CCI and CCI Both of these monthly doses were planned to achieve a PCSK9 reduction of around 90% during the dose interval and were selected to result in close to the maximum achievable effect in terms of LDL-C reduction, with the aim to show that an increase in the dose above the mid dose will not result in a clinically significant further reduction in LDL-C. The low dose, planned to be CCI was selected so as to reach a PCSK9 reduction of below 80% over the entire dose interval and was selected so as to show that decreasing the dose and PCSK9-reduction to below 80% will lead to a clinically significant lower LDL-C reduction as compared to the mid dose. The mid dose is thus selected so as to be in the therapeutic dose range. However data from the ongoing MAD study have shown that dose vs PCSK9 reduction after repeated dosing is very predictable with a consistently high PCSK9 reduction observed in the patients that received the highest dose, CCI ie the same dose that is evaluated in Part A of this study, indicating no need to include CCI in part B. Thus, sufficient data on PCSK9 and LDL-C reduction have already been generated on the high dose CCI in the ongoing MAD study (with additional data to be collected in Part A of this study and the ongoing dose-range-finding study [Study D7990C00003]), and such data is expected to show that increasing the dose above the mid dose CCI will not result in a clinically significant further reduction in LDL-C. The revised design of Part B will therefore instead include 2 active doses: the original mid dose (planned to CCI) and low dose (planned to CCI). Together with the data on the CCI dose generated in Part A (with support of data from other studies, as relevant), data from the two active doses selected for Part B is expected to be sufficient for therapeutic dose selection.

In Part B of this study, a loading dose on Day 8 has been removed. A Kinetic-Pharmacodynamic-model (Jacqmin et al 2007) was fitted to the observed PCSK9 data over time in the SAD and MAD studies. The model predicts a similar PCSK9-reduction at the end

of Week 12 with or without inclusion of the loading dose, ie for a once monthly dosing regimen. This is in line with preliminary estimates of the terminal half-life of AZD8233 full length ASOs in plasma (2-3 weeks) that indicate that close to pharmacokinetic steady state should have been reached 12 weeks after start of dosing. Thus the effect of a loading dose will be marginal, and therefore there will be no additional dose one week after the initial dose of AZD8233 in Part B.

The safety data and potentially the PCSK9 and LDL-C data after repeated (Days 1, 8, 29, and 57) dosing of AZD8233 up to CCI from other AZD8233 studies (including the ongoing D7990C00002 and D7990C00003 studies) will have been evaluated before the doses of Part B will be finally selected. Based on such emerging data of AZD8233, the planned doses in Part B may be slightly adjusted if needed to achieve the intended PCSK9 and LDL-C reduction. However, the highest dose will not exceed CCI (Days 1, 29, and 57), which is lower than the highest dose in the ongoing MAD study and the dose in Part A.

[Part C]

AZD8233 CCI will be assessed in Part C. The efficacy and safety of CCI and CCI were assessed in global phase 2 study (D7990C00003) with 3 months treatment and CCI is evaluated in an ongoing phase 2 study with 6 months treatment (D7990C00004). Based on the results from the global phase 2 study, the CCI dose resulted in a larger mean LDL-C reduction (-79% (95% CI; -83, -74)) than the CCI dose (-72% (95% CI; -78, -65) indicating that CCI dose is not fully on the plateau of the max achievable effect. Therefore, if the CCI dose is confirmed as well tolerated and no significant safety concerns are raised, the CCI is the dose planned to be selected for the phase 3 study program. The safety and tolerability of CCI is therefore planned to be assessed in Part C.

4.4 End of Study Definition

[Part A/Part B/Part C] A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to a study intervention. Participants who are enrolled but

subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Physician immediately, and a discussion should occur between the AstraZeneca Physician and the Investigator regarding whether to continue or discontinue the participant from treatment, The AstraZeneca Physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

5.1 Inclusion Criteria

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

[Part A/Part C]

Age

1 Participants must be 20 to 60 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants who have a fasting LDL-C ≥ 70 mg/dL but < 140 mg/dL at screening.

3 Participants who have fasting triglycerides < 400 mg/dL at screening.

4 Participants who should be receiving statin therapy.

5 LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during study participation. The exception to this restriction is for fenofibrate; if the participant is receiving fenofibrate, the therapy must be stable for at least 6 weeks prior to randomization at a dose that is appropriate for the duration of the study in the judgement of the Investigator. Other fibrate therapies (and derivatives) are prohibited. Non-LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during treatment period.

6 Participants who have suitable veins for cannulation or repeated venepuncture.

Weight

7 Body mass index (BMI) between 19 and 40 kg/m^2.

Sex

8 Male or female

Reproduction

9 Females must not be pregnant and must have a negative pregnancy test at screening and randomisation, must not be lactating , and must be of nonchild-bearing potential. Women

not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

(a) Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone (FSH) levels in the postmenopausal range.

(b) Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

10 Males must be surgically sterile or using, in conjunction with their female partners, a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the final follow-up visit to prevent pregnancy in a partner. Acceptable methods of contraception include birth control pills, injections, implants, or patches, intrauterine devices (IUDs), tubal ligation/occlusion, and vasectomy. A barrier method is not necessary if the female partner is sterilized. Male study participants must not donate or bank sperm during this same time period.

Rationale for LDL-C upper limit:

Based on the reference value of LDL hypercholesterolemia, as proposed by the Japan Atherosclerosis Society (JAS) guidelines.

Informed consent

11 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

12 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

[Part B]

Age

1 Participants must be 20 to 75 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Have a fasting LDL-C ≥ 70 mg/dL but < 190 mg/dL at screening (Visit 2).

3 Have fasting triglycerides < 400 mg/dL at screening (Visit 2).

4 Should be receiving statin therapy as defined in Appendix H, in accordance with the Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases.

5 LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during study participation. The exception to this restriction is for fenofibrate; if the participant is receiving fenofibrate, the therapy must be stable for at least 6 weeks prior to randomization at a dose that is appropriate for the duration of the study in the judgement of the Investigator. Other fibrate therapies (and derivatives) are prohibited. Non-LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during treatment period.

6 Have suitable veins for cannulation or repeated venepuncture.

Weight

7 BMI between 19 and 40 kg/m^2

Sex

8 Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

9 Female participants

Female participants must not be pregnant and must have a negative pregnancy test at screening and randomisation, must not be lactating, and must not be of childbearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

(a) Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.

(b) Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

10 Males participants

Males must be surgically sterile or using, in conjunction with their female partners, a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the final follow-up visit to prevent pregnancy in their partners. Acceptable methods of contraception include birth control pills, injections, implants, or patches, IUDs, tubal ligation/occlusion, and vasectomy. A barrier method is

not necessary if the female partner is sterilized. Male study participants must not donate or bank sperm during this same time period.

Informed consent

11 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

12 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses. Participants who consent only to the main study may participate in other components of the main study without participating in the optional component of the study. However, to participate in the optional component of the study, the subject must sign and date both the consent forms for the main study and optional component of the study. If a participant declines to participate in the optional component of the study, there will be no penalty or loss of benefit to the subject. The participant will not be excluded from other aspects of the study described in this protocol.

5.2 Exclusion Criteria

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

[Part A/Part C]

Medical Conditions

1 Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 using the Japanese equation. (eGFR = 194 × sCr (mg/dL) $^{-1.094}$ × Age $^{-0.287}$ × α, where α is 1 for males and 0.739 for females)

2 History or presence of gastrointestinal, hepatic, or renal disease or any other conditions known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3 Any uncontrolled or serious disease, or any medical (e.g., known major active infection or major haematological, renal, metabolic, gastrointestinal, or endocrine dysfunction) or surgical condition that, in the opinion of the Investigator, may either interfere with participation in the clinical study and/or put the participant at significant risk.

4 Blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura or symptoms of increased risk of bleeding (frequent bleeding gums or nose bleeds). Or participants receiving anti-coagulation therapy.

5 History of major bleed or high-risk of bleeding diathesis.

6 Subjects with a high 10-year risk of coronary heart disease as calculated using the Suita score (Participants classified in high risk class).

7 Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in-situ, or Stage 1 prostate carcinoma) within the last 10 years.

8 Recipient of any major organ transplant, e.g., lung, liver, heart, bone marrow, kidney.

9 LDL or plasma apheresis within 12 months prior to randomization.

10 Heart rate after 10 minutes of sitting rest < 50 or > 100 beats per minute (bpm).

11 Uncontrolled hypertension defined as sitting SBP > 140 mmHg or DBP > 90 mmHg.

12 Any laboratory values with the following deviations at the Screening Visit; test may be repeated at the discretion of the Investigator if abnormal:

- Any positive result on screening for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
- Alanine aminotransferase/transaminase（ALT) > 1.5 × upper limit of normal (ULN).
- Aspartate aminotransferase/transaminase (AST) > 1.5 × ULN.
- Creatinine > 1.5 mg/dL.
- White blood cell (WBC) < lower limit of normal (LLN).
- Hemoglobin < 12 g/dL in men or < 11 g/dL in women
- Platelet count ≤ LLN.
- Activated partial thromboplastin time (aPTT) > ULN and PT > ULN.
- Urinary albumin creatinine ratio (UACR) > 11 mg/mmol (100 mg/g).

13 Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG and any clinically important abnormalities in the 12-lead ECG as judged by the Investigator that may interfere with the interpretation of QTc interval (Corrected QT Interval by Fridericia [QTcF] > 450 ms) changes, including abnormal ST-T-wave morphology, left ventricular hypertrophy, test may be repeated at the discretion of the Investigator if abnormal.

14 Known or suspected history of drug abuse as judged by the Investigator.

15 Smokers with > 10 cigarettes/day and unable to comply with the nicotine restriction during the study.

16 History of alcohol abuse or excessive intake of alcohol as judged by the Investigator.

17 Excessive intake of caffeine-containing drinks or food (e.g., coffee, tea, chocolate,) as judged by the Investigator.

18 Use of drugs with cytochrome P450 enzyme inducing properties such as St John's Wort within 3 weeks before the first administration of IMP.

19 Antiplatelet therapy, other than low-dose aspirin ≤ 100 mg/day, within 1 month prior to randomization.

20 Mipomersen (not approved in Japan), or lomitapide within 12 months prior to randomization.

21 Previous administration of AZD8233 or other PCSK9 inhibition treatment (approved or IMP).

22 Use of any herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or 5 half-lives, whichever is longer.

23 History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or galactosamine-conjugated antisense oligonucleotides.

24 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP. History or evidence of any other clinically significant disorder (e.g., cognitive impairment), condition or disease other than those outlined above that, in the opinion of the Investigator or AstraZeneca physician, if consulted, may compromise the ability of the subject to give written informed consent, would pose a risk to subject safety, or interfere with the study evaluation, procedures, or completion.

Prior/concurrent clinical study experience

25 Participation in another clinical study with an investigational product administered in the last 3 months prior to randomisation or 5 half-lives from last dose to first administration of study intervention, whichever is the longest.

26 Received another new chemical entity (defined as a compound which has not been approved for marketing) within 30 days of last follow-up to first administration of the IMP of this study or 5 half-lives from last dose to first administration of IMP, whichever is the longest.

27 Use of other IMP or devices during the course of the study.

Other exclusions

28 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site or their close relatives).

29 Judgment by the Investigator that the patient should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

30 Previous enrolment or randomisation into the present study.

31 Participants who cannot communicate reliably with the Investigator.

32 Vulnerable participants, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

33 Plasma donation within 1 month of the Screening Visit. For male participants, donation of whole blood or significant blood loss in excess of 400 mL within 3 months prior to screening visit and for female participants, donation of whole blood or significant blood loss in excess 400 mL within 4 months prior to screening visit.

References for eGFR and SBP threshold, and The Suita score (J Atheroscler Thromb, 2018):

- eGFR - based on the mildly-decreased levels proposed by the Japanese Society of Nephrology.
- SBP - based on the hypertension criterion proposed by the Japanese Society of Hypertension.

[Part B]

Medical conditions

1 eGFR < 40 mL/min/1.73m^2 using the Japanese equation at Visit 1. (eGFR = 194 × sCr (mg/dL) $^{-1.094}$ × Age $^{-0.287}$ × α, where α is 1 for males and 0.739 for females)

2 History or presence of gastrointestinal, hepatic, or renal disease or any other conditions known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3 Any uncontrolled or serious disease, or any medical (e.g., known major active infection or major haematological, renal, metabolic, gastrointestinal, or endocrine dysfunction) or surgical condition that, in the opinion of the Investigator, may either interfere with participation in the clinical study and/or put the participant at significant risk.

4 Poorly controlled type 2 diabetes mellitus (T2DM), defined as Haemoglobin A1c (HbA1c) > 10% at Visit 1.

5 Acute ischaemic cardiovascular event in the last 12 months prior to randomization.

6 Heart failure with New York Heart Association (NYHA) Class III-IV.

7 Blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura or symptoms of increased risk of bleeding (frequent bleeding gums or nose bleeds). Or participants receiving anti-coagulation therapy.

8 High-risk of bleeding diathesis as judged by the Investigator.

9 Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in-situ, or Stage 1 prostate carcinoma) within the last 10 years.

10 Recipient of any major organ transplant, e.g., lung, liver, heart, bone marrow, renal.

11 LDL or plasma apheresis within 12 months prior to randomization.

12 Uncontrolled hypertension defined as average supine SBP > 160 mmHg or DBP > 90 mmHg at Visit 1 or Visit 3.

13 Heart rate after 10 minutes supine rest < 50 bpm or > 100 bpm at Visit 1 or Visit 3.

14 Any laboratory values with the following deviations at the Screening Visit; test may be repeated at the discretion of the Investigator if abnormal:
   - Any positive result on screening for hepatitis B, hepatitis C, or HIV
   - ALT > 1.5 ×ULN
   - AST > 1.5 × ULN

- Total bilirubin (TBL) > ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- WBC < LLN
- Hemoglobin < 12 g/dL in men or < 11 g/dL in women
- Platelet count ≤ LLN
- aPTT > ULN and PT > ULN
- UACR > 11.3 mg/mmol (100 mg/g)
- Urine protein/creatinine (UPCR) > 300 mg/g

15 Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG and any clinically important abnormalities in the 12-lead ECG as judged by the Investigator.

16 QTcF > 470 ms; high degree atrioventricular (AV)-block grade II-III and sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias.

17 Known or suspected history of drug abuse as judged by the Investigator.

18 History of alcohol abuse or excessive intake of alcohol as judged by the Investigator.

19 Mipomersen (not approved in Japan), or lomitapide within 12 months prior to randomization.

20 Previous administration of AZD8233 or other PCSK9 inhibition treatment (approved or IMP).

21 History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or galactosamine-conjugated antisense oligonucleotides.

22 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IP. History or evidence of any other clinically significant disorder (e.g., cognitive impairment), condition or disease other than those outlined above that, in the opinion of the Investigator or AstraZeneca physician, if consulted, may compromise the ability of the subject to give written informed consent, would pose a risk to subject safety, or interfere with the study evaluation, procedures, or completion.

Prior/Concurrent Clinical Study Experience

23 Participation in another clinical study with an investigational product administered in the last 3 months prior to randomisation or 5 half-lives from last dose to first administration of study intervention, whichever is the longest.

24 Received another new chemical entity (defined as a compound which has not been approved for marketing) within 30 days of last follow-up to first administration of the

IMP of this study or 5 half-lives from last dose to first administration of IMP, whichever is the longest.

25 Use of other IMP or devices during the course of the study.

Other Exclusions

26 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site or their close relatives).

27 Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

28 As judged by the Investigator, any evidence of disease conditions that, in the Investigator's opinion, make it undesirable for the participant to participate in the trial.

29 Previous enrolment or randomisation in the present study.

30 Participants who cannot communicate reliably with the Investigator.

31 Vulnerable participants, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

32 Plasma donation within 1 month of the screening visit. For male participants, donation of whole blood or significant blood loss in excess of 400 mL within 3 months prior to screening visit. For female participants, donation of whole blood or significant blood loss in excess of 400 mL within 4 months prior to screening visit.

Optional Genetic Sampling

[Part A/Part C]

Not applicable

[Part B]

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

33 Previous allogeneic bone marrow transplant.

34 Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle Considerations

For a list of prohibited medications, see Section 6.5.

5.3.1 Meals and Dietary Restrictions

[Part A/Part B/Part C]

Participants must be fasted for 10 hours prior to blood sampling for LDL-C, PCSK9, and other lipid parameters. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters.

5.3.2 Caffeine, Alcohol, and Tobacco

[Part A/Part C]

Smokers with >10 cigarettes/day (or using any other nicotine products) who are unable to comply with the nicotine restriction during the study are not allowed to participate in the study.

Participants with known or suspected history of alcohol abuse, as judged by the Investigator, are not allowed to participate in the study.

[Part B]

Participants with known or suspected history of alcohol abuse, as judged by the Investigator, are not allowed to participate in the study.

5.3.3 Activity

Participants should not start any new physical training activities or increase the intensity of their usual physical training from 5 days prior to randomization until the end of the study.

5.3.4 Reproductive Restrictions

Women of Non-Child Bearing Potential

Women of non-childbearing potential are defined as female participants who are permanently surgically sterilized or postmenopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy, but excludes bilateral tubal ligation.

Females are considered postmenopausal if they have had amenorrhea for at least 12 months or more, following cessation of all exogenous hormonal treatments, and FSH levels are in the postmenopausal range.

Restriction for Male Participants

There is no information about effects that AZD8233 could have on the development of the

fetus in humans. Therefore, it is important that women of childbearing potential who are the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male participants have attended the final follow-up visit.

As a precaution, all male participants should avoid fathering a child by either true abstinence or use (together with their female partner/spouse) a highly effective contraception form of birth control in combination with a barrier method, starting from the time of IMP administration until 3 months after the final follow-up visit. Approved/Certified measurements in Japan are combined pill, vasectomy, tubal occlusion, intrauterine device (provided coils are copper banded),and levonorgestrel intrauterine system (eg, Mirena®). Not Approved/Certified measurements in Japan are Cerazette® (desogestrel) pills , Medroxyprogesterone injections (eg, Depo-Provera®), etonogestrel implants (eg, Implanon®, Norplan®), normal and low dose combined oral pills, norelgestromin / ethinylestradiol transdermal system (eg Evra® Patch), Intravaginal device (eg, NuvaRing®)

Male participants who have been sterilized are required to use 1 barrier method of contraception (condom) from the time of IMP administration until after the final follow-up Visit. A barrier method is not necessary if the female partner is sterilized.

Sperm Donation

Male participants should not donate sperm for the duration of the study or for at least 3 months after the study follow-up visit.

Pregnancy

Participants will be instructed that if they or their partners become pregnant during the study this should be reported to the Principal investigator (PI). The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner (via the subject's request that his partner contacts the study site) and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

Blood Donation

Subject should refrain from blood donation throughout the study, including the follow-up period.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but

are not subsequently randomized to study intervention. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. At the Investigator's discretion, participants may be rescreened a further two times during the recruitment period. Rescreened participants should be assigned the same participant number as per their initial screening visit.

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Details of the identity of the investigational products are presented in Table 6 and in IMP instructions (D7990C00006) on AZD8233 solution for injection.

For Part B, an unblinded pharmacist will be assigned in case of a change of the planned doses (as described in Section 4.3).The strength of CCI /mL will be applied when a mid dose is adjusted above CCI (not exceeding CCI).

Table 6 Investigational Products

[Part A]

Arm Name	MAD Cohort 1	MAD Cohort 2
Intervention Name	AZD8233	Placebo to match AZD8233
Dose Formulation	AZD8233 solution for injection	Matching placebo solution for injection
Strength/Concentrations	CCI	Matching placebo solution for injection
Dose	CCI	Matching placebo solution for injection
Regimen	AZD8233/placebo Days 1, 8, 29 and 57	
Route of Administration	Subcutaneous injection	
Treatment Administration Guidelines	Slow injection of study intervention using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites. The anatomical location of each injection site should be documented in the electronic Case Report Form (eCRF).	
Specific device for drug administration	Syringes for injection to be provided by study site	
IMP and NIMP	IMP	
Sourcing	Provided by the Sponsor	
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	
Special Handling Requirements	Requirements will be provided in a separate document	
Availability of IMP	Will be shipped when approvals are in place	

eCRF = electric case report form

[Part B]

ARM Name	Cohort 1	Cohort 2	Cohort 3
Intervention Name	AZD8233	AZD8233	Placebo to match AZD8233
Dose Formulation	AZD8233 solution for injection		Matching placebo solution for injection
Strength/Concentrations	CCI *	CCI	Matching placebo solution for injection
Dose	CCI	CCI	Matching placebo solution for injection
Regimen	AZD8233/placebo Days 1, 29, and 57		

ARM Name	Cohort 1	Cohort 2	Cohort 3
Route of Administration	Subcutaneous injection		
Treatment Administration Guidelines	Slow injection of study intervention using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites. The anatomical location of each injection site should be documented in the eCRF.		
Specific device for drug administration	Syringes for injection to be provided by study site		
IMP and NIMP	IMP		
Sourcing	Provided centrally by the Sponsor		
Packaging and Labelling	Study intervention will be provided in vials. Each vial will be packed in a separate carton. Each vial and carton will be labeled as required per country requirement		
Special Handling Requirements	Requirements will be provided in a separate document		
Availability of IMP	Will be shipped when approvals are in place		

eCRF = electric case report form
* The strength of CCI will be applied when a mid dose is adjusted above CCI (not exceeding CCI)

[Part C]

Arm Name	MAD Cohort 1	MAD Cohort 2
Intervention Name	AZD8233	Placebo to match AZD8233
Dose Formulation	AZD8233 solution for injection	Matching placebo solution for injection
Strength/Concentrations	CCI	Matching placebo solution for injection
Dose	CCI	Matching placebo solution for injection
Regimen	AZD8233/placebo Days 1, 29 and 57	
Route of Administration	Subcutaneous injection	
Treatment Administration Guidelines	Slow injection of study intervention using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites. The anatomical location of each injection site should be documented in the electronic Case Report Form (eCRF).	
Specific device for drug administration	Syringes for injection to be provided by study site	
IMP and NIMP	IMP	
Sourcing	Provided by the Sponsor	
Packaging and Labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	

Arm Name	MAD Cohort 1	MAD Cohort 2
Special Handling Requirements	Requirements will be provided in a separate document	
Availability of IMP	Will be shipped when approvals are in place	

6.2 Preparation/Handling/Storage/Accountability

1 The head of the medical institution can delegate the control of and accountability for the study drug to an investigational product storage manager. The head of the medical institution or the investigational product storage manager must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the head of the medical institution and authorised site staff.

3 The head of the medical institution is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy manual or specified handling instructions.

6.3 Measures to Minimise Bias: Randomization and Blinding

[Part A/Part C]

This study is single-blind with regards to treatment (AZD8233 or placebo), and blinded to participants, site investigators, and site staff. The Sponsor will be unblinded to treatment allocation. Detailed blinding procedure of the SRC (Part A only) is described in Appendix A 5.

The following personnel may have access to the study randomization list or may be unblinded to treatment assignment in another way:

- AstraZeneca personnel carrying out labeling and packaging of subject-specific treatments
- AstraZeneca personnel involved in analyses and preparation of outputs for the SRC(Part A Only) and project decisions

The Investigator will ensure that all eligible subjects in accordance with the inclusion and exclusion criteria have signed the ICF. Participants who have signed the ICF will undergo

randomization to receive AZD8233 or placebo in a ratio of 8:3. All participants will be assigned to randomized study treatment using an Interactive Voice/Web Response System (IXRS). A randomization number will be provided to the randomized participants. Before the study is initiated, the log-in information and directions for the IXRS will be provided to each site.

A participant who fails to meet the inclusion criteria and meets any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a participant, who does not meet the selection criteria, is randomized in error and this is identified before dosing, he/she should be withdrawn from the study.

If a participant who does not meet the selection criteria has been dosed before the error is identified, he/she should be advised to continue safety assessments to ensure his/her safety. The PI will inform the AZ Lead Physician of the error and a joint decision will be made as to whether the participant may continue to be dosed.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. This single blinded study is blinded to the participants and investigative site personnel until all dosing, follow-up, and SRC review for all cohorts have been completed. AstraZeneca and personnel involved in PD and PK evaluation of data (to be reviewed only at select SRC meetings) may be unblinded to the evaluation of these data. Alternatively, PK and PD data will be provided in a blinded manner for the SRC review.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the investigational product and that potentially require expedited reporting to regulatory authorities.

The IXRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the participant’s best interest for the Investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant’s condition (e.g., antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blinding. The date when and reasons why the blinding was broken must be recorded in the site source documents and electronic Case Report Form (eCRF).

The laboratory vendor personnel performing the bioanalyses of the plasma/urine samples will have access to the randomization list.

[Part B]

All participants will be centrally assigned to randomized study intervention using an IXRS system. Before the study is initiated, the telephone number and call-in directions and/or the log in information & directions for the IXRS will be provided to each site. Study intervention will be dispensed at the study visits summarised in the SoA.

The IXRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IXRS user manual that will be provided to each centre.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation 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 IXRS 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 a participant’s condition (e.g., antidote available), the Investigator has the sole responsibility for determining if unblinding of the participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the participant’s intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blinding. The Investigator documents and report the action to AstraZeneca, without revealing the treatment given to the participant to the AstraZeneca staff.

The laboratory vendor personnel performing the bioanalyses of the plasma samples will have access to the randomization list.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator under medical supervision. The date, and time if applicable, of dose administered in the clinic, as well as the anatomical location of the injection site, 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 (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that the participant is receiving at the time of enrolment 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 Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate care for participants except for those medications excluded below or listed in the exclusion criteria. Specifically, participants should receive full supportive care during the study as deemed appropriate, and in accordance with local guidelines.

The following medical restrictions apply:

[Part A/Part C]

- Participants should be receiving statin therapy.

[Part B]

- Participants should be receiving statin therapy as defined in Appendix H in accordance with the JAS guidelines for prevention of atherosclerotic cardiovascular diseases.
- Participants must abstain from taking prescription or non-prescription drugs without consultation with the Investigator (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit.

[Part A/Part B/Part C]

- Medications/therapies specified in the exclusion criteria are prohibited from use for the duration of the subject's involvement in the study.
- Participants who are receiving LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during study participation. The exception to this restriction is for fenofibrate; if the participant is receiving fenofibrate, the therapy must be stable for at least 6 weeks prior to

randomization at a dose that is appropriate for the duration of the study in the judgement of the Investigator. Other fibrate therapy (and derivatives) are prohibited. Participants who are receiving non-LDL-lowering medications should be on stable dosing for ≥ 3 months prior to screening with no planned medication or dose change during treatment period.

- Participants should not be on any antiplatelet therapy other than low-dose aspirin (≤ 100 mg/day).
- Paracetamol/acetaminophen, at doses of ≤ 2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the study physician if required.
- COVID-19 vaccines are allowed to be administered as a concomitant medication during study participation. The Sponsor has no data on the co-administration of AZD8233 and respective COVID-19 vaccines. The participants should be encouraged to inform the investigator whether COVID-19 vaccination is planned and study participants become eligible for COVID-19 vaccination.
  - COVID-19 vaccination (all doses) prior to the first dose may be advisable. If possible, the first dose of AZD8233 should be given at least 14 days after the last dose of vaccine.
  - Patients should not receive COVID-19 vaccines on dosing days (+/- 7 days).
  - Ultimately, the decision to vaccinate will be based on the judgement of the treating physician taking into account the participants best interest. Any deviation from the recommendation above should be agreed with the Study Physician.

6.5.1 Rescue Medicine

The study will not supply any specific rescue medication. Please see Section 6.5 on concomitant therapy for additional instructions.

6.6 Dose Modification

No dose modification is planned.

6.7 Intervention After the End of the Study

There is no planned intervention following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive further IMP if any of the following occurs in the

participant in question:

[Part A/Part C]

Dosing for any individual participant will be stopped if he/she experiences a possible drug related SAE or a possibly drug-related significant non-serious AE, which in the opinion of the PI warrants discontinuation of the participant from the active protocol for his or her well-being. Dosing of the individual participants will also be stopped if any significant change in safety parameters as listed in **stopping rules** is met. The decision to hold or discontinue study treatment may be also based on lesser changes in these parameters observed in isolation or in association with other safety-related abnormalities. Sponsor must be informed immediately if dosing for individual participants is stopped or put on hold.

Stopping Rules

Stopping rules are applicable for the following situations if there are any safety concerns found in terms of general, cardiovascular, and laboratory criteria:

- Part A:SRC may decide not to proceed with the Part B
- Part B: iSMC may recommend not to proceed with the Part C

The following are the detailed criteria:

General Criteria

The study will be put on temporary hold (Part A: defined as cessation of Part B initiation) pending further safety data analysis if any of the following criteria occurs in participants receiving AZD8233:

- At least one SAE considered at least possibly related to the IMP administration.
- At least one severe non-serious AEs considered as, at least, possibly related to the IMP administration) in ≥ 2 participants, independent of within or not within the same System Organ Class (SOC).

The SRC will carefully review the totality of data, taking into account moderate non SAEs at least possibly related to the IMP administration in unblinded fashion and their relations to PD effects (if available), the number of participants in whom they occur, concurrency of more than one within the same participant, and potential safety signals identified for other IMPs in the same class (mechanistic and/or chemical). The SRC will also consider differences between Part A and Part B, including but not limited to dosing regimen, as well as available overall safety and PK/PD conclusions from other AZD8233 studies (including Study D7990C00002 and Study D7990C00003).

Cardiovascular Criteria

- Two or more participants who receive AZD8233, have QT (ECG interval measured from the onset of the QRS complex to the end of the T wave) interval corrected (QTc) prolongation, defined as the QT interval corrected for heart rate using Fridericia's formula (QTcF) > 500 ms, or a prolongation from baseline of > 60 ms, confirmed (persistent for at least 5 min) and determined post-dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG.
- Two or more participants who receive AZD8233, have tachycardia defined as resting supine heart rate > 125 bpm persisting for at least 10 minutes.
- Two or more participants who receive AZD8233, have symptomatic bradycardia defined as resting supine heart rate < 45 bpm or asymptomatic bradycardia defined as resting supine heart rate < 30 bpm while awake persisting for at least 10 minutes.
- Two or more participants who receive AZD8233, develop hypertension, defined as an increase by > 40 mmHg from baseline or in resting supine SBP above 180 mmHg and persisting for at least 10 minutes.
- Two or more participants who receive AZD8233 develop hypotension, defined as an asymptomatic decrease of > 20 mmHg for SBP to below 70 mmHg persisting at least 10 minutes, or a symptomatic SBP decrease of > 20 mmHg (excluding vasovagal reaction).

Laboratory Findings

- One or more participants who receive AZD8233 fulfill Hy's Law (HL) defined as an increase in AST or ALT ≥ 3 ×ULN and TBL ≥ 2 × ULN, where no other reason can be found to explain the combination of increases, e.g., elevated serum ALP indicating cholestasis, viral hepatitis, or another drug. The elevations do not have to be at the same time or within a specified time frame (see Appendix E for follow-up procedures).
- Two or more participants who receive AZD8233 have confirmed > 3 × ULN of either ALT or AST or > 2 × ULN for TBL or ALP.
- Two or more participants who receive AZD8233 have confirmed leukocyte count < 2.0 × 10^9/L.
- Two or more participants who receive AZD8233 have confirmed neutrophil count < 1.0 × 10^9/L.
- Two or more participants who receive AZD8233 have confirmed platelet count < 75 × 10^9/L.
- Two or more participants who receive AZD8233 have a platelet count reduction of 50% or more from baseline.
- Two or more participants treated with AZD8233 have confirmed increase in serum creatinine (SCr) > 0.3 mg/dL (26.5 µmol/L) from baseline.

- Two or more participants who receive AZD8233 have confirmed SCr > 2 × baseline, when there is no other reason to explain the increase.

[Part B]

- Confirmed platelet count < 75 × 10^9/L
- HL, defined as an increase in AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases
- Confirmed > 3 × ULN of either ALT or AST or > 2 × ULN for TBLor ALP
- Confirmed increase in serum creatinine of 0.3 mg/dL from baseline
- Confirmed 25% decline in eGFR from baseline
- Confirmed new-onset hematuria, albuminuria (UACR ≥ 300 mg/g), or proteinuria (UPCR ≥ 500 mg/g)
- Hypersensitivity reaction CTCAE grade 3 or higher

If a participant discontinues study treatment, he or she will be encouraged to return to the study site for the Early Discontinuation Visit (EDV) (see the SoA). Where possible, the EDV should be at the next visit according to the original visit schedule, unless consent is withdrawn from further study participation. To secure recommended safety follow-up, participants attending an EDV should also be asked to continue to return for their originally scheduled visits for a total of three months, unless they are unable to or unwilling to return. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing 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).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- 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 if he/she still agrees for existing samples to 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 out in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the 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.

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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed. Assessments scheduled at the same time may be initiated based on the sequence below.
  1 ECG
  2 Vital signs (SBP and DBP), pulse rate, and temperature, if appropriate
  3 Blood sampling
  4 Dose administration

  Pre-dose assessments may be performed within 30 minutes prior to dosing for Part A and Part C, and 60 minutes prior to dosing for Part B.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if 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.
- 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.

[Part A]

The study is divided into a treatment period and a follow-up period. The treatment period starts after the screening visits (Visit 1: Day −28 to Day −4; Visit 2: Day −1 to Day 3). During Visit 1, the participants will be checked for eligibility and enrolled in the study. Additional samples will be collected at Visit 2. Approximately 11 participants will be randomized at Visit 2 (Day 1) in an 8:3 ratio to SC injections of AZD8233 (planned doses of CCI) or matching placebo. AZD8233 or placebo will be administered subcutaneously on Days 1, 8, 29, and 57. The treatment phase will be 58 days (8 weeks) with AZD8233 or placebo. Thereafter, the participants will continue in a follow-up period for 14 weeks; the final follow-up visit will be performed on Week 24 (16 weeks after the last dose of AZD8233 or placebo).

[Part B]

The study is divided into a treatment period and a follow-up period. The treatment period starts after the screening visits (Visit 1: Day −28 to Day −10; Visit 2: Day −7 to Day −4). During Visit 1, the participants will be checked for eligibility and enrolled to the study. Additional samples will be collected at Visit 2. Approximately 60 participants will be randomized at Visit 3 (Day 1) in a 1:1:1 ratio to SC injections of AZD8233 (planned doses of

CCI , and CCI) or matching placebo. AZD8233 or placebo will be administered subcutaneously on Visits 3, 6, and 8. The treatment phase will be 84 days (12 weeks). Thereafter, the participants will continue in a follow-up period for 12 weeks; the final follow-up visit will be performed on Week 24 (up to 16 weeks after the last dose of AZD8233 or placebo).

[Part C]

The study is divided into a treatment period and a follow-up period. The treatment period starts after the screening visits (Visit 1: Day −28 to Day −4; Visit 2: Day −1 to Day 3). During Visit 1, the participants will be checked for eligibility and enrolled in the study. Additional samples will be collected at Visit 2. Approximately 11 participants will be randomized at Visit 2 (Day 1) in an 8:3 ratio to SC injections of AZD8233 (planned doses of CCI) or matching placebo. AZD8233 or placebo will be administered subcutaneously on Days 1, 29, and 57. The treatment phase will be 58 days (8 weeks) with AZD8233 or placebo. Thereafter, the participants will continue in a follow-up period for 14 weeks; the final follow-up visit will be performed on Week 24 (16 weeks after the last dose of AZD8233 or placebo).

General description of visits:

[Part A/Part C]

Visit 1 (enrollment): At Visit 1 (Day −28 to Day −4), participants will be asked to sign the informed consent. The participants' demographics and medical history, including smoking and alcohol consumption history, will be recorded in an eCRF. A complete physical examination must be performed. Vital signs, height, BMI, and ECG must be checked, as well as blood and urine sample collection.

Visit 2 (randomization): Visit 2 (Day −1 to Day 3) should be performed within 28 days of Visit 1. Participants should be admitted on Day −1 and will be discharged after the results from the 48 hours post-dose assessments have been reviewed by the Principal Investigator.

Blood sampling for LDL-C, PCSK9 and other lipid parameters should be taken in the morning after a 10 hour fasting. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters.

On Day −1, eligibility criteria must be verified by checking screening labs and inclusion/exclusion criteria. An abbreviated physical examination must be performed. Blood and urine samples will be obtained prior to administration of study intervention in fasted state. Vital signs and BMI will be checked. Cardiac telemetry should be performed for at least 4 hours.

On Day 1, he/she will be randomized in IXRS, and the study intervention will be administered

as an SC injection.

An abbreviated physical examination must be performed. Blood and urine samples will be obtained prior to administration of study intervention in fasted state. An ADA sample will be obtained pre-dose. Vital signs, ECG, and cardiac telemetry will be performed.

On Day 3, the participant will be discharged after the results from the 48 hours post-dose assessments have been reviewed by the Principal Investigator.

Visits 3 and 6 (Part A:treatment visit): Visit 3 (Day 8) and Visit 6 (Day 29 ± 1 day) are planned as clinical visits. At Visit 3 and Visit 6, the study intervention will be administered as an SC injection. Blood sampling for LDL-C, PCSK9, and other lipid parameters should be taken in the morning after a 10-hour fast. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters. Blood and urine sampling must be performed prior to administration of study intervention. PK sampling must be done pre-dose. An abbreviated physical examination, ECG, and vital signs examination must be performed prior to administration of study intervention. At Visit 6, the ADA sampling must be done pre-dose.

Visits 3 (Part C:non-treatment visit): Visit 3 (Day 8) is planned as clinical visits. Blood sampling for LDL-C, PCSK9, and other lipid parameters should be taken in the morning after a 10-hour fast. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters. Blood and urine sampling must be performed. PK sampling must be done. An abbreviated physical examination, ECG, and vital signs examination must be performed.

Visits 6 (Part C:treatment visit): Visit 6 (Day 29 ± 1 day) is planned as clinical visits. At Visit 6, the study intervention will be administered as an SC injection. Blood sampling for LDL-C, PCSK9, and other lipid parameters should be taken in the morning after a 10-hour fast. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters. Blood and urine sampling must be performed prior to administration of study intervention. PK sampling must be done pre-dose. An abbreviated physical examination, ECG, and vital signs examination must be performed prior to administration of study intervention. The ADA sampling must be done pre-dose.

Visits 4, 5, 7, and 8 (non-treatment visit): Visit 4 (Day 15 ± 1 day), Visit 5 (Day 22 ± 1 day), Visit 7 (Day 36 ± 1 day), and Visit 8 (Day 44 ± 1 day) are planned as clinical visits. At Visit 5 and Visit 8, blood sampling for platelet count must be done. Blood sampling for LDL-C, PCSK9, and other lipid parameters should be taken in the morning after a 10-hour fast. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9 and other lipid parameters. PK sampling must be done.

Visit 9 (treatment visit): Visit 9 (Days 56-59; ± 1 day) is planned for hospitalization. Participants should be admitted on Day 56 and will be discharged after the results from the 48 h post-dose assessments have been reviewed by the Principal Investigator.

On Day 56, blood sampling for platelet count must be done.

On Day 57, the study intervention will be administered as an SC injection. Weight will be checked. ADA, blood, and urine sampling must be performed prior to administration of study intervention. Blood sampling for LDL-C, PCSK9, and other lipid parameters should be taken in the morning after a 10-hour fasting. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, PCSK9, and other lipid parameters. Vital signs, ECG, and cardiac telemetry to be performed. An abbreviated physical examination must be performed 24 hours post-dose. PK sampling must be done.

Follow-up contact (Part A: Day 64 + 2 days): One telephone contact from a participant's site (or an investigator) to assess AEs.

Follow-up visits (Visits 10-16): At all follow-up visits, ECG and an abbreviated physical examination are required, and vital signs, blood, and urine samples are to be checked.

An ADA sampling is to be performed at Visit 10 (Week 2 after last dose; ± 2 days). At all follow-up visit PK sampling is to be performed.

Early Discontinuation Visit: The EDV may take place any time during the study, in case a participant discontinues study treatment prior to Visit 9 (where last dose of study treatment is administered). The same assessments as done during the final follow-up visit will be performed. See Section 7.1.

Final follow-up visit (Visit 17): The final follow-up visit will be performed in Week 16 after last dose (± 2 days). PK and ADA sampling is to be performed. A complete physical examination must be performed on the visit, and body weight, BMI, vital signs, body temperature, and ECG are to be checked. Blood and urine sampling is to be obtained.

The maximum blood volume to be drawn from each participant will not exceed 800 mL over the duration of the study period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

[Part B]

Visit 1 (enrollment) and Visit 2: At Visit 1 (Day −28 to Day −10), participants will be asked to sign the informed consent and optional informed consent for future genetic research sample. Participant demographics and medical history, including smoking and alcohol consumption history, will be recorded in the eCRF. A complete physical examination must be

performed. Vital signs, height, weight, BMI, and ECG must be checked, as well as blood and urine sample collection. Visit 2 (Day −7 to Day −4) will include an additional blood sample collection for LDL-C, PCSK9, and triglycerides.

Visit 3 (randomization): Visit 3 (Day 1) should be performed within 28 days of Visit 1. Participants are required to fast for at least 10 hours overnight prior to the visit; participants are permitted to drink water during this period of fasting until 1 hour before blood sampling. At Visit 3, the eligibility criteria must be verified by checking screening labs and inclusion/exclusion criteria. A complete physical examination must be performed. Blood and urine samples are to be obtained prior to administration of study intervention in fasted state. An ADA sample will be obtained pre-dose. Vital signs and ECG are to be checked. If the participant fulfills all inclusion criteria and none of the exclusion criteria, he/she will be randomized in IXRS, and the study intervention will be administered as an SC injection.

Treatment visits (Visits 4- 9): Visit 4 (Day 8 ± 1 day), Visit 5 (Day 22 ± 2 days), Visit 6 (Day 29 ± 2 days), Visit 7 (Day 43 ± 2 days), Visit 8 (Day 57 ± 2 days) and Visit 9 (Day 71 ± 2 days) are planned as clinical visits. At Visits 6 and 8, the study intervention will be administered as an SC injection. Participants are required to fast for at least 10 hours prior to Visits 4, 6, and 8. They are permitted to drink water during this period of fasting until 1 hour before blood sampling. Blood and urine sampling must be performed prior to administration of study intervention. PK sampling to be performed at Visits 4, 6, 7, 8, and 9. At Visits 4, 6, and 8, PK and ADA sampling must be done pre-dose when the study intervention will be administered. An abbreviated physical examination is required at the visits. Vital signs and blood and urine samples are to be taken at the visits. ECG must be performed at Visits 4, 6 and 8.

Follow-up visits (Visits 10-15): ECG must be performed at Visit 10 (Day 85 ± 2 days), Visit 11 (Day 99 ± 2 days), Visit 13 (Day 127 ± 2 days), and Visit 15 (Day 155 ± 2 days). At all follow-up visits, an abbreviated physical examination is required, and vital signs, blood, and urine samples are to be checked. PK and ADA sampling is to be performed at Visit 10, Visit 12 (Day 113 ± 2 days), and Visit 14 (Day 141 ± 2 days).

Early Discontinuation Visit: The EDV may take place any time during the study, in case a participant discontinues study treatment prior to Visit 8 (where the last dose of study treatment is administered). The same assessments as during the final follow-up visit will be performed. See Section 7.1.

Final follow-up visit: The final follow-up visit will be performed on Day 169 (± 2 days). PK and ADA sampling is to be performed. A complete physical examination must be performed at the visit, and body weight, BMI, vital signs, and ECG are to be checked. Blood and urine sampling is to be obtained.

The maximum blood volume to be drawn from each participant will not exceed 650 mL over the duration of the study period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Include the maximum amount of blood collected from each participant over the duration of the study and if any repeat or unscheduled samples may be taken, as appropriate.

8.1 Efficacy Assessments

Please see Section 8.5.3 for assessments which will be used for primary and key secondary efficacy analyses.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

- A complete physical examination will include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Body weight should be measured in light indoor clothes without shoes, after using the bathroom.

The physical examination will be performed at timepoints as specified in the SoA. BMI will be calculated at the time points specified in the SoA.

8.2.2 Vital Signs

Vital signs (blood pressure, pulse, and temperature) will be performed at timelines as specified in the SoA.

- Blood pressure and pulse measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure (BP) and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the eCRF. If the result of the

pulse is obtained automatically when BP assessed with automated device, 3 consecutive pulse readings will be recorded at intervals of at least 1 minute. For time points where ECG recording precedes vital sign measurement, the 10-minute rest in the supine position prior to the ECG suffices for the rest prior to vital sign measurement.

8.2.3 Electrocardiograms

An electrocardiogram will be performed at timepoints as specified in the SoA.

12-lead Safety Electrocardiogram

[Part A/Part C]

At the time points indicated in the SoA (Table 1 and Table 3), 12-lead safety ECGs will be obtained after the participant has rested in supine position for at least 10 minutes (can be reduced to 5 minutes at collection time points). The following parameters or time intervals will be recorded for each ECG: RR, PR, QRS, QT, QTcF, and heart rate (HR). When the 12-lead safety ECG time points coincide with the telemetry time points, the 12-lead safety ECG should be measured at the same time.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant, and the reason for the abnormality will be recorded. Throughout the study, clinically relevant new findings or worsening of a preexisting finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded. The Investigator may add additional 12-lead safety ECG assessments in case of any abnormal findings or if considered required by the Investigator for any other safety reason. These assessments should be entered as an unscheduled assessment.

[Part B]

12-lead ECG will be obtained after the participant has rested in supine position for at least 10 minutes. The following parameters or time intervals will be recorded for each ECG: RR, PR, QRS, QT, QTcF, and HR.

The same recorder should be used for each participant at each time point, if possible.

From the ECG data, the following parameters will be derived:

- QTcF will be calculated as $QTcF = QT \times RR^{-1/3}$, where the QT interval is in milliseconds and the RR interval is in seconds.
- Heart rate will be calculated, based on the RR interval as HR = 60 / RR interval, where the RR interval is in seconds.

Calculation of derived parameters will be performed after averaging of QT and RR data.

The ECG data will be averaged on an individual basis before performing the derivations above and prior to calculation of any changes from baseline or descriptive statistics. For each participant, it will be done as follows: the mean value of all measurements will be taken provided that at least 2 measurements are present (and at least 3 consecutive beats were analyzable in each ECG) or else, the averaged value at the corresponding target time point will be set to missing.

ECG results will be listed by treatment and dose level of AZD8233 for each participant and time point and will include all individual and averaged values of PR, RR, QRS, QT interval, and the derived values of QTcF and HR (RR). All averaged and derived parameters will have changes from baseline derived and presented.

Descriptive statistics will be presented by treatment and dose level of AZD8233, time point for averaged values and changes from baseline of averaged values of PR, RR, QRS, QT; derived values and changes from baseline for QTcF and HR will also be included. The baseline for the ECG measurements will be the pre-dose assessment on Day 1.

Outliers with respect to QTcF will also be tabulated for the following categories:

Absolute value > 450 ms and ≤ 480 ms

Absolute value > 480 ms and ≤ 500 ms

Absolute value > 500 ms

Increase from baseline > 30 ms and ≤ 60 ms

Increase from baseline > 60 ms

The Investigator will make an overall evaluation of the ECG as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant, and the reason for the abnormality will be recorded on the eCRF.

Abnormal values shall not be recorded as AEs unless deemed clinically significant. The printout of the ECG is to be signed, dated, and filed in the ISF along with a signed and dated copy (if the printouts are not on archive-quality paper).

The Investigator may perform additional 12-lead ECG assessments in case of any abnormal findings or if considered required by the Investigator for any other safety reason. These assessments should be entered as an unscheduled assessment.

Cardiac Telemetry

[Part A/Part C]

Real-time cardiac telemetry will be performed for 4 hours on Day −1 and from 30 minutes pre-dose until 24 hours post dose on Days 1 and 57. The telemetry monitoring system will be reviewed by the Investigator and paper printouts of any clinically important events will be stored as source data.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis will be taken at the visits indicated in the SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

All laboratory variables will be analysed at Labcorp central lab. Samples will be collected, handled, labelled, stored, and shipped as detailed in the laboratory manual.

The following laboratory variables will be measured.

[Part A/Part C]

Hematology

WBC count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Hemoglobin (Hb)	Monocytes absolute count
Hematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular haemoglobin (MCH)	Platelets absolute count
Mean corpuscular haemoglobin concentration (MCHC)	Reticulocytes absolute count

Clinical Chemistry

Sodium	ALP
Potassium	ALT
Blood urea nitrogen (BUN)	AST
Creatinine	Gamma glutamyl transpeptidase (GGT)
Calcium	Total bilirubin
Phosphate	Direct bilirubin
Glucose (fasting)	Indirect bilirubin

Creatine kinase (CK)	Glutamate dehydrogenase (GLDH)
Bicarbonate	Lactate dehydrogenase (LDH)
HbA1c	Uric acid
Serum β-human chorionic gonadotropin (β-hCG)（women only)	FSH (women only)
	Luteinizing hormone (LH) (women only)

Subject's eGFR will be calculated from serum creatinine (SCr) concentration, according to the Japanese equation as follows:
eGFR = 194 × SCr (mg/dL) $^{-1.094}$ × Age $^{-0.287}$ × α, where α is 1 for males and 0.739 for females.
Liver Panel: ALP, ALT, AST, GGT, Total bilirubin, Direct bilirubin and Indirect bilirubin

Coagulation

aPTT	Prothrombin time
	International normalized ratio (INR)

Urine renal safety biomarkers

Albumin	N-acetyl-beta-D-glucosaminidase (NAG)
Total protein	Kidney Injury Molecule-1 (KIM-1)
Creatinine	Neutrophil gelatinase-associated lipocalin (NGAL)
Clusterin[a]	Osteopontin
Cystatin-C	UACR

[a] PFC index. Refer PFC Index and Composite for details.

Other laboratory assessments

Complement activation panel (C3a [Part A only], Bb, C5a)	High-sensitive C-reactive protein (hs-CRP)
Dipstick urinalysis for hematuria	Dipstick urinalysis for human chorionic gonadotropin (hCG)(women only)

PFC Index and Composite Measure

The renal safety biomarker panel (called PFC index) will be monitored in healthy volunteers and explored in subjects with dyslipidemia. The PFC index is a Food and Drug Administration (FDA) qualified safety composite biomarker panel to be used in conjunction with traditional measures to aid in the detection of kidney tubular injury in Phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause renal tubular injury in humans. The PFC index was developed by The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Kidney Safety Biomarker Project Team and the Critical Path Institute's (C-Path) Predictive Safety Testing Consortium Nephrotoxicity Working Group

(FNIH BC/PSTC NWG). The PFC index includes clusterin, cystatin-C, osteopontin, N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL).

Composite Measure

The composite measure (CM) is a geometric mean (GM) of the fold changes from baseline of the uCr-normalised 6 urine biomarkers (called PFC index): clusterin, cystatin C, KIM 1, NAG, NGAL, and osteopontin.

The CM and the ratio between IMP and control will be calculated as follows:

- For each subject, calculate the (uCr)-normalised fold-change from baseline for each biomarker. Define this as FC_{ij} for subject i and biomarker j, where j = 1, 2,…,6.
- For each subject i, calculate CM:

$$CM_i = exp\left\{\sum_{j=1}^{6}\frac{1}{6}\log(FC_{ij})\right\}$$

- Calculate the GM of CM for cohort k (k = Drug, Control):

$$\overline{CM}_k = exp\left\{\sum_{i=1}^{m}\log(CM_i)/m\right\}$$

- Calculate the ratio of the GMs for the two cohorts:

$$GM_{ratio} = \overline{CM}_{Drug}/\overline{CM}_{Control}$$

[Part B]

Hematology

WBC count	Neutrophils absolute count
RBC count	Lymphocytes absolute count
Hb	Monocytes absolute count
HCT	Eosinophils absolute count
MCV	Basophils absolute count
MCHC	Platelets absolute count

	Reticulocytes absolute count

Clinical Chemistry

Sodium	GGT
Potassium	Total bilirubin
BUN	GLDH
Creatinine	LDH
Calcium	Bicarbonate
Phosphate	Uric acid
CK	AST
Direct bilirubin	ALT
Indirect bilirubin	FSH (women only)
ALP	LH (women only)
	β-hCG (women only)

Liver Panel: ALP, ALT, AST, GGT, Total bilirubin, Direct bilirubin and Indirect bilirubin

Coagulation

Prothrombin time	INR
aPTT	

Urinalysis

Urine human chorionic gonadotropin (hCG) (Women only)

Urinalysis dipstick test

Urinalysis (positive dipstick)

pH	Clarity/Appearance
Specific gravity	Nitrites
Glucose	Ketones
Blood	Leukocytes
Colour	Microscopic analysis (if positive for blood, nitrates or protein)
Protein	Urobilinogen

Urine renal safety biomarkers

Albumin	UPCR
Total protein	UACR
Creatinine	Estimated glomerular filtration rate (eGFR; by the Japanese equation)

Other laboratory assessments

	hs-CRP
Complement activation panel (Bb, C5a)	HbA1c

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

8.2.5 Other Screening Assessments

Other screening assessments referred to in the SoA (Table 1 ,Table 2 and Table 3) are shown below.

Viral serology (screening only)

[Part A/Part B/Part C]

HIV I	Hepatitis B surface antigen (HBsAg)
HIV II	Hepatitis C virus antibody

8.2.6 Injection Site Reactions

Injection site reactions should be reported using standard AE collection criteria. Details regarding the ISRs will be collected in a specific eCRF page.

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 can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised 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 AE and SAE Information

Adverse events will be collected from time of first dose throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing of the informed consent form.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention 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 AEs and SAEs

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. AstraZeneca 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 and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome
- Whether the AE is an injection site reaction or not

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- 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
- Description of AE

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 to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil 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 intervention, 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, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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 ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

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, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one 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 will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE

to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure (IB) for the AstraZeneca drug.

8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- 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 AstraZeneca.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/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 anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.3.8.2 Paternal Exposure

Male participants should refrain from fathering a child during the study and for 3 months following the final follow-up visit (see also Section 5.3.4). In case of pregnancy of the partner of a male participants, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following

the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. The pregnancy will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect) should, if possible, be obtained and documented.

8.3.9 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 medication error (see Section 8.3.7) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD8233 greater than the planned dose 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 on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see 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 see 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.

- Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining anti-drug antibody (ADA) sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, 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

[Part A/Part C]

Blood samples for the determination of plasma concentrations of AZD8233 and AZD8233 total full lengths ASOs will be collected for each treatment period as specified in the SoA. The concentration levels of AZD8233 total full lengths ASOs will be used to assess all the primary PK-parameters. Blood samples for a potential exploration of the plasma concentrations levels of unchanged AZD8233 will also collected as specified in the SoA.

Urine samples for the determination of urine concentrations of AZD8233 total full length ASOs will be collected for each treatment period as specified in the SoA.

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual.

[Part B]

Plasma samples will be collected for measurement of plasma concentrations of total full-length ASOs of AZD8233 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.

Plasma samples will be used to analyse the PK of AZD8233. Samples collected for this PK purpose may also be used to evaluate safety and efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

[Part A/Part C]

Blood and urine samples will be analyzed by Labcorp on behalf of AstraZeneca Research, using validated (plasma)/qualified (urine) assays, for determination of AZD8233 and AZD8233 total full lengths ASOs concentrations in plasma and AZD8233 total full lengths ASOs concentrations in urine. Full details of the analytical methods used will be described in a separate bioanalytical report.

[Part B]

Blood samples for determination of AZD8233 total full lengths ASOs concentrations in plasma will be analyzed by Labcorp on behalf of AstraZeneca Research, using validated (plasma)/qualified (urine) assays. Full details of the analytical methods used will be described in a separate bioanalytical report.

[Part A/Part B/Part C]

Placebo samples will not be analyzed, unless there is a need to confirm that correct treatment has been given to study participants.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report. In the event of safety concerns, blood samples collected for PK or PD analysis may be used for safety laboratory analysis at the discretion of the Investigator.

8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments (ADA) will be collected according to the SoA (Table 1, Table 2 and Table 3).

The presence or absence of ADAs will be determined in the plasma samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step.

Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination. Full details of the analytical method and analyses performed will be described in a separate bioanalytical report.

ADA samples may also be further tested for characterisation of the ADA response. Study results may be reported independently to ADA follow-up.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Participants that are ADA positive at the end of the study and that has more than 2-fold higher titers than at baseline with multiple dosing of AZD8233 will be asked to return to provide another sample after 3 months to evaluate whether or not ADAs persist. If positive ADA-results, and more than 2-fold higher titers than at baseline, subjects will be asked to return after an additional 3 months (i.e., 6 months after the end of study visit). If the sample is ADA positive at 6 months, the Investigator and AstraZeneca Physician will discuss additional actions and decide on future monitoring frequency. If 3 months (and 6months) have already passed at the time AstraZeneca confirmed a participant's sample of Visit 17 for Part A and Part C or Visit 16 for Part B was ADA positive, the investigator will ask the participant to return to the study site as soon as possible to provide ADA sample. Results of ADA at 3 months and 6 months after the end of study will not be recorded in the eCRF module or in the database. Participants with treatment-induced ADAs are considered ADA positive until levels have returned to within 2-fold of baseline or levels have dropped 97% from maximum.

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Blood samples will be collected for measurement of PCSK9 and dyslipidemia (Table 7). Blood samples for the determination of concentrations of PCSK9 and to evaluate the lipid parameters will be collected at the time points specified in the SoA (Table 1, Table 2 and Table 3). The results of PCSK9, LDL-C and other lipid assessments except during screening period will be masked to the subjects and sites.

Table 7 Pharmacodynamic Laboratory Assessments

[Part A/Part C]

LDL-C	PCSK9

Levels of other lipid parameters including;

TC	ApoA1
HDL-C	ApoB

Non-HDL-C	Lipoprotein(a) [Lp(a)]
VLDL-C	Triglycerides

[Part B]

LDL-C	Biomarkers analyses
PCSK9	

Levels of other lipid parameters including;

TC	ApoB
HDL-C	Lipoprotein(a) (Lp[a])
Non-HDL-C	Triglycerides
VLDL-C	Remnants cholesterol
ApoA1	

For storage, reuse, and destruction of pharmacodynamic samples, see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of mandatory samples for biomarker analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

- Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.
- Collection and storage of blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies), and tolerability related to AZD8233 treatment or cardiometabolic diseases are part of this study.
- Biomarkers to be taken:
  - Blood (plasma) and urine sample analyses
  - Targeted and unbiased -omics approaches for evaluation of plasma and/or urine samples for PD biomarkers and biomarker research relative to safety, tolerability, and PK profile related to AZD8233 treatment.

8.6.2 Collection of Optional Biomarker Samples

Not applicable.

8.6.3 Other Study Related Biomarker Research

Not applicable.

8.7 Optional Genomics Initiative Sample

[Part A/Part C]

Not applicable

[Part B]

The collection of optional samples for biomarker research is also part of this study as specified in the SoA and is subject to agreement to optional ICF.

Six mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

[Part A]

No formal statistical hypothesis will be set. However, the safety and tolerability after multiple dosing of AZD8233 CCI will be descriptively evaluated.

[Part B]

The study hypothesis to be tested is treatment effect of AZD8233 across different dose levels compared to placebo. The null hypotheses for these tests are that the absolute change in log-transformed LDL-C for AZD8233 at some dose level is equal to the absolute change in log-transformed LDL-C for placebo.

[Part C]

No formal statistical hypothesis will be set. However, the safety and tolerability after multiple dosing of AZD8233 CCI will be descriptively evaluated.

9.2 Sample Size Determination

[Part A / Part C]

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations, but on experience from similar Phase I studies previously conducted with other compounds. Eight Japanese subjects on active drug are considered to be sufficient to confirm a tendency for safety, PK, and PD data.

[Part B]

The primary endpoint is assumed to follow a log-normal distribution with a standard deviation of 0.3. Under these assumptions, at least 18 evaluable patients per arm yield more than 95% power to detect a difference of 0.693 on the log-scale (corresponding to 50% relative reduction) compared to placebo in a two-sided t-test at a 5% significance level. The same number of evaluable patients would provide approximately 89% power to detect a difference of 0.33 between the CCI group and CCI group. Accounting for 10% drop-out, 60 patients in total will be randomized.

Note: “Enrolled” means a participant’s, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered” screen failures”, unless otherwise specified by the protocol.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who signed the ICF.
Randomly assigned to study intervention	All participants who were randomized. Participants will be analyzed according to the treatment to which they were randomized.
Full Analysis Set	All randomized participants who received at least 1 dose of study intervention, in accordance with the intention-to-treat principle. Participants will be included in the analysis according to the treatment to which they were randomized. This is the primary analysis set.
Safety analysis set	All participants randomly assigned to study treatment who took at least 1 dose of study treatment and for whom any post-dose data are available. Participants will be analysed according to the treatment which they actually received. If a participant received study intervention from the wrong kit for only part of the treatment duration and then switched to another, the associated treatment group for that participant would be the treatment group that participant was randomized to.
PK analysis set	All participants who received at least one dose of study treatment and who had evaluable PK data.

Any important protocol deviations from randomized treatment will be listed and considered when interpreting the data. Important protocol deviations will be defined in the Non-compliance Handling Plan (NHP).

9.4 Statistical Analyses

The statistical analysis plan will be finalised prior to Data Base Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Unless otherwise stated, the safety analysis set will also be used for the presentation of all demographic data. If not otherwise specified, baseline refers to the last measurement prior to study intervention administration.

Statistical tests will be performed using two-sided test at a 5% significance level, if not explicitly stated otherwise. The SAS® version 9.3 or higher will be used for the data analysis. All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables. Demographic and baseline characteristics will be presented as follows: for continuous variables, the number of non-missing observations, mean, Standard Deviation (SD), Standard Error of the Mean (SEM), 95% Confidence Interval (CI) of the mean, median,

first and third quartiles, minimum and maximum as appropriate ; for categorical variables, counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by time point of assessment as appropriate.

Baseline for efficacy assessments refers to the last measurements obtained before randomization. Baseline for safety assessments refers to the last measurements obtained before the first dose of IMP.

Primary estimand is hypothetical estimand, if all the patients had continued treatment until Week 12. The primary analysis will be carried out with likelihood based repeated measure model, which would provide unbiased treatment effect under the assumption of Missing At Random. Sensitivity analyses including different type of estimands will be detailed in the statistical analysis plan.

9.4.2 Efficacy

[Part B]

The analysis and presentation of efficacy and exploratory endpoints will be based on participants in the full analysis set.

For selected efficacy variables, if not specified otherwise, a mixed model for repeated measures will be fitted using log-transformed data and results transformed back to geometric mean ratios for the purpose of presentation and interpretation. The mixed model for repeated measures will include the relevant log-transformed baseline biomarker value as a covariate. Time point (visit number), treatment, and the interaction between time point and treatment will be included as factors. The response variable will be change from baseline in log-transformed biomarker value. The model will be fitted with an unstructured covariance structure, and the Kenward-Roger correction applied to obtain the degrees of freedom. Estimation of the treatment effect will be done for each visit after baseline. In case of issues when fitting the model to the data, a hierarchical model fitting procedure will be described in the statistical analysis plan.

9.4.2.1 Primary Endpoint(s)

[Part B]

The primary efficacy endpoint is change from baseline in log-transformed LDL-C at the end of Week 12, which will be fitted using a mixed model for repeated measures.

Comparisons of the change from baseline between the treatment arms will be done using the least square mean difference between treatment groups as estimated by the fitted model.

Pair-wise comparisons will be done between each AZD8233 dose (mid and low) vs. placebo.

In addition, pair-wise comparisons between AZD8233 dose groups will also be done for reference.

The geometric mean ratio will be plotted over time by treatment group.

9.4.2.2 Secondary Endpoint(s)

[Part B]

Percent change from baseline in LDL-C in the original scale will be calculated for each participant and then compared between treatment groups using a mixed model for repeated measures.

The change from baseline of log-transformed PCSK9 will be fitted using a mixed model for repeated measures and least square mean differences between treatment groups will be estimated from the fitted model. Results will be presented on the log scale and as geometric mean ratios.

Levels of other lipid parameters will be summarized using descriptive statistics.

Development of ADA will be monitored for each participant, analysis and reporting of data related to ADA will be specified in the statistical analysis plan.

For each treatment, the mean percentage change from baseline of LDL-C and PCSK9 levels will be plotted over time.

Pharmacokinetics

[Part A/Part C]

The PK analysis set will consist of all subjects in the safety analysis set who received AZD8233 and who have evaluable PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

The exclusion of any subjects or time points from the calculation of the PK parameters will be documented by the PK scientist, including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only. Concentration data for subjects excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

[Part B]

If data permits, a population PK model will be developed, possibly with the support of PK data from studies D7990C00001 and D7990C00002 and additional clinical studies with

AZD8233, using nonlinear mixed effects regression analysis in NONMEM. Furthermore, if data allows, the population PK model may be coupled with separate PD models for PCSK9 and LDL-C.

All PK/PD modelling will be described in a separate data analysis plan. Moreover, the results of any such modelling will be provided in a separate population PK/PD report (as an appendix to the CSR or as a stand-alone report).

Plasma concentration data of AZD8233 will also be summarized by descriptive statistics per sampling time point in the CSR.

9.4.3 Safety

[Part A/Part B/Part C]

All safety analyses will be performed on the safety analysis set. Safety variables are AEs, vital signs, 12-lead ECGs, and laboratory assessments. All safety data (scheduled and unscheduled) will be presented in the data listings.

Safety variables will be summarised by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum and maximum [and geometric mean and coefficient of variation, if applicable]) for continuous data and absolute and relative frequencies for categorical data.

Adverse events will be summarised by Preferred Term and System Organ Class using MedDRA terminology. Adverse events that led to withdrawal, SAEs, AEs by severity, and causally related AEs will also be presented. All AE summaries will be done by treatment group.

Injection site reactions will be considered an AE of special interest and will be listed.

Clinical laboratory data and ECG parameters will be summarized by treatment group and visit.

Use of concomitant medication will be reported.

9.4.4 Other Analyses

Not applicable.

9.5 Interim Analyses

In Part B, an interim analysis is planned. An interim analysis will include all participants' data available until data cut-off, including the primary/secondary analysis at Week 12. The Sponsor will be unblinded at the time of interim analysis, but investigators, participants and site-staff

will not be informed of assigned treatment in order to maintain integrity as much as possible. The data cut-off date is defined as a day when all participants have completed 12 weeks of treatment (Visit 10).

9.6 Data Monitoring Committee

An iSMC will be used for monitoring of unblinded safety data in the Part B. For details on the iSMC to be used in this study, please 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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
  - Japan Ministerial Ordinance on Good Clinical Practice for drugs No. 28 of March 27, 1997 (in this Protocol called J-GCP) and the notification of amendments to the J-GCP
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) by the head of the medical institution 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.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation (CRO) but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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, IRB/ IEC, and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents]. The head of the medical institution will also receive the safety report from the sponsor 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 1 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 authorised 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 authorised representative will be required to sign a statement of informed consent that meets the requirements of J-GCP in addition to 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- 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 authorised 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 authorised representative.

- [Part A] Participants who are rescreened are required to sign a new ICF.
- [Part B/Part C] When participants will be rescreened more than 28 days from the initial informed consent, participants 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 authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use 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 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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca in consultation with AstraZeneca Patient Safety representatives. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

[Part A]

The SRC meetings will be prepared and conducted in a blinded manner to keep all attendees blinded prior and during the meeting. All personnel involved in PD and PK evaluation of data (if available) may be unblinded for the evaluation of these data. Alternatively, PK and PD data will be provided in a blinded manner for the SRC review. Separate unblinded SRC meetings may also be held as needed.

The SRC will carefully review the totality of data, taking into account moderate non-serious AEs at least possibly related to the IMP administration and their relation to PD effects (if available), the number of subjects in whom these AEs occur, concurrency of more than 1 within the same subject and potential safety signals identified for other IMPs in the same class

(mechanistic and/or chemical).

The committee will be operated in accordance with the SRC Charter.

[Part B]

An iSMC comprised of independent experts will be conducted to review the unblinded safety study data and ensure that study subjects are not exposed to undue risk. The iSMC is responsible for assessing unblinded study safety data according to an agreed upon schedule and making a recommendation to the study team. An iSMC charter gives details of precise roles and responsibilities and procedures and the committee will be operated in accordance with the iSMC Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on 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 electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator and the head of the medical institution 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- 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, Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised 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, J-GCP, 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 15 years after study completion unless local regulations or institutional policies require a longer retention period. For Japan the investigator, the study site, IRB and the sponsor should retain the records according to J-GCP. 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 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.
- Definition of what constitutes source data can be found in source data verification plan.

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 is the first site open and will be the study start date.

The sponsor 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 promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. For Japan, AstraZeneca will promptly inform the head of the medical institute, and the head of the medical institute will inform the investigators and the IECs/IRBs. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may 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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line 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 adverse event is the development of any untoward medical occurrence in a patient 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 unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example 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 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** 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 judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, 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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 judgement 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, hospitalisation, disability or incapacity but may jeopardise 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 judgement 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 anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- 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 a 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 a 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 if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs 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 aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca 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 recognised feature of overdose of the drug?
- 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 Medication Error

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

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

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/ Randomisation and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)

- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication 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 centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst 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.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle 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 AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca 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 are already analysed, AstraZeneca is not obliged to destroy the results of this 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 AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca 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 the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (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 UN 3373 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

- AstraZeneca 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 health care 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.

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 fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol 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
  - Healthy Volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

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 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 3 pre-dose. If, for any reason, the sample is not drawn pre-dose on Visit 3 (D1), it may be taken at any visit until the Final follow-up/EDV visit. 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 screening visit, 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. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

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 AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. 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 centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, 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, an AstraZeneca 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 at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organisations 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 organisations 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 (PHL) cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL 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, PHL 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 Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL 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 ≥ 3 × ULN **together with** TBL≥ 2× 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 ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL 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 PHL 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 ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

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

- Notify the AstraZeneca 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 PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention.
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL 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 Clinical Study Protocol (CSP) process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to 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. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available

#**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 total bilirubin) 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 PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca 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 AstraZeneca standard processes.

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

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL 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 HL, 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 IMP 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 HL criteria are still met. Update the previously submitted PHL 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 HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] 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 (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive

E 7 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

Appendix F Actions in Case of Development of Thrombocytopenia or Uninterpretable Platelet Counts After Administration of ASOs

Recommended actions include reassessment of platelet count, adjustment of monitoring frequency (platelet count < 100,000/μL), assessment of additional laboratory parameters (platelet count < 75,000/μL), referral to a haematologist (platelet count ≤ 50,000/μL) and start of supportive treatment with corticosteroids (platelet count ≤ 30,000/μL). **Drug discontinuation according to the defined stopping criteria is essential in participants with suspected thrombocytopenia.**

F 1 Actions in Case of Uninterpretable Platelet Count Results

Participants with uninterpretable platelet laboratory results due to clumping, haemolysis or quantity not sufficient must be reassessed within 2 days. Dosing is not allowed to proceed until the Investigator has determined that the results are within acceptable range according to the defined stopping criteria.

In a clinical study with the ASO inotersen diagnosis and treatment of severe thrombocytopenia were delayed in some participants because of uninterpretable platelet counts due to clumping of platelets in the test tube. Platelet clumping in the test tube was most likely caused by a combination of ASO-induced antiplatelet immunoglobulin G (IgG) antibodies and the anticoagulant Ethylenediaminetetraacetic Acid (EDTA). If there is suspicion of EDTA mediated platelet clumping, a repeat platelet count using a different anticoagulant, e.g., sodium citrate or heparin, should be done as soon as possible and always before a new dose is given.

Thrombocyte Monitoring Frequency

Platelet Count (per μL)	Monitoring Frequency
> 100,000	Every 2 weeks
≥ 75,000 to < 100,000 or more than 50% reduction from baseline	Every week
< 75,000	Intensified monitoring; twice weekly to daily monitoring dependent of platelet count and rate of decline

Additional Laboratory Assessments (Platelet Count < 75,000/µL)

Peripheral smear
Fibrinogen split products or D-dimer on fresh blood
Citrated sample for platelets Coagulation panel (PT/INR, aPTT) CBC with reticulocytes and mean platelet volume (MPV)
Serum B12 and folate
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG, and IgM
Complement: total C3, total C4, Bb, C5a
hs CRP
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Antithyroid
To be performed at specialty lab(s):
Antiplatelet antibodies and Anti-PF4 assay
Antidrug antibody

F 2 Referral to Expert Haematologist Care

Participants that develop thrombocytopenia with platelet counts ≤ 50,000/µL should be referred to a haematologist for diagnostic and therapeutic management. This may include the additional laboratory tests described in the table above. Additional bone marrow aspiration and biopsy should be considered.

Supportive Treatment with Corticosteroids

Treatment of severe thrombocytopenia requires close communication among consulting

specialists. For major or life-threatening bleeding, platelet transfusions should be administered without delay. Because ASOs have been associated with immune-mediated thrombocytopenia it is strongly recommended that participants with platelet counts ≤ 30,000/µL receive glucocorticoid therapy (unless contraindicated). High dose steroids have been reported to reverse platelet decline and accelerate platelet recovery. Treatment guidelines for immune thrombocytopenia recommend: Dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; Prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (may require continuation with oral steroids after methylprednisolone) (Provan et al, 2010). Platelet count should be monitored closely during corticosteroid treatment. An increased or normalized platelet count is expected within two weeks of therapy. Once the platelet count normalizes or rises significantly and plateaus > 50,000/µL, no additional therapy is needed. **Participants should be followed until platelet count has been > 100,000/µL for 1 month** (see above table for monitoring frequency).

F 3 Reference

Provan et al, 2010
Provan D et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-186.

Appendix G Guidance for Definition of Anaphylactic/Hypersensitivity Reactions and Checklist for the Investigator

The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories). Refer to Sampson et al, 2006.

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
   (a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced Peak Expiratory Flow [PEF], hypoxemia)
   (b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that participant (minutes to several hours):
   (a) Infants and children: low SBP (age specific) or greater than 30% decrease in SBP.
   (b) Adults: SBP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Hypersensitivity Reactions – Checklist for the Investigator

At least the following should be checked. If "Yes," the diagnosis (preferably not symptoms) should be recorded as AE.

	Yes	No
Skin and subcutaneous events		
Urticaria		
Erythema		

	Yes	No
Pruritus		
Face oedema		
Eye oedema		
Tongue swelling		
Angioedema		
Respiratory compromise		
Bronchospasm		
Dyspnoea		
Cough		
Choking		
Stridor		
Respiratory arrest		
Cardiovascular events		
Cardiac arrest		
Cardiovascular insufficiency		
Hypotension		

Additional Samples to be Collected in Case of an Anaphylactic-like Reaction

In case of anaphylactic-like reaction, the blood samples for tryptase assessments should be taken 30, 60, and 120 minutes after the onset of event, if feasible.

In addition, samples for analysis of ADA should be taken at the day of the anaphylactic-like reaction, if feasible.

G 1 Reference

Sampson et al, 2006
Sampson HA et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-397.

Appendix H Statin Therapy

- atorvastatin 10 to 40 mg once daily
- rosuvastatin 2.5 to 20 mg once daily
- simvastatin 10 to 20 mg once daily
- pitavastatin 1 to 4 mg once daily
- fluvastatin 60 mg once daily

These statin therapies are selected by referring to moderate- or high-intensity statin therapy in the American College of Cardiology/American Heart Association (ACC/AHA) 2018 Guideline on the Management of Blood Cholesterol, and expected to lower LDL-C levels by ≥30% in Japanese patients.

Appendix I Abbreviations

Abbreviation or special term	Explanation
ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
Apo	Apolipoproteins
aPTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase/transaminase
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CK	Creatine kinase
CSP	Clinical study protocol
CSR	Clinical study report
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EDV	Early discontinuation visit
eGFR	Estimated glomerular filtration rate
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
GLDH	Glutamate dehydrogenase
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HCT	Haematocrit

Abbreviation or special term	Explanation
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HMG-CoA	3 hydroxy 3 methyl glutarylcoenzyme A
HR	Heart rate
hs-CRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive response technology
ISR	Injection Site Reaction
iSMC	internal Safety Monitoring Committee
IUD	Intrauterine device
IXRS	Interactive Voice/Web Response System
LDL	Low-density lipoprotein
LDL C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LLN	Lower limit of normal
Lp(a)	Lipoprotein(a)
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEF	Peak expiratory flow
PD	Pharmacodynamic(s)
PHL	Potential Hy's Law
PI	Principal investigator
PK	Pharmacokinetic(s)
QTcF	Corrected QT interval by Fredericia
RBC	Red blood cell
RTSM	Randomization and trial supply management
SAE	Serious adverse event

Abbreviation or special term	Explanation
SBP	Systolic blood pressure
SC	Subcutaneous(ly)
SD	Standard deviation
SoA	Schedule of Activities
TBL	Total bilirubin
TC	Total cholesterol
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
VLDL-C	Very-low-density lipoprotein cholesterol
WBC	White blood cell

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