STATISTICAL ANALYSIS PLAN	
Study Code	D7990C00006 (Part A)
Edition Number	4.0
Date	4-Jul-2022

Statistical Analysis Plan for D7990C00006, A Phase 1 and 2 study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of AZD8233 following a multiple subcutaneous dose administration in Japanese participants with dyslipidemia (HAYATE) – Part A

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BLQ	Below limits of quantification
BMI	Body mass index
CI	Confidence interval
CM	Composite measure
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DBL	Database lock
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
HLT	High level term
IPD	Important Protocol Deviation
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
PCSK9	Proprotein convertase subtilisin/kexin type-9
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	PR interval
PT	Preferred term
QRS	QRS wave
QT	QT wave
QTcF	Corrected QT Interval using Fridericia's Formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation or Specialized Term	Definition
SD	Standard deviation
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
UNS	Unscheduled
ULN	Upper limit of normal
WHO-DD	World Health Organisation drug dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	27-Apr-2021	Initial approved SAP	N/A	N/A
Derivation of primary endpoint(s)	30-Jun-2021	4.2.1.4/ 1st bullet: Any AE → All AE	Y(V1)	Change as the result of Mock Shell review.
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.5.4: - summarized by dose level → summarized by analytes and timepoints - presented by dose level → presented by analytes and timepoints - Figures for the arithmetic mean (SD) concentration → remove "(SD)" - (SD only on the linear scale) → (SD on the linear scale and gSD on the semi-logarithmic scale)	Y(V1)	Change as the result of Mock Shell review.
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.6.4/ L2: Safety Analysis Set → PD Analysis Set for lipid parameters	Y(V1)	Correction
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.6.4/ L3: delete "alongside the individual value of the respective visit".	Y(V1)	Change as the result of Mock Shell review.
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.6.4/ L6: 95% Cis → gSD	Y(V1)	Change as the result of Mock Shell review.
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.7.4/ L2: Safety Analysis Set → PD Analysis Set	Y(V1)	Correction
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.8.4/ L2: Safety Analysis Set → PD Analysis Set	Y(V1)	Correction
Statistical analysis method for secondary endpoint(s)	30-Jun-2021	4.2.8.4/ L3: delete "alongside the individual value of the respective visit".	Y(V1)	Change as the result of Mock Shell review.
Other	30-Jun-2021	4.1.7: - prior disease → past disease - concomitant disease → current disease	Y(V1)	Change as the result of Mock Shell review.

Other	30-Jun-2021	4.6.2.2: - All overdose data will be listed → All overdose data will not be listed	Y(V1)	Change as the result of Mock Shell review.
Other	30-Jun-2021	4.6.3.2: - Any recorded abnormalities will be presented in the listings. → Any recorded abnormalities will not be presented in the listings	Y(V1)	Change as the result of Mock Shell review.
Other	15-Sep-21	Updated the analysis visits windows to coincide with the visits in the CSP	Y	Change requested.
Data presentation	15-Sep-21	Included analysis of the composite measure	Y	Change requested
Other	26-Oct-21	Summarised the lab and anti-AZD8233 antibodies analysis visit windows in a separate table	Y	Change as a result of BDR1
Data presentation	26-Oct-21	Additional summary for the liver enzyme abnormalities	Y	Change as a result of BDR1.
Other	05-Nov-21	Added detail that pre-treatment phase can be up to 28 days prior to IP administration	Y	Change requested.
Other	05-Nov-21	Added that Part C will be summarised in a separate SAP.	Y	Change requested.
Statistical analysis method for secondary endpoint(s)	23-May-22 (post-DBL)	Updated derivation of LDL-C derived by the Friedewald or Martin/Hopkins formula and added the corresponding reference	Y	To replace missing values which were negative due to formula.
Other	01-Jun-22 (post-DBL)	RAC (AUD) and RAC (Cmax) added to list of PK parameters	Y	To be in line with the parameters collected during study.
Other	04-Jul-22 (post-DBL)	Analysis visit numbers updated in Tables 1-4	Y	Updated to be in line with the CSP.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D7990C00006 – Part A, supporting the clinical study report (CSR). Additional statistical analysis plans (SAP) will be created detailing the analysis of Part B and Part C of the study.

The reader is referred to the clinical study protocol (CSP) and the electronic case report form (eCRF) for details of study conduct and data collection. This SAP is based on Version 2.0 of the CSP dated 13 November 2020 and Version 2.0 of the eCRFs dated 18 January 2021.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The Enrolled Set will be used for the summary of subject disposition instead of the Safety Analysis Set.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

A single analysis of all data from Part A will be conducted after database lock (DBL) and all results will be included in the CSR. DBL will occur after completion of all follow up visits, approximately 16 weeks after last administration of study intervention to the last ongoing subject.

3.2 Analysis Populations

3.2.1 Enrolled Set

All participants who signed the informed consent form. The Enrolled Set will be used to summarize patient disposition.

3.2.2 Randomly Assigned to Study Intervention

All participants who were randomized. Participants will be analyzed according to the treatment to which they were randomized.

3.2.3 Safety Analysis Set

All participants randomly assigned to study treatment who took at least one dose of AZD8233 or placebo and for whom any post-dose data are available. Participants will be analyzed according to the treatment which they actually received. If a participant received study intervention from the wrong kit for only part of the treatment duration and then switched to another, the associated treatment group for that participant would be the treatment group that participant was randomized to. The Safety Analysis Set will be used as the analysis set for all summaries for safety evaluation unless stated otherwise and for the analysis of the immunogenicity data.

3.2.4 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will consist of all subjects in the Safety Analysis Set who received AZD8233 and who have evaluable PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

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

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

The PK Analysis Set will be used to summarize the PK data.

3.2.5 Pharmacodynamic Analysis Set

The Pharmacodynamic (PD) Analysis Set will consist of all patients who received AZD8233 or placebo, who have at least one baseline and one post-baseline measurement for either the level of PCSK9 in plasma or the level of LDL-C in plasma, and who have no important protocol deviations thought to impact on the analysis of the data.

The available PD data for any subjects excluded from the PD analysis set will be listed only, together with a flag indicating patients excluded from the PD analysis set. Only subjects or samples in the PD analysis set will be included in the descriptive summary tables.

The PD analysis set will be used to analyse the lipid parameters (PCSK9, LDL-C and other lipids).

3.3 General Considerations

There is no formal statistical hypothesis testing in this study. Safety and tolerability after multiple dosing of AZD8233 [redacted] (or placebo) will be descriptively evaluated. The following principles will be followed throughout the study:

- Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation (SD), median, first and third quartiles, and the minimum and maximum as appropriate.

- Log-transformed continuous variables will be summarized in a similar manner. In addition, the relative change from baseline will be calculated by back-transforming the change from baseline of the logarithmic variable as necessary.

- Categorical variables will be summarized as counts (n) and percentages (%). Unless otherwise stated, percentages will be calculated using the relevant analysis set population total as the denominator. Percentages will not be presented for zero counts.

- Mean and medians will be rounded to one additional decimal place relative to the original data, the SD will be rounded to two additional decimal places, and the maximum, minimum and quartiles will be displayed with the same accuracy as the original data. 95% confidence intervals (CIs) will be presented to one more decimal place than the raw data. Percentages (proportion) will be rounded to one decimal place.

- Summaries will be provided by time point of assessment where appropriate. Where summaries are over time, study day will be calculated in relation to the date of first dose of study treatment.

- Corresponding listings will be provided for all tabulated results unless stated otherwise. Any additional listings that are required will be described in the appropriate sections of the SAP.

- SAS® version 9.3 or higher will be used for all data analyses.

3.3.1 General Study Level Definitions

3.3.1.1 Definition of Baseline

Unless otherwise specified, 'baseline' refers to the last measurement obtained before the first dose of study intervention. For lipid parameters (PCSK9, LDL-C, etc), the geometric mean of the two measures taken pre-dose at Visit 2 (Day -1 and pre-dose Day 1) will be considered as baseline.

3.3.1.2 Handling of Missing Data

In general, missing data will not be imputed and will be treated as missing unless specifically described in an analysis section. The following considerations are made for missing safety data, adverse event (AE) dates, and concomitant medication/diseases dates:

- Safety assessment values of the form '<x' or '>x' (i.e., above or below the limits of quantifications) will be imputed as 'x' in the calculation of summary statistics but displayed as '<x' or '>x' in the listings.

- Adverse events that have missing causality after data querying will be assumed to be related to study drug.

- For missing AE/concomitant medication/disease start dates, the following will be applied:

- Missing day: Impute 1st of the month unless the month is the same as that of the first dose of study drug in which case impute first dose date.
- Missing day and month: Impute 1st January unless the year is the same as that of the first dose date in which case impute first dose date.
- Missing year: Impute the year of dosing.
- Completely missing: Impute first dose date unless the end date suggests it could have started prior to this in which case impute 1st January of the same year as the end date.

- For missing AE/concomitant medication/disease end dates, the following will be applied:
  - Missing day: Impute the last day of the month unless the month is the same as that of the last dose of the study drug in which case impute the date of last dose.
  - Missing day and month: Impute 31st December unless the year is the same as that of the last dose of study drug in which case impute date of last dose.
  - Missing year: Impute the year of dosing.
  - Completely missing: Do not impute a date i.e., assume that AE/concomitant medication/disease is ongoing.

For all missing start/end dates, flags will be retained in the analysis datasets indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

If a subject is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last known date to be alive + 1 from the database and the death date using the available information provided:

- Missing day only: Use the 1st of the month.
- Missing day and month: Use 1st January.
- Missing year: Impute the year of dosing.

3.3.1.3 Study Periods

For listings of adverse events, lipid levels, laboratory values, vital signs and ECG, values will be allocated to a study period. The allocation to the study periods will be performed after any

imputation of missing dates (for AEs only) as described in Section 3.3.1.2. The study periods are defined as follows:

- Pre-treatment: Up to 28 days prior to administration of study drug (Day <1).
- Treatment Period: From Day 1 to date of last dose + 2 days (from visit 2 up to visit 9).
- Follow-up Period: From day of last dose + 3 days onwards (visit 10 to visit 17).

3.3.2 Visit Window

Study visits windows are defined in the table below.

	Screening	Treatment Period						Follow-up Period		
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact[k]**	**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days −28 to −4**	**Day −1**	**Days 1 to 3**	**Days 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	-	-	-	**± 1 day**	**± 1 day**	**± 1 day**		**+2 days**	**± 2 days**	**± 2 days**

Analysis Visit Windows

Analysis visit windows will be defined for the lipid parameters, ECG, anti-AZD8233 antibodies, laboratory results and vital signs which summarize values by visit. These analysis visit windows will be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the window will be based on the actual date and not the intended date of visit.

Analysis visit windows will be constructed such that the upper limit of the window interval falls halfway between the two scheduled visits, where the number of days between visits is odd, the additional day will be applied to the lower interval of the later date.

Table 1: Analysis visit windows for lipid parameters

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 11
Visit 4 (Day 15)	Day 15	Day 12 – Day 18
Visit 5 (Day 22)	Day 22	Day 19 – Day 25
Visit 6 (Day 29)	Day 29	Day 26 – Day 32
Visit 7 (Day 36)	Day 36	Day 33 - Day 39
Visit 8 (Day 44)	Day 44	Day 40 – Day 50
Visit 9 (Day 57 to 59)	Day 57 to Day 59	Day 51 – Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16) [c]	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment.

[c] Only blood sampling LDL-C and PCSK9 at this visit.

Table 2: Analysis visit window for ECG and vital signs

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 18
Visit 6 (Day 29)	Day 29	Day 19 – Day 42
Visit 9 (Day 57 to 59)	Day 57 to Day 59	Day 43 – Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16)	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment.

Table 3: Analysis visit window for laboratory results and anti-AZD8233 antibodies

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3) [c]	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 18
Visit 6 (Day 29)	Day 29	Day 19 – Day 42
Visit 9 (Day 57 to 59) [c]	Day 57 to Day 59	Day 43 – Day 63
Follow-up period [d]		
Visit 10 (FUP Week 2) [e]	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 98
Visit 13 (FUP Week 8)	Day 113	Day 99 – Day 126
Visit 15 (FUP Week 12)	Day 141	Day 127 – Day 154
Visit 17 (FUP Week 16) [e]	Day 169	Day 155 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment.

[c] Complement activation panels are only collected at these time points.

[d] Renal safety biomarkers and dipstick urinalysis for hematuria are not collected during follow-up period.

[e] Anti-AZD8233 antibodies are collected only at these time points.

Table 4: Analysis visit windows for platelet counts

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 14
Visit 5 (Day 22)	Day 22	Day 15 – Day 25
Visit 6 (Day 29)	Day 29	Day 26 - Day 36
Visit 8 (Day 44)	Day 44	Day 37 – Day 49
Visit 9 (Day 56)	Day 56	Day 50 - Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16)	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.
[b] Day 1 is defined as date of first dose of study treatment.

An early discontinuation visit (EDV) may take place at any point during the study up to Visit 9 (when the last dose of study treatment is to be administered). In this instance, follow-up visits (Week 2, Week 4 etc.) will begin at date of last administered treatment prior to study discontinuation. Analysis visit windows will be applied to follow-up visits in line with the example above.

If there is more than one value per subject within an analysis visit window then the closest value to the scheduled visit date will be summarized, or the earlier value if the values are equidistant from the nominal visit date. Listings will display all values contributing to a time point for a subject and will highlight the value that contributed to the summary table where feasible.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used, regardless of where it falls in an interval. For summaries at a subject level (i.e., the maximum) all values will be included regardless of whether they appear in a corresponding visit-based summary.

3.3.3 Handling of Unscheduled Visits

Visits that fall outside the visit windows defined in the CSP will be classified as Unscheduled Visits. Unscheduled visits will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in an unscheduled visit that occurs between Day 3 and Day 8, then these visits will be numbered UNS 2.1 and 2.2 in the order they occurred. The values measured at unscheduled visits will not be included in the by-visit summary tables, they will be included in the overall summary tables (for abnormalities, minimum/maximums etc.) and will be presented in the listings.

3.3.4 Multiplicity/Multiple Comparisons

Not applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

Important protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of important protocol deviations on the safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by important protocol deviations.

This estimation will be performed on a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be agreed up on by all relevant scientific experts.

During the study, a list of important protocol deviations (IPD) will be developed, which will include inclusion/exclusion/discontinuation criteria deviations, investigational product deviations and excluded medication taken. These will be taken into consideration when interpreting the data. Patients with an IPD may be excluded from the analysis of the PK data.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical and surgical history, prior and concomitant medication and study drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Not applicable.

4.1.1.2 Presentation

Subject disposition will be summarized based on the Enrolled Set and will include the following information: the number of subjects enrolled, randomized and who received at least one dose of study drug, the number and percentage of subjects who completed treatment/discontinued treatment (including reasons for IP discontinuation), and the number and percentage of subjects who completed or discontinued study (including reason for early withdrawal). Summaries will be by treatment group and overall.

A randomization listing will be presented and will include the following information: randomization number, full enrolment number, date of randomization and randomized treatment group.

Subjects affected by the COVID-19 pandemic and subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic will be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in Section 3.2.

4.1.2.2 Presentation

Analysis sets will be summarized based on the Enrolled Set. The number of subjects included and excluded (including reason for exclusion) in each analysis population will be presented by treatment group.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations (IPDs) will be defined in the Non-compliance Handling Plan and are considered as those deviations from the protocol likely to have an impact on the perceived efficacy or safety of study treatment. The final list of IPDs will be determined before DBL.

4.1.3.2 Presentation

IPDs will be summarized based on the Randomized set. The number and percentage of subjects meeting each IPD criterion will be summarized by treatment group. Subjects who deviate from a given criterion more than once will be counted once for that criterion. Any subjects with more than one IPD will be counted once in the overall summary.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age is measured in years and calculated as:

$$\text{Age (years)} = (\text{Date of randomization} - \text{date of birth} + 1) / 365.25$$

4.1.4.2 Presentation

Demographics (age, sex, race, ethnicity) will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Body mass index (BMI) is calculated as:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / \text{height}^2 \text{ (m)}$$

4.1.5.2 Presentation

Baseline characteristics (height, weight, BMI, nicotine use and alcohol use) will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.6 Disease Characteristics

4.1.6.1 Definition and Derivations

Disease characteristics are defined as the following lipid related parameters measured at baseline:

- LDL-C derived by the Friedewald formula.

- LDL-C derived by the Martin/Hopkins formula.
- Direct LDL-C.
- HDL-C and Non-HDL-C.
- VLDL-C.
- ApoA1 and ApoB.
- Lp(a).
- TG.

4.1.6.2 Presentation

Disease characteristics will be summarized based on the Safety Analysis set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical history, and concomitant (called "current") diseases are coded using MedDRA version 23.1 or higher. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded. After imputation of dates, concomitant diseases will be classified as prior (called "past") or current.

A past disease is defined as any disease with a start and end date prior to the first dose date (exclusive). A current disease is defined as any disease with an end date on or after the first dose date. A disease with a completely missing end date will be considered as current.

4.1.7.2 Presentation

Medical/surgical history and current diseases will be summarized based on the Safety Analysis Set. The number and percentage of subjects with relevant medical/surgical history/current diseases will be presented by treatment group and summarized by System Organ Class (SOC) and Preferred Term (PT). Subjects with histories in more than one SOC/PT will be counted only once in that SOC/PT. Tables will be sorted alphabetically by SOC and PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior and concomitant medications are coded using the WHO-DD. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded.

Prior medications are defined as those that stopped and started prior to the first dose date. All medications on or after the first dose date are considered as concomitant, this includes those medications that started prior to date of first dose but continued after.

4.1.8.2 Presentation

Prior and concomitant medications will be summarized based on the Safety Analysis Set. The number and percentage of subjects will be presented by treatment group and summarized by Anatomical Therapeutic Chemical (ATC) Class and Preferred Term (PT). Subjects with medications in more than one ATC class/PT will be counted only once in that ATC class/PT. Tables will be sorted alphabetically by ATC class and PT.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated for each subject and expressed as a percentage. The percent treatment compliance will be calculated as the number of doses received relative to the expected number of doses.

$$\text{Treatment compliance (\%)} = 100 \times \frac{\textbf{Number of doses received}}{\textbf{Expected number of doses}}$$

4.1.9.2 Presentation

Treatment compliance will be summarized based on the Safety Analysis Set and by treatment group, using the principles outlined in Section 3.3 for continuous variables.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the safety and tolerability of AZD8233 following subcutaneous (SC) administration of multiple doses.					
Primary	Adverse Events	Safety analysis set.	Included in the summaries regardless of treatment discontinuation	NA – descriptive statistics only	4.2.1
	Injection site reactions				4.2.3
	Clinical laboratory examinations.				4.2.4
	Vital signs, ECG and cardiac telemetry.				4.2.2
Objective 2: To characterise the PK of AZD8233 following SC administration of multiple doses.					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Secondary	Plasma and urine parameters.	PK analysis Set		NA – descriptive statistics only	4.2.5
Objective 3: To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.					
Secondary	Absolute change from baseline in log-transformed PCSK9 in plasma. Percent change from baseline in PCSK9 in plasma	PD analysis set.		NA – descriptive statistics only	4.2.6
Objective 4: To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.					
Secondary	Percent change from baseline in levels of LDL-C in serum.	PD analysis set.		NA – descriptive statistics only	4.2.7
Objective 5: To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.					
Secondary	Levels of other lipid parameters	PD analysis set		NA – descriptive statistics only	4.2.8
Objective 6: To evaluate immunogenicity of AZD8233					
Exploratory	Anti-drug antibodies (ADA) and ADA titre	Safety analysis set		NA – descriptive statistics only	4.2.9

4.2.1 Primary Endpoint – Adverse Events

4.2.1.1 Definition

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

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

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the first dose date.

4.2.1.2 Derivations

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher.

4.2.1.3 Handling of Dropouts and Missing Data

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.2.1.4 Primary Analysis of Primary Endpoint

All summaries of adverse event data will be based on the Safety Analysis Set and will be presented by treatment group. Summary tables will include TEAEs only whereas listings will include all reported AEs.

A subject-level overview of AEs (the number and percent of subjects and the number of events) will be tabulated in a single table for:

- All AE.
- AEs possibly related to study treatment.
- AEs with an outcome of death.
- AEs with outcome of death possibly related to study treatment.
- All serious adverse events (SAE).
- SAEs possibly related to study treatment.
- AEs leading to discontinuation of study treatment.
- AEs leading to discontinuation of study treatment, possibly related to study treatment.
- AEs leading to dose interruption and reduction (separately).
- AEs leading to withdrawal from the study.

Separate AE summary tables of the number and percentage of subjects with AEs and the number of events in each of the categories above will be produced by SOC and PT.

Additionally, the following tables will be presented by SOC and PT:

- AEs by the maximum reported intensity.
- AEs by causality assessment.

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.2.2 Primary Endpoint – Injection Site Reactions

4.2.2.1 Definition

Injection site reactions (ISRs) are reported using standard AE collection criteria.

4.2.2.2 Derivations

Injection site criteria will be coded using the MedDRA version 23.1 or higher.

4.2.2.3 Handling of Dropouts and Missing Data

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.2.2.4 Primary Analysis of Primary Endpoint

All summaries of injection site reactions will be based on the Safety Analysis Set and will be summarized by treatment group. The number and percentage of subjects with an injection site reaction and the number of events will be summarized by High Level Term (HLT) and preferred term.

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.2.3 Primary Endpoint – Clinical Laboratory Assessments

4.2.3.1 Definition

Clinical laboratory assessments consist of hematology parameters, clinical chemistry, coagulation, urine renal safety biomarkers (called PFC Index) and composite measure (CM), and other laboratory assessments. The parameters to be summarized are listed in Appendix 7.2.

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

4.2.3.2 Derivations

Clinical laboratory results will be assigned to analysis visits as described in Section 3.3.2.

Except for lipids (section 4.2.6.2, 4.2.7.2 and 4.2.8.2) – safety clinical laboratory results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined will be replaced with the LLOQ.

After replacements of LLOQ, the change from baseline will be calculated for all post-baseline timepoints as the respective timepoint value minus the baseline value.

Based on the respective reference range indicators, the following flags will be applied to all laboratory assessments; 'Normal' (if the value is within the normal reference range), 'Low' (if the value is below the normal reference range) or 'High' (if the values is above the normal reference range).

eGFR

Subject's eGFR will be calculated from serum creatinine (SCr) concentration, according to the Japanese equation as follows:

$$\text{eGFR} = 194 \times \text{SCr}(\text{mg/dL})^{-1.094} \times \text{Age}^{-0.287} \times \alpha$$

where α is 1 for males and 0.739 for females.

Composite measure

The CM and the ratio between treatment and placebo will be calculated as follows.

1. For each subject, calculate the (uCr)-normalised fold-change from baseline for each biomarker in the PFC index. The (uCr)-normalised concentration at a given timepoint is calculated as the concentration of the biomarker at that timepoint, divided by the concentration of urinary creatinine (uCr) at the same timepoint. The fold change from baseline is then calculated as the uCr-normalised concentration at a given timepoint, divided by the uCr-normalised concentration at baseline. Define the fold-change as FC_{ij} for subject i and biomarker j, where j = 1, 2,…,6.

2. For each subject i, calculate CM:

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

3. Calculate the GM of CM for cohort k (k = Treatment, Placebo):

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

4. Calculate the ratio of the GMs for the two cohorts:

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

Liver enzyme abnormalities

AST, ALT and TBL will be classified as follows:

AST and ALT:

- <3×ULN (or below the LLOQ).
- ≥3 to <5×ULN.
- ≥5 to < 8×ULN.
- ≥8×ULN.

TBL:

- <1×ULN (or below the LLOQ).
- ≥1 to <2×ULN.
- ≥2×ULN.

Occurrences of AST or ALT ≥3×ULN together with TBL ≥ 2×ULN are reported as SAE (Potential Hy's Law).

Reduced platelet count

Platelet count <150 (10^9/L) or percent decrease from baseline greater than 30%.

4.2.3.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.3.4 Primary Analysis of Primary Endpoint

Laboratory data will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. The number and proportion of patients with liver enzyme abnormalities and reduced platelet counts will summarized by treatment group and visit, including a summary of the maximum (for AST,ALT and TBL) or minimum value (for platelet count) recorded post-baseline.

The composite measure of the PFC index and corresponding ratio of AZD8233 to placebo will be presented by treatment group and visit. Box plots over time will be produced by treatment group for the composite measure and for the fold-change of the six individual biomarkers. A spaghetti plot over time of the fold-change of the six individual biomarkers will also be produced for each subject.

Shift tables will be presented for select laboratory parameters (clinical chemistry and hematology). Spaghetti plots over time will be produced for ALT, AST, TBIL and gamma GPT, with the corresponding reference range overlaid on top.

Clinical laboratory data will be reported in standard international units.

4.2.4 Primary Endpoint – Vital Signs, ECG and Cardiac Telemetry

4.2.4.1 Definition

Vital Signs

The vital sign measurements to be summarized are:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (oral) (ºC).

ECG

The following parameters or time intervals will be recorded for each ECG: RR, PR interval, QRS duration, QT interval, QTcF interval, and ECG mean heart rate (HR). The Investigator will judge whether the overall interpretation is ‘normal’ or ‘abnormal’.

Cardiac Telemetry

Cardiac telemetry results will be reviewed by the Investigator and clinically important results are stored.

4.2.4.2 Derivations

Vital sign measurements, ECG and cardiac telemetry results will be assigned to analysis visits as described in Section 3.3.2.

Change from baseline for vital sign measurements and ECG parameters (where applicable) will be calculated for all post-baseline visits as the respective visit value minus the baseline value.

Vital Signs

Based on the respective reference range indicators, the following flags will be applied to all vital sign measurements; 'Normal' (if the value is within the normal reference range), 'Low' (if the value is below the normal reference range) or 'High' (if the values is above the normal reference range).

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 140 mmHg
Diastolic blood pressure	50 -90 mmHg
Heart rate	50 - 100 bpm
Temperature	<=37ºC

ECG

Outlier categories with respect to QTcF will be defined as follows:

- 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

4.2.4.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.4.4 Primary Analysis of Primary Endpoint

Vital Signs

Vital signs will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1.

ECG

ECG parameters will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. Outliers with respect to QTcF will be tabulated using the categories defined in Section 4.2.4.2.

Cardiac Telemetry

Results for 12-lead ECG real-time cardiac telemetry will be listed based on the Safety Analysis Set including the overall assessment, specifics of abnormalities and the start and stop date/time.

4.2.5 Secondary Endpoint - Pharmacokinetics

4.2.5.1 Definition

Where possible, the following PK parameters will be determined.

AUC	Area under the plasma concentration-time curve from time zero extrapolated to infinity. AUC is estimated by AUC(0-last) + Clast/λz where Clast is the last observed quantifiable concentration.
$AUC_{(0\text{-}last)}$	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration.
$AUC_{(0\text{-}24)}$	Area under the concentration-time curve from time zero to 24 hours post-dose.
$AUC_{(0\text{-}48)}$	Area under the concentration-time curve from time zero to 48 hours post-dose.
AUCτ	Area under the plasma concentration-time curve during the dosing interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration.
C_{max}	Maximum observed plasma concentration.
C_{trough}	Observed trough plasma concentration
λz	Terminal rate constant, estimated by log-linear least-squares regression of the terminal part of the concentration-time curve.
MRT	Mean residence time of the unchanged drug in the systemic circulation.

RAC (AUC)	Accumulation ratio based on AUC
RAC (C_{max})	Accumulation ratio based on C_{max}
t1/2z	Half-life associated with the terminal slope (λz) of a semi-logarithmic concentration-time curve
t_{lag}	Time delay between drug administration and the first observed concentration in plasma
t_{last}	Time of last quantifiable concentration.
t_{max}	Time to reach peak or maximum observed concentration following drug
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration.

The following PK parameters will be determined, where possible, from urine concentrations.

$Ae_{(t1-t2)}$	Amount of analyte excreted unchanged in urine from time t1 to t2
$fe_{(t1-t2)}$	Percentage of analyte excreted unchanged in urine from t1 to t2
$Ae_{(0-last)}$	Cumulative amount of analyte excreted at the last sampling interval
$fe_{(0-last)}$	Cumulative percentage of dose excreted unchanged into the urine from time zero to the last measured time point for an analyte, estimated by dividing Ae(0-last) by dose
CLR	Renal clearance of drug from plasma, estimated by dividing Ae(0-24) by AUC(0-24)

Additional PK parameters may be determined where appropriate.

4.2.5.2 Derivations

The geometric mean is calculated as the exponential of the arithmetic mean calculated from the data on the natural log scale.

The percent coefficient of variation is calculated as: CV (%) = $\sqrt{(\exp(s^2) - 1}$ where s is the standard deviation of the data on a log scale.

Handling of values below the lower limit of quantification (BLQ)

Plasma concentrations below the limit of quantification (BLQ) from the time of pre dose sampling (t = 0) up to the time of the first quantifiable concentration will be set to a value of 0. After the first quantifiable concentration, BLQ plasma concentrations will be set to missing for the calculation of PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If two or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation

of the PK parameters unless there is a scientific rationale not to do so, which will be documented in the CSR.

Any embedded BLQ value (between two quantifiable concentrations) will be set to missing for the PK analysis.

If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

For descriptive statistics plasma concentrations that are below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, min, median, and max.
- The number of BLQ values (n below LLOQ) will be reported for each time point.
- Where there is no result, these will be set to missing.

Urine concentrations that are below the LLOQ will be handled as follows:

- BLQ values should be set to zero for the calculation of individual Ae.
- Any resulting Ae values equal to zero should be set to missing for the calculation of the summary statistics.

4.2.5.3 Handling of Dropouts and Missing Data

Not applicable

4.2.5.4 Primary Analysis of Secondary Endpoint

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of urine sample collection start and stop times will be provided. Urine amount and fraction of dose excreted (by interval and cumulative) will be listed.

Pharmacokinetic Concentrations

Plasma concentrations, amount excreted in urine (Ae), and fraction of dose excreted (per collection interval and cumulative) and PK parameters will be summarized by analytes and timepoints using descriptive statistic, number of non-missing observations, n below LLOQ, arithmetic mean, SD, geometric mean, geometric coefficient of variation (CV%), min, median, max and based upon the PK analysis set.

Where the actual time that a sample was taken deviates by more than the specified time allowances from the nominal time then concentration will be excluded from the summary statistics and statistical analysis.

Nominal Time	Time allowance
Pre-dose	Up to 30 minutes prior to dosing
0.5 h post dose	± 2 minutes
1 h post dose	± 5 minutes
1.5 h post dose	± 5 minutes
2 h post dose	± 5 minutes
2.5 h post dose	± 5 minutes
3 h post dose	± 10 minutes
4 h post dose	± 10 minutes
5 h post dose	± 10 minutes
6 h post dose	± 10 minutes
8 h post dose	± 10 minutes
10 h post dose	± 30 minutes
12 h post dose	± 30 minutes
24 h post dose	± 1 hour
36 h post dose	± 1 hour
48 h post dose	± 1 hour

Data from subjects excluded from the PK population will be included in the data listings, but not in the summaries or in the inferential statistics.

For t_{max} and time of last quantifiable plasma concentration (t_{last}) only n, median, minimum and maximum will be used.

Pharmacokinetic parameters will be rounded for reporting purposes in the summary tables and subject listings, as per the PK order form provided by AZ.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale, with separate plots for each subject. Plots will be based on the PK analysis set.

Combined individual plasma concentration versus actual times will be plotted in linear and semilogarithmic scale. Plots will be grouped by dose level and based on the PK analysis.

Figures for the arithmetic mean concentration-time data will be presented for all groups (pool data from all treatment groups and for placebo) overlaid on the same plot, in both a linear and semi-logarithmic scale (SD on the linear scale and gSD on the semi-logarithmic scale).

Additional graphical presentations of PK data may be added at the discretion of the PK scientist.

Pharmacokinetic data will be presented by analytes and timepoints. A listing of all concentration-time data will be presented by dose level.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

1. Source data shall be used in all derived PK concentrations without prior rounding.

2. The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.

3. Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.

4. Geometric coefficient of variation (CV) % and coefficient of variation (CV%) will be presented to one decimal place.

Graphical Presentation

For individual figures, concentrations that are BLQ will be regarded as missing, with the exception of pre-dose BLQ values which will be set to zero for linear scale plots.

For mean plots, BLQ values will be handled as described for the summary tabulations so that the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point. All mean plots will be based on the PK analysis set.

Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 6.4, or higher, (Certara) and/or SAS® Version 9.3, or higher (SAS Institute, Inc., Cary, North Carolina). All descriptive and inferential statistical computations will be performed using SAS® Version 9.3, or higher.

The actual sampling times, recorded in the raw data, will be used in the final plasma PK parameter calculations. If actual times are missing, nominal times may be used.

Nominal sampling times will be used for interim plasma PK parameter calculations.

Nominal times will be used for the calculation of urine PK parameters.

Concentration data will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount and concentration units, will be presented as they are received from the analytical laboratory.

Dose normalized parameters for AUC_{last}, AUC and C_{max} will be calculated by dividing the original parameter by dose.

The C_{max} and time to reach peak or maximum observed concentration or response following drug administration (t_{max}) will be derived directly from the plasma concentration-time profiles. For multiple peaks the highest post dose concentration will be reported as C_{max}. In the case that the multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

Terminal elimination half-life, estimated as $(\ln 2)/\lambda_z$, where λ_z refers to the terminal elimination rate constant, will be estimated by log linear least squares regression of the terminal part of the concentration-time curve.

The choice of data points used to estimate λ_z should follow the general guidelines:

- If there is more than 1 phase, use only observations from the terminal phase.
- In general, the minimum data requirements are 3 measured concentrations spanning three half-lives. Where $t_{1/2}$ is estimated over less than three half-lives, the values will be flagged in the data listings.
- Should include the last measurable concentration.
- Include only observations after C_{max}.
- The adjusted correlation coefficient (regression coefficient adjusted for λ_z, N, goodness of fit statistic for calculation of λ_z; Rsq adj) should be ≥ 0.80.

Area under the plasma concentration-curve will be calculated using trapezoidal methods when concentration is increasing and logarithmic trapezoidal method when concentrations are decreasing (linear up log down).

Three concentrations higher than the lower limit of quantification (LLOQ) are required as a minimum for the AUC parameter to be calculated.

If the pre-dose concentration prior to the first dose is missing it will be set to zero by default. If the pre-dose sample on Day 57 is missing it may be set equal to the concentration at the end of the dosing interval for the calculation of area under the plasma concentration-time curve in the dosing interval (AUCτ) assuming linear PK and steady state conditions apply.

If the sample at the end of the profile is missing on Day 57 the concentration may be set equal to the pre-dose value for the calculation of AUCτ assuming linear PK and steady state conditions apply.

If a plasma or urine concentration value is considered anomalous due to being inconsistent with the expected pharmaceutical profile it may be appropriate to exclude this data point from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the study report. Embedded BLQs may be considered anomalous depending on the characteristics of the drug.

Urine PK parameters will be calculated based on measurements with the ECL assay. In case of an incomplete urine collection in any of the specified collection intervals (eg, spilled sample), the calculation of the fraction of dose excreted into urine as well as renal clearance will be subject to discretion of the AZ study pharmacokineticist.

The amount excreted in urine (Ae) will be calculated using a urine density of 1.0 g/mL. Urine concentrations below LLOQ will be treated as numerical zero.

The amount of analyte excreted into the urine from time t1 to t2 [Ae(t1-t2)] and percentage excreted unchanged in urine from t1 to t2 [fe(t1-t2)] will be calculated by collection interval and cumulatively for all collection intervals.

4.2.6 Secondary Endpoint – Change from baseline in log-transformed PCSK9 in plasma

4.2.6.1 Definition

Not applicable.

4.2.6.2 Derivations

PCSK9 measurement will be assigned to analysis visits as described in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be

replaced by the LLOQ divided by the square root of 2. After replacement of LLOQ, PCSK9 the absolute change and percent change from baseline are calculated for each study visit.

Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. Percent change from baseline is calculated using the raw values as the visit value minus the baseline value divided by the baseline value *100.

Baseline values for PCSK9 are defined as the geometric mean of the two measures taken pre-dose at Visit 2 (Day -1 and pre-dose Day1).

4.2.6.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.6.4 Primary Analysis of Secondary Endpoint

PCSK9 endpoints will be summarized as continuous log-normal variables and based on the PD Analysis Set. The absolute change and percent change from baseline will presented. Summaries of the log-transformed variables will be presented by visit and treatment group using the principles defined in Section 3.3.

A plot of geometric means and corresponding gSD at each post-treatment visit, by treatment group will be generated.

4.2.7 Secondary Endpoint – Percent change from baseline in LDL-C

4.2.7.1 Definition

Three measures of LDL-C will be assessed; LDL-C derived by Friedewald formula, LDL-C derived by the Martin/Hopkins formula and direct LDL-C.

4.2.7.2 Derivations

LDL-C values will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2.

LDL-C derived by Friedewald or Martin/Hopkins formula are indirectly calculated and hence may take 0 mg/dL or negative values (reported as ‘Unable to Calculate’ by Central lab) (Sampson et al, 2020). LLOQs will not be defined for these indirectly calculated measurements according to Central lab. These data will be replaced by 1/square root of 2 mg/dL for the analysis and displayed as reported from Central lab in the listings. After replacement of LLOQ, the percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value * 100.

Baseline values for LDL-C are defined as the geometric mean of the two measures taken pre-dose at Visit 2 (Day -1 and pre-dose Day1).

4.2.7.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.7.4 Primary Analysis of Secondary Endpoint

LDL-C values will be summarized based on the PD Analysis Set. Summaries of the percent change from baseline and individual values will be presented by visit and treatment group using the principles defined in Section 3.3.

4.2.8 Secondary Endpoint – Other Lipid Parameters

4.2.8.1 Definition

The following lipid parameters will be summarized:

- Total cholesterol (TC).
- High-density lipoprotein cholesterol (HDL-C).
- Non-HDL-C.
- Very low density lipoprotein cholesterol (VLDL-C).
- Apolipoproteins (Apo) A1.
- ApoB.
- Lp(a)
- Triglycerides.

4.2.8.2 Derivations

Lipid parameters will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2. After replacement of LLOQ, lipid values will be log-transformed and the change from baseline, and the percent change from baseline will be calculated for each study visit.

Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. Percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value * 100.

4.2.8.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.8.4 Primary Analysis of Secondary Endpoint

Other lipid endpoints will be summarized as continuous log-normal variables and based on the PD Analysis Set. The absolute change and the percent change from baseline will presented. Summaries of the log-transformed variables will be presented by visit and treatment group using the principles defined in Section 3.3.

4.2.9 Exploratory Endpoint - Immunogenicity

4.2.9.1 Definition

Development of anti-drug antibodies (ADA) and ADA titre will be used to evaluate the immunogenicity of AZD8233. Titre evaluations are conducted only on those samples that are confirmed positive for ADA.

4.2.9.2 Derivations

ADA parameters will be assigned to an analysis visit as defined in Section 3.3.2.

4.2.9.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2

4.2.9.4 Primary Analysis of Other Endpoint

ADA endpoints will be analyzed based on the Safety Analysis Set. The number and percentage of subjects with a positive result will be tabulated for: any time in study, baseline, any time post-baseline, and by visit and treatment group along with a summary of ADA titre using the principles defined in Section 3.3.

4.3 Pharmacodynamic Endpoint(s)

Refer to Sections 4.2.6, 4.2.7 and 4.2.8.

4.4 Pharmacokinetics

Refer to Section 4.2.5.

4.5 Immunogenicity

Refer to Section 4.2.9.

Safety Analyses

The domain safety covers exposure, overdoses and physical examinations. Adverse events, clinical laboratory, vital signs, and ECG have been summarized in previous sections.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Treatment exposure will be calculated in days as the treatment duration from date of first dose to date of last dose, inclusive.

Duration of exposure (days) = last dose date – first dose date + 1

4.6.1.2 Presentation

Duration of exposure will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group using the principles outlined in Section 3.3 for continuous variables.

4.6.2 Overdose

4.6.2.1 Definitions and Derivations

An overdose is considered as any dose of AZD8233 greater than the planned dose.

4.6.2.2 Presentation

All overdose data will be listed, including randomized treatment, total dose and unit, date/time overdose started and stopped, whether it was intentional and association with AE.

4.6.3 Physical Examinations

4.6.3.1 Definitions and Derivations

The full physical examination includes an assessment of general appearance and a review 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.

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

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.

4.6.3.2 Presentation

Physical Examination data will not be solely collected and not presented in CSR.

5 INTERIM ANALYSIS

No planned interim analyses.

6 REFERENCES

Sampson, Maureen, Clarence Ling, Qian Sun, Roa Harb, Mohmed Ashmaig, Russell Warnick, Amar Sethi et al. "A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia." *JAMA cardiology* 5, no. 5 (2020): 540-548.

7 APPENDIX

7.1 Schedule of Activities

	Screening	**Treatment Period**						**Follow-up Period**		
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact** k	**10 to 16**	**17 (Final Follow up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	**+2 days**
Informed consent	X									
Inclusion/exclusion criteria [b]	X	X								
Demographic data	X									
Weight and height (BMI)[c]	X	X					X (Day 57)			X
Medical history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Drug abuse and alcohol screen [d]	X					X				
Smoking history	X									
Viral serology [e]	X									
Pregnancy test	X[O]		X[P]							

	Screening	Treatment Period						Follow-up Period		
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact k**	**10 to 16**	**17 (Final Follow up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	-	-	-	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	**+2 days**
Pregnancy and reproductive status (females only[q])	X									
Randomisation			X (Day 1)							
Study residency										
Check-in		X			X					
Check-out			X (Day 3[l])				X (Day 59)			
IMP administration			X (Day 1)	X			X (Day 57)			
Safety and tolerability										
Adverse event questioning (including collection of data for injection site reactions)	X (only SAEs)	X (only SAEs)	X	X	X	X	X	X	X	X

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

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

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

	Screening	Treatment Period						Follow-up Period		
Visit Number	**1**	**2**		**3, 6**	**4, 5, 7, 8**	**9**		**Telephone contact** k	**10 to 16**	**17 (Final Follow up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8[a], 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Day 64**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	-	-	-	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**	**+2 days**
Biobank until further analysis [i]										
Pharmacokinetics										
Plasma for AZD8233 and total full length ASOs of AZD8233 [j]			X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48h post dose)	X (pre-dose)	X		X (pre-dose and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post dose)		X	X
Urine for total full length ASOs of AZD8233			X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)				X (pre-dose and intervals 0-6, 6-12, 12-24 h post-dose)			

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

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

7.2 Clinical Laboratory Assessments

Hematology

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

Clinical Chemistry

Sodium	ALP
Potassium	ALT
Blood urea nitrogen (BUN)	AST
Creatinine	Gamma glutamyl transpeptidase (GGT)
Calcium	Total bilirubin
Phosphate	Direct bilirubin
Glucose (fasting)	Glutamate dehydrogenase (GLDH)
Creatine kinase (CK)	Lactate dehydrogenase (LDH)
Bicarbonate	Uric acid
HbA1c	FSH (women only)
Serum β-human chorionic gonadotropin (β-hCG)(women of childbearing potential only)	Luteinizing hormone (LH) (women only)
eGFR	

Coagulation

aPTT	Prothrombin time
International normalized ratio (INR)	

Urine renal safety biomarkers

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

Other laboratory assessments

Complement activation panel (C3a, Bb, C5a)	High-sensitive C-reactive protein (hs-CRP)
Dipstick urinalysis for hematuria	Dipstick urinalysis for human chorionic gonadotropin (hCG)(women of childbearing potential only)

SIGNATURE PAGE

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

Document Name: d7990c00006-sap-part-a-ed-4		
Document Title:	D7990C00006 Statistical Analysis Plan Part A Edition 4 (post-DBL)	
Document ID:	[redacted]	
Version Label:	[redacted]	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
[redacted]	[redacted]	Content Approval
[redacted]	[redacted]	Author Approval
[redacted]	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

STATISTICAL ANALYSIS PLAN	
Study Code	D7990C00006 (Part B)
Edition Number	2.0
Date	11-May-2022

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DBL	Database Lock
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDV	Early discontinuation visit
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FUP	Follow Up Period
HDL-C	High density lipoprotein cholesterol
HLT	High level term
HR	Heart rate
IP	Investigational Product
IPD	Important Protocol Deviation
IV	intravenous
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
LSM	Least Squares Mean
LSMD	Least Squares Mean Difference
MAR	Missing at Random
MCMC	Monte-Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model with repeated measures
NHP	Non-compliance Handling Plan
PCSK9	Proprotein convertase subtilisin/kexin type-9
PK	Pharmacokinetics
PT	Preferred Term
QTcF	Corrected QT Interval using Fridericia’s Formula
RR	Respiratory rate
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TBL	Total bilirubin
TC	Total cholesterol
TEAE	Treatment emergent adverse event
TG	Triglycerides
ULN	Upper limit of normal
VLDL-C	Very-low-density lipoprotein cholesterol
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	Click or tap here to enter text.	Initial approved SAP	N/A	N/A
Data presentation	18-Nov-21	Update analysis visit windows in line with schedule of activities in CSP	Y	Ease of programming.
NA	12-Apr-22	Added that an additional SAP will be produced for Part C	Y	NA
Data presentation	12-Apr-22	Removed LSM (SE) plots from primary analysis	Y	Not required.
Data presentation	12-Apr-22	Percent change derived from MMRM model, definition and summary.	Y	Ease of interpretation of the results.
Data presentation	12-Apr-22	Added additional analyses for Bleeding AEs	Y	To give more detailed summary of AEs
Data presentation	12-Apr-22	Added additional analyses for platelet counts	Y	To give more detailed summary of platelet counts
Data presentation	12-Apr-22	Added additional analyses for hematology results	Y	To give more detailed summary of hematology results

1 INTRODUCTION

AstraZeneca is developing AZD8233 [redacted] for the reduction of circulating levels of LDLs, a major risk factor of cardiovascular disease. This is a randomized, double-blind, placebo-controlled, dose-ranging Phase II study in Japanese participants with dyslipidaemia. The primary objective is to investigate the effect of AZD8233 on LDL-C across different dose levels and the primary efficacy endpoint of interest is the change from baseline in log-transformed LDL-C in serum at the end of Week 12. The study will also investigate the effect of AZD8233 on other lipid parameters including PCSK9, evaluate the pharmacokinetics of AZD8233 and assess the safety profile.

The purpose of this document is to give details for the statistical analysis of study D7990C00006 – Part B, supporting the clinical study report (CSR). A statistical analysis plan (SAP) of Part A has been created, the analysis of Part C will be detailed in a separate SAP.

The reader is referred to the clinical study protocol (CSP) and the electronic case report form (eCRF) for details of study conduct and data collection. This SAP is based on Version 4.0 of the CSP dated 2 November 2021 and Version 2.0 of the eCRFs dated 18 January 2021.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

1. 4.1 Study Population: Change from 'Safety Analysis Set' to 'Full Analysis Set' for summary of demographic data.

2. 9.4.2.1 Primary Endpoint (s): Regarding pair-wise comparisons, revised the description from 'high' to 'mid'.

3. 9.4.2.2 Secondary Endpoint (s): The analysis of levels of other lipid parameters has been updated to include an analysis using MMRM.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

- Two analyses are planned for Part B of this study. An initial analysis will be conducted after all randomized patients have completed (or discontinued from) the 12-week treatment period. The analysis for Week 12 will be considered as a primary efficacy analysis.

- To support Phase 3 development plan and also potential regulatory interaction, relevant sponsor personnel will be unblinded at the time of interim analysis.

- Investigators, other site personnel and study subjects will remain blinded to treatment assignment until the final DBL.

- The final analysis will be conducted after all randomized patients have completed the entire 24-week study period (including safety follow-up) or been withdrawn from the study.

The two analyses will have the same scope, except for PK analysis which will be included only in the final analysis.

3.2 Analysis Populations

3.2.1 Enrolled Set

All participants who signed the informed consent form. The Enrolled Set will be used to summarize patient disposition.

3.2.2 Randomly Assigned to Study Intervention

All participants who were randomized. Participants will be analyzed according to the treatment to which they were randomized.

3.2.3 Full Analysis Set (FAS)

All randomized participants who received at least one 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. For all efficacy analyses, FAS will be used.

3.2.4 Safety Analysis Set

All participants randomly assigned to study treatment who took at least one dose of study intervention and for whom any post-dose data are available. Participants will be analyzed according to the treatment which they actually received.

If a participant received study intervention from the wrong kit for only part of the treatment duration and then switched to another, the associated treatment group for that participant would be the treatment group that participant was randomized to.

The Safety Analysis Set will be used as the analysis set for all summaries for safety evaluation unless stated otherwise and for the analysis of the immunogenicity data.

3.2.5 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will consist of all subjects in the FAS who received at least one dose of AZD8233 and who have evaluable PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

The exclusion of any subjects or time points will be documented by the PK scientist, including the reasons for exclusion. The available concentration data for any participants excluded from the PK analysis set will be listed only. Concentration data for participants excluded from the PK analysis set will not be presented in the individual figures of concentration versus time plots.

The PK Analysis Set will be used to summarize the PK data and will be presented in accordance with the actual treatment received.

3.3 General Considerations

The following principles will be followed throughout the study:

- Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation (SD), median, first and third quartiles, and the minimum and maximum as appropriate.

- Log-transformed continuous variables will be summarized in a similar manner. In addition, the relative change from baseline will be calculated by back-transforming the change from baseline of the logarithmic variable as necessary.

- Categorical variables will be summarized as counts (n) and percentages (%). Unless otherwise stated, percentages will be calculated using the relevant analysis set population total as the denominator. Percentages will not be presented for zero counts.

- Mean and medians will be rounded to one additional decimal place relative to the original data, the SD will be rounded to two additional decimal places, and the maximum, minimum and quartiles will be displayed with the same accuracy as the original data. 95% confidence intervals (CIs) will be presented to one more decimal place than the raw data. Percentages (proportion) will be rounded to one decimal place.

- Summaries will be provided by time point of assessment where appropriate. Where summaries are over time, study day will be calculated in relation to Day 1, the date of first dose of study treatment.

- Corresponding listings will be provided for all tabulated results unless stated otherwise. Any additional listings that are required will be described in the appropriate sections of the SAP.

- Statistical tests will be performed using two-sided test at a 5% significance level, if not explicitly stated otherwise.

- SAS® version 9.3 or higher will be used for all data analyses.

3.3.1 General Study Level Definitions

3.3.1.1 Definition of Baseline

Unless otherwise specified, 'baseline' refers to the last measurement obtained before the first dose of study intervention. For lipid parameters (PCSK9, LDL-C, etc), the measure taken pre-dose at Visit 3 (Day 1) will be typically considered as baseline.

3.3.1.2 Handling of Missing Data

In general, missing data will not be imputed and will be treated as missing unless specifically described in an analysis section. The following considerations are made for missing safety data, adverse event (AE) dates, and concomitant medication/diseases dates:

- Safety assessment values of the form '<x' or '>x' (i.e., above or below the limits of quantifications) will be imputed as 'x' divided by the square root of 2 in the calculation of summary statistics but displayed as '<x' or '>x' in the listings.

- AEs that have missing causality after data querying will be assumed to be related to study drug.

- For missing AE start dates, the following will be applied:

    - Only partial AE start dates are imputed. Dates which are completely missing are not imputed.

    - If only the day is missing and the month and/or the year is different from the month and year of the first dose of investigational product (IP), assume 01-MMM-YYYY. If the month and year are the same as the first dose of IP month and year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date is prior to the first dose of IP, then assume the end date.

- If the month is missing and the year is different from the year of first dose of IP, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of IP year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP. If the year is the same as the first dose of IP and the end date is prior to the first dose of IP, then assume the end date.

- After applying these rules, if the imputed AE start date is after a complete AE end date then assume the same date as the complete AE end date; if the end date is missing and the imputed AE start date is after the end of study date then assume the same date as the study end date.

- For missing AE end dates, the following will be applied:

  - Completely missing AE end dates are not imputed.

  - If the AE is ongoing, the end date is set to missing.

  - If the AE is not ongoing, and if only the day is missing them assume the last day of the collected month.

  - If the AE is not ongoing, and both, the day and the month are missing then assume 31-DEC of the collected year.

  - After applying these rules, if the imputed AE end date is after the end of study date or the date of death, the AE end date is set to the earliest date between the end of study date and the date of death.

- For missing concomitant medication and concomitant procedures start dates, neither partially nor completely missing dates are imputed.

- For missing concomitant medication and concomitant procedures end dates, the following will be applied:

  - Completely missing end dates or dates for which the year is missing are not imputed.

  - If the concomitant medication is ongoing, the end date is set to missing.

  - If the concomitant medication / procedure is not ongoing, and if only the day is missing then assume the last day of the collected month.

- If the concomitant medication / procedure is not ongoing, and both, the day and the month are missing then assume 31-DEC of the collected year.
- After applying these rules, if the imputed date is after the end of study date or the date of death, the concomitant medication / procedure end date is set to the earliest date between the end of study date and the date of death.

- If a subject is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last known date to be alive + 1 from the database and the death date using the available information provided:
  - Missing day only: Use the 1st of the month.
  - Missing day and month: Use 1st January.
  - Missing year: Impute the year of dosing.

For all missing start/end dates, flags will be retained in the analysis datasets indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

3.3.1.3 Study Periods

For listings of adverse events, lipid levels, laboratory values, vital signs and ECG, values will be allocated to a study period. The allocation to the study periods will be performed after any imputation of missing dates (for AEs only) as described in Section 3.3.1.2. The study periods are defined as follows:

- Pre-treatment: Before first date of study drug (Day <1).
- On-treatment: From Day 1 to date of end of study.

3.3.2 Visit Window

Study visits windows are defined in the table below:

	Screening		Treatment Period							EDV	Follow-up period[n]	Final Follow-up Visit[n]
Visit Number	1	2	3	4	5	6	7	8	9		10, 11, 12, 13, 14, 15	16
Study Week			0	1	3	4	6	8	10		12, 14, 16, 18, 20, 22	24
Study Day	Days −28 to −10	Days −7 to −4	Day 1	Day 8	Day 22	Day 29	Day 43	Day 57	Day 71		Days 85, 99, 113, 127, 141, 155	Day 169
Visit Window				± 1 day	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days		± 2 days	± 2 days

Analysis Visit Windows

Analysis visit windows will be defined for the lipid parameters, ECG, anti-AZD8233 antibodies, laboratory results and vital signs which summarize values by visit. These analysis visit windows will be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the window will be based on the actual date and not the intended date of visit.

Analysis visit windows will be constructed such that the upper limit of the window intervals fall halfway between two scheduled visits, where the number of days between visits is odd, the additional day will be applied to the lower interval of the later date.

Table 1: Analysis visit windows for lipid parameters, laboratory parameters* and vital signs

Analysis Visits	**Scheduled visit day**	**Analysis visit window (days)**
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Day 1	Day 1	Day 1[b]
Week 1	Day 8	Day 2 – Day 14
Week 3	Day 22	Day 15 – Day 25
Week 4	Day 29	Day 26 – Day 35
Week 6	Day 43	Day 36 – Day 49
Week 8	Day 57	Day 50 – Day 63
Week 10	Day 71	Day 64 – Day 77
Follow-up period		

Week 12	Day 85	Day 78 – Day 91
Week 14	Day 99	Day 92 – Day 105
Week 16	Day 113	Day 106 – Day 119
Week 18	Day 127	Day 120 – Day 133
Week 20	Day 141	Day 134 – Day 147
Week 22	Day 155	Day 148 – Day 161
Week 24	Day 169	Day 162 onwards.

*Complement activation panel is collected pre-dose on Visits 12, 3, 6 and 8 only. Hs-CRP is collected at Visit 1, 8 and all follow-up visits.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment. Includes all measurements collected at Day 1 after the first dose of IP.

Table 2: Analysis visit windows for ECG

Analysis Visits	**Scheduled visit day**	**Analysis visit window (days)**
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Day 1	Day 1	Day 1[b]
Week 1	Day 8	Day 2 – Day 18
Week 4	Day 29	Day 19 – Day 42
Week 8	Day 57	Day 43 – Day 70
Follow-up period		
Week 12	Day 85	Day 71 – Day 91
Week 14	Day 99	Day 92 – Day 112
Week 18	Day 127	Day 113 – Day 140
Week 22	Day 155	Day 141 onwards

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment. Includes all measurements collected at Day 1 after the first dose of IP.

Table 3: Analysis visit windows for anti AZD8233 antibodies

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Day 1	Day 1	Day 1[b]
Week 1	Day 8	Day 2 – Day 18
Week 4	Day 29	Day 19 – Day 42
Week 8	Day 57	Day 43 – Day 70
Follow-up period		
Week 12	Day 85	Day 71 – Day 98
Week 16	Day 113	Day 99 – Day 126
Week 20	Day 141	Day 127 – Day 154
Week 24	Day 169	Day 155 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment. Includes all measurements collected at Day 1 after the first dose of IP.

An early discontinuation visit (EDV) may take place at any point during the study up to Week 12. In this instance, follow-up visits (Week 2, Week 4 etc.) will begin at date of last administered treatment and performed every 2 weeks after last dose prior to study discontinuation. For those patients with an early discontinuation, an additional analysis visit window will be applied to follow-up visits as follows and will be used for the summary of safety and lab data.

If there is more than one value per subject within an analysis visit window then the closest value to the scheduled visit date will be summarized, or the later value if the values are equidistant from the nominal visit date, the remaining visits will be treated as 'Unscheduled Visits' Listings will display all values contributing to a time point for a subject and will highlight the value that contributed to the summary table where feasible.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used, regardless of where it falls in an interval. For summaries

at a subject level (i.e., the maximum) all values will be included regardless of whether they appear in a corresponding visit-based summary.

3.3.3 Handling of Unscheduled Visits

Visits that fall outside the visit windows defined in the CSP will be classified as Unscheduled Visits. Unscheduled visits will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in an unscheduled visit that occurs between Day 3 and Day 8, then these visits will be numbered UNS 2.1 and 2.2 in the order they occurred.

The values measured at unscheduled visits will not be included in the by-visit summary tables, they will be included in the overall summary tables (for abnormalities, minimum/maximums etc.) and will be presented in the listings.

3.3.4 Multiplicity/Multiple Comparisons

Not applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

Important protocol deviations (IPD) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of IPDs on the safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by IPDs.

This estimation will be performed on a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be signed off by all relevant scientific experts.

The list of all IPDs is provided in the AstraZeneca Non-compliance Handling Plan (NHP). The IPD are classified per the AstraZeneca NHP. Refer to this document for all details about protocol deviations. Relevant IPDs used to exclude subject from the sensitivity analysis 1 (section 4.2.1.5) are reported below:

- All IPDs included in the category 1 - Inclusion Criteria Deviations (Subject who did not meet the below criteria. Those who entered the study even though they did not satisfy the entry criteria. If Screen failure, then this is not a protocol deviation).

- All IPDs included in the category 2 - Exclusion Criteria Deviations (Enrolled, even though subject fulfilled the below criteria. Those who entered the study even though they did not satisfy the entry criteria. If Screen failure, then this is not a protocol deviation).

- All IPDs included in the category 3 - Discontinuation Criteria for study product met but patient not withdrawn from study treatment.

- All IPDs included in the category 5 - Investigational Product (IP) Deviation, with the except of the IPD 5.02 - Subjects who were randomised but did not receive IP which is not considered relevant.

- All IPDs included in the category 6 - Excluded Medications taken.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication, and study drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Not applicable.

4.1.1.2 Presentation

Subject disposition will be summarized based on the Enrolled Set and will include the following information:

- Number of subjects enrolled.

- Number of subjects randomized,

- Number and percentage of subjects who received at least one dose of study drug,

- Number of subjects not randomized.

- Number and percentage of subjects who completed treatment/discontinued treatment (including reasons for IP discontinuation).

- Number and percentage of subjects who completed or discontinued study (including reason for early withdrawal).

Summaries will be by treatment group and overall. Percentages will be calculated using "Subjects randomized" as denominator. A randomization listing will be presented and will include the following information: randomization number, full enrolment number, date of randomization and randomized treatment group.

Subjects affected by the COVID-19 pandemic and subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic will be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in Section 3.2.

4.1.2.2 Presentation

Analysis sets will be summarized based on the Enrolled Set. The number of subjects included and excluded (including reason for exclusion) in each analysis population will be presented by treatment group.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations (IPDs) will be defined in the NHP (refer to Section 3.3.5) and are considered as those deviations from the protocol likely to have an impact on the perceived efficacy or safety of study treatment. The final list of IPDs will be determined before each DBL.

4.1.3.2 Presentation

IPDs will be summarized based on the Randomized set. The number and percentage of subjects meeting each IPD criterion will be summarized by treatment group. Subjects who deviate from a given criterion more than once will be counted once for that criterion. Any subjects with more than one IPD will be counted once in the overall summary.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age is measured in years and calculated as:

$$\text{Age (years)} = (\text{Date of randomization} - \text{date of birth} + 1) / 365.25$$

4.1.4.2 Presentation

Demographics (age, sex, ethnicity, race) will be summarized based on the Full Analysis Set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Body mass index (BMI) is calculated as:

$$\text{BMI } (kg/m^2) = \text{weight } (kg) / \text{height}^2 \ (m)$$

4.1.5.2 Presentation

Baseline characteristics (height, weight, BMI, nicotine use and alcohol use) will be summarized based on the Full Analysis Set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics are defined as the following lipid related parameters measured at baseline:

- LDL-C with reflex to PUC/beta-Quantification equals to:
    - LDL-C derived by Friedewald formula if LDL-C (Friedewald) ≥ 40mg/dL and Triglycerides (TG) < 400mg/dL.
    - LDL-C (PUC/beta-Quantification) if LDL-C (Friedewald) < 40mg/dL or TG ≥ 400mg/dL.
- LDL-C derived by Friedewald formula, without reflex, LDL-C derived by Martin/Hopkins formula and Direct LDL-C.
- HDL-C and Non-HDL-C.
- VLDL-C.
- ApoA1 and ApoB.
- Lipoprotein(a) (Lp(a)).
- Triglycerides (TG).

- Remnant cholesterol

4.1.6.2 Presentation

Disease characteristics will be summarized based on the Full Analysis set. Summaries will be presented by treatment group and according to the principles outlined in Section 3.3.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical/surgical history, and concomitant (called "current") diseases are coded using MedDRA version 24.0 or higher. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded. After imputation of dates, current diseases will be classified as prior (called "past") or current.

A past disease is defined as any disease with a start and end date prior to the first dose date (exclusive). A current disease is defined as any disease with an end date on or after the first dose date. A disease with a completely missing end date will be considered as current.

4.1.7.2 Presentation

Medical/surgical history, and current diseases will be summarized based on the Full Analysis Set. The number and percentage of subjects with relevant medical/surgical history/current diseases will be presented by treatment group and summarized by System Organ Class (SOC) and Preferred Term (PT). Subjects with histories in more than one SOC/PT will be counted only once in that SOC/PT. Tables will be sorted alphabetically by SOC and PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior (called "past") and concomitant (called "current") medications are coded using the WHO-DD. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded.

Past medications are defined as those that stopped and started prior to the first dose date. All medications on or after the first dose date are considered as current, this includes those medications that started prior to date of first dose but continued after.

4.1.8.2 Presentation

Past and current medications will be summarized based on the Full Analysis Set. The number and percentage of subjects will be presented by treatment group and summarized by Anatomical Therapeutic Chemical (ATC) Class and Preferred Term (PT). Subjects with medications in more than one ATC class/PT will be counted only once in that ATC class/PT. Tables will be sorted alphabetically by ATC class and PT.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated for each subject and expressed as a percentage. The percent treatment compliance will be calculated as the number of doses received relative to the expected number of doses.

$$\text{Treatment compliance (\%)} = 100 \times \frac{\text{Number of doses received}}{\text{Expected number of doses}}$$

4.1.9.2 Presentation

Treatment compliance will be summarized based on the Safety Analysis Set and by treatment group, using the principles outlined in Section 3.3 for continuous variables.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, safety, and exploratory endpoints including sensitivity and supportive analyses.

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the effect of different doses of AZD8233 on LDL-C versus placebo.					
Primary	Absolute change from baseline in log-transformed LDL-C in serum	Full analysis set.	The hypothetical estimand strategy will be used for the primary outcomes, therefore all subjects are assumed to have completed treatment without intercurrent events.	Mean difference in change between treatments (LSMD) at week 12	4.2.1
Objective 2: To assess the effect of different doses of AZD8233 on PCSK9 versus placebo.					
Secondary	Absolute change from baseline in log-transformed PCSK9 in plasma.	Full analysis set.	Included in the analysis regardless of	Mean difference in change	4.2.2

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	Percent change from baseline in PCSK9 in plasma.		treatment discontinuation	between treatments (LSMD) at week 12	
Objective 3: To assess the effect of different doses of AZD8233 on LDL-C versus placebo.					
Secondary	Percent change from baseline in levels of LDL-C in serum	Full analysis set.	Included in the analysis regardless of treatment discontinuation	Mean difference in change between treatments (LSMD) at week 12	4.2.3
Objective 4: To assess the effect of AZD8233 on other lipid parameters versus placebo.					
Secondary	Levels of other lipid parameters	Full analysis set.	Included in the analysis regardless of treatment discontinuation	Mean difference in change between treatments (LSMD) at week 12	4.2.4
Objective 5: To evaluate PK of AZD8233.					
Secondary	Population PK parameters	PK analysis set		NA	4.2.5
Objective 6: To evaluate the immunogenicity of AZD8233.					
Secondary	Development of antidrug antibodies (ADA) and ADA titer (if subjects are ADA positive) during treatment and follow-up.	Safety analysis set		NA	4.2.6
Objective 7: To assess the safety and tolerability of AZD8233.					
Safety	Adverse Events	Safety analysis set		NA	4.3.2
	Injection site reactions			NA	4.2.7
	Clinical laboratory examinations.			NA	4.3.3, 4.3.4, 4.3.5
	Vital signs, ECG.			NA	4.3.6, 4.3.7

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 8: To collect and store blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies) and tolerability related to AZD8233 treatment or cardiometabolic diseases.					
Exploratory	Evaluation of changes in biomarkers. Results of potential future exploratory biomarker research may be reported outside this study's CSR.	Full analysis set.		NA	

4.2.1 Primary Endpoint

The primary estimand is the hypothetical estimand, assuming all the participants had continued treatment until Week 12 without experiencing an intercurrent event. The primary analysis will be carried out with likelihood based repeated measures model, which will provide an unbiased treatment effect under the assumption of Missing At Random.

4.2.1.1 Definition

The primary efficacy endpoint is change from baseline in log-transformed LDL-C at the end of Week 12.

LDL-C with reflex to PUC/beta-Quantification will be used as the primary LDL-C variable for evaluation, this equates to:

- LDL-C derived by Friedewald formula if LDL-C (Friedewald) $\geq$ 40mg/dL and TG $<$ 400mg/dL
- LDL-C (PUC/beta-Quantification) if LDL-C (Friedewald) $<$ 40mg/dL or TG $\geq$ 400mg/dL.

LDL-C derived by the Friedewald formula without reflex, LDL-C derived by the Martin/Hopkins formula and direct LDL-C will also be presented as a supplementary analysis.

4.2.1.2 Derivations

LDL-C values will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2.

Change from baseline of the log-transformed variable will be calculated as the visit value in the natural logarithm minus the baseline value in natural logarithm.

Percent change will be derived from the MMRM estimates as:

$$\text{Mean percent change} = 100*(\exp(\text{LSMean}) - 1)$$

4.2.1.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.1.4 Primary Analysis of Primary Endpoint

The analysis and presentation will be based on subjects in the Full Analysis Set.

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

A mixed model with repeated measures will be fitted using the log-transformed LDL-C data. The model will include the log-transformed LDL-C baseline value as a covariate and 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 LDL-C. The model will be fitted with an unstructured covariance structure, and the Kenward-Roger correction applied to obtain the degrees of freedom. The primary model will include data up to and including Week 12 as a response variable.

Estimation of the treatment effect will be calculated for each visit after baseline and presented alongside the corresponding 95% confidence interval. In case of issues when fitting the model to the data, the following hierarchical model fitting procedure will be adopted:

1. The MMRM will be fitted using a spatial power covariance structure; Visit will be expressed as scheduled visit days to accomplish the variance-covariance matrix estimation.

2. The MMRM will be fitted using a compound symmetry covariance structure.

3. An ANCOVA model for Week 12 only will be used.

Comparisons of the change from baseline between the treatment groups will be conducted using the least square mean difference (LSMD) between treatment groups as estimated by

the fitted model. Pair-wise comparisons will be done for each AZD8233 dose [redacted] vs. placebo. In addition, pair-wise comparisons between AZD8233 dose groups [redacted] will also be done for reference. The p-value for each comparison will be presented alongside the LSMD and its 95% CI. In addition, LSMs and 95% CIs will be back-transformed to present as relative (geometric) difference among treatment groups and the relative change will also be presented as the percent change from baseline.

Change from baseline will be summarized by visit and treatment groups using descriptive statistics (arithmetic mean, SD, minimum, median, maximum) and based on the principles defined in Section 3.3.

The plots over the visits will be created by the treatment groups for the following cases:

- Mean (SD) for absolute value over time.
- Geometric LSMean (95% CI) based on MMRM estimates.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

Sensitivity analysis 1 will consist of repeating the MMRM assuming a log-normal distribution including only subjects who have completed the treatment period as per protocol and who have no relevant IPDs. Subjects who have completed the treatment period as per protocol are the subjects who reached week 12 and received all three scheduled doses of IP; subjects who received the wrong dose of IP or wrong treatment will be excluded. Further, relevant IPDs are defined section 3.3.5.

Sensitivity analysis 2 will consist of repeating MMRM assuming a log-normal distribution (without any back-up strategy) using the pattern-mixture model with control-based pattern imputation, if more than 20 % of data is missing this analysis will be considered.

To implement this approach, the MCMC will be used firstly to impute non monotone MAR missing data for subjects who have completed the treatment period as per protocol (reached week 12 and received all three doses of IP). Then the resulting dataset will be used to sequentially impute missing data at each visit using a monotone regression approach. Sequential imputation will be done in two ways:

1. Considering only placebo group for the estimations of missing data for placebo patients and for AZD8233 subjects at visits for which the previous scheduled dose of IP is missing or not as per protocol (wrong dose of IP or a wrong treatment)

2. Considering only the relevant AZD8233 group for the estimations of missing data for AZD8233 subjects at visits for which the previous scheduled dose of IP was taken as scheduled.

The results from each imputation set will be combined using Rubin's formulas (reference 1).

4.2.1.6 Supplementary Analyses of the Primary Endpoint

LDL-C derived by the Friedewald formula without reflex, LDL-C derived by the Martin/Hopkins formula and direct LDL-C will be analysed as described in section 4.2.1.4 above and presented as a supplementary analysis of the primary endpoint.

4.2.1.7 Subgroup Analyses

Not applicable.

4.2.2 Secondary Endpoint- Absolute change from baseline in log-transformed PCSK9 in plasma and percent change from baseline in PCSK9 in plasma

4.2.2.1 Definition

Not applicable.

4.2.2.2 Derivations

PCSK9 measurement will be assigned to analysis visits as described in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2. After replacement of LLOQ, the absolute change and percent change from baseline are calculated for each study visit.

Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. Percent change from baseline is calculated using the raw values as the visit value minus the baseline value divided by the baseline value *100.

4.2.2.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.2.4 Primary Analysis of Secondary Endpoint

The absolute change from baseline in the log-transformed PCSK9 will be fitted using the mixed model for repeated measures as described for the primary endpoint (refer to section 4.2.1.4), such that the model includes the log-transformed baseline value as a covariate, time point (visit number), treatment, and the interaction between time point and treatment as

factors. The least square mean differences between treatment groups will be estimated from the fitted model and presented alongside the corresponding 95% confidence interval. In addition, LSMs and 95% CIs will be back-transformed to present as relative (geometric) difference among treatment groups and the relative change will also be presented as the percent change from baseline.

The summary and corresponding plot of the absolute change from baseline will be generated using the same method described for the primary endpoint (refer to Section 4.2.1.4).

The percent change from baseline in PCSK9 will be analyzed using the same model as described previously without log-transformation. In addition, the summary and plot will be made using the same method.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.2.7 Subgroup Analyses

Not applicable.

4.2.3 Secondary Endpoint- Percent change in levels of LDL-C in serum

4.2.3.1 Definition

Percent change from baseline in LDL-C will be calculated on the raw scale for each subject. Reflex LDL-C will be primarily assessed and the direct LDL-C or other quantification may be considered in sensitivity analyses (refer to Section 4.2.1.1).

4.2.3.2 Derivations

LDL-C values will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2.

LDL-C derived by Friedewald or Martin/Hopkins formula are indirectly calculated and hence may take 0 mg/dL or negative values (reported as ‘Unable to Calculate’ by Central lab) (Sampson et al, 2020). LLOQs will not be defined for these indirectly calculated measurements according to Central lab. These data will be replaced by 1/square root of 2 mg/dL for the analysis and displayed as reported from Central lab in the listings. After replacement of LLOQ, the percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value * 100.

4.2.3.3 Handling of Dropouts and Missing Data

Refer to Sections 4.2.1.3.

4.2.3.4 Analysis of Secondary Endpoint

LDL-C will be analyzed using the statistical model described for the primary endpoint (refer to Section 4.2.1.4).

LDL-C endpoints will be summarized by visit and treatment group using descriptive statistics (arithmetic mean, SD, minimum, median, maximum) using the principles defined in Section 3.3.

The plot of LSMean (95% CI) based on the MMRM estimates will be produced.

Percent change from baseline for direct LDL-C will be analysed similarly.

4.2.4 Secondary Endpoint- Levels of other lipid parameters

4.2.4.1 Definition

The following lipid parameters will be summarized:

- Total cholesterol (TC).
- High-density lipoprotein cholesterol (HDL-C).
- Non-HDL-C.
- Very low density lipoprotein cholesterol (VLDL-C).
- Apolipoproteins (Apo) A1.
- ApoB.
- Lp(a)
- Triglycerides.
- Remnants cholesterol.

4.2.4.2 Derivations

Refer to Section 4.2.2.2.

4.2.4.3 Handling of Dropouts and Missing Data

Refer to Section 4.2.2.3.

4.2.4.4 Analysis of Secondary Endpoint

Other lipid endpoints will be summarized as continuous log-normal variables and based on the Full Analysis Set.

Change from baseline and percent change from baseline will be summarized by visit and treatment group using descriptive statistics (arithmetic mean, SD, minimum, median, maximum) using the principles defined in Section 3.3.

An MMRM assuming a normal distribution on percent change from baseline to week 12 will also be presented for each lipid endpoint.

The following plots by visit will be created by treatment group:

- Mean (SD) for absolute value.
- LSMean (95% CI) for percent change from baseline based on MMRM estimates.

4.2.5 Secondary Endpoint- PK

4.2.5.1 Definition

Not applicable.

4.2.5.2 Derivations

Population PK parameters are not derived and analysed within this SAP. Details on population PK analysis are provided in a separate report prepared by a dedicated pharmacometrics support group at AstraZeneca. Plasma concentrations are evaluated descriptively.

4.2.5.3 Handlings of Dropouts and Missing Data

PK concentrations will be assigned to analysis visits as defined in Section 3.3.2. PK concentrations below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ.

4.2.5.4 Analysis of Secondary Outcome

Plasma concentrations will be summarized by each analysis visit and scheduled time using descriptive statistic, number of non-missing observations, n below LLOQ, arithmetic mean, SD, geometric mean, geometric coefficient of variation (CV%), min, median and max. Plasma concentrations will also be listed for all subjects in the PK analysis set.

4.2.6 Secondary Endpoint- Development of ADA and ADA titer (if subjects are ADA positive) during treatment and follow-up.

4.2.6.1 Definition

Development of anti-drug antibodies (ADA) and ADA titre will be used to evaluate the immunogenicity of AZD8233. Titre evaluations are conducted only on those samples that are confirmed positive for ADA.

Treatment-induced ADA positive is defined as ADA negative at baseline and post-baseline ADA positive.

Treatment-boosted ADA positive is defined as ADA positive at baseline and boosted the pre-existing titre post-baseline (≥ 4-fold increase).

TE-ADA positive is defined as the sum of treatment-induced ADA positive and treatment-boosted ADA positive.

TE-ADA negative is defined as ADA positive but not fulfilling the definition of TE-ADA positive.

ADA persistently positive is defined as either ADA negative at baseline and ADA positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) either ADA positive at last post-baseline assessment.

ADA transiently positive is defined as ADA negative at baseline, having at least one postbaseline ADA positive assessment and not fulfilling the conditions of ADA persistently positive.

4.2.6.2 Derivations

ADA parameters will be assigned to an analysis visit as defined in Section 3.3.2. The median of maximum titres is calculated based on the maximum titre for each ADA positive subject within each treatment group (including both baseline and post-baseline measurements).

Missing ADA results are considered negative for the derivation of the ADA categories. The above categories will be calculated only for subjects in the ADA analysis set.

4.2.6.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2**.**

4.2.6.4 Analysis of Secondary Endpoint

ADA endpoints will be analyzed based on the Safety Analysis Set. The number and percentage of subjects with a positive result will be tabulated for: any time in study, baseline, any time post-baseline, and by visit and treatment group. ADA titre will be summarized descriptively as a continuous variable, only for ADA positive tests, with median, interquartile range, minimum, and maximum, at each visit.

ADA will also be summarized including the following:

- ADA positive at baseline and/or post-baseline (ADA prevalence)
- TE-ADA positive (ADA incidence)
- Treatment-induced ADA positive
- Treatment-boosted ADA positive
- TE-ADA negative
- Both baseline and post-baseline positive
- Only baseline positive
- ADA persistently positive
- ADA transiently positive
- TE-ADA positive with maximum titre > median of maximum titres

All immunogenicity parameters will also be reported in a listing for the full analysis set. Days from previous dose of IP will be calculated as the ADA date minus date of previous dose +1. Days from previous dose of IP for ADA measured during pre-treatment period will be set to missing. Listings of all subjects excluded from the ADA analysis set will also be provided. The listing will be based on all enrolled subjects.

The following figures will be also provided for complete analysis only:

- A spaghetti plot figure with individual plotted ADA-titres over time in subjects with any positive ADA-response, one graph per treatment group (including placebo).

- A boxplot on log-transformed data exploring ADA positive vs ADA negatives impact on PK concentrations, PCSK9 and LDL over time one graph per treatment group (including placebo).

- A figure showing the percentage of subjects with positive ADA results over time.

4.2.7 Other Endpoint – Injection Site Reactions

4.2.7.1 Definition

Injection site reactions (ISRs) are reported using standard AE collection criteria.

4.2.7.2 Derivations

Injection site criteria will be coded using the MedDRA version 24.0 or higher.

4.2.7.3 Handling of Dropouts and Missing Data

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.2.7.4 Analysis of Other Endpoint

All summaries of injection site reactions will be based on the Safety Analysis Set and will be summarized by treatment group. The number and percentage of subjects with an injection site reaction and the number of events will be summarized by High Level Term (HLT) and preferred term.

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.3 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

4.3.1 Exposure

4.3.1.1 Definitions and Derivations

Treatment exposure will be calculated in days as the treatment duration from date of first dose to date of last dose, inclusive.

$$\text{Duration of exposure (days)} = \text{last dose date} - \text{first dose date} + 1$$

4.3.1.2 Presentation

Duration of exposure will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group using the principles outlined in Section 3.3 for continuous variables.

4.3.2 Adverse Events

4.3.2.1 Definitions and Derivations

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

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

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the first dose date.

Adverse events will be coded using the MedDRA version 24.0 or higher.

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.3.2.2 Presentation

All summaries of adverse event data will be based on the Safety Analysis Set and will be presented by treatment group. Summary tables will include TEAEs only whereas listings will include all reported AEs.

A subject-level overview of AEs (the number and percent of subjects and the number of events) will be tabulated by the treatment groups in a single table for:

- Any AE.
- AEs possibly related to study treatment.
- AEs with an outcome of death.
- AEs with outcome of death possibly related to study treatment.
- All serious adverse events (SAE).
- SAEs possibly related to study treatment.

- AEs leading to discontinuation of study treatment.
- AEs leading to discontinuation of study treatment, possibly related to study treatment.
- AEs leading to dose interruption.
- AEs leading to withdrawal from the study.

Separate AE summary tables of the number and percentage of subjects with AEs and the number of events in each of the categories above will be produced by SOC and PT.

Additionally, the following tables will be presented by SOC and PT:

- AEs by the maximum reported intensity.
- AEs by causality assessment.
- Bleeding AEs (Haemorrhages (SMQ) including both "Haemorrhage laboratory terms (SMQ)" & "Haemorrhage terms (excluding laboratory terms) (SMQ)").

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.3.3 Clinical Laboratory, Blood Sample

4.3.3.1 Definitions and Derivations

In the assessments of hematology parameters, clinical chemistry and coagulation, the parameters to be summarized are listed in Appendix 7.2.

Clinical laboratory results will be assigned to analysis visits as described in Section 3.3.2.

Safety clinical laboratory results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined will be replaced with the LLOQ.

After replacements of LLOQ, the change from baseline will be calculated for all post-baseline timepoints as the respective timepoint value minus the baseline value.

Based on the respective reference range indicators, the following flags will be applied to all laboratory assessments; ‘Normal’ (if the value is within the normal reference range), ‘Low’ (if the value is below the normal reference range) or ‘High’ (if the values is above the normal reference range).

eGFR

Subject's eGFR will be calculated from serum creatinine (SCr) concentration, according to the Japanese equation as follows:

$$\text{eGFR} = 194 \times \text{SCr}(\text{mg/dL})^{-1.094} \times \text{Age}^{-0.287} \times \alpha$$

where α is 1 for males and 0.739 for females.

Liver enzyme abnormalities

AST, ALT and TBL will be classified as follows:

AST and ALT:

- <1.5×ULN (or below the LLOQ).
- ≥1.5 to <3×ULN.
- ≥3 to <5×ULN.
- ≥5 to < 8×ULN.
- ≥8×ULN.

TBL:

- <1×ULN (or below the LLOQ).
- ≥1 to <2×ULN.
- ≥2×ULN.

Occurrences of AST or ALT ≥3×ULN together with TBL ≥ 2×ULN are reported as SAE (Potential Hy's Law).

Platelet count

Platelet count will be classified as follows:

- < LLN
- > ULN

- < 50 (10^9/L)
- < 75 (10^9/L)
- < 100 (10^9/L)
- <150 (10^9/L)
- > 30% decrease from baseline
- <150 (10^9/L) and >30% decrease from baseline

Shift to minimum value on-treatment value for platelet count will be classified as follows:

- <50 (10^9/L)
- ≥ 50 and < 75 (10^9/L)
- ≥ 75 and < 100 (10^9/L)
- ≥ 100 and < 150 (10^9/L)
- ≥ 150 (10^9/L)

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.3.3.2 Presentation

Laboratory data will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. The number and proportion of patients with liver enzyme abnormalities will summarized by treatment group and visit including a summary of the maximum recorded post-baseline value. Treatment-emergent platelet count abnormalities will be summarised by treatment group and visit, including the shift to minimum value and key subject information will be presented.

Shift tables will be presented for select laboratory parameters (clinical chemistry and hematology). An additional shift table will be presented for hematology results, displaying the percent change from baseline (i.e. the relative change). Spaghetti plots over time will be produced for platelet count, ALT, AST, and TBL, with the corresponding reference range overlaid on top. The following additional plots will be presented for platelet count only:

- Empirical cumulative distribution function curves for the absolute change from baseline to minimum value.

- A spaghetti plot of the relative change from baseline in subjects with platelet count <150 (10^9/L) or > 30% decrease from baseline.

- A spaghetti plot of the absolute change from baseline in subjects with platelet count <150 (10^9/L) or > 30% decrease from baseline.

4.3.4 Clinical Laboratory, Urinalysis

4.3.4.1 Definitions and Derivations

In the assessments of urinalysis, and urinalysis (positive dipstick), the parameters to be summarized are listed in Appendix 7.2.

Clinical laboratory results will be assigned to analysis visits as described in Section 3.3.2.

Safety clinical laboratory results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined will be replaced with the LLOQ.

After replacements of LLOQ, the change from baseline will be calculated for all post-baseline timepoints as the respective timepoint value minus the baseline value.

4.3.4.2 Presentation

Laboratory data will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1.

4.3.5 Other Laboratory Evaluations

4.3.5.1 Definitions and Derivations

The parameters to be summarized are listed in Appendix 7.2.

Clinical laboratory results will be assigned to analysis visits as described in Section 3.3.2.

Safety clinical laboratory results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined will be replaced with the LLOQ.

After replacements of LLOQ, the change from baseline will be calculated for all post-baseline timepoints as the respective timepoint value minus the baseline value.

4.3.5.2 Presentation

Laboratory data will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1.

4.3.6 Vital Signs

4.3.6.1 Definitions and Derivations

The vital sign measurements to be summarized are:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (oral) (ºC).

Vital sign measurements will be assigned to analysis visits as described in Section 3.3.2.

Change from baseline for vital sign measurements (where applicable) will be calculated for all post-baseline visits as the respective visit value minus the baseline value.

Based on the respective reference range indicators, the following flags will be applied to all vital sign measurements; 'Normal' (if the value is within the normal reference range), 'Low' (if the value is below the normal reference range) or 'High' (if the values is above the normal reference range).

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 140 mmHg
Diastolic blood pressure	50 -90 mmHg
Heart rate	50 - 100 bpm
Temperature	<=37ºC

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.3.6.2 Presentation

Vital signs will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1.

4.3.7 Electrocardiogram

4.3.7.1 Definitions and Derivations

The following parameters or time intervals will be recorded for each ECG: RR, PR interval, QRS duration, QT interval, QTcF interval, and ECG mean heart rate (HR).

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

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

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

The Investigator will judge whether the overall interpretation is ‘normal’ or ‘abnormal’.

ECG results will be assigned to analysis visits as described in Section 3.3.2.

Change from baseline for ECG parameters (where applicable) will be calculated for all post-baseline visits as the respective visit value minus the baseline value.

Outlier categories with respect to QTcF will be defined as follows:

- 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

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.3.7.2 Presentation

ECG parameters will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. Outliers with respect to QTcF will be tabulated using the categories defined in Section 4.3.7.1.

4.3.8 Other Safety Assessments

Not applicable.

5 INTERIM ANALYSIS

After all randomized patients have completed (or discontinued from) the treatment period, an interim analysis will be performed for all endpoints except for PK variables. Efficacy outputs will display visits up to and including the Week 12 time point, all visits will be displayed for the safety outputs.

A limited number of Sponsor personnel will be unblinded at the time of interim analysis. Investigators, participants and site-staff will not be informed of assigned treatment or the results of the interim analysis in order to maintain study integrity. A Confidentiality List/Communication Plan will be prepared documenting unblinded personnel.

This interim analysis will be documented as an interim clinical study report.

6 REFERENCES

1. Rubin, D. B. (1987) Multiple Imputation for Nonresponse in Surveys. New York: Wiley

2. Sampson, Maureen, Clarence Ling, Qian Sun, Roa Harb, Mohmed Ashmaig, Russell Warnick, Amar Sethi et al. "A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia." *JAMA cardiology* 5, no. 5 (2020): 540-548.

7 APPENDIX

7.1 Schedule of Activities

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.2 Clinical Laboratory Assessments

Hematology

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

Clinical Chemistry

Sodium	ALP
Potassium	ALT
Blood urea nitrogen (BUN)	AST
Creatinine	Gamma glutamyl transpeptidase (GGT)
Calcium	Total bilirubin
Phosphate	Direct bilirubin
Creatine kinase (CK)	Glutamate dehydrogenase (GLDH)
Bicarbonate	Lactate dehydrogenase (LDH)
Serum β-human chorionic gonadotropin (β-hCG)(women only)	Uric acid
Luteinizing hormone (LH) (women only)	FSH (women only)
Indirect bilirubin	

Coagulation

aPTT	Prothrombin time
International normalized ratio (INR)	

Urinalysis

Urine human chorionic gonadotropin (hCG) (Women only)

Urinalysis dipstick test

Urinalysis (positive dipstick)

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

Urine renal safety biomarkers

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

Other laboratory assessments

Complement activation panel (Bb, C5a)	High-sensitive C-reactive protein (hs-CRP)
	HbA1c

SIGNATURE PAGE

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

Document Name: d7990c00006-sap-part-b-ed-1		
Document Title:	Statistical Analysis Plan Part B Edition 1	
Document ID:	[redacted]	
Version Label:	[redacted]	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
[redacted]	[redacted]	Content Approval
[redacted]	[redacted]	Author Approval
[redacted]	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

STATISTICAL ANALYSIS PLAN	
Study Code	D7990C00006 (Part C)
Edition Number	2.0
Date	3-Nov-2022

Statistical Analysis Plan for D7990C00006, A Phase 1 and 2 study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of AZD8233 following a multiple subcutaneous dose administration in Japanese participants with dyslipidemia (HAYATE) – Part C

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BLQ	Below limits of quantification
BMI	Body mass index
CI	Confidence interval
CM	Composite measure
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DBL	Database lock
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	Early discontinuation visit
eGFR	Estimated glomerular filtration rate
gSD	Geometric standard deviation
HLT	High level term
HR	Heart Rate
ICF	Informed consent form.
IMP	Investigational medicinal product
IPD	Important protocol deviation
ISR	Injection site reaction
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
PCSK9	Proprotein convertase subtilisin/kexin type-9
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QTcF	Corrected QT Interval using Fridericia's Formula
SAE	Serious adverse event

Abbreviation or Specialized Term	Definition
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
UNS	Unscheduled
ULN	Upper limit of normal
WHO-DD	World Health Organisation drug dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	02-May-2022	Initial approved SAP	N/A	N/A
Data presentation	12-Sep-2022	Added additional analyses for hematology results	Y	To give more detailed summary of hematology results
Data presentation	12-Sep-2022	Added additional analyses for platelet counts	Y	To give more detailed summary of platelet counts
Data presentation	12-Sep-2022	Added plots of mean (SD) over time for pharmacodynamic endpoints	Y	To give a graphical presentation of the results.
Data presentation	12-Sep-2022	Added additional analyses for Bleeding AEs	Y	To give more detailed summary of AEs
Data presentation	03-Nov-2022	Added plots and summary of geometric mean (gSD) for LDL-C parameters	Y	To give a graphical presentation.

1 INTRODUCTION

AstraZeneca is developing AZD8233, [redacted] for the reduction of circulating levels of LDLs, a major risk factor of cardiovascular disease. Part C is a randomized, single-blind, placebo-controlled, dose-ranging Phase I study in Japanese participants with dyslipidaemia. The primary objective is to investigate the safety and tolerability of AZD8233 following subcutaneous administration of multiple doses, which is the dosing regimen to be used in a Phase III study. The study will also investigate the pharmacokinetics and pharmacodynamics of AZD8233.

The purpose of this document is to give details for the statistical analysis of study D7990C00006 – Part C, supporting the clinical study report (CSR). Additional statistical analysis plans (SAP) have been created detailing the analysis of Part A and Part B of the study.

The reader is referred to the clinical study protocol (CSP) and the electronic case report form (eCRF) for details of study conduct and data collection. This SAP is based on Version 4.0 of the CSP dated 2 November 2021 and Version 2.0 of the eCRFs dated 18 January 2021.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

A single analysis of all data from Part C will be conducted after database lock (DBL) and all results will be included in the CSR. DBL will occur after completion of all follow up visits, approximately 16 weeks after last administration of study intervention to the last ongoing subject.

3.2 Analysis Populations

3.2.1 Enrolled Set

All participants who signed the informed consent form (ICF). The Enrolled Set will be used to summarize subject disposition.

3.2.2 Randomized Set

All participants who were randomized. Participants will be analyzed according to the treatment to which they were randomized. Important protocol deviations (IPDs) will be summarized based on the Randomized Set.

3.2.3 Safety Analysis Set

All participants randomly assigned to study treatment who took at least one dose of AZD8233 or placebo and for whom any post-dose data are available. Participants will be analyzed according to the treatment which they actually received. If a participant received study intervention from the wrong kit for only part of the treatment duration and then switched to another, the associated treatment group for that participant would be the treatment group that participant was randomized to. The Safety Analysis Set will be used as the analysis set for all summaries of baseline demographics and disease characteristics, safety evaluations unless stated otherwise and for the analysis of the immunogenicity data.

3.2.4 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will consist of all subjects in the Safety Analysis Set who received AZD8233 and who have evaluable PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

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

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

The PK Analysis Set will be used to summarize the PK data.

3.2.5 Pharmacodynamic Analysis Set

The Pharmacodynamic (PD) Analysis Set will consist of all subjects who received AZD8233 or placebo, who have at least one baseline and one post-baseline measurement for either the level of PCSK9 in plasma or the level of LDL-C in plasma, and who have no important protocol deviations thought to impact on the analysis of the data.

The available PD data for any subjects excluded from the PD analysis set will be listed only, together with a flag indicating subjects excluded from the PD analysis set. Only subjects or samples in the PD analysis set will be included in the descriptive summary tables.

The PD analysis set will be used to analyse the lipid parameters (PCSK9, LDL-C and other lipids).

3.3 General Considerations

There is no formal statistical hypothesis testing in this study. Safety and tolerability after multiple dosing of AZD8233 [redacted] (or placebo) will be descriptively evaluated. The following principles will be followed throughout the study:

- Continuous variables will be summarized by the number of non-missing observations, mean, standard deviation (SD), median, first and third quartiles, and the minimum and maximum as appropriate.

- Log-transformed continuous variables will be summarized in a similar manner where applicable. In addition, the relative change from baseline will be calculated by back-transforming the change from baseline of the logarithmic variable.

- Categorical variables will be summarized as counts (n) and percentages (%). Unless otherwise stated, percentages will be calculated using the relevant analysis set population total as the denominator. Percentages will not be presented for zero counts.

- Mean and medians will be rounded to one additional decimal place relative to the original data, the SD will be rounded to two additional decimal places, and the maximum, minimum and quartiles will be displayed with the same accuracy as the original data. 95% confidence intervals (CIs) will be presented to one more decimal place than the raw data. Percentages (proportion) will be rounded to one decimal place.

- Summaries will be provided by study visit where appropriate. Where summaries are over time, study day will be calculated in relation to the date of first dose of study treatment.

- Corresponding listings will be provided for all tabulated results unless stated otherwise. Any additional listings that are required will be described in the appropriate sections of the SAP.

- SAS® version 9.3 or higher will be used for all data analyses.

3.3.1 General Study Level Definitions

3.3.1.1 Definition of Baseline

Unless otherwise specified, ‘baseline’ refers to the last measurement obtained before the first dose of study intervention. For all lipid parameters (PCSK9, LDL-C and other lipid parameters listed in Section 4.2.8.1) the geometric mean of the two measures taken pre-dose at Visit 2 (Day -1 and pre-dose Day 1) will be considered as baseline.

3.3.1.2 Handling of Missing Data

In general, missing data will not be imputed and will be treated as missing unless specifically described in an analysis section. The following considerations are made for missing safety data, adverse event (AE) dates, and concomitant medication/diseases dates:

- Safety assessment values of the form '<x' or '>x' (i.e., above or below the limits of quantifications) will be imputed as 'x' in the calculation of summary statistics but displayed as '<x' or '>x' in the listings.

- Adverse events that have missing causality after data querying will be assumed to be related to study drug.

- For missing AE/concomitant medication/disease start dates, the following will be applied:

    - Missing day: Impute 1st of the month unless the month is the same as that of the first dose of study drug in which case impute first dose date.

    - Missing day and month: Impute 1st January unless the year is the same as that of the first dose date in which case impute first dose date.

    - Missing year: Impute the year of dosing.

    - Completely missing: Impute first dose date unless the end date suggests it could have started prior to this in which case impute 1st January of the same year as the end date.

- For missing AE/concomitant medication/disease end dates, the following will be applied:

    - Missing day: Impute the last day of the month unless the month is the same as that of the last dose of the study drug in which case impute the date of last dose.

    - Missing day and month: Impute 31st December unless the year is the same as that of the last dose of study drug in which case impute date of last dose.

    - Missing year: Impute the year of dosing.

    - Completely missing: Do not impute a date i.e., assume that AE/concomitant medication/disease is ongoing.

For all missing start/end dates, flags will be retained in the analysis datasets indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated. When imputing missing/partial dates, programmatic checks will be done to ensure a future date has not been imputed.

If a subject is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last known date to be alive + 1 from the database and the death date using the available information provided:

- Missing day only: Use the 1st of the month.
- Missing day and month: Use 1st January.
- Missing year: Impute the year of dosing.

3.3.1.3 Study Periods

For listings of adverse events, lipid levels, laboratory values, vital signs and electrocardiogram (ECG), values will be allocated to a study period. The allocation to the study periods will be performed after any imputation of missing dates (for AEs only) as described in Section 3.3.1.2. The study periods are defined as follows:

- Pre-treatment: Up to 28 days prior to administration of study drug (Day <1).
- Treatment Period: From Day 1 to date of last dose + 2 days (from visit 2 up to visit 9).
- Follow-up Period: From day of last dose + 3 days onwards (visit 10 to visit 17).

3.3.2 Visit Window

Study visits windows are defined in the table below.

	Screening	**Treatment Period**							**Follow-up Period**	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**

Analysis Visit Windows

Analysis visit windows will be defined for the lipid parameters, ECG, anti-AZD8233 antibodies, laboratory results and vital signs which summarize values by visit. The analysis visit windows will be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the window will be based on the actual date and not the intended date of visit.

Analysis visit windows will be constructed such that the upper limit of the window interval falls halfway between the two scheduled visits, where the number of days between visits is odd, the additional day will be applied to the lower interval of the later date.

Table 1: Analysis visit windows for lipid parameters

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 11
Visit 4 (Day 15)	Day 15	Day 12 – Day 18
Visit 5 (Day 22)	Day 22	Day 19 – Day 25
Visit 6 (Day 29)	Day 29	Day 26 – Day 32
Visit 7 (Day 36)	Day 36	Day 33 - Day 39
Visit 8 (Day 44)	Day 44	Day 40 – Day 50
Visit 9 (Day 57 to 59)	Day 57 to Day 59	Day 51 – Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16)	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment.

Table 2: Analysis visit window for ECG and vital signs

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 18
Visit 6 (Day 29)	Day 29	Day 19 – Day 42
Visit 9 (Day 57 to 59)	Day 57 to Day 59	Day 43 – Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16)	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.
[b] Day 1 is defined as date of first dose of study treatment.

Table 3: Analysis visit window for laboratory results and anti-AZD8233 antibodies

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3) [c, e]	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 18
Visit 6 (Day 29) [e]	Day 29	Day 19 – Day 42
Visit 9 (Day 57 to 59) [c, e]	Day 57 to Day 59	Day 43 – Day 63
Follow-up period [d]		
Visit 10 (FUP Week 2) [e]	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 98
Visit 13 (FUP Week 8)	Day 113	Day 99 – Day 126
Visit 15 (FUP Week 12)	Day 141	Day 127 – Day 154
Visit 17 (FUP Week 16) [e]	Day 169	Day 155 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.

[b] Day 1 is defined as date of first dose of study treatment.

[c] Complement activation panels are only collected at these time points.

[d] Renal safety biomarkers and dipstick urinalysis for hematuria are not collected during follow-up period.

[e] Anti-AZD8233 antibodies are collected only at these time points.

Table 4: Analysis visit windows for platelet counts

Analysis Visits	Scheduled visit day	Analysis visit window (days)
Baseline [a]	Day -28 to Day 1	≤ Day 1
Treatment period		
Visit 2 (Days 1 to 3)	Days 1 to 3	Day 1[b] – Day 3
Visit 3 (Day 8)	Day 8	Day 4 – Day 14
Visit 5 (Day 22)	Day 22	Day 15 – Day 25
Visit 6 (Day 29)	Day 29	Day 26 – Day 36
Visit 8 (Day 44)	Day 44	Day 37 – Day 49
Visit 9 (Day 56)	Day 56	Day 50 – Day 63
Follow-up period		
Visit 10 (FUP Week 2)	Day 71	Day 64 – Day 77
Visit 11 (FUP Week 4)	Day 85	Day 78 – Day 91
Visit 12 (FUP Week 6)	Day 99	Day 92 – Day 105
Visit 13 (FUP Week 8)	Day 113	Day 106 – Day 119
Visit 14 (FUP Week 10)	Day 127	Day 120 – Day 133
Visit 15 (FUP Week 12)	Day 141	Day 134 – Day 147
Visit 16 (FUP Week 14)	Day 155	Day 148 – Day 161
Visit 17 (FUP Week 16)	Day 169	Day 162 onwards.

[a] Baseline is defined as the last measurement prior to first dose of study treatment. Pre-dose values on Day 1 qualify as baseline measurements.
[b] Day 1 is defined as date of first dose of study treatment.

An early discontinuation visit (EDV) may take place at any point during the study up to Visit 9 (when the last dose of study treatment is to be administered). In this instance, follow-up visits (Week 2, Week 4 etc.) will begin at date of last administered treatment prior to study discontinuation. Analysis visit windows will be applied to follow-up visits in line with the examples above.

If there is more than one value per subject within an analysis visit window then the closest value to the scheduled visit date will be summarized, or the earlier value if the values are equidistant from the nominal visit date. Listings will display all values contributing to a time point for a subject and will highlight the value that contributed to the summary table where feasible.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used, regardless of where it falls in an interval. For summaries at a subject level (i.e., the maximum) all values will be included regardless of whether they appear in a corresponding visit-based summary.

3.3.3 Handling of Unscheduled Visits

Visits that fall outside the visit windows defined in the CSP will be classified as Unscheduled Visits. Unscheduled visits will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in an unscheduled visit that occurs between Day 3 and Day 8, then these visits will be numbered UNS 2.1 and 2.2 in the order they occurred. The values measured at unscheduled visits will not be included in the by-visit summary tables, they will be included in the overall summary tables (for abnormalities, minimum/maximums etc.) and will be presented in the listings.

3.3.4 Multiplicity/Multiple Comparisons

Not applicable.

3.3.5 Handling of Protocol Deviations in Study Analysis

Important protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of important protocol deviations on the safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by important protocol deviations.

This estimation will be performed on a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be agreed up on by all relevant scientific experts.

During the study, a list of important protocol deviations (IPD) will be developed, which will include inclusion/exclusion/discontinuation criteria deviations, investigational product deviations and excluded medication taken. These will be taken into consideration when interpreting the data. Subjects with an IPD may be excluded from the analysis of the PK and/or PD data.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical and surgical history, prior and concomitant medication and study drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Not applicable.

4.1.1.2 Presentation

Subject disposition will be summarized based on the Enrolled Set and will include the following information: the number of subjects enrolled, randomized and who received at least one dose of study drug, the number and percentage of subjects who completed treatment/discontinued treatment (including reasons for investigational medicinal product (IMP) discontinuation), and the number and percentage of subjects who completed or discontinued study (including reason for early withdrawal). Summaries will be by treatment group and overall.

A randomization listing will be presented and will include the following information: randomization number, full enrolment number, date of randomization and randomized treatment group.

Subjects affected by the COVID-19 pandemic and subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic will be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in Section 3.2.

4.1.2.2 Presentation

Analysis sets will be summarized based on the Randomized Set. The number of subjects included and excluded (including reason for exclusion) in each analysis population will be presented by treatment group.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations will be defined in the Non-compliance Handling Plan and are considered as those deviations from the protocol likely to have an impact on the perceived efficacy or safety of study treatment. The final list of IPDs will be determined before DBL.

4.1.3.2 Presentation

IPDs will be summarized based on the Randomized Set. The number and percentage of subjects meeting each IPD criterion will be summarized by treatment group. Subjects who deviate from a given criterion more than once will be counted once for that criterion. Any subjects with more than one IPD will be counted once in the overall summary.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics include age, sex, race and ethnicity. Age is measured in years and calculated as:

$$\text{Age (years)} = (\text{Date of randomization} - \text{date of birth} + 1) / 365.25$$

4.1.4.2 Presentation

Demographics will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group and overall according to the principles outlined in Section 3.3.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include height (m), weight (kg), body mass index (BMI) (kg/m^2), nicotine use and alcohol use. Body mass index (BMI) is calculated as:

$$\text{BMI } (kg/m^2) = \text{weight (kg)} / \text{height}^2 \text{ (m)}$$

4.1.5.2 Presentation

Baseline characteristics will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group and overall according to the principles outlined in Section 3.3.

4.1.6 Disease Characteristics

4.1.6.1 Definition and Derivations

Disease characteristics are defined as the following lipid related parameters measured at baseline:

- Direct LDL-C.
- LDL-C with reflex to PUC/beta-Quantification equals to:
  - LDL-C derived by Friedewald formula if LDL-C (Friedewald) ≥ 40mg/dL and Triglycerides (TG) < 400mg/dL.
  - LDL-C (PUC/beta-Quantification) if LDL-C (Friedewald) < 40mg/dL or TG ≥ 400mg/dL.
- LDL-C derived by the Friedewald formula.

- LDL-C derived by the Martin/Hopkins formula.
- Total cholesterol
- HDL-C and Non-HDL-C.
- VLDL-C.
- ApoA1 and ApoB.
- Lp(a).
- Triglycerides.

4.1.6.2 Presentation

Disease characteristics will be summarized based on the Safety Analysis set. Summaries will be presented by treatment group and overall according to the principles outlined in Section 3.3.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical/surgical history, and concomitant (called "current") diseases are coded using the Medical Dictionary for Regulatory Activities (MedDRA) [using the latest MedDRA version]. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded.

A current disease is defined as any disease with an end date on or after the first dose date. A disease with a completely missing end date will be considered as current.

4.1.7.2 Presentation

Medical/surgical history and current diseases will be summarized based on the Safety Analysis Set. The number and percentage of subjects with relevant medical/surgical history and current diseases will be presented by treatment group and overall, and summarized by System Organ Class (SOC) and Preferred Term (PT). Subjects with histories in more than one SOC/PT will be counted only once in that SOC/PT. Tables will be sorted alphabetically by SOC and PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior and concomitant medications are coded using the WHO-DD. The imputation method described in Section 3.3.1.2 will be used in the instance that partial or missing dates are recorded.

Prior medications are defined as those that stopped and started prior to the first dose date. All medications on or after the first dose date are considered as concomitant, this includes those medications that started prior to date of first dose but continued after.

4.1.8.2 Presentation

Prior and concomitant medications will be summarized based on the Safety Analysis Set. The number and percentage of subjects will be presented by treatment group and overall, and summarized by Anatomical Therapeutic Chemical (ATC) Class and Preferred Term. Subjects with medications in more than one ATC class/PT will be counted only once in that ATC class/PT. Tables will be sorted alphabetically by ATC class and PT.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated for each subject and expressed as a percentage. The percent treatment compliance will be calculated as the number of doses received relative to the expected number of doses.

$$\text{Treatment compliance (\%)} = 100 \times \frac{\textbf{Number of doses received}}{\textbf{Expected number of doses}}$$

4.1.9.2 Presentation

Treatment compliance will be summarized based on the Safety Analysis Set and by treatment group and overall, using the principles outlined in Section 3.3 for continuous variables.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the safety and tolerability of AZD8233 following subcutaneous (SC) administration of multiple doses.					
Primary	Adverse Events.	Safety analysis set.	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.1
	Injection site reactions.				4.2.3
	Clinical laboratory examinations.				4.2.4
	Vital signs, ECG and cardiac telemetry.				4.2.2
Objective 2: To characterize the PK of AZD8233 following SC administration of multiple doses.					
Secondary	Plasma and urine parameters.	PK analysis Set	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.5

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 3: To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.					
Secondary	Change from baseline in log-transformed PCSK9 in plasma. Percent change from baseline in PCSK9 in plasma	PD analysis set.	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.6
Objective 4: To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.					
Secondary	Percent change from baseline in levels of LDL-C in serum.	PD analysis set.	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.7
Objective 5: To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.					
Secondary	Levels of other lipid parameters	PD analysis set	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.8
Objective 6: To evaluate immunogenicity of AZD8233					
Exploratory	Anti-drug antibodies (ADA) and ADA titre	Safety analysis set	Included in the summaries regardless of treatment discontinuation	Descriptive statistics	4.2.9

4.2.1 Primary Endpoint – Adverse Events

4.2.1.1 Definition

An adverse event is the development of any untoward medical occurrence in a subject 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 (e.g. 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 (SAE) and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the first dose date.

4.2.1.2 Derivations

Adverse events will be coded using the latest MedDRA version.

4.2.1.3 Handling of Dropouts and Missing Data

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.2.1.4 Primary Analysis of Primary Endpoint

All summaries of adverse event data will be based on the Safety Analysis Set and will be presented by treatment group. Summary tables will include TEAEs only whereas listings will include all reported AEs.

A subject-level overview of AEs (the number and percent of subjects and the number of events) will be tabulated for:

- All AEs.
- AEs possibly related to study treatment.
- AEs with an outcome of death.
- AEs with outcome of death possibly related to study treatment.
- All serious adverse events.
- SAEs possibly related to study treatment.
- AEs leading to discontinuation of study treatment.
- AEs leading to discontinuation of study treatment, possibly related to study treatment.
- AEs leading to dose interruption and reduction (separately).
- AEs leading to withdrawal from the study.

Separate AE summary tables of the number and percentage of subjects with AEs and the number of events in each of the categories above will be produced by SOC and PT, sorted by international order for SOC and alphabetically by PT.

Additionally, the following tables will be presented by SOC and PT:

- AEs by the maximum reported intensity.
- AEs by causality assessment.
- Bleeding AEs (both laboratory and non-laboratory terms).

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.2.2 Primary Endpoint – Injection Site Reactions

4.2.2.1 Definition

Injection site reactions (ISRs) are reported using standard AE collection criteria.

4.2.2.2 Derivations

Injection site criteria will be coded using the latest version of MedDRA.

4.2.2.3 Handling of Dropouts and Missing Data

Imputation of partial dates and handling of missing data will be conducted as defined in Section 3.3.1.2.

4.2.2.4 Primary Analysis of Primary Endpoint

All summaries of injection site reactions will be based on the Safety Analysis Set and will be summarized by treatment group. The number and percentage of subjects with an injection site reaction and the number of events will be summarized by High Level Term (HLT) and preferred term, sorted by HLT and alphabetically by PT.

Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

4.2.3 Primary Endpoint – Clinical Laboratory Assessments

4.2.3.1 Definition

Clinical laboratory assessments consist of hematology parameters, clinical chemistry, coagulation, urine renal safety biomarkers (called PFC Index) and composite measure (CM), and other laboratory assessments. The parameters to be summarized are listed in Appendix 7.2.

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

4.2.3.2 Derivations

Clinical laboratory results will be assigned to analysis visits as described in Section 3.3.2.

Except for lipids (section 4.2.6.2, 4.2.7.2 and 4.2.8.2), safety clinical laboratory results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined will be replaced with the LLOQ.

After replacements of LLOQ, the change from baseline will be calculated for all post-baseline timepoints as the respective timepoint value minus the baseline value. The percent change from baseline will be calculated for hematology parameters, for all post-baseline timepoints, as the change from baseline at the respective timepoint divided by the baseline value and multiplied by 100.

Based on the respective reference range indicators, the following flags will be applied to all laboratory assessments; 'Normal' (if the value is within the normal reference range), 'Low' (if the value is below the normal reference range) or 'High' (if the values is above the normal reference range).

eGFR

Subject's eGFR will be calculated from serum creatinine (SCr) concentration, according to the Japanese equation as follows:

$$\mathrm{eGFR} = 194 \times \mathrm{SCr(mg/dL)}^{-1.094} \times \mathrm{Age}^{-0.287} \times \alpha$$

where α is 1 for males and 0.739 for females.

Composite measure

The CM and the ratio between treatment and placebo will be calculated as follows.

1. For each subject, calculate the (uCr)-normalised fold-change from baseline for each biomarker in the PFC index. The (uCr)-normalised concentration at a given timepoint is calculated as the concentration of the biomarker at that timepoint, divided by the concentration of urinary creatinine (uCr) at the same timepoint. The fold change from baseline is then calculated as the uCr-normalised concentration at a given timepoint, divided by the uCr-normalised concentration at baseline. Define the fold-change as FC_{ij} for subject i and biomarker j, where j = 1, 2,…,6.

2. For each subject i, calculate CM:

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

3. Calculate the geometric mean of CM for cohort k (k = Treatment, Placebo):

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

4. Calculate the ratio of the geometric means (GM_{ratio}) for the two cohorts:

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

Liver enzyme abnormalities

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (TBL) will be categorised as follows:

AST and ALT:

- <3 × upper limit of normal (ULN) (or below the LLOQ).
- ≥3 to <5 × ULN.
- ≥5 to < 8 × ULN.
- ≥8 × ULN.

TBL:

- <1 × ULN (or below the LLOQ).
- ≥1 to <2 × ULN.
- ≥2 × ULN.

Occurrences of AST or ALT ≥3 × ULN together with TBL ≥ 2 × ULN are reported as SAE (Potential Hy's Law).

Platelet count

Platelet count will be classified as follows:

- < LLN
- >ULN
- < 50 (10^9/L)

- < 75 (10^9/L)
- < 100 (10^9/L)
- <150 (10^9/L)
- >30% decrease from baseline
- <150 (10^9/L) and >30% decrease from baseline.

Shift to minimum value on-treatment value for platelet count will be classified as follows:

- <50 (10^9/L)
- ≥ 50 and < 75 (10^9/L)
- ≥ 75 and < 100 (10^9/L)
- ≥ 100 and < 150 (10^9/L)
- ≥ 150 (10^9/L)

4.2.3.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.3.4 Primary Analysis of Primary Endpoint

Laboratory data will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. An additional table will be presented for hematology results, displaying the percent change from baseline (i.e. the relative change), presented by treatment group and visit. The number and proportion of patients with liver enzyme abnormalities will summarized by treatment group and visit including a summary of the maximum recorded post-baseline value. Treatment-emergent platelet count abnormalities will be summarised by treatment group and visit, including the shift to minimum value and key subject information will be presented.

The composite measure of the PFC index and corresponding ratio of AZD8233 to placebo will be presented by treatment group and visit. Box plots over time will be produced by treatment group for the composite measure and for the fold-change of the six individual biomarkers. A spaghetti plot over time of the fold-change of the six individual biomarkers will also be produced for each subject.

Shift tables will be presented for select laboratory parameters (clinical chemistry and hematology). Spaghetti plots over time will be produced for ALT, AST, TBL and gamma GPT, with the corresponding reference range overlaid on top. The following plots will be presented for platelet count only:

- Empirical cumulative distribution function curves for the absolute change from baseline to minimum value.

- A spaghetti plot of the relative change from baseline in subjects with platelet count <150 (10^9/L) or > 30% decrease from baseline.
- A spaghetti plot of the absolute change from baseline in subjects with platelet count <150 (10^9/L) or > 30% decrease from baseline.

Clinical laboratory data will be reported in standard international units.

4.2.4 Primary Endpoint – Vital Signs, ECG and Cardiac Telemetry

4.2.4.1 Definition

Vital Signs

The vital sign measurements to be summarized are:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (oral) (ºC).

ECG

The following parameters or time intervals will be recorded for each ECG: RR, PR interval, QRS duration, QT interval, QTcF interval, and ECG mean heart rate (HR). The Investigator will judge whether the overall interpretation is ‘normal’ or ‘abnormal’.

Cardiac Telemetry

Cardiac telemetry results will be reviewed by the Investigator and clinically important results are stored.

4.2.4.2 Derivations

Vital sign measurements (including weight, height and BMI), ECG and cardiac telemetry results will be assigned to analysis visits as described in Section 3.3.2.

Change from baseline for vital sign measurements and ECG parameters (where applicable) will be calculated for all post-baseline visits as the respective visit value minus the baseline value.

Height is measured once at baseline and this measure is used to calculate BMI at all proceeding visits.

Vital Signs

Based on the respective reference range indicators, the following flags will be applied to all vital sign measurements; ‘Normal’ (if the value is within the normal reference range), ‘Low’

(if the value is below the normal reference range) or 'High' (if the values is above the normal reference range).

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 140 mmHg
Diastolic blood pressure	50 -90 mmHg
Heart rate	50 - 100 bpm
Temperature	<=37ºC

ECG

Outlier categories with respect to QTcF will be defined as follows:

- 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

4.2.4.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.4.4 Primary Analysis of Primary Endpoint

Vital Signs

Vital signs will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1.

Weight, height and BMI will be listed only.

ECG

ECG parameters will be summarized based on the Safety Analysis Set. Summaries of the individual values and change from baseline will be presented by treatment group and visit according to the principles outlined in section 3.3.1. Outliers with respect to QTcF will be tabulated using the categories defined in Section 4.2.4.2.

Cardiac Telemetry

Results for 12-lead ECG real-time cardiac telemetry will be listed based on the Safety Analysis Set including the overall assessment, specifics of abnormalities and the start and stop date/time.

4.2.5 Secondary Endpoint - Pharmacokinetics

4.2.5.1 Definition

Where possible, the following PK parameters will be determined.

AUC_{inf}	Area under the plasma concentration-time curve from time zero extrapolated to infinity. AUC is estimated by AUC(0-last) + Clast/λz where Clast is the last observed quantifiable concentration.
$AUC_{(0\text{-}last)}$	Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration.
$AUC_{(0\text{-}24)}$	Area under the concentration-time curve from time zero to 24 hours post-dose.
$AUC_{(0\text{-}48)}$	Area under the concentration-time curve from time zero to 48 hours post-dose.
AUCτ	Area under the plasma concentration-time curve during the dosing interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration.
C_{max}	Maximum observed plasma concentration.
C_{trough}	Observed trough plasma concentration
λz	Terminal rate constant, estimated by log-linear least-squares regression of the terminal part of the concentration-time curve.
MRT	Mean residence time of the unchanged drug in the systemic circulation.
RAC (AUC)	Accumulation ratio based on AUC
RAC (AUC) (0-48)	Accumulation ratio based on AUC from time zero to 24 hours post dose
RAC (AUC) (0-168)	Accumulation ratio based on AUC from time zero to 168 hours post dose
RAC (C_{max})	Accumulation ratio based on C_{max}
t1/2z	Half-life associated with the terminal slope (λz) of a semi-logarithmic concentration-time curve
t_{lag}	Time delay between drug administration and the first observed concentration in plasma
t_{last}	Time of last quantifiable concentration.
t_{max}	Time to reach peak or maximum observed concentration following drug
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration.

The following PK parameters will be determined, where possible, from urine concentrations.

$Ae_{(t1\text{-}t2)}$	Amount of analyte excreted unchanged in urine from time t1 to t2
$fe_{(t1\text{-}t2)}$	Percentage of analyte excreted unchanged in urine from t1 to t2

$Ae_{(0\text{-last})}$	Cumulative amount of analyte excreted at the last sampling interval
$fe_{(0\text{-last})}$	Cumulative percentage of dose excreted unchanged into the urine from time zero to the last measured time point for an analyte, estimated by dividing Ae(0-last) by dose
CLR	Renal clearance of drug from plasma, estimated by dividing Ae(0-24) by AUC(0-24)

Additional PK parameters may be determined where appropriate.

4.2.5.2 Derivations

The geometric mean is calculated as the exponential of the arithmetic mean calculated from the data on the natural log scale.

The percent coefficient of variation is calculated as: CV (%) = $\sqrt{(\exp(s^2) - 1}$ where s is the standard deviation of the data on a log scale.

Handling of values below the lower limit of quantification (BLQ)

Plasma concentrations below the limit of quantification (BLQ) from the time of pre dose sampling (t = 0) up to the time of the first quantifiable concentration will be set to a value of 0. After the first quantifiable concentration, BLQ plasma concentrations will be set to missing for the calculation of PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If two or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so, which will be documented in the CSR.

Any embedded BLQ value (between two quantifiable concentrations) will be set to missing for the PK analysis.

If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

For descriptive statistics plasma concentrations that are below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated.

- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, min, median, and max.

- The number of BLQ values (n below LLOQ) will be reported for each time point.

- Where there is no result, these will be set to missing.

Urine concentrations that are below the LLOQ will be handled as follows:

- BLQ values should be set to zero for the calculation of individual Ae.

- Any resulting Ae values equal to zero should be set to missing for the calculation of the summary statistics.

4.2.5.3 Handling of Dropouts and Missing Data

Not applicable

4.2.5.4 Primary Analysis of Secondary Endpoint

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of urine sample collection start and stop times will be provided. Urine amount and fraction of dose excreted (by interval and cumulative) will be listed.

Pharmacokinetic Concentrations

Plasma concentrations, amount excreted in urine (Ae), and fraction of dose excreted (per collection interval and cumulative) and PK parameters will be summarized by analytes and timepoints using descriptive statistic, number of non-missing observations, n below LLOQ, arithmetic mean, SD, geometric mean, geometric coefficient of variation (CV%), min, median, max and based upon the PK analysis set.

Where the actual time that a sample was taken deviates by more than the specified time allowances from the nominal time then concentration will be excluded from the summary statistics and statistical analysis.

Nominal Time	Time allowance
Pre-dose	Up to 30 minutes prior to dosing
0.5 h post dose	± 2 minutes
1 h post dose	± 5 minutes

1.5 h post dose	± 5 minutes
2 h post dose	± 5 minutes
2.5 h post dose	± 5 minutes
3 h post dose	± 10 minutes
4 h post dose	± 10 minutes
5 h post dose	± 10 minutes
6 h post dose	± 10 minutes
8 h post dose	± 10 minutes
10 h post dose	± 30 minutes
12 h post dose	± 30 minutes
24 h post dose	± 1 hour
36 h post dose	± 1 hour
48 h post dose	± 1 hour

Data from subjects excluded from the PK population will be included in the data listings, but not in the summaries or in the inferential statistics.

For t_{max} and time of last quantifiable plasma concentration (t_{last}) only n, median, minimum and maximum will be used.

Pharmacokinetic parameters will be rounded for reporting purposes in the summary tables and subject listings, as per the PK order form provided by AZ.

Individual plasma concentrations versus actual time will be plotted by analyte in linear and semi-logarithmic scale, with separate plots for each subject and study day. Plots will be based on the PK analysis set and displayed up to 48 hours post-dose.

Combined individual plasma concentration versus actual times will be plotted by analyte and study day in linear and semilogarithmic scale. Plots will be grouped by dose level, based on the PK analysis set and displayed up to 48 hours post-dose.

Figures for the arithmetic mean concentration-time data will be presented for all groups (pool data from all treatment groups) overlaid on the same plot, in both a linear and semi-logarithmic scale (SD on the linear scale and gSD on the semi-logarithmic scale) with separate plots for each study day.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist.

Pharmacokinetic data will be presented by analytes and timepoints. A listing of all concentration-time data will be presented by dose level.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

1. Source data shall be used in all derived PK concentrations without prior rounding.

2. The mean, standard deviation, geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.

3. Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.

4. Geometric coefficient of variation and coefficient of variation will be presented to one decimal place.

Graphical Presentation

For individual figures, concentrations that are BLQ will be regarded as missing, with the exception of pre-dose BLQ values which will be set to zero for linear scale plots.

For mean plots, BLQ values will be handled as described for the summary tabulations so that the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point. All mean plots will be based on the PK analysis set.

Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 8.3, or higher, (Certara) and/or SAS® Version 9.3, or higher (SAS Institute, Inc., Cary, North Carolina). All descriptive and inferential statistical computations will be performed using SAS® Version 9.3, or higher.

The actual sampling times, recorded in the raw data, will be used in the final plasma PK parameter calculations. If actual times are missing, nominal times may be used.

Nominal sampling times will be used for interim plasma PK parameter calculations.

Nominal times will be used for the calculation of urine PK parameters.

Concentration data will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount and concentration units, will be presented as they are received from the analytical laboratory.

Dose normalized parameters for AUC_{last}, AUC and C_{max} will be calculated by dividing the original parameter by dose.

The C_{max} and time to reach peak or maximum observed concentration or response following drug administration (t_{max}) will be derived directly from the plasma concentration-time profiles. For multiple peaks the highest post dose concentration will be reported as C_{max}. In the case that the multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

Terminal elimination half-life, estimated as $(\ln 2)/\lambda_z$, where λ_z refers to the terminal elimination rate constant, will be estimated by log linear least squares regression of the terminal part of the concentration-time curve.

The choice of data points used to estimate λ_z should follow the general guidelines:

- If there is more than 1 phase, use only observations from the terminal phase.
- In general, the minimum data requirements are 3 measured concentrations spanning three half-lives. Where $t_{1/2}$ is estimated over less than three half-lives, the values will be flagged in the data listings.
- Should include the last measurable concentration.
- Include only observations after C_{max}.
- The adjusted correlation coefficient (regression coefficient adjusted for λ_z, N, goodness of fit statistic for calculation of λ_z; Rsq adj) should be ≥ 0.8.

Area under the plasma concentration-curve will be calculated using trapezoidal methods when concentration is increasing and logarithmic trapezoidal method when concentrations are decreasing (linear up log down).

Three concentrations higher than the LLOQ are required as a minimum for the AUC parameter to be calculated.

If the pre-dose concentration prior to the first dose is missing it will be set to zero by default. If the pre-dose sample on Day 57 is missing it may be set equal to the concentration at the end of the dosing interval for the calculation of area under the plasma concentration-time curve in the dosing interval ($AUC\tau$) assuming linear PK and steady state conditions apply.

If the sample at the end of the profile is missing on Day 57 the concentration may be set equal to the pre-dose value for the calculation of $AUC\tau$ assuming linear PK and steady state conditions apply.

If a plasma or urine concentration value is considered anomalous due to being inconsistent with the expected pharmaceutical profile it may be appropriate to exclude this data point from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the study report. Embedded BLQs may be considered anomalous depending on the characteristics of the drug.

Urine PK parameters will be calculated based on measurements with the ECL assay. In case of an incomplete urine collection in any of the specified collection intervals (eg, spilled sample), the calculation of the fraction of dose excreted into urine as well as renal clearance will be subject to discretion of the AZ study pharmacokineticist.

The amount excreted in urine (Ae) will be calculated using a urine density of 1.0 g/mL. Urine concentrations below LLOQ will be treated as numerical zero.

The amount of analyte excreted into the urine from time t1 to t2 [Ae(t1-t2)] and percentage excreted unchanged in urine from t1 to t2 [fe(t1-t2)] will be calculated by collection interval and cumulatively for all collection intervals.

4.2.6 Secondary Endpoint – Change from baseline in log-transformed PCSK9 in plasma

4.2.6.1 Definition

Not applicable.

4.2.6.2 Derivations

PCSK9 measurement will be assigned to analysis visits as described in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2. After replacement of LLOQ, PCSK9 the absolute change and percent change from baseline are calculated for each study visit.

Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. Percent change from baseline is calculated using the raw values as the visit value minus the baseline value divided by the baseline value *100.

4.2.6.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.6.4 Primary Analysis of Secondary Endpoint

PCSK9 endpoints will be summarized as continuous log-normal variables and based on the PD Analysis Set. The absolute change and percent change from baseline will presented.

Summaries of the raw and log-transformed variables will be presented by visit and treatment group using the principles defined in Section 3.3.

Plots will be presented by treatment group for the following summaries:

- Arithmetic mean (± SD) of observed PCSK9 by visit.
- Arithmetic mean (± SD) of change from baseline by visit.
- Arithmetic mean (± SD) of percent change from baseline by visit.
- Geometric mean (± gSD) of PCSK9 by visit.

4.2.7 Secondary Endpoint – Percent change from baseline in LDL-C

4.2.7.1 Definition

Three measures of LDL-C will be assessed; LDL-C derived by Friedewald formula, LDL-C derived by the Martin/Hopkins formula and direct LDL-C.

4.2.7.2 Derivations

LDL-C values will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2.

LDL-C derived by Friedewald or Martin/Hopkins formula are indirectly calculated and hence may take 0 or negative values (reported as 'Unable to Calculate' by Central lab) (Sampson et al, 2020). LLOQs will not be defined for these indirectly calculated measurements according to Central lab. These data will be replaced by 1/square root of 2 for the analysis and displayed as reported from Central lab in the listings.

After replacements are made, the percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value * 100. Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm.

4.2.7.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.7.4 Primary Analysis of Secondary Endpoint

LDL-C values will be summarized based on the PD Analysis Set. Summaries of the change and percent change from baseline, as well as the observed values and the log-transformed variables will be presented by visit and treatment group using the principles defined in Section 3.3.

Plots will be presented by treatment group for the following summaries:

- Arithmetic mean (± SD) of observed LDL-C by visit.
- Arithmetic mean (± SD) of change from baseline by visit.
- Arithmetic mean (± SD) of percent change from baseline by visit.
- Geometric mean (± gSD) of LDL-C by visit.

4.2.8 Secondary Endpoint – Other Lipid Parameters

4.2.8.1 Definition

The following lipid parameters will be summarized:

- Total cholesterol (TC).
- High-density lipoprotein cholesterol (HDL-C).
- Non-HDL-C.
- Very low density lipoprotein cholesterol (VLDL-C).
- Apolipoproteins (Apo) A1.
- ApoB.
- Lp(a)
- Triglycerides.

4.2.8.2 Derivations

Lipid parameters will be assigned to analysis visits as defined in Section 3.3.2. Measurements below the LLOQ for which the exact value cannot be determined will be replaced by the LLOQ divided by the square root of 2. After replacement of LLOQ, lipid values will be log-transformed and the change from baseline, and the percent change from baseline will be calculated for each study visit.

Change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. Percent change from baseline is calculated on the raw scale as the visit value minus the baseline value divided by the baseline value * 100.

4.2.8.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.8.4 Primary Analysis of Secondary Endpoint

All lipid endpoints listed in Section 4.2.8.1 will be summarized as continuous log-normal variables and based on the PD Analysis Set. The absolute change and the percent change from baseline will presented. Summaries of the log-transformed variables will be presented by visit and treatment group using the principles defined in Section 3.3.

Plots will be presented by treatment group for the following summaries:

- Arithmetic mean (± SD) of observed lipid parameters by visit.
- Arithmetic mean (± SD) of change from baseline by visit.
- Arithmetic mean (± SD) of percent change from baseline by visit.

4.2.9 Exploratory Endpoint - Immunogenicity

4.2.9.1 Definition

Development of anti-drug antibodies and ADA titre will be used to evaluate the immunogenicity of AZD8233. Titre evaluations are conducted only on those samples that are confirmed positive for ADA.

4.2.9.2 Derivations

ADA parameters will be assigned to an analysis visit as defined in Section 3.3.2.

4.2.9.3 Handling of Dropouts and Missing Data

Missing data will not be imputed and only observed values will be reported in the summary tables and listings. Treatment discontinuation visit will be mapped according to Section 3.3.2.

4.2.9.4 Primary Analysis of Other Endpoint

ADA endpoints will be analyzed based on the Safety Analysis Set. The number and percentage of subjects with a positive result will be tabulated for: any time in study, baseline, any time post-baseline, and by visit and treatment group along with a summary of ADA titre using the principles defined in Section 3.3.

4.3 Pharmacodynamic Endpoint(s)

Refer to Sections 4.2.6, 4.2.7 and 4.2.8.

4.4 Pharmacokinetics

Refer to Section 4.2.5.

4.5 Immunogenicity

Refer to Section 4.2.9.

4.6 Safety Analyses

The domain safety covers exposure, overdoses and physical examinations. Adverse events, clinical laboratory, vital signs, and ECG have been summarized in previous sections.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Treatment exposure will be calculated in days as the treatment duration from date of first dose to date of last dose, inclusive.

Duration of exposure (days) = last dose date – first dose date + 1

4.6.1.2 Presentation

Duration of exposure will be summarized based on the Safety Analysis Set. Summaries will be presented by treatment group using the principles outlined in Section 3.3 for continuous variables.

4.6.2 Overdose and Medication Error

4.6.2.1 Definitions and Derivations

An overdose is considered as any dose of AZD8233 greater than the planned dose.

4.6.2.2 Presentation

All overdose data and medication errors data will be listed.

4.6.3 Physical Examinations

4.6.3.1 Definitions and Derivations

The full physical examination includes an assessment of general appearance and a review 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.

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

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.

4.6.3.2 Presentation

Physical examination data will not be presented in CSR.

5 INTERIM ANALYSIS

No planned interim analyses.

6 REFERENCES

[1] Sampson, Maureen, Clarence Ling, Qian Sun, Roa Harb, Mohmed Ashmaig, Russell Warnick, Amar Sethi et al. "A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia." *JAMA cardiology* 5, no. 5 (2020): 540-548.

7 APPENDIX

7.1 Schedule of Activities

	Screening	Treatment Period							Follow-up Period	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8 [a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**
Informed consent	X									
Inclusion/ exclusion criteria [b]	X	X								
Demographic data	X									
Weight and height (BMI) [c]	X	X						X (Day 57)		X
Medical history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Drug abuse and alcohol screen [d]	X						X			
Smoking history	X									
Viral serology [e]	X									
Pregnancy test (females only)	X [n]		X [o]							
Pregnancy and reproductive status (females only [p])	X									

	Screening	Treatment Period							Follow-up Period	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8 [a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	-	-	-	-	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**
Randomization			X (Day 1)							
Study residency										
Check-in		X					X			
Check-out			X (Day 3 [k])					X (Day 59)		
IMP Administration			X (Day 1)		X			X (Day 57)		
Safety and tolerability										
Adverse event questioning (including collection of data for injection site reactions)	X (Only SAEs)	X (Only SAEs)	X	X	X	X	X	X	X	X
Physical examination	X (complete)	X (abbr.)	X (abbr. pre-dose then 24 and 48 h post-dose)	X (abbr.)	X (abbr.; pre-dose)			X (abbr.; 24h post-dose)	X (abbr.)	X (complete)
Blood pressure and pulse rate [f]	X		X (pre-dose and then 0.25, 0.5, 1, 1.5, 2,	X	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12,	X	X

	Screening	**Treatment Period**							**Follow-up Period**	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8 [a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**
			2.5, 3, 4, 6, 8, 12, 24, 36 and 48h post-dose)					24, 36 and 48h post-dose)		
Body temperature		X	X (pre-dose)	X	X (pre-dose)			X (pre-dose)	X	X
12-lead safety ECG	X		X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48h post-dose)	X	X (pre-dose)			X (pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48h post-dose)	X	X
Cardiac telemetry		X (for at least 4h)	X (pre-dose to 24h post-dose)					X (pre-dose to 24h post-dose)		
Hematology, chemistry and coagulation including hs-CRP	X	X	X (24h post-dose)	X	X (pre-dose)			X (pre-dose)	X (Week 2, 4, 8, and 12 after last dose)	X
Sampling for renal safety biomarkers	X		X (pre-dose and then	X	X (pre-dose)			X (pre-dose)		

	Screening	Treatment Period							Follow-up Period	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8 [a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	-	-	-	-	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**
			24 and 48h post-dose)							
Sampling for dipstick urinalysis for hematuria	X		X (pre-dose and then 24 and 48h post-dose)	X	X (pre-dose)			X (pre-dose)		
Sampling for platelet count	X	X	X (24 and 48h post-dose)	X	X (pre-dose)	X (Day 22, 44)	X		X	X
Complement activation panel [h]			X (pre-dose and then 1, 2 and 4h post-dose)					X (pre-dose and then 1, 2 and 4h post-dose)		
Immunogenicity										
Samples for anti-AZD8233 antibodies			X (pre-dose)		X (pre-dose)			X (pre-dose)	X (Week 2 after last dose)	X
Pharmacodynamics										
Blood sampling for LDL-C and PCSK9	X [1]	X [1]	X [1] (pre-dose and 48h post-dose)	X [l, m]	X [l, m] (pre-dose)	X [l, m]		X [1] (pre-dose and 24h post-dose)	X [1]	X [m]

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

	Screening	Treatment Period							Follow-up Period	
Visit Number	**1**	**2**		**3**	**3,6**	**4, 5, 7, 8**	**9**		**10 to 16**	**17 (Final Follow-up Visit/ ED Visit)**
Study Day/Week	**Days -28 to -4**	**Day -1**	**Days 1 to 3**	**Day 8 [a]**	**Day 29**	**Days 15, 22, 36, 44**	**Day 56**	**Days 57 to 59**	**Weeks 2, 4, 6, 8, 10, 12, 14 (after last dose)**	**Week 16 (after last dose)**
Visit Window	**-**	**-**	**-**	**-**	**± 1 day**	**± 1 day**	**± 1 day**		**± 2 days**	**± 2 days**
			0-6, 6-12, 12-24 h post-dose)					0-6, 6-12, 12-24 h post-dose)		

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

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

[a] Day 8: no allowances.

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

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

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

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

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

[g] Allowances: pre-dose and then 0.5 h (±10 minutes), 1 h (± 10 minutes), 2 h (±15 minutes), 3 h (±15 minutes), 4 h (±15 minutes), 6h (±15 minutes), 8 h (±15 minutes), 12 h (±30 minutes), 24 h (± 1 hour), 36 h (±1 hour) and 48 h (±1 hour) post-dose.
[h] Blood samples for complement activation panel will be collected pre-dose and 1(±5 minutes), 2(±5 minutes) and 4 h (±10 minutes) post-dose so that the samples can be taken around Cmax.
[i] Plasma and urine samples for biobanking must be collected at the same hour every morning after an overnight (10-hour) fast.
[j] allowance; pre-dose and then 0.5 h (±2 minutes), 1 h (±5 minutes), 1.5 h (±5 minutes), 2 h (±5 minutes), 2.5 h (±5 minutes), 3 h (±10 minutes), 4 h (±10 minutes), 5 h (±10 minutes), 6 h (± 10 minutes), 8 h (±10 minutes), 10 h (± 30 minutes), 12 h (± 30 minutes), 24 h (± 1 hour), 36 h (± 1hour) and 48 h (± 1 hour) post dose.
[k] Participants will be discharged after the results from the 48 h post-dose assessments have been reviewed by the Investigator.
[l] The sample should be taken in a fasting state in the morning (after a 10 hour fasting) at approximately the same time point as the pre-dose sample on Day 1.
[m] Sampling to be done at approximately the same time points on the days of dosing (pre-dose) as on the non-dosing days (in the morning).
[n] Pregnancy test: Serum β-human chorionic gonadotropin (β-hCG) will be performed on all the women participants , irrespective of childbearing potential.
[o] Pregnancy test (Day1): Urine pregnancy test using dipstick will be performed before randomization on all the women participants, irrespective of childbearing potential at a local laboratory.
[p] All the women participants should have FSH and LH levels determined, irrespective of childbearing potential.

7.2 Clinical Laboratory Assessments

Hematology

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

Clinical Chemistry

Sodium	Alkaline phosphatase (ALP)
Potassium	ALT
Blood urea nitrogen (BUN)	AST
Creatinine	Gamma glutamyl transpeptidase (GGT)
Calcium	Total bilirubin
Phosphate	Direct bilirubin
Glucose (fasting)	Indirect bilirubin
Creatine kinase (CK)	Glutamate dehydrogenase (GLDH)
Bicarbonate	Lactate dehydrogenase (LDH)
HbA1c	Uric acid
Serum β-human chorionic gonadotropin (β-hCG)(women only)	FSH (women only)
eGFR	Luteinizing hormone (LH) (women only)

Coagulation

aPTT	Prothrombin time
International normalized ratio (INR)	

Urine renal safety biomarkers

Albumin	N-acetyl-beta-D-glucosaminidase (NAG)

Total protein	Kidney Injury Molecule-1 (KIM-1)
Creatinine	Neutrophil gelatinase-associated lipocalin (NGAL)
Clusterin	Osteopontin
Cystatin-C	UACR
Composite Measure	

Other laboratory assessments

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

Viral serology (screening only)

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

SIGNATURE PAGE

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

Document Name: d7990c00006-sap-ed-2		
Document Title:	Statistical Analysis Plan Part C Edition 2	
Document ID:	[redacted]	
Version Label:	[redacted]	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
[redacted]	[redacted]	Content Approval
[redacted]	[redacted]	Author Approval
[redacted]	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.