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

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AST	Aspartate aminotransferase
ASO	Antisense oligonucleotide
BMI	Body mass index
C_{max}	Maximum concentration
CI	Confidence Interval
CM	Concomitant medication
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Cardiovascular
CCI	[redacted]
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full analysis set
GST	Global Study Team
HDL-C	High-density lipoprotein cholesterol
ICE	Intercurrent event
IP	Investigational Product
IPD	Important Protocol Deviation
IRT	Interactive response technology
iSMC	Internal Safety Monitoring Committee
ISR	Injection site reaction
ITT	Intention-To-Treat
LSMD	Least Squares Mean Difference

Abbreviation or Specialized Term	Definition
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower Limit Normal
Lp(a)	Lipoprotein(a)
LTFU	Lost to follow-up
MACE	Major adverse cardiovascular events
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
Min	Minimum
MI-RD	Multiple imputation retrieved dropouts
MMRM	Mixed model repeated measures
MNAR	Missing not at random
PCSK9	Proprotein convertase subtilisin/kexin type-9
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetics
PT	Preferred term
PUC	Preparative ultracentrifugation
Q1	First Quartile
Q3	Third Quartile
Q4W	Every 4 weeks
RTSM	Randomisation and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SoA	Schedule of Activities
SOC	System Organ Class
TC	Total cholesterol
TP	Treatment Policy

Abbreviation or Specialized Term	Definition
ULN	Upper Limit Normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organisation
WOC	Withdrawal of consent

AMENDMENT HISTORY

CATEGORY* Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	02 Jul 2021	Initial approved SAP	N/A	N/A
Derivation of primary endpoint(s)	05 Jan 2022	Clarified situation when LDL-C value is obtained with PUC.	Yes	Clarified in CSP Version 2.0.
Statistical analysis method for the primary endpoint.	05 Jan 2022	Added details to primary analysis missing data handling algorithm.	Yes	To facilitate reproduction of results.
Statistical analysis method for the primary endpoint.	05 Jan 2022	Added supplementary analysis of relative change in LDL-C to end of week 16.	Yes	Relevant analysis, in particular for Interim analysis.
Statistical analysis method for the primary endpoint.	05 Jan 2022	Added details to subgroup analysis of primary endpoint.	Yes	To facilitate reproduction of results.
Statistical analysis method for the primary endpoint.	05 Jan 2022	Added comparative measurements based on time to event analysis, Kaplan-Meier estimates and Hazard ratios, to AE analyses	Yes	To align estimator with Safety estimand.
Data presentation	05 Jan 2022	Renamed IPD categories.	Yes	To align with data collection and company standards.
Data presentation	05 Jan 2022	Added HLGT and HLT levels to AE by SOC and PT tables	Yes	As suggested in FDA interaction.

CATEGORY* Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	05 Jan 2022	Added that all SOC, HLGT, HLT, and PT tables will be presented for both On-study and On-treatment period.	Yes	To align with Safety estimand and Overall summary tables.
[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
Data presentation	05 Jan 2022	Added "On-study period" definition to safety periods to denote period used for treatment emergent safety events.	Yes	No defined study period for treatment emergent safety events.
Data presentation	05 Jan 2022	Changed presentation of relative change by removing "100*"	Yes	Discrepancy between Section 3 and 4.
Data presentation	05 Jan 2022	Added PK set to Analysis set presentations.	Yes	Align with company standard outputs.
Data presentation	05 Jan 2022	Removed baseline eGFR labels.	Yes	Not clinically relevant labels.
Data presentation	05 Jan 2022	Clarified that Statin and Ezetimibe therapy at baseline I defined as ongoing use at randomisation.	Yes	Clarification of definition.
Data presentation	05 Jan 2022	Added details on outputs from primary analysis model.	Yes	To facilitate reproduction of results.
Data presentation	05 Jan 2022	Changed name of LDL-C "Enzymatic approach" to "Direct approach"	Yes	Clarification of definition.
Data presentation	05 Jan 2022	Added geometric mean and CV to Tertiary endpoint descriptive statistics	Yes	Relevant estimates for skewed distributed endpoints.
Data presentation	05 Jan 2022	Added definition of ADA positive subjects and figures of individual ADA response over time.	Yes	Clarification and addition of figures to facilitate interpretation.

CATEGORY* Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	05 Jan 2022	Added Kaplan-Meier estimates of cumulative proportion of IP discontinuation.	Yes	To facilitate interpretation.
Data presentation	05 Jan 2022	Changed categorisation of AEs by maximum intensity.	Yes	To facilitate interpretation.
Data presentation	05 Jan 2022	Added definitions of clinical laboratory parameter abnormalities and shift table categories, as well as clarified language in section.	Yes	To facilitate reproduction of results.
Data presentation	05 Jan 2022	Added figures of empirical distribution function and individual values over time for platelet count.	Yes	To facilitate interpretation.
Data presentation	05 Jan 2022	Added Potential Hy's law key subject information table.	Yes	Required company standard table.
Data presentation	05 Jan 2022	Added cross table of baseline versus each scheduled visit for coagulation parameters.	Yes	To facilitate interpretation.
Data presentation	05 Jan 2022	Added figures of individual Complement activation panel parameter values over time.	Yes	To facilitate interpretation.
Other	05 Jan 2022	Fixed typos, missing abbreviations, and other language-related issues.	Yes	Correction of errors.
Other	05 Jan 2022	Clarified that death and withdrawal of consent will be considered a study visit in the period derivation context.	Yes	Clarification for scenarios not previously handled.
Other	05 Jan 2022	Visit window definitions updated to avoid overlapping.	Yes	To facilitate interpretation.
Other	05 Jan 2022	Replaced first database lock with interim analysis, specified interim analysis section.	Yes	Changed in CSP Version 2.0.
Other	05 Jan 2022	Added that baseline definition will disregard time of day.	Yes	Clarification for scenarios not previously handled.

CATEGORY* Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	05 Jan 2022	Added that multiple measures of qualitative variables on same day will use clinically worse value in summary statistics.	Yes	Clarification for scenarios not previously handled.
Other	05 Jan 2022	Changed 1 year definition from 360 to 365 days, and removed 1 month definition (not used).	Yes	To facilitate interpretation.
Other	05 Jan 2022	Changed in concomitant medication use and total exposure definitions to be based on IP + 45 days instead of IP + 30 days.	Yes	Align with On-treatment period definition.
Other	05 Jan 2022	Changed Safety objective intercurrent event strategy in Table 2 to "Hypothetical scenario" and moved to 4.2 Safety Analysis	Yes	Correction to intercurrent event strategy and align table content with correct section.
Other	05 Jan 2022	Changed to definition of Bleeding AEs to include laboratory terms.	Yes	As suggested in FDA interaction.
Other	05 Jan 2022	Added that confirmation with consecutive HbA1C value is required for definition of new onset of diabetes.	Yes	Changed in CSP Version 2.0.
Other	05 Jan 2022	Added summary of AEs by ADA response.	Yes	To facilitate interpretation.
Other	05 Jan 2022	Changed category of eGFR in Laboratory Safety Variables Table from Urine renal safety biomarkers to Clinical chemistry	Yes	Error, fixed in CSP Version 2.0.
Statistical analysis method for the primary or secondary endpoints	28 Apr 2022	Clarified details on multiple imputation methods.	Yes	To facilitate interpretation.
Data presentation	28 Apr 2022	Updated the presentation of MMRM model, removed the redundant information and added details on figures.	Yes	To facilitate interpretation.

CATEGORY* Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	28 Apr 2022	Corrected the data included in the key subject information for subjects with haematogy abnormalities, chemistry abnormalities, or potential Hy's law.	Yes	Fixed the error.
Data presentation	28 Apr 2022	Updated rule 2b in visit window to include case of multiple assessments for qualitative variables.	Yes	To facilitate interpretation.
Data presentation	28 Apr 2022	Added Hypersensitivity to pre-defined AE categories.	Yes	To facilitate interpretation.
Data presentation	28 Apr 2022	Efficacy endpoint estimates to be presented as % by multiplying estimates by 100, including the eCDF figure.	Yes	To facilitate interpretation.
Data presentation	28 Apr 2022	Clarified the AEs with CK elevations.	Yes	To align with FDA comment.
Other	28 Apr 2022	Updated the narratives to include pre-specified AEs.	Yes	To facilitate interpretation.
Other	28 Apr 2022	MACE: Clarified the assumed order of occurrence of events when multiple events occur on the same date, and corrected typo.	Yes	To fix typo and facilitate interpretation.
Other	28 Apr 2022	Added how the missing values are treated when plotting the empirical cumulative distribution function.	Yes	To facilitate interpretation.
Other	28 Apr 2022	Clarified the references.	Yes	To present more consistently.
Other	28 Apr 2022	Adjusted the on-study period for discontinuation/interruption as patients are not at risk for these events after discontinuation.	Yes	To facilitate interpretation.
Other	28 Apr 2022	Updated the figure of study design to fix a typo and used the term "clinical data lock".	Yes	To align with CSP.

CATEGORY* Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Other	28 Apr 2022	Updated the definition of baseline diabetes.	Yes	To align with CSP.
Other	28 Apr 2022	Removed the section 5 of interim analysis and related contents on interim analysis.	Yes	To align with CSP.
Other	28 Apr 2022	Updated the definition of exposure.	Yes	To align with study period.
Other	28 Apr 2022	Clarified the global/country situation.	Yes	To clarify.
Other	28 Apr 2022	Added a non-breaking space before and after mathematical symbols.	Yes	To follow AZ authoring style guidance.
Statistical analysis method for the primary or secondary endpoints	8 Jul 2022	Updated methodology for MI-RD and provided details for placebo washout and updated subgroup analysis interaction test pooling to be based on Rubin's rules.	Yes	To update to the more robust predictive mean matching model and to facilitate interpretation.
Statistical analysis method for the primary or secondary endpoints	8 Jul 2022	Clarified the sensitivity analysis without imputing data.	Yes	To clarify.
Other	8 Jul 2022	Included MCMC, MNAR, ICE and ITT into the abbreviation list.	Yes	To clarify.
Other	8 Jul 2022	Updated the title of this SAP.	Yes	To align with CSP.
Other	8 Jul 2022	Clarified the definition of "Only baseline ADA positive".	Yes	To clarify.
Other	8 Jul 2022	Updated the boxplots to show the relative change of LDL-C and PCSK9 by ADA response instead of LDL-C and PCSK9 raw values.	Yes	To facilitate interpretation.

* Pre-specified categories are Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other.

1 INTRODUCTION

AZD8233 is a PCSK9-targeted ASO for the reduction of circulating levels of LDL-C. This is a safety and tolerability study with the aim of creating a safety database covering exposure following treatment with AZD8233 for 28 weeks (7 doses), to investigate whether any signals related to thrombocytopenia or other safety parameters are present that could potentially lead to restriction of subject populations due to safety. Efficacy of AZD8233 will also be evaluated through its ability to reduce LDL-C.

1.1 Study Design

This is a randomised, parallel, double-blind, placebo-controlled Phase 2b study to evaluate the safety and tolerability of AZD8233 as compared with placebo. The study is planned to be carried out across approximately 100 clinical sites in around 8 countries. For an overview of the study design, see **Figure 1**.

Approximately 376 subjects with hyperlipidaemia will be randomly assigned to AZD8233 CCI or matching placebo in a 1:1 ratio. Subjects will be treated with AZD8233 or placebo SC, Q4W for 28 weeks, to provide data to guide platelet monitoring for future programs. The aim is that, of the 188 subjects randomised to AZD8233 dose, at least 150 should complete the 28 weeks of planned treatment.

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

An internal safety monitoring committee (iSMC) will be used for regular review of unblinded safety data during the study. The remit of the iSMC will be detailed in the iSMC charter.

Figure 1 CCI

1.2 Randomization

All subjects will be centrally assigned to randomised study intervention using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM).

Eligible subjects will be randomly assigned to AZD8233 60 mg or matching placebo in a 1:1 ratio. Subjects will be treated with AZD8233 or placebo SC Q4W for 28 weeks.

1.3 Number of subjects

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

- AZD8233 CCI , SC Q4W, approximately 188 subjects randomly assigned
- Placebo matching dose, SC Q4W, approximately 188 subjects randomly assigned

CCI

2 CHANGES TO PROTOCOL PLANNED ANALYSES

There are no changes to protocol planned analyses.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The study is divided into a screening period of up to 28 days, a planned treatment period of 28 weeks followed by a safety follow-up period of 12 weeks. The final clinical data lock for writing the CSR will occur once all subjects have completed their full study participation or withdrawn from study.

There will be iSMC meetings scheduled approximately every 2 months after first dosing in the study. The iSMC works independent of the GST and will review unblinded study safety data and make a recommendation to GST.

3.2 General Considerations

3.2.1 General Study Level Definitions

3.2.1.1 Baseline

For analyses on the full analysis set (FAS), baseline is defined as the last non-missing value prior to or on the date of randomisation including unscheduled assessments that occurs prior to the randomisation visit.

For analyses on the safety analysis set, baseline is defined as the last non-missing value prior to or on the date of first administration of IP including unscheduled assessments.

Baseline definition will only consider date, and disregard time of day of data collection, unless pre- and post-dose assessments are collected in which case the pre-dose assessment will be used as baseline. If more than one value qualifies for baseline for any other reason, the scheduled assessment will be taken as the baseline value. If the scheduled assessment is not one of these, then the average of the non-missing values will be taken as the baseline value, unless the variable is qualitative then the clinically worse value will be taken as the baseline value.

3.2.1.2 Study periods

Study periods on the full analysis set

Enrolment period

The enrolment period starts at the date of signed informed consent and ends at the day before randomisation. For subjects enrolled but not randomised, the enrolment period ends at last visit.

Planned treatment period

The follow-up time during the planned treatment period will be calculated from the day of randomisation and to the day of end of planned treatment period visit, irrespective of if the subject has discontinued IP prior to this visit.

If the end of planned treatment period visit is missing or has occurred outside of the visit window, for the purpose of defining the planned treatment period, it will be replaced by the earliest of:

- the upper end of the visit window of the end of planned treatment period visit (Day 200),
- the date of withdrawal of consent,
- the date of death,
- the date of the last study visit,

where the date of death and withdrawal of consent will be considered a study visit in this context.

Full study period

The follow-up time for the full study period will be calculated from the day of randomisation and to the earliest of date of death, withdrawal of consent and last study visit (the date of death and withdrawal of consent will be considered a study visit in this context).

Study periods on the safety analysis set

Pre-treatment period

The pre-treatment period starts at the date of signed informed consent and ends at the day before the date of first dose of IP.

On-study period

The follow-up time for the on-study period will be calculated from the day of first dose of IP and to the earliest of date of death, withdrawal of consent and last study visit (the date of death and withdrawal of consent will be considered a study visit in this context).

On-treatment period

The follow-up time for the on-treatment period will be calculated from the day of first dose of IP and to the earliest of 45 days after last dose of IP, at date of death, withdrawal of consent or last study visit (the date of death and withdrawal of consent will be considered a study visit in this context).

3.2.1.3 Time at risk and subjects with an event included in the analysis

If a subject has an event with onset day during the study period being analysed (see Section 3.2.1.2), it will be included in the analysis. For subjects with an event, the time at risk will be derived as

- $Event\ onset\ date - date\ of\ randomisation + 1$ for the FAS,
- $Event\ onset\ date - first\ dose\ of\ IP + 1$ for the safety analysis set

For event-free subjects, the time at risk will be derived based on the study period being analysed, see the definition in Section 3.2.1.2. Event free subjects are censored on the last day of the study period.

3.2.1.4 Study Day

Study Day will be calculated from the randomisation date. Day 1 is the day of randomisation, Day -1 is the day prior to the date of randomisation, there is no Day 0.

- If the date of the event is on or after the randomisation date then:

  Study Day = date of event – date of randomisation + 1 day.
- If the date of the event is prior to the randomisation date then:

  Study Day = date of event – date of randomisation.

When converting the number of days to other units, the following conversion factor will be used: 1 year = 365 days.

3.2.1.5 Imputation of incomplete dates

The following imputed dates will only be used for analysis purposes and will remain as reported (partially or completely missing) in subject listings.

Incomplete death dates

Partially or completely missing death dates will be imputed as follows:

If only the day value of the death date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of last visit, then the date of last visit will be used.

If the day and month values of the death date are missing, January 1 will be used; unless this occurs in the same year as the date of last visit, then the date of last visit will be used.

If the death date is completely missing, the date of last visit will be used.

Incomplete concomitant medication dates

For medications that started prior to study start, start day will not be imputed. Partially or completely missing concomitant medication (CM) start dates will be imputed as follows:

If only the day value of the CM start date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of randomisation, then the date of randomisation will be used. If the day and month values of the CM start date are missing, January 1 will be used; unless this occurs in the same year as the date of randomisation, then the date of randomisation will be used.

If the CM start date is completely missing, the date of randomisation will be used.

If medication is marked as 'Treatment continues' the stop date will not be imputed. Partially or completely missing CM stop dates (where applicable) will be imputed as follows:

If only the day value of the CM stop date is missing, the last day of the month will be used; unless this occurs in the same month and year as the last visit, then the date of the last visit will be used. If the day and month values of the CM stop date are missing, December 31 will be used; unless this occurs in the same year as the last visit, then the date of the last visit will be used.

If the CM stop date is completely missing, the date of the last visit will be used.

3.2.1.6 Descriptive statistics

Summary data will be presented by treatment group and analysis visit when applicable. Quantitative data will be summarised by descriptive statistics, unless otherwise stated, including n, mean, standard deviation (SD), minimum, Q1, median, Q3 and maximum. Geometric mean and CV will be calculated in addition to arithmetic mean and SD, if appropriate. Categorical data will be summarised as the number and percentage of subjects in each treatment group for each category. When appropriate, number of missing observations will be presented, and these will not be included in the denominator when calculating percentages.

A general rule is to present descriptive summary statistics (mean, SD, median, Q1, Q3) to 1 more decimal place than the individual values. The minimum and maximum values should be reported to the same number of decimal places as the individual values.

Change from baseline will be presented similarly to summary data, with the absolute change from baseline and relative change from baseline summarised by descriptive statistics at the same timepoints, with the exception of baseline itself, in addition to the absolute values. Relative change from baseline at each timepoint will be calculated as:

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

where y_T is the value at timepoint T, and y_{BL} is the value at baseline.

All CIs will be 95%.

3.2.1.7 Subject convention

The term "Participant" is generally used to refer to language based on the CSP, vendor technology, patient-reported outcomes and publication titles. The word "subject" is more commonly encountered in the statistical sections of this SAP for consistency. Participant, patient and subject are used interchangeably.

3.2.2 Visit Window

For the purposes of analysing visit based data, analysis visit windows will be used and are based on the target date for the planned visit. The analysis visit windows are constructed based on the scheduled assessment timepoint (see Schedule of Activities in the CSP), and the range of the windows for scheduled assessments are shown in **Table 1**. Parameters are handled differently depending on the sampling frequency.

For each visit window, consider all assessments within the window and assign the visit assessment based on the following rules:

1. If the scheduled assessment is within the visit widow, then it is assigned.
2. If the scheduled assessment is not within the visit window, the closest assessment to the target date is assigned.
   a. If multiple assessments are equally close to the target date, the earliest is assigned.
   b. If there are multiple closest assessments on the same date, the mean of these assessments will be assigned for quantitative variables and the clinically worst value will be assigned for qualitative variables.
3. If there are no assessments within the visit window, then it remains missing.

Table 1 Visit windows

Scheduled assessment	Target day	Analysis visit window (days)
Platelet counts and Liver function tests		
Visit 3	15	- 13 to + 7
Visit 16	197	- 6 to + 14
Visit 17, 18	225, 281	- 13 to + 14

All other visits	See SoA	- 6 to + 7
All other parameters with a Visit 3 assessment		
Visit 3	15	- 13 to + 7
Visit 4	29	- 6 to + 14
All other visits	See SoA	- 13 to + 14
PK Plasma sample		
Visit 15	183	- 13 to + 7
Visit 16	197	- 6 to + 14
All other visits	See SoA	- 13 to + 14
All other parameters		
All visits	See SoA	- 13 to + 14

Data that are mapped to a scheduled visit will be counted in the study period (see Section 3.2.1.2) that the scheduled visit belongs, not necessarily the assessment collection date.

For summaries of extreme data at a subject level, all observations will be included regardless of whether it is included in the by-visit data presentation, e.g. when deriving a statistic such as the maximum.

3.2.3 Multiplicity/Multiple Comparisons

The formal hypotheses tests will focus on the treatment effect of AZD8233 versus placebo on the efficacy endpoints related to LDL-C and PCSK9. To maintain a family-wise Type I error rate of 5%, the hypotheses will be evaluated in a hierarchical sequence by a two-sided test at a 5% significance level until a test fails to reject the null hypothesis or until all the listed null hypotheses are rejected. Any subsequent test will be considered exploratory. Statistical tests will be done in the order as listed in **Table 2.**

Table 2 Endpoint hierarchy

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

P: Placebo; A: AZD8233.
The hypotheses are formalised using μ(*biomarker, treatment group*) to denote the mean relative reduction of *biomarker* in treatment group at the end of Week 28. For example, the mean relative reduction in concentrations of LDL-C in plasma for AZD8233 after 28 weeks is denoted with μ(LDL-C, A) and similarly for placebo with μ(LDL-C, P).

Endpoints that are not listed in **Table 2** are of an exploratory nature, and no adjustment will be made for multiple testing of these endpoints.

3.2.4 Covid-19

The impact of the COVID-19 pandemic is captured in exposure, disposition and visit data case report form pages as a general question on whether administration/subject's status/visit was impacted by global/country situation and is discussed in Appendix H, COVID-19 Specifics, in the CSP.

Subjects affected by the COVID-19 pandemic, such as efficacy and safety assessments not per CSP, will be recorded as protocol deviations and listed. Summaries of COVID-19 study disruptions and number of subject dispositions due to COVID-19 will be presented.

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

- Enrolled will be defined as a subject who signed the informed consent of the study.
- Randomised will be defined as a subject who has been randomised to a treatment group.
- Received treatment will be defined as a subject who has received at least one dose of IP.
- Completed treatment will be defined as a subject who has not permanently prematurely discontinued IP during the study. A subject who dies during follow-up without having permanently discontinued IP prior to date of death, will be considered to have completed treatment.
- Subjects who discontinued treatment is defined as subjects who have permanently prematurely discontinued IP, the reasons for discontinuation as collected on the DOSDISC eCRF will be presented. For reason collected as other, the specify field will be presented in listings but not in the disposition table.
- Completed study will be defined as a subject who has completed the end of planned treatment visit, or a later visit.
- Completed safety follow-up will be defined as a subject who has completed the final safety follow-up visit.
- Subjects who discontinued the study is defined as subjects who have withdrawn consent, have been lost to follow-up or died, the numbers for each of these categories will be presented.
- Subjects who discontinued treatment due to global/country situation, if applicable.
- Subjects who withdraw from study due to global/country situation, if applicable.

4.1.1.2 Presentation

Subject disposition and completion status will be described by treatment group and total number of subjects, for all subjects who have signed ICF for the study.

Number of subjects in each category will be presented, when applicable, percentages will also be presented.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Full Analysis Set

All subjects who were randomly assigned to study intervention. Subjects will be analysed according to their randomised study medication assignment, irrespective of the treatment actually received.

Safety Analysis Set

The safety analysis set consists of all subjects who have received at least one dose of investigational product. Erroneously treated subjects (e.g., those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A subject who has on one or several occasions received active IP is classified as active and is accounted for the active IP treatment group.

PK Analysis Set

The PK analysis set will consist of all subjects who receive at least 1 dose of AZD8233, for whom at least 1 post-dose PK concentration assessment is available as determined at the final protocol deviations meeting prior to unblinding of this study. Subjects will be presented in accordance to the actual treatment received.

4.1.2.2 Presentation

Analysis sets will be presented by number of subjects in each analysis set for all randomised subjects, by treatment group and total number of subjects. The reason for exclusion from an analysis set will be presented.

4.1.3 Study Recruitment

4.1.3.1 Definitions and Derivations

Region will be categorised by US and Europe.

4.1.3.2 Presentation

Patient recruitment by region, country and site will be summarised for all enrolled subjects, the safety analysis set, the FAS and the PK set by treatment group and total number of subjects.

4.1.4 Protocol Deviations

4.1.4.1 Definitions and Derivations

Important protocol deviations (IPDs) are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a patient's rights, safety or well-being. They will include (but are not limited to):

- Inclusion Criteria Deviations.
- Exclusion Criteria Deviations.
- Discontinuation Criteria for study product met but patient not withdrawn from study treatment.
- Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study.
- Investigational Product (IP) Deviation.
- Excluded Medications taken.
- Deviations to study procedure.
- Other Important Deviations.

All IPDs except for dosing error will be identified and documented by the study team prior to unblinding of the trial. Subjects meeting an IPD category more than once will be counted once for the corresponding IPD category. Any subject who have more than one IPD category will be counted once in the overall summary. IPDs will not be used to exclude any subject from any analysis set, nor to exclude any data from patients included in an analysis set.

IPD handling depends on detection method and are verified with site and entered/reconciled with Clinical trial management system. Further details will be described in the protocol deviation plan.

4.1.4.2 Presentation

Important protocol deviations (IPDs) will be summarised and listed for the FAS by randomised treatment group and total number of subjects. The number and percentage of patients with at least one IPD category as well as the number and percentage of patients meeting each IPD category will be provided by treatment group and in total.

4.1.5 Demographics

4.1.5.1 Definitions and Derivations

Demographic based on the FAS characteristics includes

- Age (years)
- Age group (< 65, ≥ 65 years)

- Sex (male, female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)

4.1.5.2 Presentation

Demographics will be presented for the FAS, by treatment group and total number of subjects.

Age will be presented as a continuous variable with descriptive statistics and categorically by age group. Sex, race and ethnicity will be presented as categorical variables.

4.1.6 Baseline Characteristics

4.1.6.1 Definitions and Derivations

Baseline patient characteristics includes

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI group:
  - underweight ($< 18.5\ kg/m^2$),
  - normal weight ($\geq 18.5\ kg/m^2$ and $< 25\ kg/m^2$),
  - overweight ($\geq 25\ kg/m^2$ and $< 30\ kg/m^2$) and
  - obese ($\geq 30 kg/m^2$).

BMI will be calculated based on weight and height of the subject at baseline.

4.1.6.2 Presentation

Baseline patient characteristics will be presented descriptively by randomised treatment group and overall and will be based on FAS. Height, weight and BMI will be presented as continuous variables with descriptive statistics. BMI will also be presented categorically by BMI group.

4.1.7 Baseline Disease Characteristics

4.1.7.1 Definitions and Derivations

The following disease characteristics will be presented at baseline:

- Baseline diabetes is defined according to the below criteria:
  a) Medical history of diabetes (type 1 or type 2), defined by SMQ Hyperglycemia/new onset diabetes mellitus (narrow), or

b) Measurement of HbA1c ≥ 6.5% (48 mmol/mol) confirmed by a consecutive HbA1c ≥ 6.5% (48 mmol/mol) or a fasting serum glucose ≥ 126 mg/dL (7.0 mmol/L) on or before the date of first dose of IP.

- Baseline HbA1c, grouped by < 6.5%, ≥ 6.5%
- Baseline fasting serum glucose, grouped by < 126 mg/dL, ≥ 126 mg/dL
- Baseline eGFR calculated according to CKD-EPI formula, grouped by
  - < 15 mL/min/1.73m^2,
  - ≥ 15 and < 30 mL/min/1.73m^2,
  - ≥ 30 and < 60 mL/min/1.73m^2,
    - ≥ 30 and < 45 mL/min/1.73m^2,
    - ≥ 45 and < 60 mL/min/1.73m^2,
  - ≥ 60 and < 90 mL/min/1.73m^2,
  - ≥ 90 mL/min/1.73m^2.
- Baseline PCSK9
- Baseline LDL-C
- Baseline lipoprotein(a)
- Baseline triglycerides, grouped by < 200 mg/dL, ≥ 200 mg/dL
- Statin therapy ongoing use at randomisation:
  - high intensity statin therapy (defined as atorvastatin ≥ 40 mg, or rosuvastatin ≥ 20 mg)
  - medium or low intensity statin therapy
  - no statins
- Ezetimibe therapy ongoing use at randomisation (Yes, No)

4.1.7.2 Presentation

Disease characteristics will be presented for the FAS, by treatment group and total number of subjects.

Baseline HbA1c and eGFR will be presented as continuous variables with descriptive statistics and categorically by group. Baseline PCSK9, LDL-C and Lp(a) will be presented as a continuous variable with descriptive statistics. All other variables will be presented categorically only.

4.1.8 Medical History and Concomitant Disease

4.1.8.1 Definitions and Derivations

Medical history as well as surgical history will be coded according to MedDRA and will be summarized by system organ class (SOC) and preferred term (PT) for the FAS.

4.1.8.2 Presentation

Medical and surgical history will be presented descriptively for the FAS, by treatment group and total number of subjects. Percentages will be calculated with number of subjects in the FAS as denominator. Subjects are only counted once per SOC and PT regardless of the number of occurrences within each category. PT will be presented nested within the relevant SOC and sorted by international order of SOC and alphabetically by PT.

4.1.9 Prior and Concomitant Medications

4.1.9.1 Definitions and Derivations

Prior medication is defined as any medication taken by the subject before the first dose of IP. If the end date is the day of first dose of IP, it will be defined as a prior medication.

Concomitant medication is defined as any medication taken concurrently with IP regardless of the start date of the medication. If the end date of the medication is prior to or on the day of first dose or start date of the medication is on or more than 45 days after last IP injection, the medication will not be considered to be taken concomitantly.

Disallowed concomitant medication are defined in Section 5.2, Exclusion Criteria and Section 6.5, Concomitant Therapy of the CSP. All other concomitant medications are classified as allowed.

Prior and concomitant medications will be reported by ATC classification and generic drug name (according to WHODrug).

4.1.9.2 Presentation

Prior and concomitant medications will be presented descriptively.

Prior and concomitant medications will be presented for the FAS, by treatment group and total number of subjects. Percentages will be calculated with number of subjects in the FAS as denominator. Subjects are only counted once per ATC classification and generic drug name regardless of the number of medications within each category. Generic drug name will be presented nested within the relevant ATC classification and sorted alphabetically by ATC classification and then generic drug name.

Prior medications, disallowed concomitant medications, and allowed concomitant medications will be presented separately.

4.1.10 Study Drug Compliance

4.1.10.1 Definitions and Derivations

Compliance to IP is defined by how many of the planned doses the subject has received. This will be expressed in percentage with the following formula

$$\frac{\text{Number of injections taken}}{\text{Number of expected injections}} \times 100.$$

Where number of expected injections is defined as the number of expected injections between first dose and time of completed planned treatment period or the time when IP is prematurely permanently discontinued, irrespective of temporary discontinuation of IP. Number of injections taken are defined as the number of injections taken according to the EX eCRF, for missing data see below.

The data will also be categorised in three different groups, these are

- < 80%
- ≥ 80% to < 120%
- ≥ 120%.

If the information on whether the planned dose has been administered is missing, it will be counted as if the injection was not taken irrespective of the drug was dispensed or not. Number of injections taken will be based on EX eCRF only.

4.1.10.2 Presentation

Compliance will be presented for the FAS by treatment group and total number of subjects. Compliance will be presented as a continuous variable with descriptive statistics and categorically by compliance group. Number of subjects with missing compliance will be presented.

4.2 Efficacy Analyses

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

Table 3 Efficacy, PK and Immunogenicity objectives and endpoints

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary (analysis)	Details in section
Primary Efficacy Objectives:					
Objective 1:					
To assess the effect of AZD8233 versus placebo on serum LDL-C at the end of Week 28 compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The relative change in serum LDL-C from baseline to the end of Week 28	FAS	TP	Descriptive Statistics, Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.1
Secondary Efficacy Objectives:					
Objective 2:					
To assess the effect of AZD8233 versus placebo on plasma PCSK9 at the end of Week 28 compared with baseline, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The relative change in PCSK9 from baseline to the end of Week 28	FAS	TP	Descriptive Statistics, Mean difference between treatment groups (LSMD from change from baseline, ANCOVA)	4.2.2.1
Secondary PK Objectives:					
Objective 3:					
To evaluate the PK of AZD8233	PK plasma concentration. Model population PK parameters to be reported in a separate report	PK	TP	Descriptive Statistics	4.2.2.2

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary (analysis)	Details in section
Secondary Immunogenicity Objectives:					
Objective 4:					
To evaluate the immunogenicity of AZD8233	Development of ADA and titre (if participants are ADA positive) during treatment and follow-up	SAS	TP	Descriptive Statistics	4.5
Tertiary Efficacy Objectives:					
Objective 5:					
To assess the effect of AZD8233 versus placebo on serum LDL-C over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The absolute levels, as well as the absolute and relative changes compared with baseline, in serum LDL-C over time	FAS	TP	Descriptive Statistics, Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.3.1
Objective 6:					
To assess the effect of AZD8233 versus placebo on plasma PCSK9 over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The absolute levels, as well as the absolute and relative changes compared with baseline, in PCSK9 over time	FAS	TP	Descriptive Statistics, Mean difference between treatment groups (LSMD from change from baseline, MMRM)	4.2.3.2

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary (analysis)	Details in section
Objective 7:					
To assess the effect of AZD8233 on the incidence of the 3 point MACE composite (defined as CV death, myocardial infarction, ischaemic stroke)	Time to the first occurrence of any component of the 3 point MACE composite	FAS	TP	Hazard Ratio	4.2.3.3
Objective 8:					
To assess the effect of AZD8233 on the incidence of thromboembolic events (defined as the composite of DVT and PE)	Time to first thromboembolic event	FAS	TP	Hazard Ratio	4.2.3.3
Objective 9:					
To assess the effect of AZD8233 versus placebo on other lipid parameters over time, in participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The absolute levels, as well as the absolute and relative changes compared with baseline, in other lipid parameters over time. Parameters include: • Cholesterol including TC, HDL-C, Non-HDL-C, VLDL-C, Remnants cholesterol • Triglycerides • Apo B • Apo A1 • Lp(a)	FAS	TP	Descriptive Statistics	4.2.3.4

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary (analysis)	Details in section
CCI					

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary efficacy variable of relative change in LDL-C from baseline to the end of Week 28 (Day 197/Visit 16) will be assessed through an estimand which is defined by the following attributes:

- Population: FAS, defined through inclusion and exclusion criteria.
- Treatment: AZD8233 CCI or placebo injected SC Q4W on a background of a stable dose of maximally tolerated statin and/or ezetimibe treatment.

- Intercurrent events: Non-terminal intercurrent events will be handled using a treatment policy strategy, i.e. the variable of interest is aimed to be collected and used irrespective of intercurrent events. Terminal events are expected to be few without substantial impact on the efficacy estimates and handled in the framework for missing data.
- Population-level summary: difference in variable means between treatments.

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

4.2.1.2 Derivations

The dependent variable is the relative change in LDL-C, that is

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

where y_{BL} and y_{w28} denotes the LDL-C measurements at baseline and at the end of Week 28 (Day 197).

The LDL-C value obtained using PUC will be used in the analysis of LDL-C through reflex testing when the LDL-C is < 40 mg/dL (by the Friedewald method) or if the triglycerides are ≥ 400 mg/dL. If there is no measurement taken using PUC, the calculated LDL-C value obtained using the Friedewald formula will be used [Friedewald 1972]. If neither LDL-C measured with PUC or calculated using the Friedewald formula is available, the measurement will be considered as missing.

4.2.1.3 Handling of Dropouts and Missing Data

For cases when baseline values are missing, the baseline values will be imputed by the mean value of non-missing baseline from other subjects. For post-baseline missing LDL-C values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined as missing data which constitute the end of patient follow-up, while non-monotone missing data means that there are observations made after the missing time point. Any non-monotone missing data will be replaced using PROC MI MCMC while monotone missing data will use PROC MI with a predictive mean matching model. The imputation model will include treatment group, baseline LDL-C and post-baseline LDL-C assessments at all scheduled timepoints in chronological order.

If there are sufficient retrieved dropouts per missingness-pattern by treatment group combination, pattern mixture imputation will be based on multiple imputation with retrieved dropouts (MI-RD), otherwise placebo-washout imputation will be used. Further details shown in Appendix 7.1.

4.2.1.4 Primary Analysis of Primary Endpoint

The main estimator is an ANCOVA for the relative change from baseline to the end of Week 28, including all subjects in the FAS. The model will include treatment group as a fixed categorical factor and baseline value as a continuous covariate. In this model, the dependent variable will be the relative change in LDL-C from baseline to the end of Week 28.

Available observations at baseline and the end of Week 28 will be used in the model, missing data will be imputed according to the principles outlined in Section 4.2.1.3. In addition, descriptive statistics will be presented and the distribution of missing data, number and proportions, according to each missing data pattern will be summarised per treatment arm.

Least square mean estimates for each treatment group and the difference between treatment groups, 95% CIs and p-value will be presented. In presentations, estimates based on relative change will be expressed in percent by multiplying by 100.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be conducted:

- The same approach as in Section 4.2.1.4 for the primary analysis but without imputing missing data, (i.e., subjects with missing data at baseline or end of Week 28 will be excluded).
- The same approach as in Section 4.2.1.4 for the primary analysis but LDL-C is derived from the Martin/Hopkins approach [Martin 2013].
- The same approach as in Section 4.2.1.4 for the primary analysis but LDL-C is derived from the Direct approach (direct fast determination in 24h) [Martin 2018].
- Analysis of relative reduction of LDL-C from baseline to end of Week 28 with MMRM as discussed in Section 4.2.3.1.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The following supplementary analyses will be conducted:

- Analysis of relative reduction of LDL-C from baseline to the end of Week 16, including all subjects in the FAS, using ANCOVA as estimator as described in 4.2.1.4.
- Analysis of relative reduction of LDL-C from baseline to last observation on-treatment, using ANCOVA as estimator. To assess the robustness of the main analysis of primary endpoint to the choice of intercurrent event strategy. Same approach as the primary analysis but instead of handling intercurrent events using the treatment-policy strategy, a while-on-treatment approach will be used. The last observation while-on-treatment is carried forward (LOCF) for the endpoint measurement and data after intercurrent event, i.e. last dose + 45

days, WOC, LTFU. Note that the treatment allocation with more intercurrent events may appear to have higher efficacy.

- The empirical cumulative distribution function (eCDF) within each treatment group of the endpoint variable, relative change in LDL-C from baseline to the end of Week 28, without imputing missing data, will be presented in a figure. The figure will present the cumulative probability on the y-axis and the endpoint variable on the x-axis. The x-axis will be multiplied by 100 to show relative change in percentage. Both treatment groups will be presented in the same figure.

4.2.1.7 Subgroup Analyses of the Primary Endpoint

The following baseline and demographic variables are defined for the purpose of efficacy subgroup analysis to assess consistency of effect:

- Baseline age (< 65, ≥ 65 years)
- Sex (male, female)
- Geographic region (US, Europe)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Categorical calculated baseline BMI:
  - underweight (< 18.5 kg/m^2),
  - normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2),
  - overweight (≥ 25 kg/m^2 and < 30 kg/m^2) and
  - obese (≥ 30kg/m^2).
- Baseline diabetes (Yes/No)
- Baseline categorical HbA1c (< 6.5%, ≥ 6.5%)
- Baseline fasting serum glucose (< 126 mg/dL, ≥ 126 mg/dL)
- Baseline eGFR calculated according to CKD-EPI formula ([≥ 30,< 60], [≥ 60,< 90], [≥ 90] ml/min/1.73m^2)
- Baseline PCSK9 (< median, ≥ median)
- Baseline LDL-C (< Q1, ≥ Q1 - < median, ≥ median – < Q3, ≥ Q3)
- Baseline lipoprotein(a) (< median, ≥ median)
- Baseline Triglycerides (< 200 mg/dl, ≥ 200 mg/dl)
- High intensity statin ongoing use at randomisation (Yes/No)

For each of the pre-specified subgroup variables, a separate ANCOVA model will be fitted using the same terms as used in the primary analysis in Section 4.2.1.4 but additionally including the subgroup variable and the interaction term for subgroup-by-treatment interaction. Missing values in LDL-C will be handled in the same way as in the overall analysis. Subjects with missing values in the subgroup variables is expected to be minimal, and will not be imputed but excluded before analysis. When applicable, the p-value for interaction will be derived by combining interaction test statistics from each multiple imputation ANCOVA result using Rubin's rules. Least square mean estimates for each treatment group and the difference between treatment groups per subgroup, 95% CIs and the p-value for the interaction term will be presented. Least square mean estimates for each treatment group and the differences will also be presented in a forest plot.

If any category of a subgroup variable contains less than 5% of the randomised subjects, separate ANCOVA models similar to the overall analysis will instead be fitted to subjects in each separate category, thus no p-value of interaction will be presented.

4.2.2 Secondary Endpoint

4.2.2.1 Relative change from baseline in concentrations of PCSK9

The secondary endpoint is relative change from baseline in concentrations of PCSK9 at the end of Week 28. This endpoint will be analysed with an ANCOVA model, including all subjects in the FAS, as described in Section 4.2.1.4.

4.2.2.2 PK Parameters

Evaluating the PK of AZD8233 is a secondary objective. If data permit, a population PK model will be developed, possibly with the support of PK data from studies such as D7990C00001, D7990C00002, D7990C00003 and potentially other studies, using nonlinear mixed effects modelling in NONMEM. The population PK model may be coupled with separate PD models for PCSK9 and LDL-C. All PK/PD modelling will be described in a separate data analysis plan and the results of any such modelling will be provided in a separate population PK/PD report.

AZD8233 full length ASO concentrations in plasma will be summarised by descriptive statistics by sampling time point and listed on individual level based on the PK analysis set.

Concentrations will be analysed on a natural logarithmic scale and then back-transformed to the original scale.

4.2.3 Tertiary Endpoint

4.2.3.1 Absolute values, absolute and relative changes compared with baseline, in serum LDL-C over time

For this exploratory endpoint an MMRM will be the estimator for each of the relative and absolute change in LDL-C from baseline over time. The observed relative (or absolute) change from baseline at each scheduled post baseline assessment in the planned treatment period is the dependent variable. The model will include LDL-C at baseline as the fixed effect covariate, and treatment group, visit and treatment-by-visit interaction as fixed effect categorical factors. The covariance structure used is unstructured (UN). If the model does not converge with UN, then Toeplitz, first-order autoregressive or compound symmetric covariance structure will be tried and the covariance structure will be decided based on model convergence status.

MMRM model assumes MAR for patients with missing data, missing data for participants who have discontinued IP are treated the same way as the observed measurements from participants who have not discontinued IP in the same treatment group.

Least square mean estimates from the MMRM for each treatment group and the difference between treatment groups and 95% CIs will be provided at each scheduled post baseline assessment in the planned treatment period. Figures showing absolute and relative change, respectively, from baseline to each scheduled assessment together with 95% CI in the full study period will be presented for serum LDL-C.

Descriptive statistics including n, arithmetic mean and standard deviation (SD), geometric mean and CV, minimum, Q1, median, Q3 and maximum, will be presented for the observed values, absolute and relative change from baseline for each scheduled assessment in the full study period will be presented.

In presentations, estimates based on relative change will be expressed in percent by multiplying by 100.

4.2.3.2 Absolute values, absolute and relative changes compared with baseline, in plasma PCSK9 over time

This exploratory efficacy variable is change in PCSK9 and will be analysed as described in Section 4.2.3.1. Descriptive statistics will also be presented in a similar way.

4.2.3.3 Cardiovascular outcomes: MACE and thromboembolic event

These exploratory endpoints are:

- Time to the first occurrence of any component of the 3-point MACE composite defined as CV death, myocardial infarction, ischaemic stroke.
- Time to first thromboembolic event defined as the first occurrence of DVT or PE.

The number of events and number of subjects with events in the MACE composite (CV death, MI, ischaemic stroke), and in the composite of thromboembolic events (DVT and PE) will be presented by treatment group. If there are at least 10 events in the MACE composite and thromboembolic events composite, respectively, the time to first event will also be analysed using survival analysis. Components in those endpoints are identified based on PTs for the investigator reported AEs. If there are multiple MACE with the same onset date, they will be assumed to occur in the following order: MI onset prior to stroke onset, and death onset occurs last. If there are multiple thromboembolic events, they will be assumed to occur in the following order: DVT onset prior to PE onset.

These composite endpoints will be analysed under a treatment policy intercurrent event strategy. The subjects' first event in the composite, that occurs during the planned treatment period will be included in the analysis. All subjects who are event free for the given endpoint will be censored according to the definition of planned treatment period in Section 3.2.1.3, i.e. events are included regardless of discontinuation of study medication. WOC and non-CV death which are censoring events.

In each composite endpoint, relative risk reduction between treatment groups will be compared using a Cox proportional hazards model with a factor for treatment group. The Efron method for ties will be used, and the HR, and 95% CI will be reported. Kaplan-Meier estimates of the cumulative proportion of patients with the composite event will be plotted and the estimate at Day 197 will be presented in tables.

The number of subjects with events for each component of the composites will be presented. If there are at least 10 events reported, HR with 95% CI and Kaplan-Meier estimates at Day 197 will be presented.

4.2.3.4 Change in cholesterol, triglycerides, apolipoproteins, lipoprotein

For Apo A1, Apo B, TC, HDL-C, Non-HDL-C, VLDL-C, remnant cholesterol, triglycerides and Lp(a), descriptive statistics including n, arithmetic mean and standard deviation (SD), geometric mean and CV, minimum, Q1, median, Q3 and maximum will be presented for observed values, absolute and relative change from baseline at each scheduled visit in the full study period.

These endpoints will be analysed with an ANCOVA model at the end of Week 28, including all subjects in the FAS, as described in Section 4.2.1.4 and descriptive statistics will be presented.

4.3 Pharmacodynamic Endpoint(s)

Details for these endpoints are described in Section 4.2.

4.4 Pharmacokinetics

Details are provided in Section 4.2.2.2.

4.5 Immunogenicity

Immunogenicity parameters are immunogenicity titre tested in an external laboratory. A validated screening assay will be used to determine ADA positive samples. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to AZD8233. Titre evaluation are performed on samples that are ADA positive.

Immunogenicity results are calculated for all subjects included in the Safety analysis set. The following ADA response categories will be used to categorise subjects:

- ADA positive: baseline result or ≥ 1 post-baseline result positive,
- Treatment emergent ADA positive: ≥ 1 post-baseline result positive,
- Treatment induced ADA positive: baseline result negative and ≥ 1 post-baseline result positive,
- Treatment boosted ADA positive: baseline result positive and ≥ 1 post-baseline result positive with ≥ 4-fold titre increase from baseline,
- Baseline and post-baseline ADA positive: baseline result and ≥ 1 post-baseline result positive,
- Only baseline ADA positive: baseline result positive and no post-baseline result positive,
- ADA persistently positive: baseline result negative and ≥ 2 Positive with ≥ 16 weeks between first and last positive sample, or last post-baseline result positive,
- ADA transiently positive: baseline result negative and ≥ 1 positive but not ADA persistently positive,
- Treatment emergent ADA positive with maximum titre > median of maximum titres: ≥ 1 post baseline result positive with maximum titre > median of maximum titres in all ADA positive subjects within treatment group.

Number and percentage of subjects in each ADA response category will be tabulated by treatment group and in total, with corresponding summary statistics (minimum, Q1, median, Q3, maximum) for ADA titre when applicable. Number of ADA positive subject and summary statistics for ADA titres will be tabulated by treatment group and visit. If a subject has more than one non-missing titre which qualifies for a category, the maximum titre is used in summary statistics calculations.

A figure of proportion of subjects with positive ADA response over time will be presented, with one line for each treatment group, and percentage of subjects with positive ADA response on the

y-axis and time from first dose on the x-axis. At a given time t, the curve will show the percentage of subjects with at least one positive ADA sample up until time t. For subjects with positive ADA response, ADA titres on log scale over time will be presented in a Spaghetti plot.

Summary statistics will be presented for the change in LDL-C, PCSK9 and AZD8233 full length ASO concentrations from baseline at each visit by ADA positive and negative groups. Figures with box-plots for LDL-C and PCSK9 relative change from baseline and AZD8233 full length ASO concentrations, respectively, for ADA positive vs ADA negative per visit will also be presented.

All immunogenicity parameter results will be presented in a listing.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG. Tables, figures and listings are provided for the safety analysis set.

Table 4. Safety objectives and endpoints

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary (analysis)	Details in section
Primary Safety Objectives					
Objective 1:					
To assess the safety and tolerability of AZD8233 as compared with placebo in participants with hyperlipidaemia receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations, including platelet count	SAS	Hypothetical scenario	Descriptive statistics, Difference in Kaplan-Meier risk estimate, Hazard ratio	4.6

The safety endpoints will be assessed through an estimand which is defined by the following attributes:

- Treatment: Actual treatment group, AZD8233 CCI Q4W SC injections compared to placebo on a background of a stable dose of maximally tolerated statin and/or ezetimibe treatment.
- Population: Safety analysis set (see Section 4.1.2.1)
- Variable:
  - Treatment emergent adverse event variables defined as
    - Events with an onset date on or after first dose of IP,
    - Worsening of pre-existing events on or after first dose of IP.
  - Treatment emergent vital sign, ECG, or clinical laboratory evaluation results defined as
    - Results at post-dose assessments on date of first dose of IP or at any assessments after the date of first dose of IP.
- Intercurrent events (ICEs): the risk of a safety event will in the analyses be evaluated under a hypothetical scenario where premature discontinuation of study treatment or study visits or loss to follow-up cannot happen.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure is calculated for all subjects included in the safety analysis set.

Total exposure

Total exposure (days) is calculated as the minimum of the date of last IP administration plus 45 days and last study visit minus date of first IP administration plus one, i.e.

$$\text{Total exposure (days)} = \min(\text{Last administered IP} + 45, \text{Last study visit})$$

$$-\text{First administered IP} + 1$$

Last IP administered will be extracted from the DOSDISC form, while the first dose administration are derived from the earliest administered dose collected on the EX form.

Total treatment time will be expressed in years in data presentations, defined as the sum of days of total exposure for a given treatment group divided by 365 days.

Time to permanent IP discontinuation will be analysed using survival analysis. Subjects who did not permanently discontinue IP are censored at the earliest of WOC, death, Day 172, and last dose. Kaplan-Meier estimates of the cumulative proportion of patients who discontinue IP will be calculated for each treatment group.

4.6.1.2 Presentation

Exposure will be presented by treatment group, summary statistics of total exposure will be presented, as well as total treatment time.

A figure of exposure over time will be presented, with one line for each treatment group, and percentage of subjects still exposed on the y-axis and time from first dose on the x-axis. At a given time t, the curve will show the percentage of subjects with exposure time > t.

Total exposure will also be presented categorically with cumulative categories: ≥ 4 weeks, ≥ 12 weeks, ≥ 20 weeks, ≥ 28 weeks. These categories are cumulative, and subjects will be included in all categories that apply to them.

Number of administrated doses will be presented for the given study duration by descriptive statistics and categorised based on number of injections: ≥ 1, ≥ 3, ≥ 5, ≥ 7. These categories are cumulative, and subjects will be included in all categories that apply to them.

A figure of Kaplan-Meier estimates of the cumulative proportion of subjects discontinuing IP will be plotted by treatment group.

4.6.2 Adverse Events

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

4.6.2.1 Definitions and Derivations

Each AE will be assigned to the following periods, defined in Section 3.2.1.2 based on onset date:

- Pre-treatment
- On-study
- On-treatment

For on-study the assumption is that the risk for an event is independent of continued exposure to study drug, while for on-treatment the assumption is that the ICE's are non-informative. On-study and on-treatment approaches are complementary estimands.

All AEs will be classified by SOC, HLGT, HLT and PT according to a MedDRA version not more than one older than the latest version available at the time of database lock.

Comparative measurements between treatment groups based on time to the first occurrence of any component within an AE category will be calculated using survival analysis. The subjects' first event in the composite, that occurs during the on-study or on-treatment period, respectively,

will be included in the analysis. All subjects who are event free for the given endpoint will be censored according to the definitions of study periods in Section 3.2.1.3. For on-study Kaplan-Meier estimates with patients censored at the end of study is an appropriate estimator (corresponds to ITT analysis), for analyses on-treatment Kaplan-Meier estimates with patients censored at last dose + 45 days is the estimator. For time-to-event analysis of AEs leading to discontinuation or interruption of IP, in both on-study and on-treatment analyses event-free subjects that did not complete treatment are censored 14 days following the date of last dose of IP and event-free subjects who did not die and completed treatment are censored on the date of last dose of IP.

For each AE category, relative risk reduction between treatment groups will be compared using a Cox proportional hazards model with a factor for treatment group. The Efron method for ties will be used. The absolute difference and 95% CIs in Kaplan-Meier estimates at the end of the planned treatment period (Day 197) between treatment groups will be calculated.

The following definitions and principles are to be followed:

Any AE

Defined as subjects with at least one reported AE with an onset date within the defined period.

AEs with outcome death

Defined as an AE with reported outcome as 'Fatal', there may be more than one AE with outcome death for a subject. The onset date of the AE determines the analysis period, irrespective of date of death.

AEs leading to discontinuation of IP

Defined as an AE with action taken IP reported as drug permanently discontinued. The onset date of the AE determines the analysis period, irrespective of date of discontinuation of IP.

CCI [redacted].

AEs leading to interruption of IP and the subject subsequently discontinues IP

Defined as an AE with action taken IP reported as drug interrupted and where drug has been permanently discontinued with a DOSDISC form IP discontinuation date after the date of the AE onset with action reported as drug interrupted. The onset date of the AE determines the analysis period, irrespective of date of IP discontinuation.

SAEs

Defined as an AE reported as serious, irrespective of outcome.

AEs possibly related to IP

Defined as an AE that is reported as "reasonable possibility AE caused by IP". If this causality evaluation is missing, it will be counted as an AE possibly related to IP.

AEs by maximum intensity

AEs will be classified by the reported maximum intensity (mild, moderate, and severe) and categorised in presentations as "Any", "Moderate or Severe" and "Severe". If this maximum intensity evaluation is missing, it will be counted as "Severe".

Pre-specified AE categories

For AZD8233 there is a set of pre-specified AE categories for which separate outputs will be produced. The following AE categories are pre-defined:

- Bleedings: will be identified by MedDRA Haemorrhage SMQ (broad)
- New onset or worsening of diabetes: See below.
- Injection site reactions: will be collected on specific forms where the symptoms of each reaction is collected and presented by MedDRA HLT Injection site reactions.
- AEs of thrombocytopenia: will be identified by PT/SOC (PTs: Thrombocytopenia, Immune thrombocytopenia, Platelet count abnormal, Platelet count decreased and Platelet disorder). In addition, tables based on platelet counts will be presented (see details in Section 4.6.3).
- Outcome of neurological examinations will be presented.
- AEs of hypersensitivity: will be identified by MedDRA Hypersensitivity SMQ (narrow).

New onset of diabetes

New onset of diabetes mellitus during the study is identified programmatically among patients without diabetes mellitus at baseline (for definition, see Section 4.1.7.1).

In the subset of patients without diabetes at baseline, new onset diabetes should be defined to have occurred with any of the following:

a) A post-baseline HbA1C ≥ 6.5%, confirmed by a consecutive HbA1C ≥ 6.5% (48 mmol/mol) or a fasting serum glucose ≥ 126 mg/dL (7.0 mmol/L) with both tests after date of first dose of IP, or

b) two consecutive values of fasting serum glucose ≥ 126 mg/dL (7.0 mmol/L) after date of first dose of IP, or

c) addition of a new medication for control of serum glucose after date of first dose of IP, or

d) diabetic treatment emergent adverse events identified by SMQ search (Hyperglycemia/new onset of diabetes mellitus).

If more than one of the above criteria are met, the earliest date will be considered as the onset date of the event of new onset of diabetes mellitus.

Worsening of diabetes

Worsening of diabetes mellitus during the study is identified programmatically among patients with diabetes mellitus at baseline (for definition, see Section 4.1.7.1).

a) Absolute increase in HbA1c from baseline of > 0.5% (5.5 mmol/mol) after first dose of IP, and/or
b) addition of a new antidiabetic medication or an increase in dose of current antidiabetic therapy after first dose of IP, and/or
c) diabetic treatment emergent adverse events identified by SMQ search (Hyperglycemia/new onset of diabetes mellitus).

4.6.2.2 Presentation

The number and percentage of subjects with AEs, the Kaplan-Meier estimate at Day 197, difference in Kaplan-Meier estimate at Day 197 between treatment groups and 95% CIs, and HRs ad 95% CIs will be tabulated. Unless otherwise specified, summaries of AEs will be presented for subjects in the safety analysis set, by actual treatment group, for both the on-study and on-treatment period. Percentages will be calculated with number of subjects in the analysis set as denominator, and subjects will only be counted once per category, regardless of the number of AEs satisfying each condition. Tables where AEs are presented by SOC, HLGT, HLT and PT, will be sorted by international order for SOC and alphabetical order for HLGT, HLT, and PT.

The following summaries will be presented:

Overall summary of AEs

Number of subjects with any AE, any AE with outcome of death, any serious AE, any AE leading to discontinuation of IP, any AE leading to interruption of IP, any AEs leading to interruption of IP and the subject subsequently discontinues IP, any AE possibly related to IP.

Number and percentage of subjects by treatment group, and comparative measurements based on survival analysis will be presented.

For each pre-specified AE category, an overall summary of AEs will be presented for the on-study period and the on-treatment period.

An overall summary of AEs by ADA response (positive/negative) as defined in Section 4.5 will be presented.

By SOC, HLGT, HLT and PT

Separate AE tables by SOC, HLGT, HLT and PT will be provided for: Any AE, possibly related AEs, AEs by maximum intensity, SAE with outcome death, Any SAE, AEs leading to discontinuation of IP, AEs leading to interruption of IP and the subject subsequently discontinues IP and pre-specified AE categories as relevant. New onset or worsening of diabetes will be presented by criteria, including by SOC, HLGT, HLT and PT for the AE criteria.

For each treatment group the number, percentage of subjects, and comparative measurements based on survival analysis.

Most common AEs

A table of number and percentage of subjects with most common AEs (≥ 2%) by PT will be presented.

Most common non-serious AEs

A table of non-serious AEs occurring in more than 5% of subjects in any treatment group will be presented.

Key subject information

Key subject information will be presented for subjects with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP.

Summary of injection site reactions

A table presenting number of subjects with Any, 1, 2, 3, 4, 5, and > 5 ISR AEs, symptoms and location of ISR and maximum diameter will be presented.

Listings

An AE listing will cover details for each individual AE, a separate listing will be presented for ISRs.

A listing of outcomes of neurological examinations for subjects with at least one abnormal outcome during the on-study period will be presented.

An AE listing for all randomised subjects who received at least one dose of incorrect IP will be presented, the listing will include AE onset date and date of treatment switch.

An AE listing for each individual AE in ADA positive subjects as defined in Section 4.5 will be presented. An AE listing for each individual AE in subjects with elevated complement activation panel factors (defined as C5a or Bb > ULN) at any time during the on-study period will be presented.

Narratives

Narratives will be produced for all deaths, SAEs and AEs leading to permanent discontinuation of IP. In addition, narrative will be produced for patients with ALT > 3 x ULN and AEs of bleedings, thrombocytopenia and injection site reactions of moderate or severe intensity.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry, haematology and coagulation will be collected according to the schedule of activities according to Section 1.3 of the CSP. Clinical Safety Laboratory Assessments are listed in Appendix 7.2 of the SAP.

Subjects with clinical chemistry, haematology and coagulation parameters abnormalities will be defined according to non-mutually exclusive thresholds based on reference ranges from the central lab, where applicable. In addition, the following definitions of laboratory abnormalities will be used for specific parameters:

- Platelet count will be categorised by the following, non-mutually exclusive thresholds: < 50, < 75, < 100, < 150 x 10^9/L, and > 30% decrease from baseline
- Creatine kinase (CK) elevations will be categorised by the following, non-mutually exclusive, thresholds: > 5 x ULN, > 10 x ULN and > 20 x ULN.
- Hepatic safety laboratory parameter elevations will be categorised by the following, non-mutually exclusive, thresholds:
    - ALT: > 1 x ULN, > 3 x ULN, > 5 x ULN, > 10 x ULN, > 20 x ULN
    - AST: > 1 x ULN, > 3 x ULN, > 5 x ULN, > 10 x ULN, > 20 x ULN
    - Alkaline Phosphatase: > 2 x ULN, > 3 x ULN
    - Total Bilirubin (TBL): > 2 x ULN, > 5 x ULN, > 8 x ULN
    - Direct Bilirubin: > 2 x ULN, > 5 x ULN
- International normalised ratio (INR) will be categorised by the following, non-mutually exclusive, thresholds: > 1.5 x ULN, > 3 x ULN, > 5 x ULN.
- Renal safety laboratory parameter worsening will be assessed for eGFR and Creatinine. Percent change from baseline in eGFR will be categorised by the following, non-mutually exclusive, thresholds: ≥ 25% decrease, ≥ 50% decrease and ≥ 75% decrease.

Creatinine will be categorised by the following, non-mutually exclusive thresholds: ≥ 1.5 x baseline, ≥ 2 x baseline and ≥ 3 x baseline.

The risk difference $R = p_A - p_p$ is defined as the difference in proportions between AZD8233 treatment group p_A and placebo group p_P. The 95% CI for the risk difference is given by

$$p_A - p_P \pm z \cdot \sqrt{\frac{p_A \cdot (1 - p_A)}{n_A} + \frac{p_P \cdot (1 - p_P)}{n_P}}$$

where n_A, n_P represent the number of subjects in AZD8233 and placebo group, respectively, and z is the $1 - \frac{\alpha}{2}$ quantile of the standard normal distribution where $\alpha = 0.05$.

In shift tables, all parameters will be categorized according to the following mutually exclusive categories based on central laboratory ranges (when applicable): Low (< LLN), Normal (≥ LLN and ≤ ULN), High (> ULN). In addition, platelet count will be categorised according to categories : < 50, ≥ 50 and < 75, ≥ 75 and < 100, ≥ 100 and < 150, and ≥ 150 x 10^9/L.

Potential Hy's law is defined as AST ≥ 3 x ULN or ALT ≥ 3 x ULN and Total bilirubin ≥2 x ULN, where at least one time Total bilirubin ≥ 2 x ULN occurred on or after the date of the first occurrence of ALT ≥ 3 x ULN or AST ≥ 3 x ULN and on or after the date of first administration of IP.

Assessed values of the form '<x' (below the lower limit of quantification) or '>x' (above the upper limit of quantification will be imputed as 'x' in the calculations of summary statistics but displayed as '<x' or '>x' in listings.

4.6.3.2 Presentations

All laboratory data will be presented during the on-study period, for the safety analysis set and in SI or conventional units.

Clinical laboratory parameters will be presented by treatment group and scheduled visit, separately for haematology, chemistry and coagulation parameters. All parameters will be presented as continuous variables with descriptive statistics for all visits at which an assessment is scheduled. Observed value, absolute change and relative change from baseline will be presented using descriptive statistics for all scheduled assessments after baseline.

The number of subjects with treatment-emergent laboratory parameter abnormalities will be presented categorically by treatment group, alongside risk differences with 95% CIs for each category of elevation, according to the categories defined in Section 4.6.3.1. Safety laboratory

parameter abnormality categories are cumulative and subjects will be included in all categories for which they have a qualifying assessment during the on-study period.

Key subject information will be presented for subjects with haematology abnormalities, chemistry abnormalities, or potential Hy's law in separate tables.

Shift tables from baseline to maximum and minimum value during the on-treatment period will be presented, by treatment group, according to the mutually exclusive categories defined in Section 4.6.3.1.

The empirical cumulative distribution function within each treatment group of change from baseline to the minimum platelet count measurement after first dose of IP will be presented in a figure. Time course of recovery of platelet counts after thrombocytopenia will be displayed by spaghetti plots showing platelet count by visit for subjects with $<150 \times 10^9$/L or with decrease from baseline >30% at any time during the on-study period.

Subjects with CK elevations will be presented categorically by treatment group. For subjects meeting the criteria for CK elevations, an AE listing for each individual AE will be produced and CK values over time will be presented in a Spaghetti plot.

For subjects with eGFR worsening, the eGFR values over time will be presented in a Spaghetti plot.

A descriptive table for maximum on-treatment ALT and AST versus maximum on-treatment bilirubin for each treatment group in the safety analysis set will be shown.

Coagulation parameter results will further be presented as a cross table with number and percentages in categories Low (< LLN), Normal (≥ LLN and ≤ ULN), High (> ULN), by treatment group for baseline versus each scheduled post-baseline visit.

A listing including variables, such as assessment date and value, change from baseline, LLN, ULN, reference range indicator will be created. Percentages will be calculated with number of subjects with available assessment at each visit as denominator.

Parameters will be presented in alphabetical order.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urinalysis (dipstick), urinalysis (positive dipstick) and urine renal safety biomarkers will be taken according to the schedule of activities according to Section 1.3 of the CSP. Clinical Safety Laboratory Assessments are listed in Appendix 7.2.

Subjects with treatment emergent urinalysis parameter abnormalities in quantitative parameters will be defined according to the non-mutually exclusive thresholds based on central laboratory ranges (when applicable): < LLN, > ULN.

Assessed values of the form '<x' (below the lower limit of quantification) or '>x' (above the upper limit of quantification will be imputed as 'x' in the calculations of summary statistics but displayed as '<x' or '>x' in listings.

4.6.4.2 Presentations

Clinical laboratory parameters for urinalysis will be presented for the safety analysis set by treatment group and scheduled visit, separately for urinalysis parameters and urine renal safety biomarkers parameters. All parameters will be presented with descriptive statistics for all visits at which an assessment is scheduled. Absolute change from baseline will be presented for continuous variables using descriptive statistics for all scheduled assessments after baseline.

Shift tables from baseline to maximum and minimum value during the on-treatment period will also be presented.

Parameters will be presented in alphabetical order.

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

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

4.6.5.2 Presentations

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

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

ECG assessment is limited to overall ECG evaluation, i.e. normal, abnormal not clinically significant and abnormal clinically significant.

4.6.6.2 Presentations

ECG results will be presented as a cross table with number and percentages, by treatment group for baseline versus each scheduled post-baseline visit. Frequency tables will show the interpretation of the ECG reading (normal, abnormal - clinically not significant, abnormal - clinically significant) at each timepoint. Change from baseline to last on-treatment value will be presented in shift tables for the overall ECG evaluation.

4.6.7 Other Safety Assessments

4.6.7.1 Definitions and Derivations

Other laboratory measurements are composed of complement activation panel (Bb, C5a), high-sensitivity C-reactive protein (hs-CRP).

4.6.7.2 Presentations

Measurements will be presented in the same way as blood samples in Section 4.6.3.2.

Results will further be presented as a cross table with number and percentages in categories Low (< LLN), Normal (≥ LLN and ≤ ULN), High (> ULN), by treatment group for baseline versus each scheduled post-baseline visit when applicable.

For subjects with C5a elevations, the C5a and Bb values over time will be presented in a Spaghetti plot. For subjects with Bb elevations, the Bb values over time will be presented in a Spaghetti plot.

5 INTERIM ANALYSIS

Interim Analysis is not planned for this study.

6 REFERENCES

[Crooke 2017] The Effects of 2'-O-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials. Nucleic Acid Ther. 2017; 27:121-129.

[Friedewald 1972] Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499-502.

[Martin 2013] Comparison of a Novel Method vs the Friedewald Equation for Estimating Low-Density Lipoprotein Cholesterol Levels From the Standard Lipid Profile. JAMA. 2013; 19:2061-2068.

[Martin 2018] Comparison of Low-Density Lipoprotein Cholesterol Assessment by Martin/Hopkins Estimation, Friedewald Estimation, and Preparative Ultracentrifugation. JAMA cardiology. 2018; 8: 749-753.

7 APPENDIX

7.1 Missing data handling: MI-RD and placebo-washout imputation sensitivity analysis

For cases when baseline values are missing, the baseline values will be imputed by the mean value of baseline. For post-baseline missing LDL-C values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined on a subject level as missing data that constitutes the end of subject follow-up, while non-monotone missing data means that observations exist after the time point with the missing data. The steps of the imputation algorithm is described in **Table 5.**

Table 5 ANCOVA missing data imputation algorithm

Step		**Description**
Step 1	Impute non-monotone missing data	Impute all non-monotone missing data using the Markov chain Monte Carlo (MCMC) method assuming missing data are missing at random (MAR). This is performed using PROC MI in SAS, stratified by treatment group, with the IMPUTE=MONOTONE and CHAIN=MULTIPLE options in the MCMC statement. The imputation model will include baseline LDL-C and all scheduled post-baseline LDL-C assessments in chronological order. In this step, 1000 imputation datasets will be generated using the seed 674752, each of which will now solely contain missing data of the same monotone pattern.
Step 2	Impute monotone missing data	For each of the 1000 imputed datasets, impute all monotone missing LDL-C data sequentially using the pattern mixture model assuming missing data are missing not at random (MNAR) with the seed 6747521. The preferred method of imputation will be to use MI-RD, where imputation of missing data will be performed after stratifying for each combination of treatment group and on-treatment status. To impute missing data at *Time t,* subjects are categorised as either as on-treatment (= subject for whom *Time t* is during the on-treatment period), or as treatment discontinuers (= subject for whom *Time t* is outside the on-treatment period). The pattern mixture model imputation with a predictive mean matching model is preformed using PROC MI in SAS with the MONOTONE statement set to the REGPMM option. The statement is repeated sequentially for each measured timepoint, including baseline value and all previous timepoints. Subjects who had

		missing data imputed at previous timepoints will contribute to the imputation for the current timepoint.
Step 3	Fit ANCOVA models	Fit the pre-specified ANCOVA model to each imputed dataset, each now without any missing data, using PROC MIXED and store the 1000 resulting least square mean estimates for each treatment group and the difference between treatment groups, and corresponding standard errors for each model.
Step 4	Pool ANCOVA model estimates	Pool results using Rubin's rules in PROC MIANALYZE in SAS to provide the final least square mean estimates, 95% CIs, and p-value for the difference between treatment groups.

This MI-RD approach described in Step 2 in **Table 5** will be used as long as the number of retrieved dropouts for each combination of treatment group and on-treatment status is sufficient to construct imputation models. The distribution of missing data, number and proportions, according to each missing data pattern will be summarised per treatment group.

If MI-RD cannot be used due to an insufficient number of retrieved dropouts, missing data at the end of Week 28 in the placebo group will be replaced based on subjects in the same group using standard MI and assuming missing at random, including baseline value and observations between baseline and the end of Week 28 in the imputation model. Missing values in the active treatment group will be replaced by washout multiple imputation. In washout multiple imputation, the end of Week 28 data are imputed based on observed values in the placebo group only, including baseline value in the imputation model but not accounting for any observations after baseline. A total of 1000 datasets will be imputed. The seed for imputing non-monotone missing data will be the same as in the MI-RD analysis (i.e., 674752). For the imputation of monotone missing data, seed 101010 will be used for the placebo group and seed 201010 will be used for the AZD8233 group.

7.2 Laboratory Safety Variables

Laboratory measurements according to Section 8 of the CSP:

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
White blood cell (WBC) count	Sodium
Red blood cell (RBC) count	Potassium
Haemoglobin (Hb)	Blood urea nitrogen (BUN)
Haematocrit (HCT)	Creatinine
Mean-corpuscular volume (MCV)	Calcium

Mean corpuscular haemoglobin concentration (MCHC)	Phosphate
Neutrophils absolute count	Creatine kinase (CK)
Lymphocytes absolute count	Direct bilirubin
Monocytes absolute count	Alkaline phosphatase (ALP)
Eosinophils absolute count	Alanine aminotransferase (ALT)
Basophils absolute count	Aspartate aminotransferase (AST)
Platelets absolute count	Gamma glutamyl transpeptidase (GGT)
Reticulocytes absolute count	Total bilirubin (TBL)
	Glutamate dehydrogenase (GLDH)
Urinalysis (dipstick)	Bicarbonate
Urinalysis (positive dipstick)	Uric acid
pH	Follicle stimulating hormone (FSH[women only])
Specific gravity	Luteinising hormone (LH) (women only)
Glucose	haemoglobin A1c, glycated haemoglobin (HbA1c)
Blood	p-glucose
Colour	Estimated glomerular filtration rate (eGFR) by CKD-EPI formula)
Protein	
Clarity/Appearance	**Coagulation**
Nitrites	Prothrombin time
Ketones	Activated partial thromboplastin time (aPTT)
Leukocytes	International normalised ratio (INR)
Microscopic analysis (if positive for blood, nitrites or protein)	
Urobilinogen	**Urine renal safety biomarkers**
	Albumin
Other Laboratory Assessments	Total protein
Complement activation panel (Bb, C5a)	Creatinine
High-sensitivity C-reactive protein (hs-CRP)	Urine protein to creatinine ratio (UPCR)
	Urine albumin to creatinine ratio (UACR)

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