Clinical Study Protocol

Study Intervention	AZD0780
Study Code	D7960C00006
Version	3.0
Date	15 January 2024

A Phase IIb, Multicenter, Randomized, Parallel-group, Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of AZD0780 in Participants with Dyslipidemia

Sponsor Name: AstraZeneca K.K

Legal Registered Address: 3-1 Ofukacho, Kita-ku, Osaka, 530-0011, Japan

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): EU CT number: 2023-506197-12-00

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

Protocol Number: D7960C00006

Amendment Number: Not Applicable

Investigational Product: AZD0780

Study Phase: Phase IIb

Brief Title: A study to investigate the effect of different doses of AZD0780 on LDL-C levels compared with placebo and its safety and tolerability in participants 18 to 75 years of age with dyslipidemia

Study Clinical Lead Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 2 (Amendment 1)	01 December 2023
Version 3 (Amendment 2)	15 January 2024

Amendment 1 (01 December 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU. Amendment 1 is applicable to European EU CTR countries only.

Overall Rationale for the Amendment

This substantial modification is created in response to the EU CTR Part I RFIs.

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
1.2, Table 1, Schedule of Activities	Added HbA1C testing at Week 12	To monitor for variation in glycaemic control	Substantial
5.2, Exclusion Criteria	Added exclusion criteria in relation to medication that causes QT prolongation	Medication that is known to cause QT prolongation should be restricted during the study	Substantial
6.4.1, Methods for Ensuring Blinding	a) Clarified that the randomization codes are generated by a validated IT-system, that the Sponsor cannot influence the randomization to study intervention, and that the information is access controlled. b) Clarified that the Investigator will not have access to the complete randomization list. c) Removed a paragraph referring to methods for unblinding, merging the information into section 6.4.2.	a) In the prior version, it was not clear how the randomization codes were generated and managed. b) The previous wording regarding access to the randomization list could be misinterpreted. c) The information was originally written in the wrong section.	Non-substantial
6.4.2, Methods of Unblinding	The section is rewritten to introduce further detail of the process and methods for emergency unblinding.	The previous text was not as informative and could be misinterpreted.	Non-substantial
6.9, Prior and Concomitant Therapy	Added details of prohibited medication that cause QT prolongation	Medication that is known to cause QT prolongation should be restricted during the study	Substantial

8.3.9, Reporting of SAEs	Added wording to indicate compliance with safety reporting requirements to EudraVigilance database.	Wording required to indicate compliance with safety reporting requirements to EudraVigilance database.	Non-substantial
8.3.1, Time Period and Frequency for Collecting AE and SAE Information	Changed AE collection time from first dose instead of from signature of ICF	Correction of error, alignment with Schedule of Activities, aligning with Sponsor policy	Non-substantial

Amendment 2 (15 January 2024)

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

Overall Rationale for the Amendment

This substantial modification is created in response to FDA feedback, to clarify items throughout and the addition of a potential interim analysis.

Section Number and Name	**Description of Changes**	**Brief rationale**	**Substantial/ Non-substantial**
List of Abbreviations	Abbreviations added - Coronary artery bypass graft surgery (CABG) & Percutaneous coronary intervention (PCI)	These abbreviations are referenced in exclusion criteria #5 but not originally included in list of abbreviations.	Non-substantial
Section 5.2 Exclusion Criteria	Coronary artery bypass graft surgery & Percutaneous coronary intervention added prior to use of abbreviation	Full wording added due to first use of the abbreviations.	Non-substantial
Table 1 Schedule of activities, 8.2.3 Electrocardiograms	Addition of clarification that triplicate ECG recordings are required throughout the study	Clarification	Non-substantial
2.1 Study Rationale	Clarification of wording of standard of care therapy regarding statins	Clarification	Non-substantial
Table 1 Schedule of activities, Table 6 Laboratory Safety Variables	Clarification provided that FSH and LH are to be obtained only at screening visit. Clarification that serum beta HCG test is to be analysed at central laboratory.	Clarification	Non-substantial
Section 3 Objective and Endpoints, table 3	Clarify objectives and add additional secondary objectives, including corrections of grammar	Update based on FDA recommendation	Substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 3 Objective and Endpoints, table 3	Revision to Exploratory objective to align with Appendix D Optional Genomics Initiative	Correction/revision	Substantial
Section 3 and Section 9.4.2	Update the wording for estimand description, clarify intercurrent events of interest for both estimands, and update the terminology corresponding to the estimand to align with clinical question and interest and ICH E9(R1)	Add clarification and improve readability	Non-substantial
Section 5.1 Inclusion criteria 6	Removal of upper BMI limit	Update based on FDA recommendation	Substantial
Section 5.1 Inclusion criteria 9	Clarification regarding sperm donation	Clarification of wording	Non-Substantial
Section 5.2 Exclusion criteria 10	Change: Uncontrolled hypertension defined as average sitting DBP > 90 mmHg changed from DBP > 100 mmHg, at Visit 1.	To allow sufficient window between exclusion criteria and stopping criteria.	Substantial
Section 5.2 Exclusion criteria 12	Potassium < LLN added to exclusion criteria	Update based on FDA recommendation	Substantial
Section 5.2 Exclusion criteria 13	Addition of further detail to exclusion criteria	Update based on FDA recommendation	Substantial
Section 5.2 Exclusion criteria 22	Addition of exclusion of fibrate therapy & derivatives	Previously mentioned incorrectly as part of inclusion criteria 5	Substantial
Section 6.1.1, Table 4, Investigational Products	Clarification on tablet shape	Clarification	Non-substantial
Section 6.1.1 Investigational Products	Addition of composition of the placebo.	Update based on FDA recommendation	Non-substantial
Section 6.3 and Section 9.4.1	Clarify randomization for Japan and rest of the world	Add clarity on randomisation set up	Non-substantial
Section 7.1.1 liver chemistry stopping criteria	Addition of criteria	Update based on FDA recommendation	Substantial
Section 7.1.2. cardiac stopping criteria	Addition of clarification that ECGs will be triplicate	Clarification	Non-Substantial
Section 7.1.3 respiratory stopping criteria	Clarification of criteria	Update based on FDA recommendation	Substantial

Section Number and Name	Description of Changes	Brief rationale	Substantial/ Non-substantial
Section 8 Study Assessments and procedures	Added: The approximate amount of blood collected from each participant over the duration of the study is around 300ml (approximately 20 tablespoons)	Add clarity on approximate blood collection	Non-substantial
Section 8.1, Table 5 and Section 9.4.2.2: Statistical Analysis, Efficacy, Secondary Endpoint(s)	Added clarification that the VLDL-C will be calculated from standard lipid profile.	Clarification	Non-substantial
Section 8.2.3 Electrocardiograms	Change: The participant should be in a resting, seated position for at least 10 minutes	Updated duration of resting position to align with cardiac stopping criteria	Substantial
Section 8.4 Pharmacokinetics	Clarification regarding collection of PK samples	Clarification	Non-Substantial
Table 6	Removal of annotation mark corresponding to Leukocyte differential count	Correction due to no corresponding footnote	Non-substantial
Section 9.2	Update the sample size and the rationale for the choice of sample size	Update based on FDA recommendation	Substantial
Section 9.5 & Appendix A5	Added potential Interim Analysis and details on Unblinded Review Committee	Interim analysis added with the purpose of informing further development of the clinical programme	Substantial
Appendix A5	Details of unblinded review committee added	Added in line with potential Interim Analysis	Substantial
Appendix C2	Clarification regarding sample handling in instances of withdrawal of consent for donated biological samples	Clarification	Non-Substantial
Appendix C3	Correction of outdated link	Correction	Non-Substantial

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B-100
AST	Aspartate Aminotransferase/Transaminase
BP	Blood Pressure
bpm	Beats Per Minute
CABG	Coronary artery bypass graft surgery
CFR	Code of Federal Regulations
Cmax	Maximum Concentration of Drug Observed after Administration
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DUS	Disease Under Study
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDV	Early Discontinuation Visit
EU CT	EU Clinical Trial
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HDL-C	High-density lipoprotein cholesterol
hERG	human Ether-a-go-go-Related Gene
HIV	Human Immunodeficiency Virus
hsCRP	High-sensitivity C-reactive protein
IATA	International Air Transport Association

Abbreviation or special term	Explanation
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHD	Ischemic Heart Disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	Ischemic Stroke
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	LDL Receptor
Lp(a)	Lipoprotein (a)
LS	Least Squares
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NOAEL	No-observed-adverse-effect
PCI	Percutaneous coronary intervention
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
QTcF	Corrected QT Interval
RTSM	Randomization and Trial Supply Management
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit of Normal
VLDL-C	Very-Low-Density Lipoprotein Cholesterol

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IIb, Multicenter, Randomized, Parallel-group, Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of AZD0780 in Participants with Dyslipidemia

Brief Title:

A study to investigate the effect of different doses of AZD0780 on LDL-C levels compared with placebo and its safety and tolerability in participants 18 to 75 years of age with dyslipidemia.

Regulatory Agency Identifier Number(s):

EU CT number: 2023-506197-12-00

Rationale:

AZD0780 is a small molecule, oral inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) for the reduction of circulating levels of low-density lipoprotein cholesterol (LDL-C). This study aims to evaluate the dose-dependent reduction in LDL-C as well as the associated adverse effects profile after oral administration of multiple doses of AZD0780 on background standard of care therapy including medium to high-intensity statins. The data generated will be used to guide choice of doses, dosing regimens, and sample sizes, as well as safety and pharmacodynamic (PD) monitoring in the further clinical development program.

Objectives, Endpoints, and Estimands:

This study is designed to explore the efficacy, safety, tolerability, and pharmacokinetics (PK) across different dose levels of AZD0780, a small molecule PCSK9 inhibitor, administered orally for up to 12 weeks in participants with elevated LDL-C. The study will randomize approximately 375 participants.

Objectives	Endpoints
Primary	
• To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "ideal" scenarios in which intercurrent events would not occur (hypothetical estimand will be considered)	• Percent change from baseline of LDL-C at Week 12
Secondary	

• To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "real-world" conditions (treatment policy estimand will be considered)	• Percent change from baseline of LDL-C at Week 12
• To assess the PK of AZD0780	• AZD0780 plasma concentrations summarized by sampling timepoint
• To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "ideal" scenarios in which intercurrent events would not occur (hypothetical estimand will be considered)	• Percent change from baseline at Week 12 in: ◦ Total cholesterol ◦ HDL-C ◦ Triglycerides ◦ Non-HDL-C ◦ VLDL-C ◦ ApoA1 ◦ ApoB ◦ Lp(a) ◦ Remnant cholesterol ◦ hsCRP
• To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "real-world" conditions (treatment policy estimand will be considered)	• Percent change from baseline at Week 12 in: ◦ Total cholesterol ◦ HDL-C ◦ Triglycerides ◦ Non-HDL-C ◦ VLDL-C ◦ ApoA1 ◦ ApoB ◦ Lp(a) ◦ Remnant cholesterol ◦ hsCRP
Safety	
• To assess the safety and tolerability of AZD0780	• Safety and tolerability will be assessed in terms of AEs, vital signs, ECG, and clinical laboratory evaluations

AE = adverse event; ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B-100; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); PK = pharmacokinetic(s); VLDL-C = very-low-density lipoprotein cholesterol.

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

Overall Design Synopsis:

This is a randomized, multicenter, parallel-group, double-blind, placebo-controlled, dose-ranging, Phase IIb study in approximately 375 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD0780 on LDL-C levels across different dose levels. An overview of the study design is provided in Figure 1. The study will be conducted at up to 65 sites in up to 8 countries.

The study population will consist of male and female participants of non-childbearing potential, 18 to 75 years of age with a fasting LDL-C of ≥ 70 (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening.

The screening period will be up to 3 weeks prior to randomization. Once participants have fulfilled the eligibility criteria, they can be randomized at any time between Day -21 and Day -1. Participants with a fasting LDL-C of ≥ 70 mg/dL and < 190 mg/dL, and triglycerides< 400 mg/dL at screening will be eligible.

Participants will also be receiving moderate or high-intensity statin therapy for at least 2 months prior to screening (please refer to Appendix F). Eligible participants will attend 6 visits during the treatment period and one additional visit in the follow-up period.

Eligible participants will be randomized across 5 different treatment arms in a 1:1:1:1:1 ratio for a 12-week treatment period. The planned treatments arms are AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, and placebo.

Blood samples will be collected for analysis of LDL-C (Friedewald calculation + reflex testing for triglycerides > 400 mg/dL and/or LDL-C < 40 mg/dL) to assess the effects of AZD0780 on these parameters. Blood samples for analysis of lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides, apolipoprotein B-100 [ApoB], lipoprotein (a) [Lp(a)], apolipoprotein A-1 [ApoA1]) will be obtained to assess the effects of AZD0780 on these parameters. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual.

The study is double-blind and AZD0780 and placebo will be matched for appearance. Participants will begin treatment (placebo or AZD0780) on Day 1 and continue for 12 weeks. After the treatment period, participants will have one follow-up visit 2 weeks post last dose. For detailed information, please refer to the Schedule of Activities (SoA; Table 1).

Brief Summary:

The purpose of this study is to measure the effect of different daily doses of AZD0780 on LDL-C levels compared with placebo in participants with dyslipidemia.

The study will comprise 3 periods totaling up to 17 weeks:

- A screening period of up to 3 weeks
- A treatment period of 12 weeks
  - Dispensing visits will be at Week 1, Week 4, and Week 8
  - The visit frequency will be at Week 1, Week 2, and Week 4; then once monthly up to Week 12
- A final follow-up visit at Week 14

Disclosure Statement:

This is a randomized, multicenter, parallel-group, double-blind, placebo-controlled, dose-ranging Phase IIb study with 5 treatment arms that will evaluate the safety, tolerability, PK, and efficacy of multiple doses of AZD0780 administered orally for up to 12 weeks in participants with elevated LDL-C.

Number of Participants:

Approximately 650 participants will be screened/enrolled to achieve approximately 375 participants randomly assigned to AZD0780 or placebo.

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 Arms and Duration:

Participants will be randomized to once daily dosing of placebo or one of the AZD0780 doses. Dosing should be supervised and documented by study staff when study intervention is administered in the clinic. Eligible participants will be randomized across 5 different treatment arms in a 1:1:1:1:1 ratio for a 12-week treatment period. The planned treatments arms are AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, and placebo.

The study will comprise 3 periods totaling up to 17 weeks:

- A screening period of up to 3 weeks
- A total treatment period of 12 weeks
- A safety follow-up period of 2 weeks

Statistical Methods

Sample Size Estimation

The study will randomize approximately 375 participants in order to have approximately 320 evaluable participants who complete the 12-week treatment period to support the evaluation of the primary endpoint (the discontinuation rate is assumed to be approximately 15%). Participants will be randomized in a 1:1:1:1:1 manner to receive AZD0780 [redacted] mg, [redacted] mg, [redacted] mg, [redacted] mg, or corresponding placebo.

The sample size is driven by the objective to assess the safety and tolerability of AZD0780. The chosen sample size is believed to be sufficient for the creation of a robust safety database.

The sample size of approximately 64 evaluable participants who complete the 12-week treatment period in each arm will provide more than 90% power for the test of each dose of AZD0780 versus placebo to detect a difference of [redacted] in percent change from baseline in LDL-C to Week 12. The calculations assume SD = [redacted] and a 2-sided alpha level of 0.05 and are based on a t-test with normal approximation for percent change from baseline.

Primary Endpoint Analysis

The primary objective is to demonstrate superiority of AZD0780 compared to placebo on LDL-C. To support the primary objective, the primary endpoint is percent change from baseline of LDL-C at Week 12.

The hypothetical estimand will be used for the primary analysis.

The summary measure for the primary endpoint will be least squares mean of percent change from baseline. The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) based on the full analysis set (FAS) population. The model will include the fixed effects of baseline, treatment, visit, and treatment-by-visit interaction, and the random effect (random intercept) of participant. The Restricted Maximum Likelihood estimation approach will be used with a compound symmetry covariance structure for repeated measures. The treatment effects will be summarized by the difference in least squares means, 95% confidence interval, and p-value.

To strongly control the familywise error rate at the 0.05 level, the alpha expenditure of 0.05 (2-sided) will be allocated to the following hypotheses (H) for the primary endpoint:

- H1: $\mu_{\text{AZD0780 [redacted] mg}} = \mu_{\text{placebo}}$
- H2: $\mu_{\text{AZD0780 [redacted] mg}} = \mu_{\text{placebo}}$
- H3: $\mu_{\text{AZD0780 [redacted] mg}} = \mu_{\text{placebo}}$

- H4: $\mu_{\text{AZD0780}\blacksquare\text{mg}} = \mu_{\text{placebo}}$

Where μ denotes the percent change from baseline of LDL-C at Week 12.

A hierarchical testing strategy (closed testing procedure) will be employed. H1 will be tested first using the full test mass alpha. If H1 is rejected, then the full test mass will be recycled to test H2. If H2 is rejected, then H3 will be tested with full alpha, and if H3 is rejected, H4 will be further tested with full alpha. Further details of multiplicity testing are provided in the statistical analysis plan (SAP).

Secondary Endpoint Analyses

As a secondary endpoint the percent change from baseline of LDL-C at Week 12 will be estimated under "real-world" conditions. The treatment policy estimand will be used for this analysis. With the treatment policy estimand the analysis will include all measurements taken regardless of the occurrence of intercurrent events (ICEs). Participants will be analyzed according to their randomized investigational medicinal product (IMP) assignment irrespective of the treatment they received.

The summary measure will be least squares mean of percent change from baseline. The analysis will be the same as for the primary endpoint.

Other secondary endpoints include:

- Percent change from baseline to Week 12 in:
  - Non-HDL-C
  - Very-low-density lipoprotein cholesterol (VLDL-C) (calculated from standard lipid profile)
  - ApoA1
  - ApoB
  - Total cholesterol
  - LDL-C
  - HDL-C
  - Triglycerides
  - Lp(a)
  - Remnant cholesterol (calculated from standard lipid profile)
  - High-sensitivity C-reactive protein (hsCRP)

The percent change from baseline of these parameters at Week 12 will be estimated under both "ideal" scenarios in which intercurrent events would not occur (i.e., hypothetical strategy) and "real-world" conditions (i.e., treatment policy strategy).

The FAS will be used in the analysis of the secondary efficacy endpoints. The statistical analyses will in general consist of the following 4 pairwise treatment comparisons:

- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo

In general, multiple testing adjustment will not be applied to the secondary endpoints except for the "percent change from baseline of LDL-C at Week 12 " endpoint (under "real-world" conditions), in which case the multiplicity adjustment method will be the same as that for the primary endpoint for comparison purposes.

Safety Analysis

Safety data will be summarized descriptively and will not be formally tested. All safety data will be presented in data listings.

Adverse events (AEs) will be summarized by preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs that led to withdrawal will be made and the number of participants who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized.

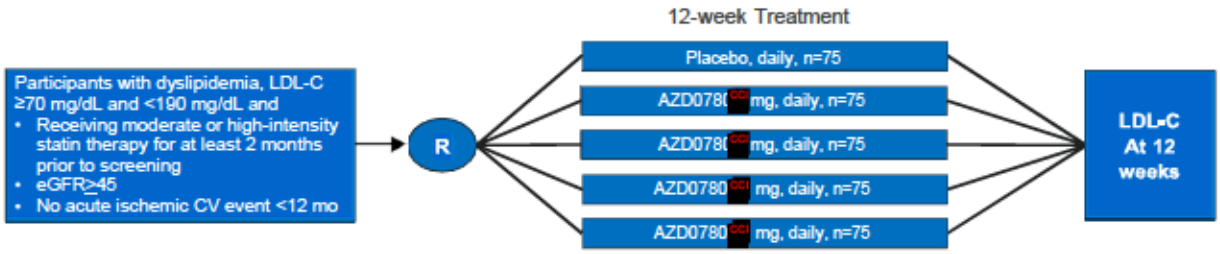
Tabulations and listings of data for vital signs, clinical laboratory tests will be presented. Results from safety electrocardiograms (ECGs) will be listed. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

Out-of-range values for safety laboratory will be flagged in individual listings as well as summarized descriptively.

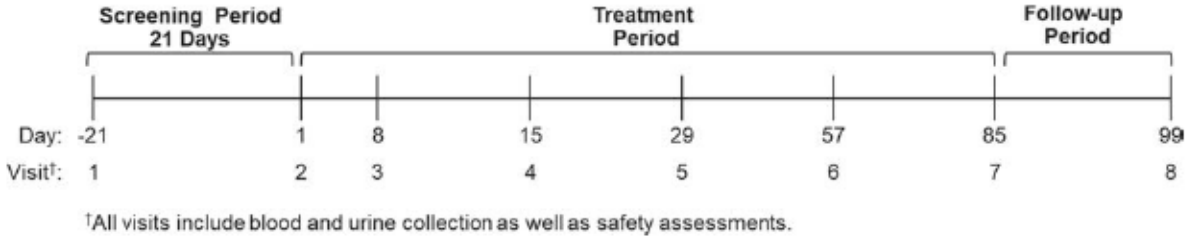
Schema

Figure 1 Study Design

Study Design



Study Schedule



CV = cardiovascular; eGFR = estimated glomerular filtration rate; LDL-C = low density lipoprotein cholesterol; MAD = multiple ascending dose.

1.2 Schedule of Activities

The Schedule of Activities (SoA) is provided in Table 1.

Table 1 Schedule of Activities

	Screening	Treatment period						Final follow-up/EDV
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day	**D -21 to D -1**	**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D99**
Visit window			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical history	X							
Height, weight, and BMI (height at screening only)	X	X	X	X	X	X	X	X
Drugs of abuse screening[a]	X							
Urine pregnancy test (local)[b]	X	X						
FSH	X							
LH	X							
HbA1c	X						X	
Serology	X							
COVID-19 test[c]	X	X						
Concomitant medication review	X	X	X	X	X	X	X	X
Dispensing of AZD0780/Placebo (35 tablets per bottle)		X			X	X		
Study intervention administration (AZD0780/Placebo)		X (Once daily oral dosing; Day 1 through Day 84)						

Table 1 Schedule of Activities

	Screening	Treatment period						Final follow-up/EDV
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day	**D -21 to D -1**	**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D99**
Visit window			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
Safety and Tolerability								
Adverse event review	X (SAEs only)	X (AEs as of dosing)	X	X	X	X	X	X
Physical examination (full)	X	X						X
Physical examination (brief)			X	X	X	X	X	
Vital signs (BP, pulse and temperature, respiratory rate, pulse oximetry)[d]	X	X	X	X	X	X	X	X
12-lead safety ECG[e]	X	X	X	X	X	X	X	X
Clinical safety laboratory evaluations (chemistry, hematology, coagulation, urinalysis)	X	X	X	X	X	X	X	X
Urine renal safety biomarkers: albumin, creatinine, total protein	X	X	X	X	X	X	X	X
Efficacy/Pharmacokinetics/Pharmacodynamics (fasted)[f]								
Lipid profile (TC, HDL-C, non-HDL-C, triglycerides)	X	X	X	X	X	X	X	X
LDL-C	X	X	X	X	X	X	X	X
ApoB		X	X	X	X	X	X	X

Table 1 Schedule of Activities

	Screening	Treatment period						Final follow-up/EDV
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study day	**D -21 to D -1**	**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D99**
Visit window			**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
ApoA1		X			X	X	X	X
Lp(a)		X			X	X	X	X
hsCRP		X			X	X	X	X
PK plasma samples[f]			X	X	X	X	X	
Exploratory								
Blood sample for total PCSK9		X						
Blood (serum) sample for biomarker analyses		X			X	X	X	X
Blood (plasma) sample for biomarker analyses		X			X	X	X	X
Urine sample for biomarker analyses		X			X	X	X	X
Sample for Genomic Initiative (optional) [g]		X						

[a] Screening for drugs of abuse may be performed as per guidelines at local site.
[b] Eligibility is confirmed by negative urine pregnancy test. Confirmatory serum test analyzed at the central laboratory is indicated if urine test is positive at Visit 1.
[c] COVID-19 tests will be performed as per investigator's discretion and according to the study centers' local procedures.
[d] Three consecutive BP and pulse readings should be recorded at intervals of at least 2 minutes.
[e] 12-lead ECGs should be obtained in triplicate.
[f] Blood samples must be obtained pre-dose of IMP for each applicable visit.
[g] Consent and sample collection for genetic testing will only be conducted in countries where genetic testing is allowed in this study. If sample is not collected at Visit 2, it can be collected at any subsequent visit until the last study visit; to be collected per local guidelines.

Participants are required to fast for at least 8 hours overnight prior to all study visits (including screening). Participants are permitted to drink water during this period of fasting until 1 hour before blood sampling.

AE = adverse event; ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B-100; BMI = body mass index; BP = blood pressure; COVID-19 = Coronavirus disease 2019; ECG = electrocardiogram; EDV = early discontinuation visit; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IMP = investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; Lp(a) = lipoprotein (a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetic(s); SAE = serious adverse event; TC = total cholesterol.

2 INTRODUCTION

2.1 Study Rationale

AZD0780 is a small molecule inhibitor of PCSK9 for the reduction of circulating levels of LDL-C. This study aims to evaluate the dose-dependent reduction in LDL-C as well as the associated adverse effects profile after oral administration of multiple doses of AZD0780 on background standard of care therapy including medium to high-intensity statins. 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.

2.2 Background

2.2.1 Dyslipidemia

Dyslipidemias are alterations to the plasma lipid profile that are often associated with clinical conditions. Hypercholesterolemia due to elevated LDL-cholesterol levels is a common form of dyslipidemia and is a major causal factor for IHD and IS in both the developed and the developing world. Elevated LDL-C can be genetically determined (primary or familial dyslipidemias) or secondary to other conditions (such as diabetes mellitus, obesity or an unhealthy lifestyle), the latter being more common. The global burden of dyslipidemia has increased over the past 30 years (Pirillo et al 2021). Cardiovascular disease (CVD), principally IHD and IS, is the leading cause of global mortality and a major contributor to disability. Prevalent cases of CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019 (Pirillo et al 2021). The global trends for disability-adjusted life years and years of lost life also increased significantly due to IHD and IS. Cardiovascular disease burden continues its decades-long rise for almost all countries (Roth et al 2020). Elevated LDL-C remains the main interventional and pharmacologic target for prevention of CVD (Pirillo et al 2021, Ference et al 2018, Roth et al 2020).

Statins are the first-line therapy for lowering of LDL-C recommended by the latest dyslipidemia guidelines (Mach et al 2020; Reiter-Brennan et al 2020). Reduction of LDL-C levels by statins leads to significant reduction in cardiovascular events including coronary artery disease and other cardiovascular related deaths (Collins et al 2016). However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C target levels. Current guidelines call for LDL-C to be lowered ≥ 50% with maximally tolerated statins in patients with existing atherosclerotic CVD (Atar et al 2021). Additional evidence demonstrates that aggressively lowering LDL-C levels to < 40 mg/dL lowers CVD risk in a wider range of patients (Marston et al 2021). This underscores the medical need for developing new cost-effective LDL-C lowering medicines to achieve the most recent dyslipidemia guidelines for primary and secondary prevention of CVD.

2.2.2 AZD0780

An important discovery in the regulation of LDL-C levels has been the identification of PCSK9. Loss-of-function mutations in PCSK9 have been associated with low LDL-C levels and protection from CVD (Cohen et al 2005). PCSK9 is produced in the liver and promotes degradation of the LDLR. Therefore, reduction or inhibition of PCSK9 increases LDLR levels and consequently lowering plasma circulating LDL-C levels. As such, PCSK9 has been the subject of intense research as a pharmacologic target. Two PCSK9 neutralizing monoclonal antibodies, alirocumab and evolocumab, have been approved as LDL-C lowering therapies. These antibodies lower LDL-C by as much as 60% and lowers cardiovascular event rates (Sabatine et al 2017). More recently, a small interfering RNA (siRNA) molecule targeting PCSK9, inclisiran, has been shown to reduce LDL-C by approximately 50% (Ray et al 2020). The US FDA recently approved inclisiran injection (Leqvio®) to be used with diet and statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD who require additional lowering of LDL-C has also been approved (FDA approved add-on therapy to lower cholesterol among certain high-risk adults).

Despite the interest in PCSK9 as a target to lower LDL-C, no orally available therapy has been successfully developed. AstraZeneca is developing a small molecule, AZD0780, to inhibit PCSK9 and lower LDL-C levels. AZD0780 may provide a novel, oral, cost-effective medication as an alternative to the current approved injectable PCSK9 inhibitors.

2.2.3 Supportive Nonclinical Data

Briefly, AZD0780 binds human and cynomolgus monkey PCSK9 specifically with high affinity inhibiting its activity on the LDL-receptors. In vitro studies and in vivo toxicology studies demonstrated acceptable safety profiles. The NOAELs were established at CCI mg/kg/day in rat and CCI mg/kg/day in cynomolgus monkey after 28 days of once daily oral dosing.

AZD0780 has been evaluated for genotoxicity potential in both in vitro and in vivo studies. Potential mutagenic activity has been assessed in bacteria cells in vitro by the Bacterial Reverse Mutation (Ames) test. The genotoxic potential of AZD0780 has been assessed in in vitro and in vivo micronucleus tests in the L5178Y mouse lymphoma cell line and in rat, respectively. Based on the weight of evidence from all genetic toxicology studies conducted with AZD0780, it was concluded that AZD0780 is not mutagenic or clastogenic.

AZD0780 was not phototoxic in the NRU 3T3 Phototoxicity Assay.

A detailed description of the nonclinical pharmacology, PK, drug metabolism, and toxicology can be found in Section 4 of the IB.

2.2.4 Supportive Clinical Data

An ongoing Phase I study (Study D7960C00001) is a first in human (FIH) study to assess the safety, tolerability, PK and PD of single and MADs of AZD0780, administered orally as tablets, in healthy participants with or without elevated LDL-C.

Following single (CCI mg dose) and multiple ascending (CCI mg dose) administration of AZD0780 to healthy participants with or without elevated LDL-C levels, interim data from Study D7960C00001 have demonstrated an acceptable safety profile.

2.3 Benefit/Risk Assessment

In order to evaluate the clinical benefit/risk balance for AZD0780, nonclinical and clinical data were taken into consideration, as well as review of the available information for PCSK9 inhibitors that are approved and marketed, or in development, for the treatment of dyslipidemia.

More detailed information about the known and expected benefits and potential risks of AZD0780 can be found in the IB.

2.3.1 Risk Assessment

This study has been designed with appropriate measures in place to monitor and minimize any potential health risks to participants.

Details of the risk assessment in this study are presented in Table 2. Refer to the IB for detailed information on the risks of AZD0780.

Table 2 Risk Assessment of AZD0780

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
QT-prolongation	In an in vitro assay, AZD0780 was shown to be an inhibitor of the hERG channel (human ether-a-go-go-related gene). hERG channel inhibition can cause QT-prolongation and potentially cardiac arrhythmia, including Torsade de Pointes. Based on the in vitro data, modeling predicted a high likelihood of QT-prolongation at free plasma levels of AZD0780 at doses to be investigated in AZD0780 clinical studies. In the cardiovascular safety studies and the 1 month toxicology study of AZD0780 in cynomolgus monkeys, although QT-prolongation was observed, the pre-clinical data were consistent with a reversible mode of hERG channel inhibition and QT-prolongation. There were no observations of AZD0780 related arrythmias in the in vivo studies at the dose levels tested. No ECG findings of safety concern have been identified in the ongoing phase 1 clinical study (Study D7960C00001) at single doses of up to CCI mg or repeated doses up to CCI mg once daily.	• Exclusion of participants with clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any clinically important abnormalities in the 12 lead ECG; QTcF > 450 ms; AV-block grade II-III; sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias (exclusion criteria 13-14). • Regular ECG recordings and assessment. • Individual stopping criteria have been defined to consider QTc and QTcF values outside pre-specified ranges.
Blood pressure elevation	In the cardiovascular safety studies of AZD0780 in cynomolgus monkeys, a transient increase in arterial BP was observed between 0.5h – 8h post dose at the highest tested dose of CCI mg/kg (free C_{max} of CCI µmol/L).	• Only participants within a defined range of BP will be included in the study (exclusion criterion 10). • It is recommended that antihypertensive treatment is considered/initiated at the PI's discretion and in accordance with applicable clinical guidelines in order to optimize blood pressure for participants with hypertension during the clinical study.BP will be monitored throughout the study.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Dyspnea	In in vitro studies, AZD0780 is an adenosine transport inhibitor (IC50 ~15 µM). Inhibition of adenosine transporters can result in dyspnea and bronchospasm in patients with respiratory disease. In addition, inhibition of α1A adrenoceptors (Ki=18 µM and functional IC50 ~47 µM) identified in AZD0780 in vitro studies, can result in dyspnea, observed in clinical trials with α-adrenoceptor antagonists. The respiratory safety pharmacology study with AZD0780 in rats did not show any effect on respiratory parameters as assessed by plethysmography.	• Exclusion of participants with any uncontrolled or serious disease, or any medical (eg, known major active infection or major hematological, renal, metabolic, gastrointestinal, respiratory, 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 (exclusion criterion 3). • Adverse events, physical examinations and vital signs, including respiratory rate and pulse oximetry, will be monitored throughout the study. • Individual stopping criteria have been defined to consider exacerbation of respiratory disease.
Effects on Reproduction	AZD0780 was shown to be an antagonist of the serotonin receptor 5-hydroxytryptamine receptor 2B (5-HT_{2B}). Possible adverse effects of 5-HT_{2B} receptor antagonism include developmental toxicity (based on complete knockout). AZD0780 inhibits α_{1A} adrenoceptor. In clinical studies α_{1A} adrenoceptor antagonism has resulted in a reduction of uterine and vas deferens contractility and AE reports of abnormal ejaculation. Nonclinical developmental toxicity studies for AZD0780 have not yet been performed.	• Women of childbearing potential will be excluded from the study (inclusion criteria 1 and 8). • Reproductive restrictions will be in place throughout the study.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Vomiting	In in vitro studies, AZD0780 was shown to be an antagonist of the serotonin receptor 5-HT_{2B} (Ki = 9.4 µM, functional IC50 >100 µM). This receptor is expressed in the gastrointestinal tract and mediates smooth muscle contraction. Inhibition may reduce gastric motility and result in symptoms such as nausea and vomiting. In the 1-month toxicology study with AZD0780 in cynomolgus monkeys, vomiting was observed and was a dose-limiting factor. Nausea/emesis may translate to humans but since the mechanism for the vomiting observed with AZD0780 treatment is unknown, there is no understanding of the PK/PD relationship for predicting translatability to human.	• Potential gastrointestinal effects will be monitored throughout the study by the reporting of AEs. • Physical examinations and vital signs will be monitored throughout the study.

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; hERG = human ether-a-go-go-related gene; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QTcF = corrected QT interval.

AZD0780 is an inhibitor of PCSK9. Several drugs (siRNA and antibody based) aimed at lowering PCSK9 levels are either on the market or in clinical development. So far no safety concerns related to inhibition of PCSK9 has been reported in the literature (Ray et al 2020, Karatasakis et al 2017, Geng et al 2021).

In human PCSK9 polymorphisms with low or no PCSK9 expression, no adverse phenotypes are described (Schmidt et al 2019).

Potential risks of the study procedures are the following:

- Blood draws
  - Routine blood draws have a well-established risk profile. Risks will be mitigated by following institutional/study site guidelines.
- Electrocardiogram
  - Routine ECGs are noninvasive, safe, and painless procedures. Participants will be informed that they may develop a mild rash or skin irritation where the electrodes were attached.

2.3.2 Benefit Assessment

The purpose of this Phase IIb study is to evaluate the safety, tolerability, PK, and efficacy of AZD0780 in participants with dyslipidemia.

Participants will be required to continue on stable doses of their dyslipidemia maintenance

therapy (SoC) throughout the study to minimize the risk of disease worsening during the study.

For participants randomized to AZD0780, there is a potential benefit in terms of reduction of circulating levels of LDL-C. Plasma samples for analysis of lipid profile (total cholesterol, HDL-C, triglycerides, ApoB, Lp(a), ApoA1) will also be obtained to assess the effects of AZD0780 on these parameters.

Two PCSK9 neutralizing monoclonal antibodies, alirocumab and evolocumab, have been approved as LDL-C lowering therapies. These antibodies lower LDL-C by as much as 60% and lowers cardiovascular event rates (Sabatine et al 2017). More recently, an siRNA molecule targeting PCSK9, inclisiran, has been shown to reduce LDL-C by approximately 50% (Ray et al 2020). While the clinical effect of AZD0780 in participants with dyslipidemia is yet to be determined, it is conceivable that treatment with AZD0780 will lead to similar improvement. However, it is possible that participants will not receive any individual benefit from participating in this study. All participants in this clinical study, irrespective of whether treated with AZD0780 or placebo, will be receiving SoC and closer medical attention compared to ordinary medical practice.

2.3.3 Overall Benefit/Risk Conclusion

The overall goal of the study is to examine if PCSK9 inhibition by AZD0780 is safe and clinically efficacious in dose-dependent reduction in LDL-C levels after oral administration of multiple doses of AZD0780 in participants with dyslipidemia.

Based on the available information regarding the potential risks of AZD0780, the safety data available to date, the inclusion/exclusion criteria, and additional precautions implemented in the clinical study, the prospect of individual benefit based on the IMP's mechanism of action, and the clinical efficacy observed with administration of LDL-C lowering therapies targeting PCSK9 inhibition, the benefit-risk profile for study participants is considered acceptable.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives and endpoints for the study are detailed in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "ideal" scenarios in which intercurrent events would not occur	• Percent change from baseline of LDL-C at Week 12
Secondary	
• To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "real-world" conditions	• Percent change from baseline of LDL-C at Week 12
• To assess the PK of AZD0780	• AZD0780 plasma concentrations summarized by sampling timepoint
• To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "ideal" scenarios in which intercurrent events would not occur	• Percent change from baseline at Week 12 in: ◦ Total cholesterol ◦ HDL-C ◦ Triglycerides ◦ Non-HDL-C ◦ VLDL-C ◦ ApoA1 ◦ ApoB ◦ Lp(a) ◦ Remnant cholesterol ◦ hsCRP
• To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "real-world" conditions	• Percent change from baseline at Week 12 in: ◦ Total cholesterol ◦ HDL-C ◦ Triglycerides ◦ Non-HDL-C ◦ VLDL-C ◦ ApoA1 ◦ ApoB ◦ Lp(a) ◦ Remnant cholesterol ◦ hsCRP
Safety	

• To assess the safety and tolerability of AZD0780	• Safety and tolerability will be assessed in terms of AEs, vital signs, ECG, and clinical laboratory evaluations
Exploratory	
• To assess baseline PCSK9 levels	• Results of baseline PCSK9 levels may be reported outside of the CSR
• To collect and store plasma, serum, and urine samples for potential future exploratory biomarkers involved in PK, PD, safety and tolerability related to AZD0780 treatment and/or cardiometabolic diseases	• Results of potential future exploratory biomarkers may be reported outside of the CSR
• To explore how genetic variations may affect clinical parameters, risk and prognosis of diseases and the response to medications as detailed in Appendix D Optional Genomics Initiative. Note: The sample is taken from consented participants for DNA isolation and storage. Results will not be reported in the CSR.	• Exploratory endpoints are related to the data generated from the genetic analysis of part or all of the participant's genetic information

AE = adverse event; ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B-100; CSR = clinical study report; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic(s); PK = pharmacokinetic(s); VLDL-C = very-low-density lipoprotein cholesterol.

Estimand for efficacy endpoints

Intercurrent events (ICE) are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. In this study, ICEs of interest for efficacy evaluation include treatment discontinuation, change in background therapy, and intake of prohibited medication.

Estimand for the primary objective

The primary clinical question of interest is:

What is the difference in means of percent change in LDL-C from baseline to Week 12 in eligible participants with dyslipidemia treated with AZD0780 vs placebo in "ideal" scenarios in which intercurrent events would not occur?

The estimand is described by the following attributes:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia.

- Endpoint: Percent change in LDL-C from baseline to Week 12.
- Population-level summary measure: Difference in means of percent change in LDL-C from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The hypothetical strategy will be used for the primary analysis. With this strategy, efficacy assessments obtained after ICEswill not be used for treatment effect estimation.

Estimand for secondary objectives

For the objective "To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in “real-world” conditions "

The clinical question of interest is:

What is the difference in means of percent change in LDL-C from baseline to Week 12in eligible participants with dyslipidemia treated with AZD0780 vs placebo, regardless of the occurrence of ICEs?

The estimand is described by the following attributes:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia.
- Endpoint: Percent change in LDL-C from baseline to Week 12.
- Population-level summary measure: Difference in means of percent change in LDL-C from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The treatment policy strategy will be used for this analysis. With this strategy, efficacy assessments are used for treatment effect estimation regardless of the occurrence of ICEs.

For the objective "To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in “ideal” scenarios in which intercurrent events would not occur"

The clinical question of interest is:

What is the difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 in eligible participants with dyslipidemia treated with AZD0780 vs placeboin “ideal” scenarios in which intercurrent events would not occur ?

The estimand is described by the following attributes:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia.
- Endpoint: Percent change in other lipid parameters and inflammatory markers from baseline to Week 12.
- Population-level summary measure: Difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The hypothetical strategy will be used for these analyses. With this strategy, efficacy assessments obtained after ICEs will not be used for treatment effect estimation.

For the objective "To evaluate the effects of different doses of AZD0780 on other lipid parameters and inflammatory markers versus placebo in “real-world” conditions"

The clinical question of interest is:

What is the difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 in eligible participants with dyslipidemia treated with AZD0780 vs placebo, regardless of the occurrence of ICEs?

The estimand is described by the following attributes:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia.
- Endpoint: Percent change in other lipid parameters and inflammatory markers from baseline to Week 12.
- Population-level summary measure: Difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The treatment policy strategy will be used for this analysis. With this strategy, efficacy assessments are used for treatment effect estimation regardless of the occurrence of ICEs.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, multicenter, parallel-group, double-blind, placebo-controlled, dose-ranging, Phase IIb study in approximately 375 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD0780 on LDL-C levels across different dose levels. An overview of the study design is provided in Figure 1. The study will be conducted at up to 65 sites in up to 8 countries.

The study population will consist of male and female participants of non-childbearing potential, 18 to 75 years of age with a fasting LDL-C of ≥ 70 (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening.

The screening period will be up to 3 weeks prior to randomization, ie, participants will be randomized at any time between Day -21 and Day -1 providing all eligibility criteria have been met. Participants with a fasting LDL-C of ≥ 70 mg/dL and < 190 mg/dL, and triglycerides < 400 mg/dL at screening will be eligible. Participants will also be receiving moderate or high-intensity statin therapy for at least 2 months prior to screening (please refer to Appendix F). Eligible participants will attend 6 visits during the treatment period and one additional visit in the follow-up period. Eligible participants will be randomized across 5 different treatment arms in a 1:1:1:1:1 ratio for a 12-week treatment period. The planned treatments arms are AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, and placebo.

Blood samples will be collected for analysis of LDL-C (Friedewald calculation + reflex testing for triglycerides > 400 mg/dL and/or LDL-C < 40 mg/dL) will be obtained to assess the effects of AZD0780 on these parameters. Blood samples for analysis of lipid profile (total cholesterol, HDL-C, triglycerides, ApoB, Lp(a), ApoA1) will be obtained to assess the effects of AZD0780 on these parameters. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual.

The study is double-blind and AZD0780 and placebo will be matched for appearance. Participants will begin treatment (placebo or AZD0780) on Day 1 and continue for 12 weeks. After the treatment period, participants will have one follow-up visit 2 weeks post last dose. For detailed information, please refer to the SoA (Table 1).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Selection of Participant Population

AZD0780 is a potential first-in-class oral small molecule PCSK9 inhibitor, and this study is part of a program to confirm if AZD0780 will lower cardiovascular risk in both primary and secondary prevention, when taken once daily along with SoC.

The population included in this study comprises male or female participants of non-childbearing potential, 18 to 75 years of age with a fasting LDL-C of ≥ 70 (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening. Each participant should meet all the inclusion criteria and none of the exclusion criteria to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (Section 5.4).

4.2.2 Rationale for Selection of Primary Endpoint

Statins are the first-line therapy for lowering of LDL-C recommended by the latest dyslipidemia guidelines (Mach et al 2020; Reiter-Brennan et al 2020). Reduction of LDL-C levels by statins leads to significant reduction in cardiovascular events including coronary artery disease and other cardiovascular related deaths (Collins et al 2016). However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C target levels. Current guidelines call for LDL-C to be lowered ≥ 50% with maximally tolerated statins in patients with existing atherosclerotic CVD (Atar et al 2021). Additional evidence demonstrates that aggressively lowering LDL-C levels to < 40 mg/dL lowers CVD risk in a wider range of patients (Marston et al 2021). This underscores the medical need for developing new cost-effective LDL-C lowering medicines to achieve the most recent dyslipidemia guidelines for the prevention of CVD.

4.2.3 Rationale for Selection of Comparator

The comparator in this study is placebo. Both AZD0780 and placebo will be administered on top of moderate or high-intensity statin therapy; therefore, the treatment of the placebo group will correspond to current SoC for participants with dyslipidemia.

The use of placebo will allow for a double-blinded treatment period and to provide a control arm, so as to enable a continued comparison of efficacy, in particular the comparison of dose-dependent change in LDL-C after oral administration of multiple doses of AZD0780, and to act as a comparator to contextualize safety observations.

4.2.4 Rationale for Selection of Study Duration

The treatment length in the study is 12 weeks. Based on data from a MAD study (Study D7960C00001), steady state in plasma exposure of AZD0780 was reached after one week of once daily dosing with AZD0780, while steady state in the LDL-C lowering effect was reached within approximately 2 weeks of treatment. With a treatment length of 12 weeks participants are predicted to be at least 10 weeks on stable LDL-C lowering effect, allowing for a robust assessment of the lipid effects of AZD0780. Twelve weeks of dosing is also predicted to allow for a robust assessment of safety, tolerability and the PK of AZD0780 to guide dose selection for further clinical development of AZD0780.

4.3 Justification for Dose

Single doses of AZD0780 up to [CCI] mg and multiple doses of AZD0780 up to [CCI] mg once daily for up to 4 weeks of dosing have been evaluated and shown to be well tolerated in participants with elevated LDL-C (ongoing Study D7960C00001). The doses for the current study were selected based on the observed safety, tolerability, and LDL-C reducing data from the MAD cohorts.

The mid and high dose, planned to be [CCI] mg and [CCI] mg AZD0780, were selected to reach close to maximum achievable reduction in LDL-C. The aim with the highest dose ([CCI] mg) is to show that an increase above the [CCI] mg dose will not result in any further clinically significant reduction in LDL-C compared to [CCI] mg AZD0780. Due to the uncertainty in dose/exposure response at doses below [CCI] mg, two lower doses were also selected for this study, [CCI] mg and [CCI] mg. The aim is to have at least one dose that shows a clinically significant lower LDL-C reduction as compared to the [CCI] mg and [CCI] mg doses. The 2 mid doses, [CCI] mg and [CCI] mg, were thus selected for the potential to be in the therapeutic dose range.

Prior to the start of dosing in the current study, safety and tolerability data from multiple dosing of [CCI] mg AZD0780 once daily for 4 weeks will have been evaluated in the ongoing Study D7960C00001 in participants with elevated LDL-C.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit.

5 STUDY POPULATION

Participants will be males and females of non-childbearing potential (ie, postmenopausal or surgically sterile), aged 18 to 75 years (inclusive), with a fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) and< 190 mg/dL (4.9 mmol/L), fasting triglycerides < 400 mg/dL (< 4.52 mmol/L), and have a BMI at or above 19.0 kg/m^2.

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

Each participant should meet all the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion Criteria

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

Age

1 Males, and females of non-childbearing potential, 18 to 75 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with a fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) and < 190 mg/dL (4.9 mmol/L) at screening.

3 Participants with fasting triglycerides < 400 mg/dL (< 4.52 mmol/L) at screening.

4 Should be receiving moderate or high-intensity statin therapy for ≥ 2 months prior to screening, according to ACC/AHA guidelines on blood cholesterol management, or to local guidelines, eg, Japanese Atherosclerosis Society guidelines.

5 There should be no planned medication or dose change during study participation.

Weight

6 Body mass index at or above 19.0 kg/m^2.

Sex

7 Male participants:

(a) Males must be surgically sterile or using, in conjunction with their female partner, 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, 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.

8 Female participants:

(a) Female participants must not be pregnant and must have a negative pregnancy test at screening and randomization, must not be lactating, and must not be of childbearing potential. Women not of childbearing potential are defined as women who are either permanently sterilized (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 randomization without an alternative medical cause. The following age-specific requirements apply:

(i) Women < 50 years of age 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.

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

9 Restrictions for male participants

(a) All male participants should avoid fathering a child by either true abstinence or by using (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 study intervention administration until 3 months after the Final Follow-Up visit. Acceptable methods of preventing pregnancy include birth control pills, injections, implants, or patches, IUDs, tubal ligation/occlusion, and vasectomy.

(b) Male participants who have been sterilized are required to use 1 barrier method of contraception (condom) from the time of study intervention administration until after the Final Follow-Up Visit. A barrier method is not necessary if the female partner is sterilized.

(c) Male participants should not donate sperm for the duration of the study and for at least 3 months post last follow-up visit.

Informed Consent

10 Capable of giving signed informed consent as described in Appendix A 3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

11 Provision of signed and dated, written ICF 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 participant 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 participant. The participant will not be excluded from other aspects of the study described in this protocol.

Other Inclusion Criteria

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

5.2 Exclusion Criteria

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

Medical Conditions

1 Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2 using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-Epi 2021(Age, Sex)) equation at Visit 1.

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 (eg, known major active infection or major hematological, renal, metabolic, gastrointestinal, respiratory, 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, defined as HbA1c > 10% at Visit 1.

5 Acute ischemic cardiovascular event in the last 12 months prior to randomization however patients can be included if it is > 6 months from coronary artery bypass graft surgery (CABG) surgery and > 3 months after percutaneous coronary intervention (PCI).

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

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, eg, lung, liver, heart, bone marrow, renal.

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

10 Uncontrolled hypertension defined as average sitting SBP > 160 mmHg or DBP > 90 mmHg at Visit 1. It is recommended that antihypertensive treatment should be considered/initiated at the PI's discretion and in accordance with applicable clinical guidelines in order to optimize blood pressure for participants with hypertension during the clinical study.

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

12 Any laboratory values with the following deviations at Screening Visit 1; test may be repeated at the discretion of the investigator if abnormal:

(a) Any positive result on screening for hepatitis B, hepatitis C or HIV.

(b) ALT > 1.5 × ULN

(c) AST > 1.5 × ULN

(d) TBL > ULN

(e) Hemoglobin < 12 g/dL in men or < 11 g/dL in women

(f) Potassium < LLN

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 including shortened QTcF< 340ms; family history of long QT syndrome; PR interval shortening < 120 ms; PR interval prolongation >220 ms, intermittent second or third degree AV block or AV dissociation; persistent or intermittent complete bundle branch block, incomplete bundle branch, or interventricular conduction delay with QRS > 110 ms.

14 QTcF > 450 ms; high degree atrioventricular-block grade II-III and sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias.

15 Known or suspected history of drug abuse as judged by the investigator.

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

17 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.

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

Prior/Concomitant Therapy

19 Current/previous administration of inclisiran.

20 Lomitapide within 12 months prior to randomization.

21 Previous administration of PCSK9 inhibition treatment within 12 months prior to randomization (approved or investigational).

22 Fibrate therapy and derivatives are prohibited.

23 Receiving or has received within 14 days of screening, medication that contains a black box warning for significant QT prolongation.

Prior/Concurrent Clinical Study Experience

24 Participation in another clinical study with a study intervention administered in the last 3 months prior to randomization or 5 half-lives from last dose to first administration of study intervention, whichever is the longest.

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

26 Use of other investigational products or investigational devices during the course of the study.

Other Exclusions

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

28 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

29 As judged by the investigator, any evidence of disease conditions that, in the investigator's opinion, makes it undesirable for the participant to participate in the trial.

30 Previous screening in the present study.

- 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 once during the recruitment period.

31 Participants who cannot communicate reliably with the investigator.

32 Vulnerable participants, eg, 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 at the clinic or any blood donation/blood loss > 500 mL (> 400 mL in Japan only) during the 3 months prior to screening visit.

Optional Genetic Sampling

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

(a) Previous allogeneic bone marrow transplant.

(b) Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle Considerations

5.3.1 Pregnancy

Participants will be instructed that if they or their partner becomes pregnant during the study this should be reported to the investigator. The investigator 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 participant is included in the study, then consent will be sought from the partner (via the participant's request that their partner contact 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.

5.3.2 Meals and Dietary Restrictions

For all study visits (including screening), participants must be fasted for 8 hours prior to blood sampling for LDL-C and other lipid profile. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C and other lipid profile.

5.3.3 Caffeine, Alcohol, and Tobacco

Participants who use alcohol may participate in the study unless their consumption is deemed excessive by the investigator.

5.3.4 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.

5.3.5 Other Restrictions

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

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomly assigned to study intervention/entered in the study. 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.

Participants may be rescreened once if the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits). Rescreened participants should be assigned the same participant number as for the initial screening. Individuals who do not meet a specific criterion may have this parameter retested if the investigator determines there is a reason to believe that this was caused by a temporary/transient reason.

5.5 Criteria for Temporarily Delaying Administration of Study Intervention – Not Applicable

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Investigational medicinal product will be allocated via an IRT system and study-site staff will dispense proper bottles to the participants. Additional information regarding the administration of IMP is provided in the Pharmacy Manual.

Table 4 includes a description of the IMPs used in this study, their dose formulation, unit dose strength, dosage level, route of administration, use, sourcing, and packaging and labeling.

Table 4 Investigational Products Administered

Arm name	AZD0780	Placebo
Intervention name	AZD0780	Placebo
Type	Drug	Placebo
Dose formulation	Round tablet	Round tablet
Unit dose strength(s)	CCI mg	Placebo to match
Dosage level(s)	CCI mg	Placebo to match
Route of administration	Oral	Oral
Regimen	QD	QD
Use	Experimental	Placebo
IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labeling	Study treatment will be provided in plastic bottles. Labels for study intervention supplied by AstraZeneca will be prepared in accordance with GMP and local regulatory guidelines	Study treatment will be provided in plastic bottles. Labels for study intervention supplied by AstraZeneca will be prepared in accordance with GMP and local regulatory guidelines

GMP = Good Manufacturing Practice; IMP = investigational medicinal product; QD = once daily.

The placebo to match contains cellulose microcrystalline/microcrystalline cellulose and sodium stearyl fumarate. The film-coat contains poly(vinyl alcohol)/polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide yellow/ferric oxide, iron oxide red/ferric oxide, and iron oxide black/ferrosoferric oxide.

Details of the batch numbers will be included in the trial master file and final CSR.

6.2 Preparation, Handling, Storage, and Accountability

The IMP will be supplied by AstraZeneca as labeled bottles (QP released by AstraZeneca) with a study specific label. The labels will fulfill Good Manufacturing Practice Annex 13 requirements and medical device directive for labeling.

No special procedures for the safe handling of AZD0780/placebo are required.

The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying the Sponsor (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by the Sponsor (or designated party).

Only participants randomized in the study may receive study intervention, and only authorized site staff may dispense proper IMP to participants. Prior to dispensing to study participants, all IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized site staff. Participants will be given instructions around storage of IMP and self-administering IMP at home.

The investigator, or delegated, authorized site staff, is responsible for the IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records, provided that the blind of the study is not compromised.

Further guidance and information for the final disposal of unused study interventions are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. The participant numbers will be obtained during screening for all participants, after the signature of the ICF, while the randomization codes will be assigned only to the participants proceeding to the treatment phase of the study. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site in the IRT/RTSM user manual.

In case of rescreening, the rescreened participants should be assigned the same participant number as for the initial screening.

Participants will be randomized to once daily dosing of placebo or different dose levels of AZD0780. Dosing should be supervised and documented by study staff when study intervention is administered in the clinic. Eligible participants will be randomized across 5 different treatment arms (approximately 75 participants in each arm) in a 1:1:1:1:1 ratio for a

12-week treatment period. The planned treatments arms are AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, AZD0780 [redacted] mg, and placebo. A minimum of 5 participants and a maximum of 10 participants in each arm (a minimum of 25 in total and a maximum of 50 in total) will be allocated to sites in Japan. Separate randomization lists will be generated for Japan and for the rest of the world.

Investigational medicinal product will be available as film-coated oral tablets in labeled bottles containing either AZD0780 tablets or placebo tablets (35 tablets in a bottle).

Returned study intervention should not be re-dispensed to participants.

6.4 Blinding

6.4.1 Methods for Ensuring Blinding

This is a double-blind study in which the investigational site staff and participants remain blinded during the clinical study.

All packaging and labeling of IMP will be done in such a way as to ensure blinding for all participants, Sponsor, and investigational site staff. Investigators, blinded Sponsor, and investigational site staff and participants will remain blinded to each participant's assigned IMP throughout the course of the study.

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

A Sponsor site monitor will perform IMP accountability. In the event that the treatment allocation for a participant becomes known to the investigator or other study staff involved in the management of study participants, or needs to be known to treat an individual participant for an AE, the Sponsor must be notified immediately by the investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list during the study, prior to database lock:

- Those carrying out the packaging and labeling of IMP.
- Those generating the randomization list.
- The Sponsor supply chain department.
- The Investigator in case of a medical emergency where the treatment needs to be revealed due to safety reasons, and then only for the at one concerned participant(s).
- Labcorp Bioanalytical Services LLC (responsible for analyzing the samples).
- In the event of an interim analysis, designated sponsor personnel will be unblinded as part of the Unblinded Review Committee as described in Appendix A5.

The information in the randomization list will be kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at the Sponsor, or any CRO handling data, will have access to the randomization scheme during the conduct of the study. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The randomization codes are generated by a validated IT-system and are provided by a third party vendor, who provides and manages the RTSM system.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4.2 Methods for Unblinding

The Investigator has sole responsibility for the medical care of the individual study participants throughout the clinical trial duration. It is the Investigator's independent decision to break the randomization code in the event of an emergency that requires a rapid response. This action does not require the Sponsor's representative approval. To maintain the blinding of the assigned study intervention of other participants the emergency unblinding is performed via a specifically programmed transaction within the RTSM system that only reveals the assigned study intervention of the concerned participant(s). The specific process will be described in the RTSM user manual that will be provided to each site.

Access to the transaction is restricted and emergency unblinding can only be performed by appropriate users. The Sponsor applies two options for emergency unblinding: primary line and secondary line.

The primary line for emergency unblinding grants access only for medically qualified site personnel:

- Principal Investigator (PI)
- Sub-Investigator (SI)

Note: Study Coordinators (SC) and any other non-medically qualified site personnel are not allowed to perform emergency unblinding.

In the unlikely event that the Investigator is unable to access the RTSM system for e.g. technical issues or loss of log-in details, there is an IRT Helpdesk service available to assist, which is available 24 hours per day, 7 days per week.

The secondary line for emergency unblinding is a local back-up solution which only allows an appointed user (Local Safety Unblinder) to reveal the study participant's assigned study

intervention when the primary line point of contact is not available. The local back-up solution is available 24 hours per day, 7 days per week.

If a participant's assigned study intervention is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The unblinding action is reported to the Sponsor without revealing the assigned study intervention to the Sponsor staff.

In conjunction with the investigator, the Sponsor can request unblinding of the assigned study intervention for participant(s) with SAEs that are unexpected and are suspected to be causally related to IMP. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the quantity of AZD0780 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Continued Access to Study Intervention After the End of the Study

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

6.8 Treatment of Overdose

For this study, any dose of AZD0780 greater than planned will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the treating physician should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.3.12 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant (except for screen failures) is receiving at the time of enrollment or receives during the study, or other specific categories of interest such as cholesterol lowering therapy within the last 12 months must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route.

Participants will be required to continue on stable doses of their dyslipidemia maintenance therapy (SoC) throughout the study to minimize the risk of disease worsening during the study.

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medications that contain a black box warning for significant QT prolongation are prohibited within this study.

Fibrate therapy and derivatives are prohibited.

Paracetamol at doses of £ 2 grams/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 Clinical Lead if required.

6.9.1 Rescue Medicine – Not Applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

It may be necessary for a participant to permanently discontinue study intervention. Note that discontinuation from study intervention is not the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

7.1 Discontinuation of Study Intervention

An individual participant will not receive further IMP if any of the following occur in the participant in question:

- Hy's Law (HL) defined as 'an increase in AST of ALT ≥ 3 x ULN and TBL ≥ 2 x ULN' where no other reason, other than IMP, can be found to explain the combination of increases.
- A severe hypersensitivity reaction.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- An SAE that is assessed as possibly related to the study intervention by the Investigator.
- An AE or other safety reasons as judged by the investigator and/or sponsor where continued treatment may put the participant at undue risk.
- Severe noncompliance with the CSP.
- Pregnancy; if a participant becomes pregnant during the study the study intervention should be discontinued immediately and a Sponsor representative notified.
- Signs or symptoms of severe hepatic impairment, as described in Section 7.1.1.
- Cardiovascular findings, as described in Section 7.1.2.
- Respiratory symptoms, as described in Section 7.1.3

If a participant discontinues IMP, he or she will be encouraged to return to the study site for the Early Discontinuation Visit (EDV; see Table 1). Where possible, the EDV should be at the next visit according to the original visit schedule, unless consent is withdrawn from further study participation, or the participant is lost to follow-up. Participants attending an EDV should also be asked to return for a follow-up visit (Visit 8, as if they have completed all doses) unless they are unable or unwilling to return.

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study. See the SoA (Section 1.2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined below or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the investigator believes that it is in best interest of the participant.

- ALT and/or AST are > 3 × ULN and TBL > 2 × ULN
- ALT and/or AST are > = 5 × ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
- ALT and/or AST are > 8 × ULN
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALT or AST > 3 x ULN and INR > 1.5 (applicable for participants with a baseline INR ≤ 1.1)

Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

7.1.2 Cardiac Stopping Criteria

Discontinuation of study intervention for abnormal cardiac tests is required by the investigator when a participant meets one of the conditions outlined below:

- Average absolute (regardless of baseline value) cardiac QTc interval corrected for heart rate by QTcF > 500 msec, or an increase of QTcF > 60 msec above the baseline value, confirmed (persistent for ≥ 5 minutes) on repeat triplicate 12-lead ECGs.

Any one of the following:

- Tachycardia, defined as resting supine pulse rate > 125 beats per minute persisting for at least 10 minutes.
- Symptomatic bradycardia, defined as resting supine pulse rate < 40 beats per minute while awake, persisting for at least 10 minutes.
- Asymptomatic bradycardia, defined as resting supine pulse rate < 30 beats per minute while awake persisting for at least 10 minutes.
- Hypertension, defined as an increase from baseline in resting supine systolic > 40 mmHg or above 180 mmHg and persisting for at least 10 minutes and/or increase from baseline in resting supine diastolic BP > 20 mmHg or above 100 mmHg and persisting for at least 10 minutes.

7.1.3 Respiratory stopping criteria

Discontinuation of study intervention is required by the investigator when a participant with respiratory disease meets the condition below:

- Exacerbation of known respiratory disease that requires hospital admission.
- Note: If any respiratory problems arise such as ongoing infection (for example, bronchitis, bronchiolitis or mild pneumonia, or acute dyspnea due to new onset arrhythmia), or change in respiratory medications is needed, to include, starting, or an increase in frequency of use of inhaler therapy, it is up to the Investigator to determine whether the participant may remain in the study whilst adjusting the other therapies or to permanently discontinue the participant from the study intervention.

7.2 Participant Discontinuation/Withdrawal from the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant 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 the participant withdraws from the study, the Sponsor may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counseled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or 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, texts, emails, 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, the participant will be considered to have been lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with the investigator 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of HBS 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 HBS see Appendix C.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements.

Laboratory and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The approximate amount of blood collected from each participant over the duration of the study is around 300ml (approximately 20 tablespoons), and the maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL (approximately 33 tablespoons). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.2).

Laboratory efficacy variables are shown in Table 5.

Table 5 Laboratory Efficacy Variables

Primary endpoint	Secondary endpoints
• Percent change from baseline of LDL-C at Week 12 (in "ideal" scenarios where intercurrent events would not occur)	• Percent change from baseline of LDL-C at Week 12 (in "real-world" conditions) • Percent change from baseline at Week 12 (in "ideal" scenarios) in: ° Total cholesterol ° HDL-C ° Triglycerides ° Non-HDL-C ° VLDL-C* ° ApoA1 ° ApoB ° Lp(a) ° Remnant cholesterol* ° hsCRP • Percent change from baseline at Week 12 (in "real-world" conditions) in: ° Total cholesterol ° HDL-C ° Triglycerides ° Non-HDL-C ° VLDL-C* ° ApoA1 ° ApoB ° Lp(a) ° Remnant cholesterol* ° hsCRP

* Calculated from standard lipid profile.
ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B-100; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); VLDL-C = very-low-density lipoprotein cholesterol.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

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.

8.2.1 Physical Examinations

A complete physical examination will be performed and 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.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

New or worsening abnormalities may qualify as AEs; see Section 8.3 for details

Height will be assessed using locally available tools without the participant wearing shoes. Weight will be assessed using the same scale (properly maintained and calibrated), and with the participant wearing a similar amount of clothes (eg, underwear only or light indoor clothing only) at each time.

Physical examination will be performed at timepoints as specified in the SoA (Section 1.2).

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Section 1.2). Vital signs will be assessed before any interventional study procedures (blood sampling, ECG, IMP administration). The participant should be in a resting, seated position for at least 5 minutes prior to the collection of vital sign, as follow:

- Body temperature (measured in Celsius). Oral measurement is preferred, but other methods are acceptable as per local standards of care
- Heart (pulse) rate
- Respiratory rate
- Oxygen saturation (SpO_2) measured by pulse oximetry
- Blood pressure (systolic and diastolic)

Blood pressure and pulse measurements should be taken by an adequately trained health care professional and assessed with a completely automated device (a calibrated sphygmomanometer is preferred). If not available, another device calibrated carefully in

proportion to a mercury sphygmomanometer should be used. The use of aneroid manometers should be avoided. An appropriate cuff size must be used to ensure accurate measurement. The disappearance of sound (Korotkov Phase V) should be used for the diastolic reading.

Blood pressure and pulse measurements should be assessed with the participant rested in a seated position, their back supported and feet on the ground. Three consecutive blood pressure and pulse readings should be recorded at intervals of at least 2 minutes. The average of the SBP, DBP and pulse readings should be recorded in the eCRF.

8.2.3 Electrocardiograms

12-lead ECG will be performed at timepoints as specified in the SoA (Section 1.2).

All 12-lead ECGs will be obtained in triplicate with no more than a 5-minute interval between each reading using a properly maintained and calibrated machine. The mean value from the three ECG readings will be recorded in the eCRF. The recordings should be done after the participant has been lying down to rest for at least 10 minutes. For participants with pacemakers, ECG variables should be read manually. ECGs may also be performed according to clinical judgment or as indicated based on any symptoms or clinical events (eg, cardiac arrhythmia).

The following ECG parameters should be collected: PR interval, RR interval, QRS duration, QT and QTcF intervals, and heart rate. An overall evaluation of the ECG results should also be performed.

8.2.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.2).

The clinical chemistry, hematology, coagulation, and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes will be described in the Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

Drugs of abuse screening will be performed at a central laboratory, unless the investigator performs these locally per each study site’s guidelines.

The following laboratory variables will be measured (Table 6).

Table 6 Laboratory Safety Variables

Hematology/Hemostasis/Glycaemic control

- Blood
  - Hematocrit
  - Hb
  - Leukocyte count
  - Leukocyte differential count (absolute count)
  - MCV
  - MCH
  - MCHC
  - Platelet count
  - RBC
  - Reticulocyte absolute count
  - Coagulation
  - HbA1C

Urinalysis

- Microscopy including white blood cell/RBC and casts
- Urine
  - Appearance and color
  - Urobilinogen
  - Blood
  - Glucose
  - Ketones
  - Leukocytes
  - Nitrites
  - pH
  - Protein
  - Specific gravity
- Urine renal safety biomarkers
  - Albumin
  - Creatinine
  - eGFR
  - Total protein

Clinical Chemistry

- Plasma/Serum
  - Albumin
  - ALP
  - ALT
  - AST
  - Bilirubin, total
  - Bicarbonate
  - Blood urea nitrogen
  - Creatinine
  - GGT
  - High sensitivity CRP
  - Potassium
  - Sodium
  - Total Protein

Endocrinology

- Serum
  - FSH (women only, at screening)
  - LH (women only, at screening)

Pregnancy Dipstick Test

- Pregnancy test (urine human chorionic gonadotropin)[a]

Viral Serology (screening only)

- HIV I
- HIV II
- HBsAg
- Hepatitis C virus antibody

ALP = alkaline phosphatase; ALT = alanine aminotransferase/transaminase; AST = aspartate aminotransferase/transaminase; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; GGT = gamma glutamyl transpeptidase; Hb = hemoglobin; HIV = human immunodeficiency virus; HBsAg = hepatitis B surface antigen; LH = luteinizing hormone; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell.

[a] Confirmatory serum test analyzed at the central laboratory is indicated if local urine pregnancy test is positive at visit 1.

In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix E, for further instructions.

8.3 AEs, SAEs, and Other Safety Reporting

The Principal Investigator 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.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

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.

Serious Adverse Events will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, 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. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

- Adverse Event (verbatim). Note: for COVID-19 related events, the investigator should add 'COVID' as part of the verbatim term
- The date and time when the AE started and stopped
- Maximum intensity
- Intensity grading: mild, moderate, or severe
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)

- AE caused participant's withdrawal from the study (yes or no)
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between IMP 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 IMP?'

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

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

8.3.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs, should only be reported as AEs if they meet any of the following:

- Fulfil any of the SAE criteria
- Are the reason for discontinuation of the IMP
- Are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign

will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia vs low hemoglobin 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 DUS.

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

8.3.5 AEs Based on Signs and Symptoms

All signs or symptoms 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.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of symptoms of DUS are those which might be expected to occur as a result of dyslipidemia (eg, increase in blood lipid levels) should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.3.8 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of dyslipidemia. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP.

8.3.9 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate Sponsor representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor 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 the Sponsor representative 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 Sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate Sponsor representative.

When the EDC is temporarily not accessible, the Sponsor Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP.

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All suspected unexpected serious adverse reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.3.10 Pregnancy

Participants will be instructed that if they or their partner becomes pregnant during the study this should be reported to the investigator. The investigator 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 participant is included in the study, then consent will be sought from the partner (via the participant's request that their partner contact 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.

8.3.10.1 Maternal Exposure

Females of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the study intervention should be discontinued immediately, and the pregnancy reported to the Sponsor.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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 during the study, then the investigator or other site personnel informs the appropriate Sponsor representative immediately but no later than **24 hours** after he or she becomes aware of it.

The designated Sponsor 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 pregnancies associated with SAEs (Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 3 months following the last follow-up visit.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 10 months after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form.

Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate Sponsor representative within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **one** (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 event of medication error, drug abuse, or misuse (Section 8.3.9) and **within 30 days** for all other events.

8.3.11.2 Medication Error

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

The full definition and examples of medication error can be found in Appendix B 4.

8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.12 Reporting of Overdose

For this study, any dose of AZD0780 greater than the planned dose within the planned study period will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/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 IMP occurs in the course of the study, the investigator or other site personnel inform the appropriate Sponsor representative immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor 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 (Section 8.3.9) and **within 30 days** for all other overdoses.

Refer to Section 6.8 for definition and treatment of overdose.

8.4 Pharmacokinetics

8.4.1 Collection of Samples for Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of AZD0780 as specified in the SoA (Section 1.2). On days where PK samples are to be collected the patient should refrain from taking the study medication prior to coming to the clinic. The PK samples are to be collected prior to administering the study medication at the clinic.

Plasma concentrations will be summarized by treatment (dose level of AZD0780) for each sampling time point, using descriptive statistics based on the PK analysis set and included in the CSR.

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

PK data from this study, possibly together with data from other studies, may be used for population PK/PD analysis. The results of any such modeling activity will be provided in a separate report (as an appendix to the CSR or as a stand-alone report).

8.4.2 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by Labcorp Bioanalytical Services LLC on behalf of the Sponsor, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Only samples from participants on active treatment will be analyzed, unless there is a need to confirm the correct treatment has been given to study participants.

Incurred sample reproducibility analysis or additional assay development work, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5 Pharmacodynamics

8.5.1 Collection of Samples for Pharmacodynamics

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

Blood samples will be collected for measurement of LDL-C, lipid profile, ApoA1, ApoB, Lp(a), hsCRP, and PK profile at the time points specified in the SoA (Table 1).

For storage, re-use, and destruction of samples for PD see Appendix C.

8.6 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the optional genetic research information ICF.
The blood sample for genetic research will be obtained at Visit 2, subject to participant agreement in the optional genetic research information ICF.

Blood samples for DNA isolation will be collected from participants who have consented to participate in the genomic analysis component of the study. Participation is optional. Participants who do not wish to participate in genomic research may still participate in the study.

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

8.7 Biomarkers

8.7.1 Mandatory Biomarker Sample Collection

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 (Section 1.2).
- Samples will be tested for safety, PK/PD, and for exploratory research to evaluate their association with the observed clinical responses to AZD0780.

8.7.2 Other Study-related Biomarker Research

Already collected samples may be analyzed on different biomarkers thought to play a role in dyslipidemia, lipid metabolism, metabolic disorders, and/or ASCVD including, but not limited to, blood (plasma and serum) and urine sample analysis to evaluate their association with observed clinical responses to study intervention. Targeted and unbiased metabolomic, lipidomic, and/or proteomic approaches may be used for PD biomarkers and biomarker research relevant to safety, tolerability, PK profile, and efficacy related to AZD0780 treatment.

For storage, re-use, and destruction of biomarker samples see Appendix C.

8.8 Immunogenicity Assessments

Immunogenicity samples are not collected in this study.

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

8.10 Study Participant Feedback Questionnaire

A study participant feedback questionnaire is not included in this study.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The primary objective is to demonstrate superiority of AZD0780 compared to placebo on LDL-C. To support the primary objective, the primary endpoint is percent change from baseline of LDL-C at Week 12. To strongly control the familywise error rate at the 0.05 level (2-sided), the alpha expenditure will be allocated to test the following null hypotheses (H) for the primary endpoint:

- H1: $\mu_{\text{AZD0780 [CCI] mg}} = \mu_{\text{placebo}}$
- H2: $\mu_{\text{AZD0780 [CCI] mg}} = \mu_{\text{placebo}}$
- H3: $\mu_{\text{AZD0780 [CCI] mg}} = \mu_{\text{placebo}}$
- H4: $\mu_{\text{AZD0780 [CCI] mg}} = \mu_{\text{placebo}}$

Where μ denotes the percent change from baseline of LDL-C at Week 12.

A hierarchical testing strategy (closed testing procedure) will be employed. H1 will be tested first using the full test mass alpha. If H1 is rejected, then the full test mass will be recycled to test H2. If H2 is rejected, then H3 will be tested with full alpha, and if H3 is rejected, H4 will be further tested with full alpha. Further details of multiplicity testing are provided in the statistical analysis plan (SAP).

9.2 Sample Size Determination

The study will randomize approximately 375 participants in order to have approximately 320 evaluable participants who complete the 12-week treatment period to support the evaluation of the primary endpoint (the discontinuation rate is assumed to be approximately 15%).

Participants will be randomized in a 1:1:1:1:1 manner to receive AZD0780 [redacted] mg, [redacted] mg, [redacted] mg, [redacted] mg, or corresponding placebo.

The sample size is driven by the objective to assess the safety and tolerability of AZD0780. The chosen sample size is believed to be sufficient for the creation of a robust safety database.

The sample size of approximately 64 evaluable participants who complete the 12-week treatment period in each arm will provide more than 90% power for the test of each dose of AZD0780versus placebo to detect a difference of [redacted] in percent change from baseline in LDL-C to Week 12. The calculations assume SD = [redacted] and a 2-sided alpha level of 0.05, and are based on a t-test with normal approximation for percent change from baseline

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF.
Randomly Assigned to Study Treatment Set	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 one dose of study intervention. Participants will be included in the analysis according to the treatment to which they were randomized.
Safety Analysis Set	All randomized participants who received at least one dose of study intervention. Participants will be included in the analysis according to the treatment they actually received.
PK Analysis Set	All participants who received at least one dose of AZD0780 and who had evaluable PK data. Participants will be included in the analysis according to the treatment they actually received.

ICF = informed consent form; PK = pharmacokinetic(s).

9.4 Statistical Analyses

9.4.1 General Considerations

Separate randomization lists will be generated for Japan and for the rest of the world. No stratification factor will be used for statistical analysis.

Statistical tests will be performed using 2-sided tests at the 5% significance level, if not explicitly specified otherwise.

The baseline value is defined as the last non-missing value prior to the administration of the first dose of study intervention unless otherwise stated.

Participant disposition will be summarized and will include the following information (also including the percentage for each category): number of participants randomized, number of participants who received treatment, number of participants who did not receive any treatment, number of participants who completed treatment, number of participants completing the study and the number of participants who were withdrawn (including reasons for withdrawal). Participants and/or data excluded from the analysis set will be listed including the reason for exclusion.

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by participant. Demographic characteristics (age, gender, race and ethnicity) and participant characteristics (height, weight, and BMI) will be summarized by treatment (dose level of AZD0780 and placebo) for all randomized participants.

A more comprehensive description of statistical procedures and assessments will be available in the SAP.

9.4.2 Efficacy

Unless otherwise specified, participants will be analyzed according to their randomized IMP assignment, irrespective of the treatment they actually received. Participants who were randomized and received at least 1 dose of study intervention will be included in the FAS population. The FAS will be considered the primary analysis set for the primary and secondary endpoints unless otherwise specified.

Efficacy data will be listed for each participant and summarized descriptively (including, but not limited to, mean, SD, minimum, median, maximum; geometric mean and geometric coefficient of variation will be presented where appropriate) by treatment and time point/visit. Figures of the mean response (absolute change from baseline and/or percent change from baseline where appropriate) may be used to visualize the average PD response over time.

Further details for analyses of efficacy endpoints will be found in the SAP.

9.4.2.1 Primary Endpoint(s)

The primary endpoint is percent change from baseline of LDL-C at Week 12. This will be assessed for each dose of AZD0780 versus placebo. The hypothetical estimand will be used for this endpoint. With the hypothetical estimand, LDL-C measurements taken after the occurrence of intercurrent events would not be used for effect estimation. More details on estimand are provided in Section 3.

The summary measure for the primary endpoint will be least squares mean of percent change from baseline of LDL-C at Week 12. The primary endpoint will be analyzed using a MMRM based on the FAS population. The model will include the fixed effects of baseline, treatment, visit, and treatment-by-visit interaction, and the random effect (random intercept) of participant. The Restricted Maximum Likelihood estimation approach will be used with a compound symmetry covariance structure for repeated measures. The treatment effects will be summarized by the difference in least squares means, 95% confidence interval, and p-value.

The hierarchical testing strategy will be employed to strongly control the familywise error rate at the 0.05 level (2-sided), as described in Section 9.1.

9.4.2.2 Secondary Endpoint(s)

For secondary efficacy endpoints, the statistical analyses will in general consist of the following 4 pairwise treatment comparisons:

- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo
- Comparison of AZD0780 [redacted] mg versus placebo

The treatment policy estimand will be used for the secondary endpoint the percent change from baseline of LDL-C at Week 12 (in "real-world" conditions). With the treatment policy estimand, LDL-C assessments are used for treatment effect estimation regardless of the occurrence of intercurrent events. Details on the handling of missing data and will be described in SAP. Participants will be analyzed according to their randomized IMP assignment, irrespective of the treatment they actually received. The summary measure for this secondary endpoint will be least squares mean of percent change from baseline of LDL-C at Week 12. The analysis will be the same as for the primary endpoint. The same multiplicity adjustment method as for the primary endpoint will be applied to this secondary endpoint for comparison purposes.

Other secondary endpoints include:

- Percent change from baseline to Week 12 in:
  - Non-HDL-C
  - VLDL-C (Calculated from standard lipid profile)
  - ApoA1
  - ApoB
  - Total cholesterol
  - HDL-C
  - Triglycerides
  - Lp(a)
  - Remnant cholesterol (Calculated from standard lipid profile)
  - hsCRP

The percent change from baseline of these parameters at Week 12 will be estimated under both "ideal" scenarios in which intercurrent events would not occur (i.e., hypothetical strategy) and "real-world" conditions (i.e., treatment policy strategy). Details on the handling of missing data will be described in SAP.

These endpoints will be analyzed using MMRM based on the FAS. The model will include the fixed effects of baseline, treatment, visit, and treatment-by-visit interaction, and the random effect (random intercept) of participant. Restricted Maximum Likelihood will be used with a compound symmetry covariance structure for repeated measures. Treatment effects will be summarized by the difference in lsmeans, 95% confidence interval, and p-value. Multiplicity adjustment will not be applied to these endpoints.

9.4.2.3 Exploratory Endpoints

The analysis of the exploratory objectives, where required, may be presented in the SAP or a separate exploratory analysis plan.

9.4.3 Safety

Safety data will be summarized descriptively and will not be formally tested.

Safety data will be presented in the data listings.

Adverse events will be summarized by PT and SOC using MedDRA vocabulary.

Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of participants who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized.

Tabulations and listings of data for vital signs, clinical laboratory tests be presented. Results from safety ECGs will only be listed. Any new or aggravated clinically relevant abnormal

medical physical examination finding compared to the baseline assessment will be reported as an AE.

Out-of-range values for safety laboratory will be flagged in individual listings as well as summarized descriptively.

Safety analyses will be performed using the safety analysis set unless otherwise specified. Details of safety analyses will be provided in the SAP.

9.4.4 Other Analyses

Pharmacokinetics

One secondary objective is to assess the PK of AZD0780.

PK analyses will be based on the PK analysis set unless otherwise specified.

Plasma concentration data of AZD0780 will be summarized by treatment (dose level of AZD0780) for each sampling timepoint using descriptive statistics.

If data permits a population PK model may be developed, possibly with the support of PK data from other studies, using nonlinear mixed effects regression analysis in NONMEM.

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

9.5 Interim Analyses

The Sponsor will potentially conduct an interim analysis with the purpose of informing further development of the clinical programme, including but not limited to dose selection for Phase 3. The interim analysis will be performed when at least 175 randomized participants have completed 12 weeks of treatment. An Unblinded Review Committee (URC) will review the interim analysis. The outcome of the interim analysis will have no impact on study conduct.

The unblinded interim analysis will be conducted by an independent team who are not involved in the conduct of the study. The members who will review the results from the interim analysis will be described in relevant charter and/or the study integrity plan. . All necessary steps will be taken to ensure the integrity of the trial by keeping the study team blinded throughout the study.

Details on the planned interim analysis will be prospectively described in relevant charter and/or SAP.

9.6 Data Monitoring Committee

If an interim analysis is performed, an Unblinded Review Committee will be used in this study.

For details on the Unblinded Review Committee, refer to Appendix A5.

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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with the Sponsor.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, 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 an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Adherence to 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the Sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representative immediately after he or she becomes aware of it.
- In certain regions/countries, the Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - The Sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU CT Regulation 536/2014 applies, the Sponsor is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to the Sponsor or delegated party, through the contacts (email address or telephone number) provided by the Sponsor.

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 study and for one year after completion of the study.

A 3 Informed Consent Process

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

Participants who are rescreened are required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The investigator or authorized 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 their 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymized. The General Data Protection Regulation defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 5 Committees Structure

If an interim analysis is performed, an Unblinded data Review Committee (URC) will be used in this study.

Unblinded Review Committee: A URC consisting of a limited number of sponsor personnel will be formed to review data for an interim analysis should it be performed, with the purpose of informing further development of the clinical programme, including but not limited to dose selection phase 3. The URC will review the risk/benefit profile and make recommendations on the dose for phase 3.

A 6 Dissemination of Clinical Study Data

Any results, both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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 study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on 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 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, including definition of study-critical data items and processes (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 included in the Monitoring Plan.
- The Sponsor or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail 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, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. 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 and its origin can be found in the Monitoring 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 the 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 IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 multicenter 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 AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE 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 unfavorable 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 it's considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and 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 SAEs

An SAE 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-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

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

Life-threatening

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

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, 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 judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used. The following are examples of an Important Medical Event:

- 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 ER or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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

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

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant 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 etiology 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? The Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the 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 DUS has deteriorated due to lack of effect should be

classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or Sponsor NIMP 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** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as 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, eg, 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 refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/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 led 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

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or Sponsor NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or Sponsor NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Sponsor NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn

consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and the study site is notified.

C 3 International Air Transport Association Guidance Document 62nd edition

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport 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 are 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.
- AstraZeneca 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 eligible adult 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 protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genomic 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 genomic 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 protocol and Appendix C2.

Collection of Samples for Genetic Research

- The optional blood sample for this genetic research will be obtained from the participants at Visit 2 after randomization. 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 Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study, subject to consent.

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 will be 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 samples either before or at the time of sample processing (DNA extraction), replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the Sponsor genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at the AstraZeneca or designated organizations. The link will be used to identify the relevant 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 genomics 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 originals filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

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

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

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver anomalies can be found in Section 8.3.6 of the CSP.

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

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

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

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

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

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase 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

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

E 3 Identification of Potential Hy's Law Cases

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

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

Central Laboratories Being Used:

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

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

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

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

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

Local Laboratories Being Used:

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

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

E 4 Follow-up

10.1.1 E 4.1 Potential Hy's Law Criteria not met

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

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

10.1.2 E 4.2 Potential Hy's Law Criteria met

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

- Notify the Sponsor representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the investigator, to provide guidance, discuss, and agree an approach for the study participant's 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. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. This includes deciding which tests available in the Hy's Law laboratory kit should be used.
  - Complete the 3 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 TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the Sponsor 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 Sponsor standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide 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 protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol 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 Laboratory 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) [c]
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 [c] 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.
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

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Appendix F Statin Inclusion Criteria

F 1 Statin Inclusion Criteria (excluding participants from Japan)

High and Moderate-intensity Statin Therapy

High-dose Statin Therapies	Moderate-dose Statin Therapies
• atorvastatin 40 to 80 mg once daily • rosuvastatin 20 to 40 mg once daily	• atorvastatin 10 to 20 mg once daily • lovastatin 40 mg once daily • pravastatin 40 mg once daily • rosuvastatin 5 to 10 mg once daily • simvastatin 40 mg once daily

Based on the American College of Cardiology / American Heart Association 2018 Guideline on the Management of Blood Cholesterol.
Grundy et al. J Am Coll Cardiol. Nov 2018: DOI: 10.1016/j.jacc.2018.11.003

F 2 Statin Inclusion Criteria (participants from Japan only)

Statin Therapy

- atorvastatin 10 to 40 mg daily
- rosuvastatin 2.5 to 20 mg 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 refering to moderate- or high-intensity statin therapies in the American College of Cardiology/American Heart Association 2018 Guideline on the Management of Blood Cholesterol, and expected to lower LDL-C levels by ≥ 30% in Japanese patients.

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