Clinical Study Protocol	
Study Intervention	AZD8233
Study Code	D7990C00004
Amendment Number	1
Date	08 Feb 2022

A Randomised, Parallel, Double-Blind, Placebo-Controlled Phase 2b Study to Assess the Safety, Tolerability and Efficacy of AZD8233 Treatment in Participants with Hyperlipidaemia (SOLANO)

Sponsor Name: AstraZeneca AB

Legal Registered Address:151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): EudraCT number, 2020-005845-18; IND number, 138348

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

Protocol Number: D7990C00004

Amendment Number: 1.0

Study Intervention: AZD8233
Study Phase: Phase 2b

Short Title: A Phase 2b Study to Assess the Safety, Tolerability and Efficacy of AZD8233 Treatment in Participants with Hyperlipidaemia.

Study Name: SOLANO

Study Physician name and contact information will be provided separately.

International co-ordinating investigators:

PPD
PPD

PPD
PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	08-Feb-2022
Original Protocol	21-Apr-2021

Amendment 1 08 February 2022

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

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Title page, 1.1 Synopsis (multiple places). 4.1 Overall design	Tolerability and efficacy words order changed in multiple places across the document	To keep consistency across the document	Non-substantial
Figure 1 footnote, Objectives and endpoints table footnote	Low-density lipid cholesterol changed to low-density lipoprotein cholesterol	To keep consistency across the document	Non-substantial
Table 1 (footnote i)	Visit 1 changed to visit 2 in footnote i SoA	To align with description of visits and guidance	Non-substantial
Table 1 (footnote j), 8 Study Assessments and Procedures	"± 15 minutes" added to post-dose sample collection in footnote j	To align guidance to sites and to define PD	Non-substantial
Table 1 explanations	IP, investigational product removed from explanations	To keep consistency, IP is not used in the table	Non-substantial
5.1 Inclusion criteria	"At screening" wording added to inclusion criteria 4	To clarify start of medication timeframe	Non-substantial
Table 4	Wording changed from "… to be provided by Clinical Site" to "… to be provided by Labcorp central laboratory"	To be consistent with process	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
6.3 Measures to Minimise Bias: Randomisation and Blinding	Section "Handling of database locks" removed	Sequential clinical data locks replaced by single final lock at end of study	Non-substantial
6.5 Concomitant Therapy	"Patients who are completely intolerant to statin therapy will be allowed to participate as the maximum tolerated dose is none." added to medical restrictions	To clarify inclusion criteria for patients intolerant to statin therapy	Non-substantial
7.1 Discontinuation of Study Intervention	Discontinuation of study intervention criteria updated	To clarify the process	Non-substantial
7.1 Discontinuation of Study Intervention	Follow-up for participants who have discontinued IMP section had been updated. Name of section: "Modified follow-up for participants who have discontinued IMP" had been removed	To clarify follow-up process for patients who have discontinued IMP	Non-substantial
8 Study Assessments and Procedures	Neurologic exam and IMP ISR assessment added to list of assessments	To clarify the process	Non-substantial
8 Study Assessments and Procedures	Neurological examination added to visit 2 and follow-up visits assessments description	To clarify the process	Non-substantial
8 Study Assessments and Procedures	Wording for visit 16 changed	To be consistent with SoA	Non-substantial
8.2.3 Assessments for AEs, including new onset/worsening of diabetes AEs	Assessments for hyperglycemia-related AEs wording had been updated	To clarify criteria basing on FDA recommendation	Non-substantial
8.2.6 Clinical Safety Laboratory Assessments	Central Laboratory name changed from COVANCE to Labcorp	To keep consistency as vendor legal name changed during course of the study	Non-substantial
Table 5	eGFR moved to Clinical chemistry column	To be consistent with the process	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
8.3.2 Follow-up of AEs and SAEs	Word "time" removed from AE variables	To be consistent with the process	Non-substantial
8.3.5 Adverse Events Based on Examination and Tests	Wording about physical examination evaluation added	To clarify process regarding physical examination/neurological examination	Non-substantial
8.3.8 Pregnancy	"AE" changed to "adverse event"	To align CSP template 6.0	Non-substantial
8.3.8 Pregnancy	"abnormalities" changed to "anomalies"	To align CSP template 6.0	Non-substantial
8.3.10 IMP Injection Site Reactions	Section renamed by adding "IMP" to the name and to the section wording	To be consistent across the document	Non-substantial
8.5.2 Immunogenicity Assessments	ADA positive participants follow-up wording had been adjusted	To clarify the ADA positive patients follow-up process	Non-substantial
Table 6	Word "dose" removed from a footnote	To be consistent across the document	Non-substantial
Table 7	PK Analysis set added	To be consistent with SAP	Non-substantial
9.4.1 General Considerations	Wording about using of PUC had been added	To clarify the process	Non-substantial
9.4.2.1 Primary Endpoints	Wording changed	To be consistent with SAP	Non-substantial
Appendix I Abbreviations	ADA and LDL-C explanation changed	To be consistent across the document	Non-substantial
Multiple places	Typographical errors were corrected in multiple places in the protocol	To be consistent across the document	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Randomised, Parallel, Double-Blind, Placebo-Controlled Phase 2b Study to Assess the Safety, Tolerability and Efficacy of AZD8233 Treatment in Participants with Hyperlipidaemia.

Short Title: A Phase 2b Study to Assess the Safety, Tolerability and Efficacy of AZD8233 Treatment in Participants with Hyperlipidaemia

Rationale:

AZD8233 is a CCI for the reduction of circulating levels of LDL-C. Elevated plasma LDL-C is a main risk factor for cardiovascular disease. Genetic studies have identified PCSK9 as an important HMG-CoA-independent, circulating regulator of LDL-C. Circulating PCSK9 is derived mainly from the liver and increases LDL-C by promoting degradation of hepatic LDL receptors. Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a human CCI CCI to specifically inhibit CCI expression in the liver.

Objectives and Endpoints:

Objectives	Endpoints
Primary Safety	
• To assess the safety and tolerability of AZD8233 as compared with CCI in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations, including CCI count
Primary Efficacy	
• To assess the effect of AZD8233 versus CCI on CCI at the end of CCI compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The relative change in CCI from baseline to the CCI

Objectives	Endpoints
Secondary Efficacy	
• To assess the effect of AZD8233 versus CCI on plasma CCI the end of CCI compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The relative change in CCI from baseline to the end of CCI
Secondary PK	
• To evaluate the PK of AZD8233	• Model population PK parameters
Secondary immunogenicity	
• To evaluate the immunogenicity of AZD8233	• CCI during treatment and follow-up

CCI; AE, adverse event; ECG, electrocardiogram; LDL-C, low-density lipoprotein cholesterol; CCI PK, pharmacokinetic(s)

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

Overall Design:

This is a randomised, parallel, double-blind, placebo-controlled Phase 2b study to evaluate the safety and tolerability of AZD8233 as compared with CCI. The study is planned to be carried out across approximately 100 clinical sites in around 8 countries.

Approximately 376 participants with hyperlipidaemia will be randomly assigned to AZD8233 CCI or matching CCI in a CCI ratio. Participants will be treated with AZD8233 or CCI, to provide data to guide CCI monitoring for future programs. The effect of AZD8233 on concentrations of LDL-C in serum will also be evaluated.

Disclosure Statement:

This is a parallel group treatment study with 2 arms that is participant, investigator, and sponsor blinded.

Number of Participants:

Of around 530 participants screened/enrolled, approximately 376 participants will be randomly assigned to study intervention with around 188 participants allocated to each of AZD8233 CCI and placebo groups. The aim is that, of the participants randomised to AZD8233, at least 150 should complete the CCI of planned treatment.

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.

Intervention Groups and Duration:

It is planned to have 2 intervention groups: an AZD8233 group and a CCI group. There will be an initial screening period starting up to CCI prior to randomisation. The study is divided into a planned treatment period of CCI followed by a safety follow-up of CCI Overall, this makes a total study participation time of CCI once participants are randomly assigned into the trial.

Data Monitoring Committee:

An internal Safety Monitoring Committee will be used for monitoring of unblinded safety data in the ongoing study.

Statistical Methods:

The primary safety objective is to assess the safety and tolerability of AZD8233 as compared with CCI in participants with hyperlipidaemia. This will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations, including CCI Safety analyses will be performed using the safety analysis set and will be presented using descriptive statistics unless otherwise specified.

Primary and secondary efficacy variables (change from baseline in LDL-C, PCSK9) will be assessed through a Treatment Policy Estimand. This approach will assess the effect of the treatment policy of AZD8233 and comparators, regardless of discontinuation of study medication. The main estimator is an CCI for the relative change from baseline to the end of CCI including all participants in the FAS. The model will include treatment group as a fixed categorical factor and baseline value as a continuous covariate.

1.2 Schema

Figure 1 Study Design

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Planned Treatment Period [a]					Safety Follow-up	
	Enrolment	Randomisation	Post First Dose assessment Visit	Dosing Visits	Safety Monitoring Visits [b]	End of Planned Treatment Period Visit	First Safety Follow-up Visit	Final Safety Follow-up Visit
CCI								
Informed consent	X							
CCI								
Verify eligibility criteria	X	X [d]						
Enrolment in IRT/RTSM	X							
Randomisation in IRT/RTSM		X						
Medical history	X							
Concomitant medication review	X	X	X	X	X	X	X	X
Demographics	X							
Body weight [e]	X	X						X
Height	X							
HbA1c	X	X				X		X

Table 1 Schedule of Activities

Procedure	Screening	Planned Treatment Period [a]					Safety Follow-up	
	Enrolment	Randomisation	Post First Dose assessment Visit	Dosing Visits	Safety Monitoring Visits [b]	End of Planned Treatment Period Visit	First Safety Follow-up Visit	Final Safety Follow-up Visit
Visit Number	**1**	CCI						
CCI	CCI							
Blood glucose		X		X		X		X
Viral serology	X							
Drug and alcohol screen	X							
Pregnancy test	X (serum)							
LH/FSH (females only)	X							
IMP administration (AZD8233/Placebo)		X		X				
Safety Assessments								
Adverse event review	X (SAE only)	X	X	X	X	X	X	X
IMP ISR assessment [f]		X	X	X	X	X	X	X
Complete physical examination	X	X						X
Abbreviated physical examination			X	X	X	X	X	
Neurological examination [g]		X		X		X		X

Table 1 Schedule of Activities

Procedure	Screening	Planned Treatment Period [a]					Safety Follow-up	
	Enrolment	Randomisation	Post First Dose assessment Visit	Dosing Visits	Safety Monitoring Visits [b]	End of Planned Treatment Period Visit	First Safety Follow-up Visit	Final Safety Follow-up Visit
CCI								
Vital signs [h] (blood pressure, pulse and temperature)	X	X	X	X		X	X	X
ECG [i]	X	X		X (Visits 8 and 14)			X	X
Serum chemistry	X	X	X	X		X	X	X
Haematology	X	X	X	X		X	X	X
Coagulation parameters [j]	X	X		X		X	X	X
CCI	X	X	X	X	X	X	X	X
Liver function tests [l]					X			
hs-CRP	X	X	X	X		X	X	X
Complement activation panel [j]		X		X				
Urinalysis	X	X	X	X		X	X	X
eGFR, UACR, UPCR	X	X	X	X		X	X	X
Urine renal safety biomarkers: albumin, creatinine, total protein	X	X	X	X		X	X	X

Table 1 Schedule of Activities

Procedure	Screening	Planned Treatment Period [a]					Safety Follow-up	
	Enrolment	Randomisation	Post First Dose assessment Visit	Dosing Visits	Safety Monitoring Visits [b]	End of Planned Treatment Period Visit	First Safety Follow-up Visit	Final Safety Follow-up Visit
Visit Number	**1**	**2**	**3**	**4, 6, 8, 10, 12, 14**	**5, 7, 9, 11, 13, 15**	**16**	**17**	**18**
Study Week		**1**	**3**	**5, 9, 13, 17, 21, 25**	**7, 11, 15, 19, 23, 27**	**29**	**33**	**41**
Study Day	**D-28 to D-1**	**D1**	**D15**	**D29, 57, 85, 113, 141, 169**	**D43, 71, 99, 127, 155, 183**	**D197**	**D225**	**D281**
Visit Window (days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 6**	**± 6**
Pharmacodynamics [m]								
LDL-C	X	X		X		X		X
PCSK9	X	X		X		X		X
Triglycerides	X	X		X		X		X
Other lipid parameters [n]	X	X		X		X		X
Exploratory Biomarker Analysis								
CCI [redacted]								
Pharmacokinetics								
PK plasma sample				X CCI [redacted]	X (Visit 15 only)	X CCI [redacted]		
Immunogenicity								

Table 1 Schedule of Activities

Procedure	Screening	Planned Treatment Period [a]					Safety Follow-up	
	Enrolment	Randomisation	Post First Dose assessment Visit	Dosing Visits	Safety Monitoring Visits [b]	End of Planned Treatment Period Visit	First Safety Follow-up Visit	Final Safety Follow-up Visit
Visit Number	CCI							
CCI								
Samples for anti-AZD8233 [a]		X		X		X		X
CCI								

[a] If COVID-19 vaccination is planned prior to entering a study, the first dose of AZD8233 should be given at least 30 days after the last dose of vaccine. In participants already undergoing dosing with AZD8233, vaccination should be separated from AZD8233 dosing by at least 7 days. AE reporting in the study should use standard reporting.

[b] Safety monitoring visits (with the exception of Visit C, when a PK sample is to be obtained) may be undertaken at the participant's home or any other appropriate location using home nursing capability. Other visits (CCI) may also be undertaken at the participant's home or any other appropriate location if deemed applicable, following consultation with the sponsor.

[c] CCI

[d] Check screening laboratory assessments and inclusion/exclusion criteria.

[e] Weight should be measured in light indoor clothes, without shoes, after a prior visit to the bathroom.

[f] IMP ISR assessments will be collected as AEs, and detailed information regarding symptoms etc, will be collected on a specific eCRF.

[g] The neurological exams should be comprehensive and include peripheral sensory and motor evaluation, and an assessment of gait, pain, position, strength and reflexes.

[h] Vital signs to be performed pre-dose on dosing visits.

[i] At CCI ECG to be performed in triplicate; all ECGs to be done pre-dose

[j] Samples will be taken around C_{max} and are to be collected pre-dose and 2 hours (± 15 minutes) post-dose (applies to dosing visits)

[k] CCI count results must be available within CCI prior to all subsequent dosing following CCI
[l] AST, ALT, TBL, direct bilirubin, GGT, ALP
[m] Samples to be collected pre-dose where applicable, in a fasted state.
[n] Lipoprotein profile. Other lipid parameters include cholesterol (TC, HDL-C, non-HDL-C, VLDL-C, remnants cholesterol), Apo B, Apo A1, and Lp(a).
[o] Samples to be collected pre-dose in a fasted state with an additional sample 2 hours post-dose at CCI .

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Apo A1, apolipoprotein A1; Apo B, Apolipoprotein B; AST, aspartate aminotransferase; ECG, electrocardiogram; D, Day; eGFR, estimated glomerular filtration rate; FSH, follicle stimulating hormone; GGT, gamma glutamyl transferase; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); hs-CRP, high sensitivity C-reactive protein; IMP, investigational medicinal product; CCI ; IVRS/IWRS, interactive voice response system/interactive web response system; LDL-C, low-density lipoprotein cholesterol; LH, luteinising hormone; PCSK9, proprotein convertase subtilisin/kexin type 9; PK, pharmacokinetic; SAE, serious adverse event; TBL, total bilirubin; TC, total cholesterol; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio; VLDL-C, very low-density lipoprotein cholesterol

Note: Participants are required to fast for at least 8 hours overnight prior to CCI and C CI. Participants are permitted to drink water during this period of fasting. On days where participants attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of IMP.

2 Introduction

2.1 Study Rationale

AZD8233 is a [redacted] This is a safety and tolerability study with the aim of creating a safety database covering exposure following treatment with AZD8233 for [redacted], to investigate whether any signals related to [redacted] or other safety parameters are present that could potentially lead to restriction of participant populations due to safety. Efficacy of AZD8233 will also be evaluated through its ability to reduce LDL-C.

2.2 Background

Elevated plasma LDL-C, is a main risk factor for cardiovascular disease and is typically caused by a combination of environmental and genetic factors. Statin therapy is the standard lipid lowering medication for both primary and secondary prevention of cardiovascular disease. Reduction of LDL-C by statins leads to a significant reduction in cardiovascular events (Collins et al 2016). Statins reduce LDL-C by inhibiting HMG CoA reductase, the rate-limiting enzyme of hepatic cholesterol synthesis. However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C target goals.

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

Two [redacted] ([redacted]) have been successfully developed to pharmacologically inhibit PCSK9. [redacted] of these compounds lowers LDL-C levels by approximately 60%, even in patients already receiving maximum dose statin therapy (Sabatine et al 2017). Furthermore, [redacted] was found to lower PCSK9 (69.1%) and LDL (52.6%) levels in patients at high cardiovascular risk who had elevated LDL-C levels (Ray et al 2017).

Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a [redacted] that specifically [redacted] expression in the liver (Prakash et al 2014). Potential risks for AZD8233 based on [redacted] class have been identified (see Table 2) and will be evaluated in this study. AZD8233 may provide novel treatment options for patients with hyperlipidaemia.

In the ongoing SAD (Study D7990C00001), global MAD (Study D7990C00002), Japanese MAD (D7990C00006 [HAYATE]), and global dose ranging (Study D7990C00003

[ETESIAN]) studies, > 120 participants have been exposed to multiple doses of CCI administration of AZD8233.

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

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

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

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

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the current IB.

2.3 Benefit/Risk Assessment

Potential risks of AZD8233 and mitigation strategy are shown in Table 2. More detailed information about the known and expected benefits and potential risks of AZD8233 can be found in the current IB.

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (AZD8233)		
Thrombocytopenia	Severe, reversible thrombocytopenia has been observed in some CCI programs in clinical trials although it is not known whether other members of the class may be affected (Crooke et al 2017). One case of severe thrombocytopenia was observed in the non-human primate toxicology study with AZD8233.	Monitoring of CCI . In cases of severe thrombocytopenia, the action plan detailed in Appendix F will be followed.
Kidney Injury	Kidney is an oligonucleotide high-uptake tissue. Tubular necrosis has been observed CCI CCI (van Meer et al 2017, van Poelgeest et al 2013, 2015). This was not predicted in toxicological studies with AZD8233	Monitoring of S-creatinine, BUN, urine albumin and urine total protein as well as calculation of eGFR.
Liver Toxicity - Transaminase Elevations	Liver is an oligonucleotide high-uptake tissue (Hung et al 2013). Oligonucleotide treatment may cause transient transaminase elevations in mice, monkeys, and humans at therapeutic exposures (Burdick et al 2014, Hagedorn et al 2013, Hildebrandt-Eriksen et al 2012). AZD8233 is a GalNAc-conjugated oligonucleotide, utilizing the ASGP-R to enhance uptake by hepatocytes. In the 6-month mouse chronic toxicology study, higher levels in liver enzymes (AST and ALT) in males and/or in females was observed and minimal to mild histopathological changes in few animals at high doses, however deemed not to be adverse. In ongoing clinical studies with AZD8233, transient increases in transaminases have been seen in 6 participants (see Section 2.2 for details).	Monitoring of a panel of liver safety biomarkers including transaminases.

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (AZD8233)		
CCI	CCI	
Injection Site Reactions	ISRs may occur following subcutaneous administration of ASOs and other biologics and is regarded as a class effect. Most often they are mild with only slight erythema and are rapidly reversible and tolerated by patients. They are also dose-dependent. There have been reports in some ASO programs of a few cases of severe ISRs with a high incidence of discomfort to the patient that have led to withdrawal from treatment. In the ongoing clinical programme for AZD8233, mild ISRs have been observed in a few participants (see Section 2.2 for details).	Monitoring for ISRs.
Complement Activation	This is a known class effect of oligonucleotides and appears to be directly plasma concentration (C_{max}) driven. Monkeys are considered more sensitive to complement activation than humans (Crooke et al 2016). In the 9-month monkey study, minimal to mild higher complement Bb was observed at ≥ 6 mg/kg/occasion at the end of the study and correlated microscopically with mononuclear cell (predominantly lymphocytic) infiltration/inflammation observed in multiple tissues, including the administration site.	Assessment of complement activation around C_{max} (C5a, Bb).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (AZD8233)		
Inhibition of Intrinsic Coagulation Pathway	Increases in aPTT, in the absence of clinical or pathological sequelae, have been observed with ASOs (Burel et al 2013, Henry et al 1997). Mechanistically, interaction of ASOs with the intrinsic tenase complex and thrombin results in a selective inhibition of the intrinsic clotting cascade and hence increases in aPTT (Henry et al 2017, Sheehan and Lan 1998, Sheehan and Phan 2001). Changes in activity of the intrinsic clotting pathway reverse when ASOs are cleared from plasma. Transient prolongation of aPTT has been described in man and was observed to correlate in a linear manner with the C_{max} at the end of infusion (Sewell et al 2002). There were no treatment related changes in any coagulation parameters in the nonclinical toxicology studies.	Assessment of aPTT and Prothrombin Time around C_{max} Collection of AEs related to bleeding.
Hypersensitivity and Anaphylactic Reaction	Similar to any foreign biological agent, administration of AZD8233 may induce hypersensitivity reactions. These acute reactions are important because they may be severe but are considered rare.	Monitoring for immunogenicity effects (severe allergy and hypersensitivity reactions and ADA), see Appendix G.
Flu-like Reactions	Flu-like symptoms (chills, myalgia, arthralgia, feeling hot, and body temperature increase) are rather common for some ASOs. No indications of systemic inflammatory effects induced by AZD8233 have been seen in the toxicology studies.	Monitoring for any flu-like reactions and assessment of hs-CRP.
Study procedures		
CCI	Pain near the injection site (for 1 or 2 days) is the most common complication CCI	Slow CCI of AZD8233 using gentle pressure (at least 5 seconds duration is recommended) and CCI

CCI

[redacted]

2.3.2 Benefit Assessment

AZD8233 is expected to lower circulating PCSK9 in this study in all AZD8233-treated participants (see Section 4.3). Pharmacologic inhibition of PCSK9 is known to increase catabolism of LDL-C and reduce circulating LDL-C. Low levels of LDL-C are associated with a lower risk of incident atherosclerotic CVD events, providing an important clinical benefit to individuals with hyperlipidaemia.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the IB.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with AZD8233 are justified by the anticipated benefits that may be afforded to participants with hyperlipidaemia. Furthermore, findings from this study may serve to ameliorate the perception of risk potentially associated with AZD8233 around thrombocytopenia and guide recommendations for monitoring.

3 Objectives and Endpoints

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary Safety	
• To assess the safety and tolerability of AZD8233 as compared with placebo in participants with hyperlipidaemia receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations, including platelet count
Primary efficacy	
• To assess the effect of AZD8233 versus placebo on serum LDL-C at the end of Week 28 compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The relative change in serum LDL-C from baseline to the end of Week 28
Secondary efficacy	
• To assess the effect of AZD8233 versus placebo on plasma PCSK9 at the end of Week 28 compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The relative change in PCSK9 from baseline to the end of Week 28
Tertiary efficacy	
• To assess the effect of AZD8233 versus placebo on serum LDL-C over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The absolute levels, as well as the absolute and relative changes compared with baseline, in serum LDL-C over time
• To assess the effect of AZD8233 versus placebo on plasma PCSK9 over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The absolute levels, as well as the absolute and relative changes compared with baseline, in PCSK9 over time
• To assess the effect of AZD8233 on the incidence of the 3 point MACE composite (defined as CV death, MI, ischaemic stroke)	• Time to the first occurrence of any component of the 3 point MACE composite
• To assess the effect of AZD8233 on the incidence of thromboembolic events (defined as the composite of DVT and PE)	• Time to first thromboembolic event

Table 3 Objectives and Endpoints

Objectives	Endpoints
• To assess the effect of AZD8233 versus placebo on other lipid parameters over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	• The absolute levels, as well as the absolute and relative changes compared with baseline, in other lipid parameters over time. Parameters include: – Cholesterol: o TC o HDL-C o Non-HDL-C o VLDL-C o Remnants cholesterol – Triglycerides – Apo B – Apo A1 – Lp(a)
Secondary PK	
• To evaluate the PK of AZD8233	• Model population PK parameters to be reported in a separate report
Secondary immunogenicity	
• To evaluate the immunogenicity of AZD8233	• Development of ADA and titre (if participants are ADA positive) during treatment and follow-up
Exploratory	
• CCI	
• CCI	• CCI

ADA, anti-drug antibodies; AE, adverse event; Apo A1, apolipoprotein A1; Apo B, Apolipoprotein B; CSR, clinical study report; CV, cardiovascular; CCI DVT, deep vein thrombosis; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type-9; PD, pharmacodynamics; PE, pulmonary embolism; PK, pharmacokinetics; TC, total cholesterol; VLDL-C, very-low-density lipoprotein cholesterol

4 Study Design

4.1 Overall Design

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

This is a randomised parallel, double blind, placebo controlled Phase 2b study to evaluate the safety, tolerability and efficacy of AZD8233 as compared with placebo. The study is planned to be carried out across approximately 100 clinical sites in around 8 countries.

Approximately 376 participants with hyperlipidaemia will be randomly assigned to AZD8233 CCI or matching placebo in a 1:1 ratio. Participants will be treated with AZD8233 or placebo SC, Q4W for 28 weeks, to provide data to guide platelet monitoring for future programs. The aim is that, of the participants randomised to AZD8233 doses, at least 150 should complete the 28 weeks of planned treatment.

The effect of AZD8233 CCI administered SC, Q4W for 28 weeks, on concentrations of LDL-C in serum will also be evaluated.

There will be an initial screening period starting up to 28 days before and ending on the day before the randomisation visit (ie, Day -1). The study is divided into a planned treatment period of 28 weeks followed by a safety follow-up of 12 weeks. Overall, this makes a total study participation time of 40 weeks once participants are randomly assigned into the trial.

An iSMC will be used for regular review of unblinded safety data during the study (see Appendix A 5). The remit of the iSMC will be detailed in the iSMC charter.

4.2 Scientific Rationale for Study Design

Elevated plasma LDL-C, is a main risk factor for CVD and is caused by a combination of environmental and genetic factors. Statin therapy is the standard lipid lowering medication for both secondary and primary prevention of CVD, as an adjunct to diet. Reduction of LDL-C by statins leads to a significant reduction in cardiovascular events (Collins et al 2016). Statins reduce LDL-C by inhibiting HMG-CoA reductase, the rate- limiting enzyme of hepatic cholesterol synthesis. However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C target goals and some continue to be at residual risk despite maximum doses.

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

Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a

PCSK9 -targeted, GalNAc-conjugated ASO that specifically inhibits intracellular PCSK9 expression in the liver (Prakash et al 2014). Severe, reversible thrombocytopenia has been observed in some ASO programs in clinical trials, but it is not known whether all members of the class have this characteristic (Crooke et al 2017). This study will evaluate platelet count, over time, in AZD8233-treated participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy, compared with placebo. The aim of the study is to see if any thrombocytopenia signal is observed, and whether it is feasible to reduce platelet monitoring frequency and maintain patient safety.

4.3 Justification for Dose

The therapeutic goal of AZD8233 is to lower LDL-C by 70% during the entire dosing interval. PCSK9 reduction causes LDL-C reduction by a well-known and previously quantified mechanism, and lowering PCSK9 by 90% has been shown to reduce LDL-C by 70% (Gibbs et al 2017, Kathman et al 2018, Sokolov et al 2019).

4.4 End of Study Definition

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

5 Study Population

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

5.1 Inclusion Criteria

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

Age

1 Participants must be 18 to 75 years of age inclusive, at the time of signing the informed consent form.

Type of Participant and Disease Characteristics

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

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

4 Participants are receiving a stable dose (≥ 3 months) of maximally tolerated statin and/or ezetimibe therapy as defined by the investigator for that participant at screening.

Sex

5 Male or female of non-childbearing potential.

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

- Male participants:

  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, intrauterine devices (IUDs), tubal ligation/occlusion and vasectomy. These methods of contraception should be combined with a barrier method except for when the female partner is sterilized. Male study participants must not donate or bank sperm during this same time period.

- Female participants:

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

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

Informed Consent

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

7 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.

8 CCI [redacted]

5.2 Exclusion Criteria

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

Medical Conditions

1 As judged by the investigator, any evidence of a condition, which in the investigator's opinion, makes it undesirable for the participant to participate in the study.

2 eGFR < 40 mL/min/1.73m^2 using the CKD-EPI.

3 History or presence of gastrointestinal, hepatic or renal disease or any other conditions known to interfere with absorption, distribution, metabolism or excretion of drugs, per the investigator's judgement.

4 Any uncontrolled or serious disease, or any medical (eg, known major active infection or major haematological, renal, metabolic, gastrointestinal or endocrine dysfunction) or surgical condition that, in the opinion of the investigator, may either interfere with participation in the clinical study and/or put the participant at significant risk (according to the investigator's judgment) if he/she participates in the clinical study.

5 Poorly controlled T2DM, defined as HbA1c > 10%.

6 Acute ischaemic cardiovascular event, including stroke, within 30 days, or heart failure with New York Heart Association (NYHA) Class III to IV.

7 Blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura or symptoms of increased risk of bleeding (frequent bleeding gums or nose bleeds).

8 High-risk of bleeding diathesis or any anti-platelet therapy other than low dose aspirin (≤ 100 mg/day).

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

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

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

12 Uncontrolled hypertension defined as average sitting SBP > 160 mmHg or DBP > 90 mmHg.

13 Heart rate after 10 minutes sitting rest < 50 or > 100 bpm.

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

- Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV)
- ALT > 1.5 × ULN
- AST > 1.5 × ULN
- TBL > ULN
- ALP > 1.5 × ULN
- WBC < lower limit of normal (LLN).
- Haemoglobin < 12 g/dL in males or < 11 g/dL in females
- Platelet count ≤ LLN
- aPTT > ULN or Prothrombin Time > ULN
- UACR > 11 mg/mmol (100 mg/g)
- UPCR > 300 mg/g

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

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

17 Known or suspected history of drug abuse or a positive screen for drugs of abuse at the Screening Visit, likely to impact participant safety or compliance with study procedures, at the discretion of the Investigator.

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

Prior/Concomitant Therapy

19 Use of warfarin, direct and indirect thrombin inhibitors or factor Xa inhibitors

20 Mipomersen, or lomitapide within 12 months prior to randomisation.

21 Any fibrate therapy other than fenofibrate; if the participant is on fenofibrate therapy, the dose should be stable for at least 6 weeks prior to randomisation.

22 Previous administration of AZD8233/AZD6615 or inclisiran (LEQVIO®, Novartis).

23 Use of evolocumab (REPATHA®, Amgen) and alirocumab (PRALUENT®, Regeneron) within 3 months of screening.

24 History of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or GalNAc-conjugated ASOs.

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

Prior/Concurrent Clinical Study Experience

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

27 Participants with a known hypersensitivity to AZD8233 or any of the excipients of the product.

28 Use of other IMP or investigational devices during the course of the study.

Other Exclusions

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

30 Judgment 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.

31 Previous randomisation into the present study.

32 Participants who cannot communicate reliably with the investigator.

33 Participants (eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order).

34 Plasma donation within 1 month of the visit at the clinic or any blood donation/blood loss > 500 mL during the 3 months prior to screening visit.

CCI [redacted]

CCI [redacted]

35 CCI [redacted]

36 CCI [redacted]

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants are required to fast for at least 8 hours overnight prior to Visits 1, 2, 4, 6, 8, 10, 12, 14, 16, and 18. Participants are permitted to drink water during this period of fasting. On days where participants attend the clinic in a fasted state, blood and urine samples should be

obtained prior to administration of IMP.

5.3.2 Caffeine, Alcohol, and Tobacco

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

5.3.3 Reproductive restrictions

Women of Non-Child Bearing Potential

Women of non-child bearing potential are defined as female participants who are permanently surgically sterilized or postmenopausal (see inclusion criteria, Section 5.1).

Restriction for Male Participants

There is no information about any potential effect of AZD8233 on development of the foetus in humans. Therefore, it is important that women of child bearing potential who are the partners of male participants do not become pregnant during the study and for a total period of 3 months after the male participant has attended the final follow-up visit.

As a precaution, 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.

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.

Sperm Donation

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

Pregnancy

Male participants will be instructed that if 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.

5.3.4 Blood donation

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. At the investigator's discretion, participants may be rescreened once during the recruitment period. Participants who are rescreened are required to sign a new ICF and should be assigned the same participant number as per their initial screening visit.

6 Study Intervention

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Details of the identity of the investigational products are presented in Table 4 and in the study specific IMP handling instructions.

Table 4 Investigational Medicinal Products

Arm name	Cohort 1	Cohort 2
Intervention name	**AZD8233**	**Placebo**
Dose formulation	AZD8233 solution for injection	Matching placebo solution for injection
Unit dose strength(s)[a]	CCI [redacted]	Placebo, CCI [redacted]
Dosage level(s)[b]	CCI [redacted] Q4W	Placebo, CCI [redacted]
Regimen	AZD8233/Placebo, Days 1, 29, 57, 85, 113, 141, 169	
Route of administration	SC injection	
Treatment Administration Guidelines	SC injection in either abdominal region (avoid a 5 cm radius around umbilicus), arm, thigh or buttock is to be used. Slow injection of study intervention using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites. The anatomical location of each injection site should be documented in the eCRF.	
Specific device for drug administration	Syringes and needles for injection to be provided by Labcorp central laboratory	
Use	Experimental	Placebo
IMP and NIMP	IMP	
Sourcing	Vials provided centrally by the Sponsor	
Packaging and labelling	CCI [redacted]	
Special Handling Requirements	Requirements will be provided in a separate document.	
Availability of IMP	Will be shipped when approvals are in place	

[a] AZD8233 is also available as a 55 mg/mL solution to give flexibility should a lower strength be needed. The required injection volumes are described in the study specific handling instructions.
[b] Planned dose
eCRF, electronic case report form; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; Q4W, every 4 weeks; SC, subcutaneous

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants randomised into the study may receive study intervention and only when an assessment of platelet count has been made. All participants must meet inclusion criteria for platelet count based on laboratory values from Visit 1 in order

to be dosed at randomisation (Visit 2); after randomisation, participants must have platelet count assessed within 14 (+/-3) days of each subsequent dose administration.

3 Only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

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

5 Further guidance and information for the final disposition of unused study interventions are provided in the study specific handling instructions.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised study intervention using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM). Before the study is initiated, the log in information & directions for the IRT/RTSM will be provided to each site.

Eligible participants will be randomly assigned to AZD8233 CCI or matching placebo in a 1:1 ratio. Participants will be treated with AZD8233 or placebo SC Q4W for 28 weeks.

Study intervention will be dispensed at the study visits summarised in the SoA. Returned study intervention should not be re-dispensed to the participants.

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

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

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

The RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a

determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

Data for the pharmacodynamic parameters in the lipid panel listed in Section 8.5.3 are considered potential unblinding information. Therefore, any such results taken post randomisation will be kept confidential and blinded to site staff as sponsor personnel. The exceptions are laboratory vendor and data management personnel assigned in unblinded role

The laboratory vendor personnel performing the bioanalyses of the plasma samples will have access to the randomisation list. The laboratory vendor will receive instructions on blinding of specific pharmacodynamic biomarkers, such as LDL-C, to laboratory results accessed by sites and sponsor. Additionally, guidance will be provided to investigators to advise participants and their clinicians to adhere to recommended guidelines for lipid monitoring and avoid additional assessment when not clinically indicated.

6.4 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, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Safety monitoring visits may be undertaken at the participant's home or any other appropriate location using home nursing capability. Other visits may also be undertaken at the participant's home or any other appropriate location if deemed applicable, following consultation with the sponsor. Once the home visit is complete, the hard copy of the source document will be securely mailed to the site for data entry into the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine, including any approved or emergency use authorised COVID-19 vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

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

Specific guidance for COVID-19 vaccination can be found in Appendix H.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate care for participants except for those medications excluded below or listed

in the exclusion criteria. Specifically, participants should receive full supportive care during the study as deemed appropriate, and in accordance with local guidelines.

The following medical restrictions apply:

- Medications/therapies specified in the exclusion criteria are prohibited from use for the duration of the participant's involvement in the study.
- Participants should be receiving a stable dose (≥ 3 months) of maximally tolerated statin and/or ezetimibe therapy as defined by the investigator for that participant. Because the therapeutic window of statin therapy may vary between patient in accordance to known or potential risks for side effects, the maximum tolerated dose of statin therapy will be defined by the investigator for each patient based on clinical judgement. Patients who are completely intolerant to statin therapy will be allowed to participate as the maximum tolerated dose is none.
- For participants on fenofibrate therapy, the dose must be stable for at least 6 weeks prior to randomisation at a dose that is appropriate for the duration of the study in the judgement of the investigator. Other fibrate therapy (and derivatives) are prohibited.
- Use of icosapent ethyl (Vascepa), bempedoic acid (Nexletol), bile acid sequestrants and nicotinic acid are permitted; however, participants should be receiving a stable dose (≥ 3 months) prior to randomisation. Initiating these medications after a participant is enrolled is not permitted.
- Participants should not be on any anti-platelet therapy other than low-dose aspirin (≤ 100 mg/day).
- Participants must abstain from making dose changes and taking new prescription or non-prescription drugs without consultation with the investigator (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit.
- Paracetamol/acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Study Physician if required.
- The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medicine

The study will not supply any specific rescue medication.

The date and time of any rescue medication administration or respective dose change must be recorded including:

- Name of medication;
- Reason for use or change;

- Dates of administration including start and end dates;
- And dosage information including dose and frequency.

6.6 Dose Modification

No dose modification is allowed.

6.7 Intervention After the End of the Study

There is no planned intervention following the end of the study. However, should a participant develop thrombocytopenia during the safety follow-up that remains unresolved after the study ends, further evaluation may be necessary as outlined in Appendix F.

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.

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:

- Participant decision. The participant is free at any time to discontinue IMP treatment, without prejudice to further treatment
- AE precluding further therapy (where the investigator thinks continued treatment may put the patient at undue risk, regardless of whether the AE is thought to be related to IMP)
- Investigator's decision, including but not limited to these examples:
  - Incorrectly randomised patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
  - Severe non-compliance to Clinical Study Protocol
- Pregnancy
- Platelet count $< 75 \times 10^9$/L, confirmed by taking a second measurement (Appendix F)
- Hy's Law defined as 'an increase in AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases', as defined in Appendix E.
- Confirmed:
  - ALT or AST $> 8 \times$ ULN
  - ALT or AST $> 5 \times$ ULN for > 2 weeks
  - ALT or AST $> 3 \times$ ULN and TBL $> 2 \times$ ULN or INR > 1.5
  - ALT or AST $> 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).

- Confirmed by repeat testing increase in serum creatinine of 0.3 mg/dL from baseline at the discretion of the investigator
- Confirmed by repeat testing 25% decline in eGFR from baseline at the discretion of the investigator
- Confirmed by repeat testing new onset haematuria of unknown etiology, albuminuria (urine albumin/creatinine ratio [UACR] ≥ 300 mg/g), or proteinuria (urine protein/creatinine [UPCR] ≥ 500 mg/g) at the discretion of the investigator
- Anaphylactic reaction or severe hypersensitivity reaction suspected to be related to study intervention.

Follow-up for participants who have discontinued IMP

Participants who are prematurely and permanently discontinued from receiving IMP will be encouraged to continue their study participation by following the original visit schedule, without taking IMP, with the exception of the safety monitoring visits during the treatment period.

If the participant is unwilling to comply with the visit schedule, a modified follow-up schedule can be offered, which should at a minimum include the following visits:

- The next scheduled visit, using the original visit schedule.
- Visit 8 (if the participant discontinues prior to Visit 8) and Visit 16 (end of planned treatment period) per the SoA.
- Safety follow-up visits (to include SoA procedures for Visit 17 and Visit 18), adjusted to occur 8 and 16 weeks after last dose, respectively.

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

7.1.1 Temporary Discontinuation

If a participant temporarily discontinues IMP for any reason, the participant may restart the medication at any time during the dosing period in accordance with the dosing schedule, but only when an assessment of platelet count has been made within 14 (+/-3) days of planned administration and re-assessment of the participants clinical status. No additional doses will be administered to make up for missed doses. The reason for any temporary IMP interruption will be collected in the eCRF.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request without prejudice to further treatment. In exceptional circumstances, the participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (telephone contact, contact with a relative or the treating physician, information from medical records or modification of the SoA as described in Section 7.1).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulations. The investigator must inform the Global Study Team immediately and document the decision on use of existing samples in the site study records.

7.3 Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.

- 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.
- Platelet count results must be available within 14 days (+/-3) prior to all subsequent dosing following Visit 2

- Assessments scheduled at the same time may be initiated based on the sequence below (where applicable):
  1 ECG
  2 Vital signs (SBP, DBP, pulse rate, and temperature), and physical exam, including neurologic exam and AE review including IMP ISR assessment
  3 PK, PD and safety blood and urine sampling
  4 Dose administration. Pre-dose assessments may be performed up to 60 minutes prior to dosing
  5 Where applicable, 2-hour (±15 minutes) post-dose assessments, including complement activation profile, coagulation parameters and PK (Visit 12)
- Immediate safety concerns should be discussed with the sponsor upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The study is divided into a screening period of 28 days, a planned treatment period of 28 weeks followed by a safety follow-up period of 12 weeks, with the first visit in the safety follow-up period occurring 8 weeks after the last dose of IMP is administered. On the screening visit (Visit 1), participants are checked for eligibility, enrolled into the study, and examinations and samples taken according to the SoA. At Visit 2, after study assessments and additional blood and urine samples are taken, participants are randomly assigned to AZD8233 or matching placebo in a 1:1 ratio. The first dose will be administered at randomisation Visit 2. Participants will then receive a further dose every 4 weeks on 6 more occasions. The end of the planned treatment period Visit will occur on Visit 16 followed by the first safety follow-up Visit 4 weeks later. The final safety follow-up visit takes place 8 weeks after the first safety follow-up visit.

General Description of Study Visits

Visit 1 (enrolment): At Visit 1, participants will be asked to sign the informed consent. Participants are required to be fasting for at least 8 hours overnight prior to the visit. Participant eligibility criteria will be reviewed and demographics, medical history, including, drug and alcohol consumption history, as well as concomitant medication review will be recorded in the eCRF. A complete physical examination must be performed. Vital signs, height, weight, and ECG will be checked, as well as blood and urine sample collection, per the SoA. Serum pregnancy, FSH, and LH tests will be taken for female participants. All laboratory tests performed at Visit 1 should be reviewed for eligibility prior to the participant returning for Visit 2. Enrolment will be performed in IRT/RTSM.

Visit 2 (randomisation): At Visit 2, participants are required to be fasting for at least 8 hours overnight prior to the visit; participants are permitted to drink water during this period until 1 hour before blood sampling. Eligibility criteria must be verified by checking screening laboratory assessments and inclusion/exclusion criteria. CCI [redacted] A complete physical examination, neurologic examination and vital sign assessments will be performed. Blood samples, including those needed for efficacy and pharmacodynamics, ADA and urine samples will be obtained in accordance with the SoA. ECG will be checked. If the participant fulfils all inclusion criteria and none of the exclusion criteria, the participant will be randomised in IRT/ RTSM and IMP will be administered as a SC injection. Post-dose assessments (complement activation profile and coagulation parameters) will take place 2 -hours after dosing of IMP.

Visit 3: At Visit 3, concomitant medications, AEs, and an assessment for ISRs will be reviewed, as well as an abbreviated physical exam and assessment of vital signs. Blood and urine samples, and platelet count, will be obtained in accordance to the SoA.

Dosing Visits (Visits 4, 6, 8, 10, 12, 14): At dosing visits, participants are required to be fasting for at least 8 hours overnight prior to the visit; participants are permitted to drink water during this period until 1 hour before blood sampling. Concomitant medications, AEs and an assessment for ISRs will be reviewed. An abbreviated physical exam a neurologic examination and assessment of vital signs will be performed. Review of the most recent platelet count within 14 (+/-3 days) prior to the visit. ECG, blood samples, including those needed for efficacy and pharmacodynamics, and urine samples will be collected in accordance with the SoA. Blood samples for ADA will be collected. PK samples will be collected pre-dose on Visits 4, 8, and 12. Study intervention will then be administered. Post-dose assessments (coagulation panel and complement activation profile; PK at Visit 12) will be obtained 2 hours after dosing of IMP.

Safety Monitoring Visits (Visits 5, 7, 9, 11, 13, 15): At safety visits, concomitant medications, AEs and an assessment for ISRs will be reviewed. Platelet count and liver function tests will be obtained. A PK sample will be obtained on Visit 15. Participants do not have to be fasting for this visit. Where applicable, the safety monitoring visit may be performed via home visits.

End of Planned Treatment Period Visit (Visit 16): At the end of treatment visit, the participants are required to be fasting for at least 8 hours overnight prior to the visit. Concomitant medications, AEs and an assessment for ISRs will be reviewed. An abbreviated physical exam, a neurologic examination and assessment of vital signs will be performed. Blood samples, including those needed for efficacy and pharmacodynamics, PK and ADA, as well as urine samples, will be collected. Coagulation parameters will also be assessed.

Safety Follow-up Visits (Visit 17, 18): At the safety follow-up visits, participants are required to be fasting for at least 8 hours overnight prior to Visit 18 (not necessary for Visit 17). Concomitant medications and AEs will be reviewed. An abbreviated physical examination and assessment of vital signs will be performed on Visit 17 and a complete

physical examination, a neurologic examination and assessment of vital signs on Visit 18. Additionally, ECG will be obtained. Blood and urine samples, including ADA, will be collected in accordance with the SoA. For participants who have prematurely discontinued IMP, these visits will be adjusted to occur 8 and 16 weeks after the last dose of IMP, as described in Section 7.1.

8.1 Efficacy Assessments

Please see Section 8.5.3 for the pharmacodynamic assessments, which will be used for primary and key secondary efficacy analyses. Primary efficacy will be determined by relative change from baseline in LDL-C at the end of Week 28. Secondary efficacy will be determined by relative change from baseline in PCSK9 at the end of Week 28.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. The safety follow-up period will be defined as the time from the end of treatment Visit to the final safety follow-up Visit.

8.2.1 Physical Examination

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

Physical examination will be performed at timepoints as specified in the SoA.

8.2.2 Neurological Examination

- A complete neurological examination will include peripheral sensory and motor evaluation, as well as an assessment of gait, pain, position, strength and reflexes. Appropriate training to be given at the investigators' Meeting.
- Neurological examination will be performed at timepoints as specified in the SoA.

8.2.3 Assessments for AEs, including new onset/worsening of diabetes AEs

An assessment of AEs will be performed at the time points specified in the SoA. These AEs will also include any worsening of previously documented medical conditions as determined by the investigator.

Additionally, assessments for hyperglycemia-related AEs should be included with the

assessment for concomitant medications and AEs. This should include:

Any report of 'New onset of diabetes' in which participants with no medical history of diabetes are found to have any of the following:

- a post-baseline HbA1C ≥6.5%, confirmed by a consecutive HbA1C value ≥6.5% (48 mmol/mol) or a fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), **or**
- two consecutive values of fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), **or**
- addition of a new concomitant medication for control of plasma glucose (if additional information provided to the investigator supports the diagnosis), **or**
- adverse events suggestive of diabetes (e.g. typical diabetes manifestations, signs, symptoms, complications).

Any report of 'Worsening of the glycemic control' or 'diabetic complications' in which participants with a medical history of diabetes are found to have:

- Absolute increase in HbA1c from baseline of > 0.5% (5.5 mmol/mol), and/or
- A new concomitant antidiabetic medication or an increase in dose of current antidiabetic therapy in response to uncontrolled diabetes, or any confirmation of uncontrolled diabetes/worsening glycemic control from clinical data collected by the investigator

8.2.4 Vital Signs

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

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

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

8.2.5 Electrocardiograms

ECG will be performed pre-dose where applicable, at timepoints specified in the SoA.

- At randomisation (Visit 2), the baseline 12-lead ECG will be obtained on three consecutive occasions after the participant has rested in supine position for at least 10 minutes

- During the treatment period and safety follow-up, a single 12-lead ECG will be obtained after the participant has rested in supine position for at least 10 minutes
- The same recorder should be used for each participant at each time point, if possible

The investigator (or qualified designee) will make an overall evaluation of the ECG as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not clinically significant, and the reason for the clinically significant abnormality will be recorded on the eCRF.

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

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

8.2.6 Clinical Safety Laboratory Assessments

Laboratory variables will be analysed at Labcorp central laboratory. Any local laboratory variables, performed for safety assessment, such as platelet count, must be confirmed by central laboratory assessment. Samples will be collected, handled, labelled, stored and shipped as detailed in the laboratory manual.

The following laboratory variables will be measured.

Table 5 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
White blood cell (WBC) count	Sodium
Red blood cell (RBC) count	Potassium
Haemoglobin (Hb)	Blood urea nitrogen (BUN)
Haematocrit (HCT)	Creatinine
Mean-corpuscular volume (MCV)	Calcium
Mean corpuscular haemoglobin concentration (MCHC)	Phosphate
Neutrophils absolute count	Creatine kinase (CK)
Lymphocytes absolute count	Direct bilirubin
Monocytes absolute count	Alkaline phosphatase (ALP)
Eosinophils absolute count	Alanine aminotransferase (ALT)
Basophils absolute count	Aspartate aminotransferase (AST)
Platelets absolute count	Gamma glutamyl transpeptidase (GGT)
Reticulocytes absolute count	Total bilirubin (TBL)

Table 5 Laboratory Safety Variables

	Glutamate dehydrogenase (GLDH)
Urinalysis (dipstick)	Bicarbonate
Urinalysis (positive dipstick)	Uric acid
pH	Follicle stimulating hormone (FSH[women only])
Specific gravity	Luteinising hormone (LH) (women only)
Glucose	Haemoglobe A1c, glycated haemoglobin (HbA1c)
Blood	Glucose
Colour	Estimated glomerular filtration rate (eGFR) by CKD-EPI formula)
Protein	
Clarity/Appearance	**Coagulation**
Nitrites	Prothrombin time
Ketones	Activated partial thromboplastin time (aPTT)
Leukocytes	International normalised ratio (INR)
Microscopic analysis (if positive for blood, nitrites or protein)	
Urobilinogen	**Urine renal safety biomarkers**
	Albumin
	Total protein
Other Laboratory Assessments	Creatinine
Complement activation panel (Bb, C5a)	Urine protein to creatinine ratio (UPCR)
High-sensitivity C-reactive protein (hs-CRP)	Urine albumin to creatinine ratio (UACR)

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

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method for determining the occurrence of AEs.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from randomisation, (Visit 2*)* and SAEs from signing the ICF (Visit 1). Both AEs and SAEs will continue to be collected throughout the treatment period and including the follow-up period (Visit 18).

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

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild, moderate, severe)
- Whether the AE is serious or not
- Whether the AE required treatment
- Whether the AE was assessed as an ISR
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death if applicable
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation 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 to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

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

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

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

Any finding from physical examination (including neurological examination) should be evaluated as normal/abnormal. If the abnormal physical finding (including neurological examination) started prior to enrolment, it must be recorded as medical history. If the abnormal physical finding (including neurological examination) started or worsened after

enrolment, it must be recorded as an Adverse Event.

8.3.6 Hy's Law

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

8.3.7 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

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

Investigators or other site personnel send relevant CRF modules by fax (PPD) or email (PPD to AstraZeneca Patient Safety Data Entry Site, Tata Consultancy Services.

The reference document for definition of expectedness/listedness is the IB for AZD8233.

8.3.8 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

The pregnancy report module in the eCRF is used to report the pregnancy and the paper-based pregnancy outcome module is used to report the outcome of the pregnancy.

8.3.8.1 Paternal Exposure

Male participants should refrain from fathering a child during the study and for 3 months following the final follow-up visit (see also Section 5.3.3).

In case of pregnancy of the partner of a male participants, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should, if possible, be obtained and documented.

8.3.9 Medication Error

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

The designated AstraZeneca 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 five** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.7) and **within 30 days** for all other medication errors.

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

8.3.10 IMP Injection Site Reactions

Any reactions at the IMP injection site(s) (ie, ISRs) will be collected as AEs and detailed information regarding symptoms etc, will be collected on a specific CRF.

8.4 Overdose

For this study, any dose of AZD8233 greater than the planned dose will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see section 8.3.7) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

- PK samples (assessing AZD8233 total full length ASOs) will be disposed of after Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consent is obtained for future analyses.
  - PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

Plasma samples will be collected for measurement of concentration of AZD8233 (total full length ASOs) as specified in the SoA.

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

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

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

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration (AZD8233 total full length ASOs) in plasma will be assayed at bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

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

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

Incurred sample reproducibility analysis or additional assay development/validation 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.

8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments (ADA) in plasma will be collected according to the SoA (Table 1).

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

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

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

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

Participants with treatment-emerging ADA-positive titres at the last study visit, and that has a titer of at least 800 that is > 2 dilution steps higher than at baseline, may be asked to return to provide another sample in the time frame approximately 3-6 months after the last study visit.

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Blood samples will be collected for measurement of LDL-C and other lipids, which will be measured in serum using a validated analytical method. Plasma PCSK9 levels will be measured using a validated analytical method.

Pharmacodynamic laboratory assessments include:

- LDL-C
- PCSK9
- Triglycerides
- Lipoprotein profile (particle size and number)
- Biomarker analyses

And other lipid parameters:

- Total cholesterol
- HDL-C
- Non-HDL-C (Calculated)
- VLDL-C
- Remnants cholesterol (calculated)
- Apo B
- Apo A1
- Lp(a)
- LDL-C/Apo B

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of mandatory samples for biomarker analysis

By consenting to take part in the study, the participant consents to take part in 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 (Table 1).
- CCI [redacted]
- Biomarkers to be taken:
  - Blood (for plasma and serum) and urine sample analyses
  - Plasma and/or urine samples will be collected for targeted and unbiased -omics approaches, PD biomarkers and biomarker research relative to safety, tolerability and PK profiles, to evaluate their association with the observed clinical responses to AZD8233 treatment.

8.7 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.8 Health Economics

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

9 Statistical Considerations

9.1 Statistical Hypotheses

The formal hypotheses tests will focus on the treatment effect of AZD8233 versus placebo on the efficacy endpoints related to LDL-C and PCSK9 (Table 6). To maintain a family-wise

Type I error rate of 5%, the hypotheses will be evaluated in a hierarchical sequence by a two-sided test at a 5% significance level until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected. Any subsequent test will be considered exploratory. Statistical tests will be done in the order as listed in Table 6.

Table 6 Hierarchical Order for Statistical Testing

Order	Null hypothesis	Alternative hypothesis
1	μ(LDL-C, A) = μ(LDL-C, P)	μ(LDL-C, A) $\neq$ μ(LDL-C, P)
2	μ(PCSK9, A) = μ(PCSK9, P)	μ(PCSK9, A) $\neq$ μ(PCSK9, P)

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type-9; P, Placebo; A, AZD8233
The hypotheses are formalised using μ(*biomarker, treatment group*) to denote the mean relative reduction of *biomarker* in treatment group at the end of Week 28. For example, the mean relative reduction in concentrations of LDL-C in plasma for AZD8233 after 28 weeks is denoted with μ(LDL-C, A) and similarly for placebo with μ(LDL-C, P).

Endpoints that are not listed in Table 6 are of an exploratory nature, and no adjustment will be made for multiple testing of these endpoints.

9.2 Sample Size Determination

Approximately 530 participants will be enrolled to achieve 376 participants randomly assigned to study intervention. Participants will be randomly assigned at a 1:1 ratio to one of the 2 treatment arms listed below:

- AZD8233 CCI , CCI approximately 188 participants randomly assigned
- Placebo matching dose, CCI , approximately 188 participants randomly assigned

CCI [redacted]

CCI [redacted]

CCI [redacted]

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent

process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned/assigned in the study, are considered" screen failures", unless otherwise specified by the protocol.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 7 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF
Full Analysis Set (FAS)	All participants who were randomly assigned to study intervention. Data from participants will be analysed according to the treatment to which they were randomly assigned.
Safety analysis set (SAS)	The Safety analysis set consists of all participants who have received at least one dose of investigational product. Erroneously treated participants (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A participant who has on one or several occasions received active IMP is classified as active and is accounted for the active IMP treatment group.
PK Analysis Set	The PK analysis set will consist of all subjects who receive at least 1 dose of AZD8233, for whom at least 1 post-dose PK concentration assessment is available as determined at the final protocol deviations meeting prior to unblinding of this study. Subjects will be presented in accordance to the actual treatment received.

9.4 Statistical Analyses

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

9.4.1 General Considerations

Handling of multiple methods for measuring LDL-C

The LDL-C value obtained using PUC will be used in the analysis of LDL-C through reflex testing when the LDL-C is < 40 mg/dL (by the Friedewald method) or if the triglycerides are ≥400 mg/dL. If there is no measurement taken using PUC, the calculated LDL-C value obtained using the Friedewald formula will be used (CCI [redacted]). If neither LDL-C measured with PUC or calculated using the Friedewald formula is available, the measurement will be considered as missing. Further details or any additional measurement methods will be described in the SAP.

Baseline

For analyses based on the SAS, the baseline value is defined as the last non-missing value prior to or on the date of administration of the first dose of IMP. For analyses based on the FAS, the baseline value is defined as the last non-missing value prior to or on the date of randomisation. Details are described in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary efficacy variable of relative change in LDL-C from baseline to the end of CCI (visit 16) will be assessed through an estimand which is defined by the following attributes:

- Population: FAS, defined through inclusion and exclusion criteria
- Treatment: AZD8233 CCI or placebo injected CCI on a background of a stable dose of maximally tolerated statin and/or ezetimibe treatment
- Intercurrent events: Non-terminal intercurrent events will be handled using a treatment policy strategy, i.e. the variable of interest is aimed to be collected and used irrespective of intercurrent events. Terminal events are expected to be few without substantial impact on the efficacy estimates and handled in the framework for missing data.
- Population-level summary: difference in variable means between treatments

This estimand requires that to the extent possible, randomised participants are followed up regardless of study intervention compliance.

The main estimator is an ANCOVA for the relative change from baseline to the end of CCI C CI, including all participants in the FAS. The model will include treatment group as a fixed categorical factor and baseline value as a continuous covariate. Additional covariates may be added to the model if deemed necessary, but will be prespecified in the SAP. In this model, the dependent variable will be the relative change in endpoint from baseline to the end of CCI, that is:

$$\frac{(y_{w28} - y_{BL})}{y_{BL}},$$

where y_{w28} and y_{BL} are the measurements of LDL-C at the end of CCI and baseline (BL), respectively.

Available observations at baseline and the end of CCI will be used in the model. Missing observations will be imputed. Any missing baseline values will be imputed based on existing values, disregarding the treatment group. For post-baseline missing values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined as missing data which constitute the end of patient follow-up, while non-monotone missing data means that there are observations made after the missing time

point.

Any non-monotone missing data will be replaced using the procedure, PROC MI in the SAS Software, with the Markov Chain Monte Carlo method. The imputation model will include timepoint, baseline value and treatment group.

For monotone missing data, pattern mixture models will be used, assuming missing data are not missing at random. Imputation of monotone missing data will be done separately for each treatment arm.

The preferred method of imputation for monotone missing data will be to use MI-RD for each distinct pattern. Missing data patterns at the end of CCI are defined as:

- Missing data without discontinuation of treatment (including deaths as discontinuation of treatment) prior to the end of CCI
- Missing data after discontinued treatment prior to the end of CCI

For both of these missing data patterns, monotone missing values will be imputed sequentially by visit; for pattern a) based on completers (ie, had follow-up until the end of CCI) in the same treatment arm who had not discontinued treatment, and for pattern b) based on completers in the same treatment arm who had discontinued treatment. The baseline value will be included in the imputation models and data up to each missing visit will be accounted for. This MI-RD approach will be used as long as the number of retrieved dropouts for each combination of treatment arm and missing data pattern is sufficient to construct imputation models. The distribution of missing data, number and proportions, according to each missing data pattern will be summarised per treatment arm.

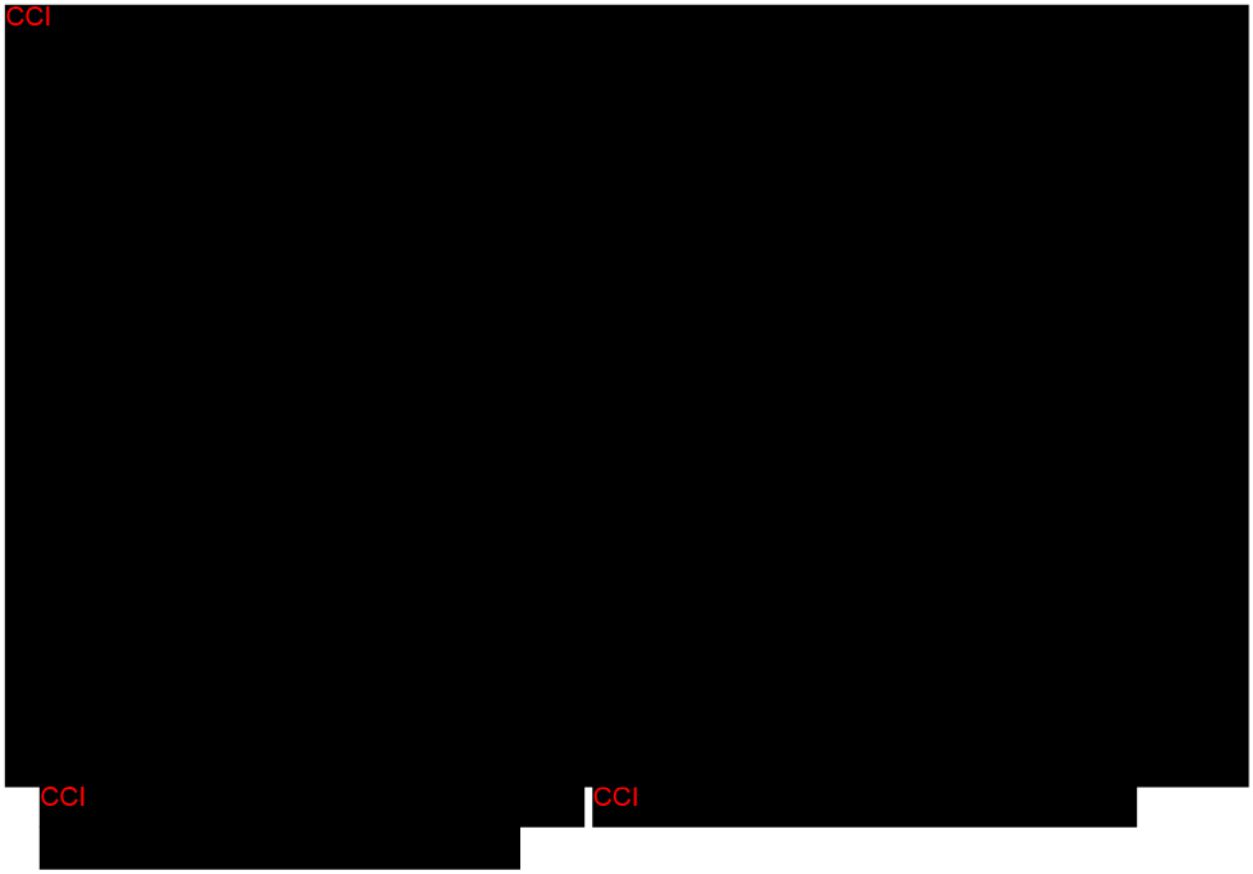
The ANCOVA model described above will be used to provide least-squares means, least-squares mean differences and corresponding standard errors for each of the multiple imputed datasets. These results are then pooled according to Rubin's rules in PROC MIANALYZE in SAS to provide the final estimates as well as p-value.

If MI-RD cannot be used due to an insufficient number of retrieved dropouts, missing data at the end of CCI in the placebo arm will be replaced based on participants in the same arm using standard MI and assuming missing at random, including baseline value and observations between baseline and the end of CCI in the imputation model. Missing values in the active treatment arm will be replaced by washout multiple imputation. In washout multiple imputation, the end of CCI data are imputed based on observed values in the placebo group only, including baseline value in the imputation model but not accounting for any observations after baseline.

9.4.2.2 Secondary Endpoint(s)

Relative change from baseline in concentrations of PCSK9 in plasma at the end of CCI, will be analysed similar to the analysis of the primary endpoint as outlined in Section 9.4.2.1.

9.4.2.3 Tertiary Endpoint(s)



9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

9.4.3.1 Primary Endpoint(s)

Adverse Events

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

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

Adverse events will be summarised by PT and SOC using MedDRA vocabulary. Adverse events that led to discontinuation of IMP, SAEs, AEs by severity and causally related AEs will also be presented. All AE summaries will be done by treatment group. Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AZ.

AEs will be presented for each treatment group by SOC, PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IMP, as well as AEs leading to IMP interruptions.

AEs of ISRs will be summarised separately.

Separate AE tables will be provided taking into consideration relationship to IMP as assessed by the investigator, seriousness, death and events leading to discontinuation of IMP and other significant adverse events and timing of events.

An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency $\geq$ x%) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment group.

Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IMP.

An AE listing for the safety analysis set will cover details for each individual AE; an AE listing for participants who were not exposed to IMP is presented separately.

Full details of AE analyses will be provided in the SAP.

AEs occurring prior to start of IMP and treatment emergent AEs will be presented separately.

Treatment emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IMP
- Worsening of pre-existing events on or after first dose of IMP

Vital signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Details of vital sign analyses will be provided in the SAP.

Thrombocytopenia

Analyses related to platelet counts will include summaries of the following, by treatment group:

- Absolute platelet counts
- Percentage decline of the platelet count from baseline (mean, median, range, and measures of variance)
- Time course of recovery of platelet counts following an event of thrombocytopenia.

In addition, separate summaries of AEs related to thrombocytopenia such as bleeding events, bruising, and petechiae will be provided.

Laboratory

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all serum chemistry, haematology, coagulation, platelet, urinalysis, urine renal safety biomarker, and other laboratory assessments (see Table 5) as well as platelet count will be presented for observed values as well as change from baseline.

Elevation in liver parameters for assessment of Hy's Law will be done and reported appropriately if potential cases are identified during the course of the study.

Electrocardiogram

Electrocardiogram parameters will be presented for each treatment group. Frequency tables will show the interpretation of the ECG reading (normal, abnormal - clinically not significant, abnormal - clinically significant) at each timepoint. Shift tables (compared to baseline) may also be generated.

9.4.4 Other Analyses

PK endpoints

This is secondary endpoint. If data permit, a population PK model will be developed, possibly with the support of PK data from studies D7990C00001, D7990C00002, D7990C00003, using nonlinear mixed effects modeling in NONMEM. Furthermore, if data allow, the population PK model may be coupled with separate PD models for PCSK9 and LDL-C.

All PK/PD modelling will be described in a separate data analysis plan. Moreover, the results of any such modelling will be provided in a separate population PK/PD report (as an

appendix to the CSR or as a stand-alone report).

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

9.5 Interim Analyses

Interim Analysis is not planned for this study.

9.6 Data Monitoring Committee

An iSMC will be used for monitoring of unblinded safety data in the ongoing study. For details on the iSMC to be used in this study, please refer to Appendix A 5.

10 Supporting Documentation and Operational Considerations

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, 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 amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will

review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.
- Participants who are rescreened are required to sign a new ICF and should be assigned the same participant number as per their initial screening visit.
- The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Internal Safety Monitoring Committee

An iSMC will be established for this study. The iSMC shares responsibility with GST for monitoring subject safety and ensuring that study subjects are not exposed to undue risk. The iSMC is responsible for periodically assessing unblinded study safety data according to an agreed upon schedule (as well as on an ad-hoc basis) and making a recommendation to GST. An iSMC charter is in place and gives details of precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the study team.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the 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 (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan. The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in 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 investigator may include but are not limited to:

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

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

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

A 10 Publication Policy

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

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

B 1 Definition of Adverse Events

An 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 unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including CCI or CCI periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

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

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

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

Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

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

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

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

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

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

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

B 4 Medication Error

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

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

Medication error includes situations where an error.

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

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

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding 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 lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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 analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The investigator:

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

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

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

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

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

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

Appendix D CCI

D 1 CCI

- CCI
-
-
-

D 2 CCI

CCI

- CCI

CCI

CCI

- CCI

CCI

- CCI

CCI

- CCI

CCI

- CCI
- CCI
- CCI

CCI

- CCI

CCI

- CCI

CCI

CCI

- CCI
-

CCI

- CCI
-
- CCI

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 PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

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

E 2 Definitions

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

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

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

E 3 Identification of Potential Hy's Law Cases

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

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

Identification of PHL cases may be through central laboratories and/or local laboratories.

Central Laboratories Being Used:

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

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

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

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

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

Local Laboratories Being Used:

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

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Appendix E 6)

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
  - Complete the three Liver eCRF Modules as information becomes available

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

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

The instructions in this Section should be followed for all cases where PHL criteria are met.

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

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

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

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

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

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

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

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine

whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [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

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

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

F 1 Actions in case of uninterpretable platelet count results

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

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

Thrombocyte Monitoring Frequency

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

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

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

F 2 Referral to Expert Haematologist Care

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

Supportive Treatment with Corticosteroids

Treatment of severe thrombocytopenia requires close communication among consulting specialists. For major or life-threatening bleeding, platelet transfusions should be administered without delay. Because ASOs have been associated with immune-mediated thrombocytopenia it is strongly recommended that participants with platelet counts **≤ 30,000/µL** receive glucocorticoid therapy (unless contraindicated). High dose steroids have

been reported to reverse platelet decline and accelerate platelet recovery. **Treatment guidelines for immune thrombocytopenia recommend: Dexamethasone** 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; **Prednis(ol)one** 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (may require continuation with oral steroids after methylprednisolone) (PPD). Platelet count should be monitored closely during corticosteroid treatment. An increased or normalized platelet count is expected within two weeks of therapy. Once the platelet count normalizes or rises significantly and plateaus > 50,000/µL, no additional therapy is needed. **Participants should be followed until platelet count has been > 100,000/µL for 1 month** (see above table for monitoring frequency).

F 3 Reference

PPD

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

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

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

Hypersensitivity Reactions – Checklist for The investigator

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

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

Additional Samples to be Collected in Case of an Anaphylactic-like Reaction
In case of anaphylactic-like reaction, the blood samples for tryptase assessments should be taken 30, 60, and 120 minutes after the onset of event, if feasible.

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

G 1 Reference

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

Appendix H COVID-19 Specifics

H 1 Background to COVID-19

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

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline on the management of clinical trials during the COVID-19 (coronavirus) pandemic v4.

H 2 AZD8233 and COVID-19 vaccinations

H 2.1 Mode of Action

AZD8233 is an ASO that inhibits the production of PCSK9 in the liver. AZD8233 is directed to the liver by enhanced uptake mediated by the ASGP-receptor present on hepatocytes. Circulating PCSK9 is mainly produced in the liver and regulates circulating levels of LDL-C by interfering with LDL-R recycling in hepatocytes. here are two approved PCSK9 monoclonal antibody inhibitors approved for lipid lowering as well as an PCSK9 siRNA inhibitor, all both with good efficacy and safety profiles. The ASO platform has been associated with a mild pro-inflammatory effect in some participants, including ISRs and flu-like symptoms.

H 2.2 Potential interference with COVID-19 vaccines

There is no biological rationale that inhibition of PCSK9 would reduce immune response to vaccines.

H 2.3 Degree of potential impact (low, medium, high)

AZD8233 is predicted to have a low risk of influencing COVID-19 vaccine effectiveness, and no additional safety concerns are identified at this early stage in development.

H 2.4 Recommendation

Participants enrolled in studies with AZD8233 can take part in vaccination programs for COVID-19. Administration of COVID-19 vaccines should be in accordance with the label for the vaccine and local guidelines for administration should be followed. COVID-19 vaccination should be recorded in the eCRF as concomitant medication. If COVID-19 vaccination is planned prior to entering a study, the first dose of AZD8233 should be given at least 30 days after the last dose of vaccine. In participants already undergoing dosing with AZD8233, vaccination should be separated from AZD8233 dosing by at least 7 days when possible. Adverse Events (AE) reporting in the study should use standard reporting.

I 3 Risk Assessment for COVID-19 Pandemic

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

- This study will start enrolling only when the Sponsor and CRO, in collaboration, deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. The decision to continue with the study interventions in the event of participants showing symptoms of COVID-19 infection will be per the investigator's discretion
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory
  - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on investigator's discretion
  - Requesting all participants are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, participants are asked for details of any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment
  - Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement
  - Where physical distancing is not possible, PPE will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves,

protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements

- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing

H 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to Screening Visit 1, potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

H 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site, when necessary, will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required and any adjustments needed in response to the COVID-19 pandemic will be documented as such.

H 5 References

1. Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

2. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on April 16, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix I Abbreviations

Abbreviation or special term	Explanation
ANCOVA	analysis of covariance
Apo A1	apolipoprotein A1
Apo B	apolipoprotein B
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
ASGP-R	asialoglycoprotein receptor
AST	aspartate aminotransferase/transaminase
BP	blood pressure
C_{max}	maximum concentration
CKD-EPI	chronic kidney disease epidemiology collaboration
COVID-19	coronavirus disease 2019
CRO	contract research organisation
CSP	clinical study protocol
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DBP	diastolic blood pressure
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic Acid
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	good clinical practice
GGT	gamma glutamyl transferase

Abbreviation or special term	Explanation
HbA1c	haemoglobin A1c, glycated haemoglobin
HDL-C	high-density lipoprotein cholesterol
HL	Hy's Law
HMG-CoA	3-hydroxy-3-methyl-glutarylcoenzyme A
IB	Investigator's Brochure
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	institutional review board
IRT	interactive response technology
iSMC	internal Safety Monitoring Committee
LDL	low-density lipid
LDL-C	low-density lipoprotein cholesterol
LH	luteinising hormone
Lp(a)	lipoprotein(a)
MACE	major adverse cardiovascular events
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MI-RD	multiple imputation retrieved dropouts
NIMP	non-investigational medicinal product
PD	pharmacodynamic(s)
PE	pulmonary embolism
PEF	peak expiratory flow
PHL	potential Hy's Law
PCSK9	proprotein convertase subtilisin/kexin type-9
PI	principal investigator
PK	pharmacokinetic(s)
PREGOUT	pregnancy outcome
PREGREP	pregnancy report
PT	preferred term
PUC	preparative ultracentrifugation
Q4W	every 4 weeks
RTSM	randomisation and trial supply management

Abbreviation or special term	Explanation
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SC	subcutaneous
SoA	schedule of activities
SOC	system organ class
TBL	total bilirubin
TC	total cholesterol
UACR	urinary albumin creatinine ratio
ULN	upper limit of normal
UPCR	urinary protein creatinine ratio
URC	unblinded review committee
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell count
WHO	World Health Organization

11 References

Burdick et al 2014
Burdick AD, Sciabola S, Mantena SR, Hollingshead BD, Stanton R, Warneke JA et al. Sequence motifs associated with hepatotoxicity of locked nucleic acid--modified antisense oligonucleotides. Nucleic Acids Res. 2014;42(8):4882-91.

Burel et al 2013
Burel SA, Han SR, Lee HS, Norris DA, Lee BS, Machemer T et al. Preclinical evaluation of the toxicological effects of a novel constrained ethyl modified antisense compound targeting signal transducer and activator of transcription 3 in mice and cynomolgus monkeys. Nucleic Acid Ther. 2013;23(3):213-27.

Cohen et al 2005
Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37(2):161-5.

Cohen et al 2006
Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354(12):1264-72.

Collins et al 2016
Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532-61.

Crooke et al 2016
Crooke ST, Baker BF, Kwoh TJ, Cheng W, Schulz DJ, Xia S et al. Integrated Safety Assessment of 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides in NonHuman Primates and Healthy Human Volunteers. Mol Ther. 2016;24(10):1771-82.

Crooke et al 2017
Crooke ST, Baker BF, Witztum JL, Kwoh TJ, Pham NC, Salgado N et al. The Effects of 2'-O-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials. Nucleic Acid Ther. 2017;27(3):121-9.

Friedewald 1972
Friedewald. Estimation of the Concentrationof Low-Density Lipoprotein Cholesterol Plasma,Without Use of the Preparative Ultracentrifuge. Journal of Clinical Chemistry. 1972;18499-502.

Gibbs et al 2017
Gibbs JP, Doshi S, Kuchimanchi M, Grover A, Emery MG, Dodds MG et al. Impact of Target-Mediated Elimination on the Dose and Regimen of Evolocumab, a Human Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). J Clin Pharmacol. 2017;57(5):616-26.

Hagedorn et al 2013
Hagedorn PH, Yakimov V, Ottosen S, Kammler S, Nielsen NF, Hog AM et al. Hepatotoxic potential of therapeutic oligonucleotides can be predicted from their sequence and modification pattern. Nucleic Acid Ther. 2013;23(5):302-10.

Henry et al 1997
Henry SP, Novotny W, Leeds J, Auletta C, Kornbrust DJ. Inhibition of coagulation by a phosphorothioate oligonucleotide. Antisense Nucleic Acid Drug Dev. 1997;7(5):503-10.

Henry et al 2017
Henry SP, Narayanan P, Shen L, Bhanot S, Younis HS, Burel SA. Assessment of the Effects of 2'-Methoxyethyl Antisense Oligonucleotides on Platelet Count in Cynomolgus Nonhuman Primates. Nucleic Acid Ther. 2017;27(4):197-208.

Hildebrandt-Eriksen et al 2012
Hildebrandt-Eriksen ES, Aarup V, Persson R, Hansen HF, Munk ME, Orum H. A locked nucleic acid oligonucleotide targeting microRNA 122 is well-tolerated in cynomolgus monkeys. Nucleic Acid Ther. 2012;22(3):152-61.

Hung et al 2013
Hung G, Xiao X, Peralta R, Bhattacharjee G, Murray S, Norris D et al. Characterization of target mRNA reduction through in situ RNA hybridization in multiple organ systems following systemic antisense treatment in animals. Nucleic Acid Ther. 2013;23(6):369-78.

Kathman et al 2018
Kathman S, Bellibas SE, Kallend DG, Ray KK, Wheeler J, Wijngaard P. Population dose-response modeling of inclisiran, a novel siRNA inhibitor to PCSK9, in patients at high cardiovascular risk with elevated LDL cholesterol. Clin Pharmacol Ther. 2018;103: S72.

Prakash et al 2014
Prakash TP, Graham MJ, Yu J, Carty R, Low A, Chappell A et al. Targeted delivery of antisense oligonucleotides to hepatocytes using triantennary N-acetyl galactosamine improves potency 10-fold in mice. Nucleic Acids Res. 2014;42(13):8796-807.

Ray et al 2017
Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. N Engl J Med. 2017;376(15):1430-40.

Sabatine 2017
Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-22.

Sewell et al 2002
Sewell KL, Geary RS, Baker BF, Glover JM, Mant TG, Yu RZ et al. Phase I trial of ISIS 104838, a 2'-methoxyethyl modified antisense oligonucleotide targeting tumor necrosis factor-alpha. J Pharmacol Exp Ther. 2002;303(3):1334-43.

Sheehan et al 1998
Sheehan JP, Lan HC. Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex. Blood. 1998;92(5):1617-25.

Sheehan et al 2001
Sheehan JP, Phan TM. Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex by an allosteric mechanism. Biochemistry. 2001;40(16):4980-9.

Sokolov 2019
Sokolov V, Helmlinger G, Nilsson C, Zhudenkov K, Skrtic S, Hamren B et al. Comparative quantitative systems pharmacology modeling of anti-PCSK9 therapeutic modalities in hypercholesterolemia. J Lipid Res. 2019;60(9):1610-21.

van Meer et al 2017
van Meer L, van Dongen M, Moerland M, de Kam M, Cohen A, Burggraaf J. Novel SGLT2 inhibitor: first-in-man studies of antisense compound is associated with unexpected renal effects. Pharmacol Res Perspect. 2017;5(1):e00292.

van Poelgeest et al 2013
van Poelgeest EP, Swart RM, Betjes MG, Moerland M, Weening JJ, Tessier Y et al. Acute kidney injury during therapy with an antisense oligonucleotide directed against PCSK9. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;62(4):796-800.

van Poelgeest et al 2015
van Poelgeest EP, Hodges MR, Moerland M, Tessier Y, Levin AA, Persson R et al. Antisense-mediated reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9): a first-in-human randomized, placebo-controlled trial. Br J Clin Pharmacol. 2015;80(6):1350-61.

SIGNATURE PAGE

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

Document Name: d7990c00004-csp-amendment-1		
Document Title:	D7990C00004 Clinical Study Protocol Amendment 1	
Document ID:	PPD	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
14-Feb-2022 14:22 UTC	PPD	Content Approval
09-Feb-2022 13:41 UTC	PPD	Content Approval
09-Feb-2022 13:24 UTC	PPD	Author Approval
10-Feb-2022 15:00 UTC	PPD	Content Approval

Notes: (1) PPD .