Clinical Study Protocol	
Study Intervention	AZD8233
Study Code	D7990C00003
Version	2.0
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A Randomized, Parallel, Double-blind, Placebo-controlled, Dose-ranging, Phase 2b Study to Evaluate the Efficacy, Safety and Tolerability of AZD8233 Treatment in Participants With Dyslipidemia

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): EudraCT number 2020-000767-23

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: 2.0

Amendment Number: 1

Study Intervention: AZD8233

Study Phase: Phase 2b

Short Title: A Phase 2b Study of AZD8233 in Participants With Dyslipidemia

Medical Monitor Name and Contact Information will be provided separately

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Parallel, Double-blind, Placebo-controlled, Dose-ranging, Phase 2b Study to Evaluate the Efficacy, Safety and Tolerability of AZD8233 Treatment in Participants With Dyslipidemia

Short Title: A Phase 2b Study of AZD8233 in Participants With Dyslipidemia

Rationale: To evaluate low-density lipoprotein cholesterol reduction at steady state at different doses of AZD8233 in order to select a therapeutic dose.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of different doses of AZD8233 on LDL-C versus placebo	• Absolute change from baseline in log-transformed LDL-C in plasma
Secondary	
• To assess the effect of different doses of AZD8233 on PCSK9 versus placebo	• Absolute change from baseline in log-transformed PCSK9 in plasma.
• To assess the effect of different doses of AZD8233 on LDL-C versus placebo	• Percentage change from baseline in levels of LDL-C in plasma
• To assess the effect of AZD8233 on other lipid parameters versus placebo	• Levels of other lipid parameters, including: – TC – HDL-C – Non-HDL-C – VLDL-C – ApoA1 – ApoB – Lp(a) – Triglycerides – Remnants cholesterol

Objectives	Endpoints
• To evaluate the PK of AZD8233	• Plasma parameters: population PK parameters to be reported in a separate report.
• To evaluate the immunogenicity of AZD8233	• Development of ADA and titer (if participants are ADA positive) during treatment and follow-up
Safety	
• To assess the safety and tolerability of AZD8233	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations including platelet count

AE = adverse event; ADA = anti-drug antibodies; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type-9; PK = pharmacokinetics; TC = total cholesterol; VLDL-C = very-low-density lipoprotein cholesterol

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

Overall Design

This is a randomized parallel, double-blind, placebo-controlled, dose-ranging Phase 2b study in approximately 108 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD8233 on LDL-C across different dose levels. The study will be conducted at up to 25 sites in up to 4 countries.

The screening period starts up to 42 days before the randomization visit and ends on Day -1. Some participants routinely come fasting to the clinic. In the event that participants come fasting at their own initiative, sites may choose to combine Visit 1 and Visit 2. In case Visit 1 and Visit 2 are combined, the combined visit must take place between -7 to -1 days prior to randomization. Eligible participants will attend 7 visits during the treatment period and 7 additional visits during the safety follow up period. Eligible participants are randomized across four different treatment arms in a 1:1:1:1 ratio for a 12-week treatment period. The planned treatment arms are AZD8233 CCI , AZD8233 CCI , AZD8233 CCI , and Placebo. Participants will be dosed SC on Days 1, 8, 29, and 57.

Disclosure Statement: This is a parallel group treatment study with 4 arms that is participant and Investigator blinded.

Number of Participants:

Approximately 108 participants will be randomly assigned to the four study arms so that at

least 80 evaluable participants completed treatment up until and including visit 10 (week 12).

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:

The screening period starts up to 42 days before the randomization visit and ends on Day -1. Eligible participants will attend 7 visits during the treatment period and 7 additional visits during the safety follow up period. Eligible participants are randomized across four different treatment arms at a 1:1:1:1 ratio for a 12-week treatment period. The planned treatment arms are: AZD8233 CCI , AZD8233 CCI , AZD8233 CCI , and Placebo. Participants will be dosed SC on Days 1, 8, 29, and 57.

Data Monitoring Committee:

A data monitoring committee will not be used in this study.

Statistical methods

The primary objective of this study is to compare absolute change from baseline in log-transformed LDL-C across different dose levels of AZD8233.

The key secondary objective of this study is to compare absolute change form baseline in log-transformed PCSK9 across different dose levels of AZD8233.

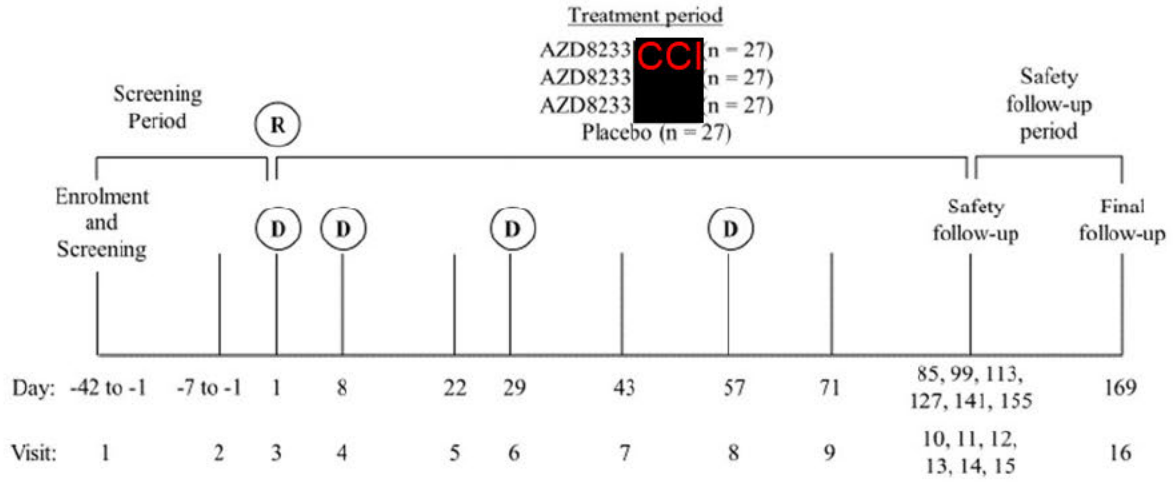
Both log-transformed LDL-C and log-transformed PCSK9 will be analysed by fitting a mixed model for repeated measures to the data with baseline as covariate and treatment, time (visit number), and interaction between treatment and time as factors.

The participants will be analysed according to the treatment to which the participant was randomised. Participants will be analysed with respect to the intention to treat principle using the full analysis set which contains data from each participant who received at least one dose of placebo or AZD8233.

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

1.2 Schema

Figure 1 Study Design



Note: All visits include blood and urine sample collection as well as safety assessment, except for Visit 2, which includes only blood sample collection.
D = dosing day; R = randomization

1.3 Schedule of Activities

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

Dosing of participants should only be carried out if all required assessments have been performed and evaluated. Dosing is not allowed to proceed until the Investigator has determined that the results are within acceptable range according to the defined stopping criteria; see Section 7.1. Laboratory assessment results should also be reviewed at every visit to ensure that stopping criteria have not been met.

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

1 ECG
2 Vital signs (SBP and diastolic blood pressure [DBP]), pulse rate, and temperature, if appropriate)
3 PK and PD blood sampling
4 Dose administration

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

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**		**10, 11[a], 12, 13[a], 14, 15[a]**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**D-42 to D-1[1]**	**D-7 to D-1**	**D1**	**D8**	**D22**	**D29**	**D43**	**D57**	**D71**		**D85, D99, D113, D127, D141, D155**	**D169**	
Visit Window				**± 1 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Informed consent	X												Appendix A 3
Optional Informed consent for future genetic research sample	X												Appendix D
Verify eligibility criteria	X		X[b]										Sections 5.1, 5.2
Enrolment in RTSM	X												Sections 6.3, 8
Randomisation in RTSM			X										Sections 6.3, 8
Medical history	X												Section 8
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Demographics	X												Section 9.4.1
Height	X												

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**		**10, 11[a], 12, 13[a], 14, 15[a]**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**D-42 to D-1[1]**	**D-7 to D-1**	**D1**	**D8**	**D22**	**D29**	**D43**	**D57**	**D71**		**D85, D99, D113, D127, D141, D155**	**D169**	
Visit Window				**± 1 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Body weight[c]	X		X		X		X			X	X	X	Section 8.2.1
BMI	X									X		X	Section 8.2.1
HbA1c	X												Section 8.2.5
Viral serology	X												Section 8.2.5
Pregnancy and reproductive status (females only, pre-dose)	X		X										Section 8.2.4
Study intervention administration (AZD8233/Placebo)			X	X		X		X					Section 6.1.1
Safety Assessments													
Adverse event review	X (SAE only)	X (SAE only)	X	X	X	X	X	X	X	X	X	X	Section 8.3

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**		**10, 11[a], 12, 13[a], 14, 15[a]**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**D-42 to D-1[1]**	**D-7 to D-1**	**D1**	**D8**	**D22**	**D29**	**D43**	**D57**	**D71**		**D85, D99, D113, D127, D141, D155**	**D169**	
Visit Window				**± 1 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Injection site reactions [d]			X	X	X	X	X	X	X	X	X	X	Section 8.2.6
Complete physical examination	X		X							X		X	Section 8.2.1
Abbreviated physical examination				X	X	X	X	X	X		X		Section 8.2.1
Vital signs (blood pressure, pulse and temperature) [e]	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.2
ECG [e]	X		X	X		X		X		X	X[f]	X	Section 8.2.3
Serum chemistry	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Hematology	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Coagulation parameters [g]	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
hs-CRP	X		X					X		X	X	X	Section 8.2.4

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	**1**	**2**	**3**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**		**10, 11[a], 12, 13[a], 14, 15[a]**	**16**	
Study Week			**0**	**1**	**3**	**4**	**6**	**8**	**10**		**12, 14, 16, 18, 20, 22**	**24**	
Study Day	**D-42 to D-1[1]**	**D-7 to D-1**	**D1**	**D8**	**D22**	**D29**	**D43**	**D57**	**D71**		**D85, D99, D113, D127, D141, D155**	**D169**	
Visit Window				**± 1 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		**± 2 days**	**± 2 days**	
Complement activation panel [g]			X	X		X		X					Section 8.2.4
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Urine renal safety biomarkers	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Pharmacodynamics													
LDL-C [h]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
PCSK9 [h]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
Triglycerides [h]		X	X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
Other Lipid parameters [h]			X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1
Lipoprotein profile [h]			X	X	X	X	X	X	X	X	X	X	Section 8.5.3.1

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	1	2	3	4	5[a]	6	7[a]	8	9[a]		10, 11[a], 12, 13[a], 14, 15[a]	16	
Study Week			0	1	3	4	6	8	10		12, 14, 16, 18, 20, 22	24	
Study Day	D-42 to D-1[l]	D-7 to D-1	D1	D8	D22	D29	D43	D57	D71		D85, D99, D113, D127, D141, D155	D169	
Visit Window				± 1 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days		± 2 days	± 2 days	
Pharmacokinetics													
PK plasma sample [i]				X		X	X	X	X	X	X [i]	X	Section 8.5.1
Immunogenicity													
Samples for anti-AZD8233 antibodies [j]			X	X		X		X		X	X [j]	X	Section 8.5.2
Exploratory biomarker analysis													
Biomarker analyses (plasma) [h]	X		X	X	X	X	X	X	X	X	X	X	Section 8.6.1
Biomarker analyses (urine) [h]			X	X	X	X	X	X	X	X	X	X	Section 8.6.1
Genomics Initiative optional, exploratory genetic sample [k]			X										Section 8.7

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	1	2	3	4	5[a]	6	7[a]	8	9[a]		10, 11[a], 12, 13[a], 14, 15[a]	16	
Study Week			0	1	3	4	6	8	10		12, 14, 16, 18, 20, 22	24	
Study Day	D-42 to D-1[1]	D-7 to D-1	D1	D8	D22	D29	D43	D57	D71		D85, D99, D113, D127, D141, D155	D169	
Visit Window				± 1 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days		± 2 days	± 2 days	

Note: Participants are required to fast for at least 8 hours overnight prior to all study visits except for Visit 1; Participants are permitted to drink water during this period of fasting until 1 hour before blood sampling. On days where participants attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of IP.

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

[a] Home visits: may be undertaken at the participant's home or any other appropriate location by site staff or by qualified external service provider. Other visits currently not designated as 'home visits' may also be undertaken at the participant's home or any other appropriate location if deemed applicable, following consultation with the Investigator and the sponsor. Home visits performed by qualified external service provider (i.e. not by clinical trial site personnel) may only be performed starting Visit 5 (D22), excluding dosing visits (Visit 6 (D29) and Visit 8 (D57)).

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

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

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

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

[f] ECG to be performed during the safety follow up period at Visits 10 (D85), 11 (D99), 13 (D127), and 15 (D155).

[g] Blood samples for complement activation panel and coagulation parameters will be taken around Cmax and are to be collected pre-dose and 2 hours post-dose.

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

Table 1 Schedule of Activities (SoA)

	Screening		Treatment Period							EDV	Safety Follow-up period	Final Follow-up Visit	Details in CSP Section or Appendix
Visit Number	1	2	3	4	5[a]	6	7[a]	8	9[a]		10, 11[a], 12, 13[a], 14, 15[a]	16	
Study Week			0	1	3	4	6	8	10		12, 14, 16, 18, 20, 22	24	
Study Day	D-42 to D-1[l]	D-7 to D-1	D1	D8	D22	D29	D43	D57	D71		D85, D99, D113, D127, D141, D155	D169	
Visit Window				± 1 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days		± 2 days	± 2 days	

[i] PK sampling to be performed at Visits 4 (D8), 6 (D29), 7 (D43), 8 (D57), 9 (D71), 10 (D85), 12 (D113) and 14 (D141) and final follow-up visit/EDV. Schedule of sampling for Visits 4 (D8), 6 (D29), 8 (D57) are shown below.
Visit 4 (Day 8; Loading dose): pre-dose
Visit 6 (Day 29; Dose 3): pre-dose
Visit 8 (Day 57; Final dose): pre-dose

[j] ADA sampling to be performed at Visits 3 (D1), 4 (D8), 6 (D29), 8 (D57), 10 (D85), 12 (D113), and 14 (D141), and final follow-up visit/EDV. ADA samples to be collected pre-dose on all dosing days.

[k] If, for any reason, the sample is not drawn pre-dose on Visit 3 (D1), it may be taken at any visit until the Final follow-up/EDV visit.

[l] Visit 1 and visit 2 may be combined.

BMI = body mass index; CSP = clinical study protocol; D = day; ECG = electrocardiogram; EDV = early discontinuation visit; HbA1c = haemoglobin A1c; LDL-C =low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTSM = Randomization and Trial Supply Management.

2. INTRODUCTION

2.1 Study Rationale

AZD8233 is a PCSK9-targeted ASO for the reduction of circulating levels of LDL-C. This study aims to evaluate the dose-dependent reduction in LDL-C after SC administration of multiple doses of AZD8233 as well as the associated adverse effects profile. The data generated will be used to guide choice of doses, dosing regimens, and sample sizes, as well as safety and PD monitoring in the further clinical development program.

2.2 Background

Dyslipidemia, particularly elevated levels of plasma LDL-C, is a main risk factor for CVD. Hypercholesterolemia is typically caused by a combination of environmental and genetic factors. Statin therapy is the standard lipid lowering medication for both secondary and primary prevention of CVD, as an adjunct to diet. Reduction of LDL-C by statins leads to a significant reduction in cardiovascular events (**Collins R et al 2016**). Statins reduce LDL-C by inhibiting 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 CVD risk despite maximum doses.

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

Two monoclonal antibodies (evolocumab [Amgen] and alirocumab [Sanofi/Regeneron]) have been successfully developed to pharmacologically inhibit circulating PCSK9. Injection of these compounds lowers LDL-C levels by approximately 60%, even in clinical study participants already receiving maximum dose statin therapy (**Sabatine MS et al 2017**, **Ray KK et al 2017**). Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a PCSK9-targeted, N-acetylgalactosamine-conjugated ASO specifically inhibiting intracellular PCSK9 expression in the liver (**Prakash TP et al 2014**). AZD8233 may provide novel treatment options for participants with dyslipidemia.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the Investigator's Brochure (**Investigator's Brochure 2019**).

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 may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy (refer to IB Section 5.5 for further detail)
Study Intervention		
Thrombocytopenia	Severe thrombocytopenia has been observed in some ASO programs and it is not known whether other members of the class may be affected (**Crooke ST et al 2017**). One case of severe thrombocytopenia was observed in the non-human primate toxicology study with AZD8233.	Monitoring of platelet count. In case of severe thrombocytopenia, the action plan detailed in Appendix F will be followed.
Acute Kidney Injury	Kidney is an oligonucleotide high-uptake tissue. Tubular necrosis has been observed with ASOs including an ASO inhibiting PCSK9. This was not observed in toxicological studies with AZD8233 (**Van Poelgeest EP et al 2013**, **Van Poelgeest EP et al 2015**, **Van Meer L et al 2017**).	Monitoring of S-creatinine, BUN, urine albumin and urine total protein as well as calculation of eGFR.
Transaminase Elevation	Liver is an oligonucleotide high-uptake tissue (**Hung G et al 2013**). Oligonucleotide treatment may cause transient transaminase elevations in mice, monkeys and humans at therapeutic exposures (**Burdick AD et al 2014**, **Hagedorn PH et al 2013**, **Hildebrandt Eriksen ES et al 2012**). AZD8233 is a GalNAc conjugated oligonucleotide, utilizing the ASGP-R to enhance the uptake by hepatocytes. There was however no treatment related histological changes in the liver or changes in liver injury biomarkers	Monitoring a panel of liver safety biomarkers including transaminases.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy (refer to IB Section 5.5 for further detail)
	in the non-clinical toxicology studies.	
Anti-drug Antibodies	There is a potential risk for antibody formation. Emergence of ADA has been observed in a proportion of clinical study participants after repeated oligonucleotide treatment, leading to change in PK profile. To date, no apparent association of ADA with loss of efficacy or safety findings have been observed.	Assessment of ADAs and monitoring for immunogenicity effects (including hypersensitivity reactions and ADA effect on PK/PD). Guidance on the definition of an anaphylactic reaction and the action plan that needs to be followed with regards to ADA sampling is presented in Appendix G.
Injection Site Reactions	As with any exogenous substance, injection site reactions may occur as a response to the SC injection of AZD8233. Possible risks associated with SC administration are redness, swelling, pain, induration, and sometimes infection at the administration site. Although observed for some ASOs, injection site reactions are not generally a clinical problem for newer generation ASOs.	Monitoring for injection site reactions
Complement Activation	This is a known class effect of oligonucleotides and appears to be directly plasma concentration (C_{max}) driven. Monkeys are considered more sensitive to complement activation than humans (**Crooke ST et al 2016**). No indication of complement activation induced by AZD8233 have been observed in toxicology studies.	Assessment of complement activation around C_{max} (C3a, C5a, Bb)
Increased Bleeding Risk	Increases in aPTT, in the absence of clinical or pathological sequelae, have been observed with ASOs (**Burel S et al 2013**, **Henry SP et al 1997**). Mechanistically, interaction of ASOs with the intrinsic tenase complex and thrombin results in a selective inhibition of the intrinsic clotting	Assessment of aPTT and PT

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy (refer to IB Section 5.5 for further detail)
	cascade and hence aPTT (**Henry SP et al 2017**, **Sheehan JP, Lan HC 1998**, **Sheehan JP, Thao PM 2001**). Changes in activity of the intrinsic clotting pathway reverse when ASOs are cleared from plasma. Transient prolongation of aPTT has been described in man and was observed to correlate in a linear manner with the C_{max} at the end of infusion (**Sewell KL et al 2002**).	
Systemic Inflammatory Effects	Systemic inflammation with flu like symptoms has been seen in some oligonucleotide programs. No indications of systemic inflammatory effects induced by AZD8233 have been seen in the toxicology studies.	Monitoring for any flu like symptoms and assessment of hsCRP
Study Procedures		
Subcutaneous Injection	Pain near the injection site (for 1 or 2 days) is the most common complication of subcutaneous injections.	Slow injection of AZD8233 using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites.

ADA = anti-drug antibody; aPTT = activated partial thromboplastin time ASGP-R = asialoglycoprotein receptor; ASO = antisense oligonucleotide; BUN = blood urea nitrogen; C_{max} = maximum plasma concentration; eGFR = estimated glomerular filtration rate; hsCRP = high sensitivity C reactive protein; PCSK9 = ; PT = prothrombin time; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous

2.3.2 Benefit Assessment

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

A multiple ascending dose study of AZD8233 is ongoing (Study D7990C00002).

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

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

2.3.3 Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of different doses of AZD8233 on LDL-C versus placebo	• Absolute change from baseline in log-transformed LDL-C in plasma
Secondary	
• To assess the effect of different doses of AZD8233 on PCSK9 versus placebo	• Absolute change from baseline in log-transformed PCSK9 in plasma
• To assess the effect of different doses of AZD8233 on LDL-C versus placebo	• Percentage change from baseline in levels of LDL-C in plasma
• To assess the effect of AZD8233 on other lipid parameters versus placebo	• Levels of other lipid parameters including: - TC - HDL-C - Non-HDL-C - VLDL-C - ApoA1 - ApoB - Lp(a) - Triglycerides - Remnants cholesterol
• To evaluate the PK of AZD8233	• Plasma parameters: population PK parameters to be reported in a separate report.
• To evaluate the immunogenicity of AZD8233	• Development of ADA and titer (if participants are ADA-positive) during treatment and follow-up
Safety	
• To assess the safety and tolerability of AZD8233	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and

Objectives	Endpoints
	clinical laboratory evaluations including platelet count
Tertiary/Exploratory	
• To assess lipoprotein profile following SC administration of AZD8233	• Lipoprotein profile, including particle size and number
• To collect and store blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including anti-platelet antibodies) and tolerability related to AZD8233 treatment or cardiometabolic diseases	• Results of potential future exploratory biomarker research may be reported outside this study's CSR
• Optional: To store DNA from blood samples according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response to treatment.	• Results of possible future genetic research may be reported outside this study's CSR.

AE = adverse event; ADA = anti-drug antibodies; ApoA1 = apolipoprotein A1; ApoB = Apolipoprotein B; CSR = clinical study report; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type-9; PD = pharmacodynamics; 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 randomized, parallel, double-blind, placebo-controlled, dose-ranging Phase 2b study in approximately 108 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD8233 on LDL-C across different dose levels. The study will be conducted at up to 25 sites in up to 4 countries.

The screening period starts up to 42 days before the randomization visit and ends on Day -1. Some participants routinely come fasting to the clinic. In the event that participants come fasting at their own initiative, sites may choose to combine Visit 1 and Visit 2. In case Visit 1 and Visit 2 are combined, the combined visit must take place between -7 to -1 days prior to randomization. Eligible participants will attend 7 visits during the treatment period and 7 additional visits during the safety follow up period. Eligible participants are randomized across four different treatment arms in a 1:1:1:1 ratio for a 12-week treatment period. The planned treatment arms are AZD8233 CCI SC, AZD8233 CCI SC, AZD8233 CCI SC, and Placebo SC on Days 1, 8, 29, and 57.

This study is double-blind with regards to treatment (AZD8233 or placebo) at each dose level. AZD8233 and placebo will be matched for appearance. Participants randomized to placebo will receive a volume of injection that will not differ substantially from participants on active drug. From randomization, every second visit is planned to be a site visit and the visits in-between may be home visits. Home visits are optional, and all visits could be conducted as on-site visits, if this is preferred. Home visits may be undertaken at the participant's home or any other appropriate location by site staff or qualified external service provider. Other visits that are currently not designated as 'home visits' may also be undertaken at the participant's home or at any other appropriate location if deemed applicable, following consultation with the Investigator and the sponsor. Home visits performed by qualified external service provider (i.e. not by clinical trial site personnel) may only be performed starting Visit 5 (D22), excluding dosing visits (Visit 6 (D29) and Visit 8 (D57)).

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

For detailed information please refer to the SoA (Table 1).

4.2 Scientific Rationale for Study Design

AstraZeneca is developing AZD8233 for the treatment of dyslipidemia. This study aims to

evaluate the effect of different doses of AZD8233 on LDL-C at steady state to select a therapeutic dose for further clinical development.

The scheduled 12 weeks dosing should be sufficient to reach close to steady state conditions in the tissues at the end of the dosing period (estimated terminal half-life of the full length ASO in plasma is 2-3 weeks). Based on these data and the expected time course for PCSK9 and LDL-C reduction, 12 weeks of dosing is predicted to allow for a robust assessment of safety, tolerability, PK, as well as PCSK9 and LDL-C reduction to guide dose selection for further clinical development of AZD8233.

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

Dosing in the current study will only start after AZD8233 is concluded safe and tolerable by the Safety Review Committee in Study D7990C00002. The definition of safe and tolerable is that none of the pre-specified safety stopping criteria in Study D7990C00002 have been met.

4.3 Justification for Dose

Single SC doses of up to CCI AZD8233 have been well tolerated in participants with elevated LDL-C (Study D7990C00001). The doses for the current study have been selected based on observed PCSK9 and LDL-C reduction in the single ascending dose study (D7990C00001) and the predicted PCSK9 and LDL reduction at steady state of the selected doses taking expected accumulation into account for a Q4W dosing regimen that includes a loading dose at Day 8. The mid and high dose, planned to CCI and CCI (Days 1, 8, 29, and 57) were selected to achieve a PCSK9 reduction of around 90% during the dose interval and is expected to result in close to maximum achievable effect in terms of LDL-C reduction, with the aim to show that an increase in dose above the mid dose will not result in a clinically significant further reduction in LDL-C. The low dose, planned to CCI (Days 1, 8, 29, and 57) was selected to reach a PCSK9 reduction of below 80% over the entire dose interval and was selected to show that decreasing the dose and PCSK9-reduction to below 80% will lead to a clinically significant lower LDL-C reduction as compared to the mid dose. The mid dose was thus selected to be in the therapeutic dose range. Prior to the start of dosing in the current study, safety data after two repeated doses of AZD8233 CCI (in Study D7990C00002) as well as safety and potentially PCSK9 and LDL-cholesterol data after repeated (Days 1, 8, 29, and 57) dosing of AZD8233 CCI (Study D7990C00002) will have been evaluated. Based on the results from these cohorts, the planned doses in the current study may be slightly adjusted if needed to achieve the intended PCSK9 and LDL-C reduction. However, the highest dose will not exceed CCI (Days 1, 8, 29, and 57), which is the highest dose planned to be evaluated in Study D7990C00002.

4.4 End of Study Definition

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

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

5. STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

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

3 Have fasting triglycerides < 400 mg/dL (< 4.52 mmol/L) at screening (Visit 2).

4 Should be receiving moderate- or high-intensity statin therapy (refer to Appendix H) as defined by the ACC/AHA guidelines on blood cholesterol management, or according to local guidelines.

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

Weight

6 Body mass index between 19 and 40 kg/m^2.

Sex

7 Male or female.

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

(a) 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, IUDs, tubal ligation/occlusion, and vasectomy. A barrier method is not necessary if the female partner is sterilized. Male study participants must not donate or bank sperm during this same time period.

(b) Female participants:

- Female participants must not be pregnant and must have a negative pregnancy test at screening and randomisation or be post-menopausal, must not be lactating, and must not be of childbearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - 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

8 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.

9 Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses. Participants who consent only to the main study may participate in other components of the main study without participating in the optional component of the study. However, to participate in the optional component of the study, the participant must sign and date both the consent forms for the main study and optional component of the study. If a participant decline 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.

5.2 Exclusion Criteria

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

Medical Conditions

1 Estimated glomerular filtration rate < 40 mL/min/1.73m^2 using the Chronic Kidney Disease-Epidemiology Collaboration equation at Visit 1.

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

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

4 Poorly controlled type 2 diabetes mellitus, defined as HbA1c > 10% at Visit 1.

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

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

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

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

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

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

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

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

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

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

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

   (b) ALT > 1.5 × ULN.

   (c) AST > 1.5 × ULN.

   (d) TBL > ULN

   (e) ALP > 1.5 × ULN

   (f) WBC < LLN.

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

   (h) Platelet count ≤ LLN.

   (i) aPTT > ULN and PT > ULN.

   (j) UACR > 11.3 mg/mmol (100 mg/g).

   (k) 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-block grade II-III and sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias.

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

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

19 Mipomersen, or lomitapide within 12 months prior to randomization.

20 Previous administration of AZD8233/AZD6615 or other PCSK9 inhibition treatment (approved or investigational).

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

22 Any clinically important illness, medical/surgical procedure or trauma within 4 weeks of the first administration of study intervention. History or evidence of any other clinically significant disorder (eg, cognitive impairment), condition, or disease other than those outlined above that, in the opinion of the Investigator or 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

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

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

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

Other Exclusions

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

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

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

29 Previous enrolment or randomisation in the present study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. At the Investigator's discretion, participants may be rescreened a further two times during the recruitment period.

30 Participants who cannot communicate reliably with the Investigator.

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

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

Optional Genetic Sampling

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

33 Previous allogeneic bone marrow transplant.

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

5.3 Lifestyle Considerations

For a list of prohibited medications, see Section 6.5.

5.3.1 Meals and Dietary Restrictions

Except for Visit 1, participants must be fasted for 8 hours prior to blood sampling for LDL-C and other lipid parameters, PCSK9, and lipoprotein profile. No fluids will be allowed apart from water, which can be given until 1 hour before blood sampling for LDL-C, other lipid parameters, PCSK9, and lipoprotein profile.

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 Activity

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

5.3.4 Reproductive restrictions

Women of Non-Child Bearing Potential

Women of non-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 effects that AZD8233 could have on the 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

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

5.3.5 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 randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography,

screen failure details, eligibility criteria, and any SAE.

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) 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 Handling Instructions D7990C0003, AZD8233 solution for injection. In case of a change of the planned doses (as described in Section 4.3), the investigational product strength/concentrations may be used for other cohorts than presented in Table 4, in order to minimize injection volume.

Table 4 Investigational Products

ARM Name	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Intervention Name	AZD8233	AZD8233	AZD8233	Placebo to match AZD8233
Dose Formulation	AZD8233 solution for injection			Matching placebo solution for injection
Strength/Concentrations	CCI	CCI	CCI	Matching placebo solution for injection
Dose	CCI	CCI	CCI	Matching placebo solution for injection
Regimen	AZD8233/Placebo Days 1, 8, 29, and 57			
Route of Administration	Subcutaneous injection			

Table 4 Investigational Products

Treatment Administration Guidelines	Subcutaneous abdominal region injection is the preferred region; avoid a 5 cm radius around umbilicus. Other regions might be used if needed, as decided by the investigator (thigh or buttock). Slow injection of study intervention using gentle pressure (at least 5 seconds duration is recommended) and rotation of injection sites. The anatomical location of each injection site should be documented in the eCRF.	
Specific device for drug administration	Syringes for injection to be provided by Clinical Team	
Use	Experimental	Placebo to match AZD8233
IMP and NIMP	IMP	
Sourcing	Provided centrally by the Sponsor	
Packaging and Labelling	Study Intervention will be provided in vials. Each vial will be packed in a separate carton. Each vial and carton will be labelled as required per country requirement	
Special Handling Requirements	Requirements will be provided in a separate document	
Availability of IMP	Will be shipped when approvals are in place	

6.2 Preparation/Handling/Storage/Accountability of Interventions

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

3 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).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Study Drug Packaging Agreement.

6.3 Measures to Minimise Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using a RTSM

system. Before the study is initiated, the telephone number and call-in directions and/or the log in information & directions for the RTSM will be provided to each site.

To simplify supply of study drug, randomization will be stratified based on the region in which the site is located. This will achieve greater balance within each region compared to simple randomization. Currently, two regions are planned: Europe and North America.

Study intervention will be dispensed at the study visits summarized in SoA.

The 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 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.

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

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic, as well as the anatomical location of the injection site, will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the

study site staff other than the person administering the study intervention.

Dosing visits may be undertaken as home visits by site staff. If participants are dosed at home, they will receive study intervention directly from site staff The dose administered at home will be recorded in the source documents.

6.5 Concomitant Therapy

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

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

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.
- All study participants should be receiving moderate-or high-intensity statin therapy as defined by the ACC/AHA guidelines on blood cholesterol management, or according to local guidelines.
- Participants should be on stable medication for ≥ 3 months prior to screening with no planned medication or dose change during study participation. The exception to this restriction is for fenofibrate; if the participant is receiving fenofibrate, the therapy must be stable for at least 6 weeks prior to randomization at a dose that is appropriate for the duration of the study in the judgement of the Investigator. Other fibrate therapy (and derivatives) are prohibited.
- Participants 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 of 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 (Visit 3) until completion of the follow-up visits.

- 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 Medical Monitor if required.
- The Medical Monitor 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. Please see Section 6.5 on concomitant therapy for additional instructions.

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

- Name of medication;
- Reason for use / change;
- Dates of administration including start and end dates;
- And dosage information including dose and frequency.

6.6 Dose Modification

No dose modification is planned.

6.7 Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

- Confirmed platelet count < 75,000/µL (see Appendix F in case of uninterpretable platelet count)
- Hy's Law defined as 'an increase in AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN', where no other reason, other than the study treatment, can be found to explain the combination of increases
- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for > 2 weeks
- ALT or AST > 3 × ULN and TBL > 2 x ULN or INR > 1.5

- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5 %)
- Confirmed increase in serum creatinine of 0.3 mg/dL from baseline
- Confirmed 25% decline in eGFR from baseline
- Confirmed new-onset haematuria, albuminuria (UACR ≥ 300 mg/g), or proteinuria (UPCR ≥ 500 mg/g)
- Hypersensitivity reaction CTCAE grade 3 or higher

Participants may be discontinued from study intervention in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the CSP

If a participant discontinues study treatment, he or she will be encouraged to return to the study site for the EDV (see Table 1). Where possible, the EDV should be at the next visit according to the original visit schedule, unless consent is withdrawn from further study participation. To secure recommended safety follow-up, participants attending an EDV should also be asked to continue to return for their originally scheduled visits for a total of three months, unless they are unable to or unwilling to return. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

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

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EDV should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team/CRA.

7.3 Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

  Pre-dose assessments may be performed up to 60 minutes prior to dosing.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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 one treatment period and one safety follow up period. The treatment period starts after the screening visits (Visit 1: Day -42 to Day -1; Visit 2: Day -7 to Day -1). During Visit 1, the participants will be checked for eligibility and enrolled to the study. Additional samples will be collected on Visit 2. Approximately 108 participants will be randomized at Visit 3 (Day 1) in a 1:1:1:1 ratio to SC injections of AZD8233 (planned doses CCI , CCI , and CCI) or matching placebo. AZD8233 or placebo will be administered SC on Visit 3, 4, 6, and 8. The participants will be treated for 84 days (12 weeks) with AZD8233 or placebo. Thereafter, the participants will continue in a safety follow up period for 12 weeks; the final follow up visit will be performed on Week 24 (16 weeks post last dose of AZD8233 or placebo).

General description of visits:

Visit 1 (enrolment) and Visit 2: At Visit 1 (Day -42 to Day -1), participants will be asked to

sign the informed consent and optional informed consent for future genetic research sample. Participant demographics, medical history including smoking and alcohol consumption history will be recorded in the eCRF. A complete physical examination must be performed. Vital signs, height, BMI and ECG must be checked, as well as blood and urine sample collection. Enrolment will be performed in RTSM. Visit 2 (Day -7 to Day -1) will include an blood sample collection for LDL-C, PCSK9, and triglycerides.

Visit 3 (randomization): Visit 3 (Day 1) should be performed within 42 days of Visit 1. Participants are required to fast 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. At Visit 3, eligibility criteria must be verified by checking screening labs and inclusion/exclusion criteria. A complete physical examination must be performed. Blood and urine samples to be obtained prior to administration of study intervention in fasted state. ADA sample will be obtained pre-dose. Vital signs and ECG to be checked. If the participant fulfils all inclusion criteria and none of the exclusion criteria, they will be randomized in RTSM and study intervention will be administered as SC injection.

Visit 4, 6, and 8: Visit 4 (Day 8 ± 1 day), Visit 6 (Day 29 ± 2 days), and Visit 8 (Day 57 ± 2 days) are planned as clinical visits but may also be undertaken at the participant's home or any other appropriate location if deemed applicable, by site staff, following consultation with the sponsor. At Visits 4, 6, and 8, study intervention will be administered as SC injections. Participants are required to fast for at least 8 hours prior to Visits 4, 6, and 8. Participants are permitted to drink water during this period of fasting until 1 hour before blood sampling. Blood and urine sampling must be performed prior to administration of study intervention. PK sampling to be performed at Visits 4, 6, and 8. On Visits 4, 6, and 8, PK and ADA sampling must be done pre-dose. An abbreviated physical examination is required at the visits as well as ECG and vital signs examination.

Visit 5, 7, and 9: For Visit 5 (Day 22 ± 2 days), Visit 7 (Day 43 ± 2 days), and Visit 9 (Day 71 ± 2 days), are planned as clinical or home visits that may be undertaken at the participant's home or any other appropriate location by site staff or by qualified external service provider. PK sampling to be performed at Visits 7 and 9. An abbreviated physical examination is required at the visits. Vital signs, blood and urine samples to be taken at the visits.

Safety follow up visits (Visit 10-15): ECG must be performed at Visit 10 (Day 85 ± 2 days), Visit 11 (Day 99 ± 2 days), Visit 13 (Day 127 ± 2 days) and Visit 15 (Day 155 ± 2 days). At all safety follow up visits, an abbreviated physical examination is required, and vital signs, blood, and urine samples are to be checked. PK and ADA sampling are to be performed at Visit 10 (Day 85 ± 2 days), Visit 12 (Day 113 ± 2 days) and Visit 14 (Day 141 ± 2 days). Visit 11, 13, and 15 are listed as home visits in the SoA. Those visits may be undertaken at the participant's

home or any other appropriate location. Other visits currently not designated as “home visits” may also be undertaken at the participant's home or any other appropriate location if deemed applicable, following consultation with the sponsor.

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

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

The maximum blood volume to be drawn from each subject should not exceed 550 mL over an 8-week period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

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

8.2 Safety Assessments

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

8.2.1 Physical Examinations

- A complete physical examination will include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). During the home visits, the abbreviated physical exam can be conducted via a 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 the time points specified in the SoA. BMI will be calculated at the time points specified in the SoA.

8.2.2 Vital Signs

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

- Blood pressure and pulse measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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.

8.2.3 Electrocardiograms

ECG will be performed at the time points specified in the SoA.

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

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

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

- QTcF will be calculated as QTcF=QT*RR^-1/3, where the QT interval is in milliseconds and the RR interval is in seconds.

- Heart rate will be calculated, based on the RR interval as HR=60/RR interval, where the RR interval is in seconds.

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

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

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

changes from baseline derived and presented.

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

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

Absolute value > 450 ms and ≤ 480 ms.

Absolute value > 480 ms and ≤ 500 ms.

Absolute value > 500 ms.

Increase from baseline > 30 ms and ≤ 60 ms.

Increase from baseline > 60 ms.

The Investigator (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 abnormality will be recorded on the eCRF.

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

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

8.2.4 Clinical Safety Laboratory Assessments

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

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

All laboratory variables will be analysed at Covance central lab. 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)
	Glutamate dehydrogenase (GLDH)
Urinalysis (dipstick)	Bicarbonate
Urinalysis (positive dipstick)	Uric acid
pH	FSH (women only)
Specific gravity	LH (women only)
Glucose	
Blood	***Coagulation***
Colour	Prothrombin time
Protein	Activated partial thrombin time (aPTT)
Clarity/Appearance	International normalized ratio (INR)
Nitrites	
Ketones	***Urine renal safety biomarkers***
Leukocytes	Albumin
Microscopic analysis (if positive for blood, nitrites or protein)	Total protein
Urobilinogen	Creatinine
	Urine protein to creatinine ratio (UPCR)
Other Laboratory Assessments	Urine albumin to creatinine ratio (UACR)
Complement activation panel (C3a, Bb, C5a)	Estimated glomerular filtration rate (eGFR; by CKD-EPI formula)
High-sensitivity C-reactive protein (hs-CRP)	

NB. In case 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.

8.2.5 Other Screening Assessments

Other screening assessments referred to in the SoA (Table 1) are shown in

Table 6 Other Screening Assessments

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Table 6 Other Screening Assessments

HbA1c	
Viral Serology Screen	
Human immunodeficiency virus (HIV) I	Hepatitis B surface antigen (HBsAg) Hepatitis B virus DNA (HBV DNA)
HIV II	Hepatitis C virus antibody Hepatitis C virus RNA (HCV RNA)

8.2.6 Injection Site Reactions

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

8.3 Adverse Events and Serious Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the contents of this section

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

Serious adverse events will be recorded from the time of signing of the ICF.

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

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to the study intervention
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

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

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

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

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 study intervention or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE (see also Section 8.3.7).

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

8.3.6 Hy's Law

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

8.3.7 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform 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 (+46 317-763-734) or email (AEMailboxClinicalTrialTCS@astrazeneca.com) to AstraZeneca Patient Safety Data Entry Site, Tata Consultancy Services.

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

8.3.8 Pregnancy

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

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

8.3.8.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study. Should a

pregnancy still occur, the investigational product should be discontinued immediately, and the pregnancy reported to AstraZeneca.

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

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

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

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.8.2 Paternal Exposure

Male participants should refrain from fathering a child during the study and for 3 months following the final follow-up visit (see also Section 5.3.4).

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

8.3.9 Medication Error

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

The designated AstraZeneca representative works with the Investigator to ensure that all

relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.7) and within 30 days for all other medication errors.

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

8.4 Overdose

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

In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.7. For other overdoses, reporting must occur within 30 calendar days.

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 Sample, see Appendix C.

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

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled, or individual PK samples to

further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the 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 plasma concentrations of AZD8233 as specified in the SoA.

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

Plasma samples will be used to analyse the PK of AZD8233. Samples collected for analyses of AZD8233 concentration 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 full lengths 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) 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 will be asked to return to provide another sample 3 months after the first positive sample to evaluate whether ADAs persist. If the sample taken 3 months later is ADA-positive, the participant will be asked to return to provide a sample in another 3 months. If the sample is ADA-positive at 6 months, the Investigator and the medical monitor will discuss additional actions and decide on future monitoring frequency. Participants with treatment-induced ADAs are considered ADA-positive until levels have returned to baseline or levels have dropped 97% from maximum.

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Blood samples will be collected for the assessment of PCSK9 and dyslipidemia (

Table 7). Blood samples for the determination of concentrations of PCSK9 and to evaluate the lipid parameters and lipoprotein profile (particle size and number) will be collected at the time points specified in the SoA (Table 1).

Table 7 Pharmacodynamic Laboratory Assessments

LDL-C	PCSK9
Lipoprotein profile (particle size and number)	Biomarkers analyses
Other lipid parameters including:	
Total cholesterol	HDL-C
non-HDL-C	VLDL-C
ApoA1	ApoB
Lp(a)	Triglycerides
Remnants cholesterol	

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type-9; VLDL-C = very-low-density lipoprotein cholesterol

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.
- Collection and storage of blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including anti-platelet antibodies) and tolerability related to AZD8233 treatment or cardiometabolic diseases is part of this study.
- Biomarkers to be taken:
  - Blood (plasma) and urine sample analyses
  - Targeted and unbiased -omics approaches for evaluation of plasma and/or urine samples for PD biomarkers and biomarker research relative to safety, tolerability and PK profile related to AZD8233 treatment.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

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

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

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

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

The main statistical test to perform has the null hypothesis that the absolute change in log-transformed LDL-C for AZD8233 CCI dose is equal to the absolute change in log-transformed LDL-C for AZD8233 CCI dose.

9.2 Sample Size Determination

Approximately 108 participants will be randomly assigned to the four study arms so that at least 80 evaluable participants completed treatment up until and including visit 10 (week 12). Any participant who receives at least one dose of study intervention is considered evaluable and is included in the full analysis set. Participants are randomly assigned to study treatment cohorts in a ratio of 1:1:1:1.

The sample size of 20 participants per arm will provide 90% power in a two-sided t-test at 5% significance level to detect a difference of 0.33 on the log scale; 0.33 on the log scale is considered sufficient to distinguish the effect of the CCI dose from the effect of the CCI dose. The common SD for log-transformed LDL-C is assumed to be 0.3.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

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

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

9.4 Statistical Analyses

The statistical analysis plan will be finalised prior to first participant first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The statistical analysis plan will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

9.4.1 General Considerations

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

Statistical tests will be performed using two-sided test at a 5% significance level, if not explicitly stated otherwise. The SAS® version 9.3 or higher will be used for the data analysis.

A complete set of raw data listings will be appended to the final CSR. All tables, figures and listings will be presented in portable document format (PDF) without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables. Demographic and baseline characteristics will be presented as follows; for continuous variables, the number of non-missing observations, mean, SD, SEM, 95% CI of the mean, median, first and third quartiles, minimum and maximum, will be presented; for categorical variables: counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by time point of assessment as appropriate.

9.4.2 Efficacy

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

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

9.4.2.1 Primary Endpoint(s)

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

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

For active treatment in the study, the geometric mean ratio will be plotted over time.

9.4.2.2 Secondary Endpoint(s)

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

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

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

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

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

Pharmacokinetics

If data permits a population PK model will be developed, possibly with the support of PK data from studies D7990C00001 and D7990C00002, using nonlinear mixed effects regression analysis in NONMEM. Furthermore, if data allows, the population PK model may be coupled with separate PD models for PCSK9 and LDL-C.

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

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

9.4.3 Safety

All safety analyses will be performed on the Safety analysis set. Safety variables are AEs, vital signs, 12-lead ECGs and laboratory assessments.

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

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

Injection site reactions will be considered an AE of special interest and will be listed separately. Listing of injection site reactions will include information about size, colour and itching status and will be grouped by participant and time point (visit).

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

Use of concomitant medication will be reported.

9.5 Interim Analyses

There are no plans to perform any interim analyses during the study.

9.6 Data Monitoring Committee

A data monitoring committee will not be used in this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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.

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.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure 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 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or 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 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the 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 6 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 physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of 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, CRO).
- 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 7 Source Documents

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

A 8 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 CROs 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 9 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 participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

B 2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that 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 abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events 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 drug 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 RTSM errors)
- Wrong drug administered to participant (excluding RTSM errors)

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

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

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The Investigator:

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

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

C 3 International Airline Transportation Association (IATA) 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, for example, 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, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

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

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.

The results of genetic analyses may be reported in the CSR or in a separate study summary. The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on AZD8233 or other AstraZeneca Study treatments of this class or for this indication continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

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

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection
- Healthy Volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of consent for genetic research:

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal of consent are outlined in Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research will preferably be obtained from the participants at Visit 3 predose. If, for any reason, the sample is not drawn pre-dose on Visit 3 (D1), it may be taken at any visit until the Final follow-up/EDV visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an adverse event (AE), such participants would be important to include in any genetic analysis. If for any reason the sample is not drawn at the screening visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The process adopted for the single coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

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

Informed consent

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

Participant data protection

AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the

results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

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 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 study intervention.

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

E 2 Definitions

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

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

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

elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

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

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

Central laboratories being used:

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

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

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

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the participant has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the Global Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; 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. This includes deciding which of the tests available in the HL lab kit should be used.
  – Complete the three Liver eCRF Modules as information becomes available

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

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether

there is an alternative explanation for meeting PHL criteria other than DILI caused by the study treatment, 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 PHL 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 study treatment:

- 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 study treatment 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 References

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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 (PT/INR, aPTT) CBC with reticulocytes and mean platelet volume (MPV)
Serum B12 and folate
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG, and IgM
Complement: total C3, total C4, Bb, C5a
hs-CRP
Serology for:
HBV, HCV, HIV (if not done for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
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) (Provan et al, 2010). Platelet count should be monitored closely during corticosteroid treatment. An increased or normalized platelet count is expected within two weeks of therapy. Once the platelet count normalizes or rises significantly and plateaus > 50,000/µl, no additional therapy is needed. **Participants should be followed until platelet count has been > 100,000/µl for 1 month** (see above table for monitoring frequency).

F 3 Reference

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

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

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized 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, hypoxemia)
   (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, generalized 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 subcutaneous 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 High- and Moderate-intensity Statin Therapy

Participants should be receiving moderate- or high-intensity statin therapy as defined by the ACC/AHA guidelines on blood cholesterol management, or according to local guidelines. Below are examples of high- and moderate-intensity statin therapy for reference.

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

Appendix I Abbreviations

Abbreviation or special term	Explanation
ACC/AHA	American College of Cardiology/American Heart Association
AE	Adverse Event
ADA	Anti-drug antibody
ALP	Alkaline Phosphatase
ALT	Alkaline Aminotransferase
Apo	Apolipoproteins
aPTT	Activated Partial Thromboplastin Time
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CK	Creatine Kinase
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EDV	Early Discontinuation Visit
eGFR	Estimated Glomerular Filtration Rate
FDA	U.S. Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase

Abbreviation or special term	Explanation
GLDH	Glutamate Dehydrogenase
Hb	Haemoglobin
HbA1c	Haemoglobin A1c
HCT	Haematocrit
HDL-C	High-density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HMG-CoA	3-hydroxy-3-methyl-glutarylcoenzyme A
HR	Heart Rate
hs-CRP	High sensitive C-reactive Protein
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
ISR	Injection Site Reaction
IUD	Intrauterine Device
LDL	Low-density Lipoprotein Cholesterol
LDL-C	Low-density Lipoprotein Cholesterol
LH	Luteinizing Hormone
LLN	Lower Limit of Normal
Lp(a)	Lipoprotein(a)
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemaglobin Concentration
MCV	Mean Corpuscular Volume
NHP	Non-compliance Handling Plan
PCSK9	Proprotein Convertase Subtilisin/Kexin type-9
PEF	Peak Expiratory Flow
PD	Pharmacodynamic
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic
QTcF	Corrected QT Interval by Fredericia
RBC	Red Blood Cell
RTSM	Randomization and Trial Supply Management

Abbreviation or special term	Explanation
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SD	Standard Deviation
SEM	Standard Error of the Mean
SoA	Schedule of Activities
TBL	Total Bilirubin
TC	Total cholesterol
UACR	Urine Albumin to Creatinine Ratio
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
VLDL-C	Very-low-density lipoprotein cholesterol
WBC	White Blood Cell

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