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

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B-100
AST	Aspartate Aminotransferase/Transaminase
ATC	Anatomic Therapeutic Chemical
ATP	According to Protocol
BMI	Body mass index
BP	Blood Pressure
bpm	Beats Per Minute
CI	Confidence Interval
Cmax	Maximum Concentration of Drug Observed after Administration
CM	Concomitant Medication
CRF	Case Report Form
CRP	C-Reactive Protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDV	Early Discontinuation Visit
ENR	Enrolled Participants
EOT	End of Treatment
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
gSD	Geometric Standard Deviation

Abbreviation or Specialized Term	Definition
Hb	Haemoglobin
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
hsCRP	High-sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICE	Intercurrent Events
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
LDL-C	Low-Density Lipoprotein Cholesterol
LH	Luteinizing Hormone
LLOQ	Lower Limit of Quantification
Lp(a)	Lipoprotein (a)
LSMD	Least Squares Mean Difference
MCAR	Missing Completely at Random
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI-RD	Multiple Imputation – Retrieved Dropout
MNAR	Missing not at random
MMRM	Mixed Model for Repeated Measures
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PD	Pharmacodynamic
PK	Pharmacokinetics
PKS	PK Analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile

Abbreviation or Specialized Term	Definition
QTcF	Corrected QT Interval
RAND	Randomly Assigned to Study Treatment Set
RBC	Red Blood Cell
RDMS	Regulatory Document Management System
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SoA	Schedule of Activities
SOC	System Organ Class
TA	Therapeutic Area
TBL	Bilirubin, Total
ULOQ	Upper Limit of Quantification
ULN	Upper Limit of Normal
UNS	Unscheduled Visit
URC	Unblinded Review Committee
VLDL-C	Very-Low-Density Lipoprotein Cholesterol

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	4/16/2024	Initial approved SAP	N/A	N/A
Change to Protocol planned Analysis	11/18/2024	Section 2: added further clarifications on ICEs.	No	Study team's decision: to clarity ICEs considered in this study.
General Definitions	11/18/2024	Section 3.3.1.2: the baseline definition was updated to include clarification on scenarios where time is unavailable.	Yes	To ensure baseline definition covers the scenarios where time is unavailable.
General Definitions	11/18/2024	Section 3.3.1.4: added ICE i.e., "Initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy" and "Any concomitant medication not explicitly specified in the above categories".	Yes	Study team's decision: the initiation, change, or discontinuation of Ezetimibe and/or Bempedoic acid after treatment initiation in the PURSUIT study should be considered an intercurrent event. Moreover, an additional ICE was added to account for possible concomitant medications not covered by the adjusted definitions of ICEs related to other intakes.

General Definitions	11/18/2024	Section 3.3.2: the analysis visit window for efficacy endpoints was aligned with the analysis visit window for safety endpoints, and corresponding specifications for unscheduled visits were added.	Yes	To align with AZ standards.
Disease Characteristics	11/18/2024	Section 4.1.6 added non-prohibited background lipid-lowering non-statin therapy, LDL-C (Friedewald method) and HbA1c at baseline to reporting as disease characteristics.	Yes	Study team's decision: to report baseline intake of ezetimibe and/or bempedoic acid, as well as additional disease characteristics not previously included.
Study Drug Compliance	11/18/2024	Section 4.1.9 compliance definition was updated, and compliance categories restored.	Yes	Study team's decision: to clarify compliance will be calculated based on Drug Accountability form following the standard approach. Additionally, the instructional font was removed to resolve a visibility issue in the PDF, where categories had unintentionally disappeared.
Statistical analysis method for primary endpoint(s)	11/18/2024	Section 4.2.1.1 and 4.2.1.2 : definition and derivation updated to clarify the handling of intercurrent events.	Yes	To improve clarity.

Statistical analysis method for primary endpoint(s)	11/18/2024	Section 4.2.1.4: added the list of fixed effects for the ANCOVA model.	Yes	To clarify which fixed effects will be included in the ANCOVA model.
Statistical analysis method for primary endpoint(s)	11/18/2024	Section 4.2.1.7: added subgroup analyses based on the use of Ezetimibe at baseline and direct LDL-C level categories at baseline.	Yes	Study team's request.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.2.1 and 4.2.2.2 : definition and derivation updated to clarify the handling of intercurrent events.	Yes	To improve clarity.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.2.3: added specification of a new missing data imputation as the primary approach for treatment policy using either the MMRM or ANCOVA model.	Yes	Study team's decision: to distinguish the imputation methodology for monotone missing values that occur prior to ICE and monotone missing values that occur on or after ICE.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.2.5: sensitivity analyses added for multiple imputation under MNAR assumption and without explicit missing data imputation.	Yes	Study team's decision: to assess the impact of missing data imputation.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.2.6: Supplementary analyses were added, replacing direct LDL-C with LDL-C derived from the Friedewald method.	Yes	Study team's request.

Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.2.7, 4.2.3.7 and 4.2.2.6: Subgroup analyses repeated using the treatment policy strategy.	Yes	Study team's request.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.3.1: definition updated to clarify the handling of intercurrent events.	Yes	To improve clarity.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.3.7 and 4.2.2.6: Subgroup analyses added based on baseline Lp(a) values.	Yes	Study team's request.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 4.2.3.7 and 4.2.2.6: Subgroup analyses repeated on treatment policy strategy.	Yes	Study team's request.
Exposure	11/18/2024	Section 4.6.1: Formula updated based on DA form instead of EXL.	Yes	Study team's decision.
Safety Analysis	11/18/2024	Section 4.6.3: - updated categories and parameter thresholds; - added shift tables from baseline to minimum on-treatment and on-study value.	Yes	Study team's decision: to clarify the definitions and improve the completeness of outputs.
Safety Analysis	11/18/2024	Section 4.6.4: updated the list of variables and categories for the urinalysis analysis.	Yes	Study team's request.

Safety Analysis	11/18/2024	Section 4.6.5: added definitions for "Abnormalities in Vital Signs" and shift tables.	Yes	The definitions were missing.
Safety Analysis	11/18/2024	Section 4.6.6: shift tables added.	Yes	The presentation was missing.
Statistical analysis method for secondary endpoint(s)	11/18/2024	Section 7.1: imputation approach extended to all efficacy parameters.	Yes	Study team's decision: to ensure consistency throughout the methodology for secondary endpoints.
Other	11/18/2024	Throughout the document: minor clarifications, changes, and typographical corrections were made, particularly with regard to the removal of the term 'standard of care' and the addition of 'lipid-lowering' in the ICE definitions for both statin and non-statin therapies.	Yes	To enhance clarity and readability.

1 INTRODUCTION

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

This is a randomized, multicenter, parallel-group, double-blind, placebo-controlled, dose-ranging, Phase IIb study in approximately 375 participants with dyslipidemia. The primary objective of the study is to investigate the effect of AZD0780 on LDL-C levels across different dose levels.

The screening period will be up to 3 weeks prior to randomization. Participants with a fasting LDL-C of ≥ 70 mg/dL and < 190 mg/dL, and triglycerides < 400 mg/dL at screening will be eligible. Eligible participants will attend 6 visits during the treatment period and one additional visit in the follow-up period. Eligible participants will be randomized across 5 different treatment groups in a 1:1:1:1:1 ratio for a 12-week treatment period. The planned treatments arms are AZD0780 1 mg, AZD0780 3 mg, AZD0780 10 mg, AZD0780 30 mg, and placebo.

Throughout the document and the subsequent statistical deliverables phrases “subject” and “participant” are used as synonyms and are interchangeable.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

- ECG parameters will be presented descriptively, treatment emergent abnormalities will be summarized, shift tables will be produced and key subject information will be listed.
- Multiplicity adjustments will not be applied for any of the secondary endpoints, and will have nominal p-values presented only.
- Two subcategories of the intercurrent event ‘change in background therapy’ are introduced:
  - ‘Change in background lipid lowering statin therapy’
  - ‘Initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy’ to account for non-statin therapies (such as ezetimibe and bempedoic acid) when assessing the treatment effects.
- The ICE ‘Prohibited medication intake’ is clarified as ‘intake of prohibited medication affecting lipid parameters’.
- Addition of the ICE ‘Prohibited medication not affecting lipid parameters’, ‘intake of any other concomitant medication’, and ‘death’.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The final clinical data lock will occur once all randomised participants have completed their full study participation or withdrawn from study.

The Sponsor may potentially conduct an interim analysis after at least 175 participants had completed 12 weeks of study treatment with the purpose of informing further development of the clinical programme.

3.2 Analysis Sets

A minimum of 5 participants and a maximum of 10 participants in each arm (a minimum of 25 in total and a maximum of 50 in total) will be allocated to sites in Japan. Separate randomization lists will be generated for Japan and for the rest of the world to support exploratory investigation of subgroups, if required outside of CSR and to ensure compliance with the Japanese regulations.

Analysis sets are groups of participants who contributed data points to this clinical trial. Analysis sets are defined in Table 1.

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

- the AZD0780 group if the participant has received any dose of AZD0780 and placebo,
- the AZD0780 treatment group the participant had the longest exposure to if a participant has received multiple doses of AZD0780.

Table 1 – Definition of Analysis Sets

Population/analysis set	Description
Enrolled (ENR)	All participants who sign the ICF.
Randomly Assigned to Study Treatment Set (RAND)	All participants who were randomized. Participants will be analyzed according to the treatment to which they were randomized.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of study intervention. Participants will be included in the analysis according to the treatment to which they were randomized.
Safety Analysis Set (SAS)	All randomized participants who received at least one dose of study intervention. Participants will be included in the analysis according to the treatment they actually received.

PK Analysis Set (PKS)	All participants who received at least one dose of AZD0780 and who had evaluable PK data. Participants will be included in the analysis according to the treatment they actually received.

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

3.3 General Considerations

In the following sections general aspects that are to be considered for the data analysis are described.

3.3.1 General Study Level Definitions

Unless otherwise stated, the general principles described below are followed throughout the study:

- Continuous endpoints are summarised by the number of observations, mean, standard deviation (SD), median, first (Q1) and third quartiles (Q3) (as applicable), minimum, and maximum. For data that requires log-transformation (e.g. PK data), we present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical endpoints are summarised by frequency counts and percentages for each category.

- Unless otherwise stated, summaries will be presented by treatment group and the following categories will be included:

Table 2 - Presented Treatment groups per Analysis Category

Treatment Group	Study Population	Efficacy Analyses	PK Analyses	Safety Analyses
AZD0780 1 mg	X	X	X	X
AZD0780 3 mg	X	X	X	X
AZD0780 10 mg	X	X	X	X
AZD0780 30 mg	X	X	X	X
AZD0780 Total	X			X
Placebo	X	X		X
Total	X			

- For continuous data, descriptive summary statistics (mean, median, Q1, Q3, SD, 95% confidence intervals (CIs)) are rounded to 1 additional decimal place compared to the original data.

- Minimum and maximum are displayed with the same accuracy as the original data.

- For categorical data, percentages are rounded to 1 decimal place.

- In case of efficacy endpoints, the unscheduled analysis visits are not summarized in tables and figures. They are presented in listings.

- In case of safety endpoints, presentations that are by visit will include data points mapped to scheduled analysis visit windows. For other types of safety outputs, all measured data points will be considered in tables, figures and listings.

- Statistical tests will be performed using 2-sided tests at the 5% significance level, if not explicitly specified otherwise.
- SAS® version 9.4 (as a minimum) is used for all analyses.

3.3.1.1 Study Day

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

If the date of the event is on or after the first study treatment administration date, then:

Study Day = date of event – date of first study treatment administration + 1.

If the date of the event is prior to the first study treatment administration date, then:

Study Day = date of event – date of first study treatment administration.

3.3.1.2 Baseline

For analyses on the full analysis set (FAS) and the safety analysis set (SAS), baseline is defined as the last non-missing value prior to or on the date of study treatment administration including unscheduled assessments that occur prior to first administration of study treatment.

Baseline definition will consider date, and time of data collection (if available). The pre-dose assessment will be used as baseline. If time of first study treatment administration is unavailable, the measurement will be assumed to be pre-dose unless the CSP suggests otherwise. Additionally, if there is only one visit eligible to assess participant status at baseline and it occurs on the date of randomization without a recorded time for the assessment, we should also assume it is a baseline assessment unless the CSP suggests otherwise. If more than one assessment is conducted before the first study treatment

administration, assessment conducted closest to the first study treatment intake will be taken as the baseline value.

If there are more than one assessment that meet the baseline criteria (for example, several assessments on the same date prior to first administration and occurring either at the same time or one or all of them without collected time), the average of these values will be used as a baseline. In case of qualitative variables, the clinically least abnormal value will be taken as the baseline value.

Missing baseline values will not be imputed.

3.3.1.3 Definition of study periods

The following periods are defined in this study:

1. Screening

   Start: Signing of the ICF

   End: Day prior to first study treatment administration

2. On-treatment period

   The on-treatment analysis period starts on the date of the first administration of study treatment and ends on the earliest of 10 days following the date of last dose of study treatment or the end of the on-study analysis period.

   Start: Day of first study treatment administration

   End: Day of last study treatment dose + 10 days

   OR

   End of on-study analysis period

   Whichever occurs earlier

3. Follow-up period

   Start: The day after the end of the treatment period

   End: Last day in the study as recorded on the End of Study (EOS) form

4. On-study period

   The on-study analysis period starts on the date of the first administration of study treatment and ends on the End of Study date as recorded on the EOS form, unless the participant dies while under follow-up, then the date of death is taken as the end of the on-study analysis period, as reported on the EOS form. No data should be collected after withdrawal of consent. If a participant withdraws consent to continue in the study, then the on-study analysis period ends on this date at the latest.

   Start: Day of the first study treatment administration

   End: Last day in the study as recorded on the End of Study (EOS) form

The allocation to the study periods is performed after the imputation of date as in Section 3.3.1.6.

3.3.1.4 Intercurrent Events

Intercurrent events (ICEs) are events that happen after treatment initiation and affect either the existence or interpretation of planned measurements.

The intercurrent events, and the applied analysis strategy considered in this SAP are summarized in Table 3.

Table 3– Expected ICEs and the Corresponding Statistical Considerations by Estimand

ICEs	Hypothetical strategy for ICEs defined in the CSP	Treatment policy strategy for ICEs defined in the CSP	Handling in the safety analysis	
			On-treatment	On-study
1. Premature and permanent discontinuation of study treatment	Hypothetical strategy	Treatment policy strategy	Hypothetical strategy	Treatment policy strategy
2. Change in background lipid lowering statin therapy	Hypothetical strategy	Treatment policy strategy	Treatment policy strategy	
3. Initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy	Hypothetical strategy	Treatment policy strategy	Treatment policy strategy	
4. (a) Prohibited medication affecting lipid parameters	Hypothetical strategy	Treatment policy strategy	Treatment policy strategy	
(b) Prohibited medication not affecting lipid parameters	Treatment policy strategy		Treatment policy strategy	
5. Any concomitant medication not explicitly specified in the above categories	Treatment policy strategy		Treatment policy strategy	

6. Death	Hypothetical strategy	Hypothetical strategy	Hypothetical strategy	Hypothetical strategy

ICEs – Intercurrent Events

The occurrence of any ICE does not automatically trigger premature and permanent study discontinuation as described in Section 7. of the latest approved CSP. In case of still applying consent, the participants are expected to attend assessments as described in the Schedule of Activities.

The following ICEs are considered:

1 Premature and permanent discontinuation of study treatment

2 Change in background lipid lowering statin therapy

The allowed background lipid lowering statin therapies are described in Appendix F of the last approved version of CSP and the latest approved version of the Statin eligibility memo. Background therapy is recorded in the EDC as prior medication.
Possible mechanisms of change in background lipid lowering statin therapy include:

(a) Discontinue statin therapy
(b) Change to a different statin therapy in the same intensity category
(c) Change between two statin therapy in allowed intensity category
(d) Change the dose of the statin therapy
(e) Change to a statin therapy in a non-allowed intensity category

3 Initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy.

Substances to be considered as non-prohibited background lipid lowering non-statin therapies:

(a) Ezetimibe
(b) Bempedoic acid

4 Prohibited medication

Prohibited medications are defined in Section 5 of the latest version of the CSP and the latest approved version of the Protocol Deviation Plan.
Prohibited medication is recorded in the EDC as concomitant medication. Prohibited medication intake will be identified by comparison with the substance list found in the

Appendix of the latest approved Prohibited Medication Memo. In this study we distinguish the prohibited medications according to the following categories:

(a) Prohibited medication affecting lipid parameters

These medications interfere with the interpretation of the efficacy endpoints in the study. As such, their effect on the efficacy endpoints will be investigated according to the ICE handling strategies in Table 3.

(b) Prohibited medication not affecting lipid parameters

These medications do not interfere with the interpretation of the efficacy endpoints in the study. As such, they will be handled with the treatment policy strategy, as defined in Table 3.

5 Any concomitant medication not explicitly specified in the above categories

6 Death

3.3.1.5 Definition of study treatment

Study treatment is defined as the randomly assigned study treatment. For details regarding the background lipid lowering statin therapy please refer to Section 5.1 and Appendix F of the latest approved CSP and the Statin eligibility memo.

The study treatment is dispensed in 3 bottles as represented in Table 4. The participant is instructed to take 1 tablet/bottle/day. Treatment compliance is defined in Section 4.1.9.

Table 4 – Representation of the Drug Dispensing Scheme

	Bottle A	Bottle B	Bottle C
1 mg	AZD0780 1 mg	Placebo	Placebo
3 mg	AZD0780 1 mg	AZD0780 1 mg	AZD0780 1 mg
10 mg	AZD0780 5 mg	AZD0780 5 mg	Placebo
30 mg	AZD0780 20 mg	AZD0780 5 mg	AZD0780 5 mg
Placebo	Placebo	Placebo	Placebo

3.3.1.6 Imputation of incomplete dates

For imputations of incomplete dates the latest recommendations of the PhUSE Working Group will be followed.

If date of first administration of study treatment is missing, incomplete AE and CM start and end dates will not be imputed.

Imputation of date of first dose of study treatment

Date and time of first dose of study treatment are mandatory eCRF fields recorded in the Study Treatment Log (EXL). No imputations are expected. In the rare cases of missing date, the date of first dose of study treatment will be imputed if both the following criteria are met:

- There is at least one tablet (including kit number) recorded in the eCRF EXL form
- The first recorded tablet has a missing or partial missing date.

If that is the case, the date of first dose of study treatment is imputed with the date of eCRF Visit 2 (Day 1). Completely missing time and time where only hour is missing is imputed to 00:00. If only minutes are missing, it will be imputed to HH:00.

Imputation of date of last dose of study treatment

Date of last dose of study treatment are mandatory eCRF fields recorded in the Study Treatment Log (EXL). No imputations are expected. In the rare cases of missing date, the date of last dose of study treatment is imputed if both the following criteria are met:

- There is at least one tablet (including kit number) recorded in the eCRF EXL
- The last recorded dose has a missing or partial missing date

If that is the case, the date of last dose of study treatment is imputed with the date in which the participant ended the treatment phase recorded in the End of Treatment (EOT) eCRF.

Imputation of AE end date

The imputation of dates is used to decide the study period the AE falls into. The imputed dates should not be used to calculate durations.

Completely missing AE end dates are not imputed. Partial missing AE end dates are handled as below:

- AE is ongoing

- Set the end date as missing.

- AE is not ongoing
  - Only the day is missing: impute last day of the month of data collection.
    - Check whether end of study date or date of death is earlier than imputed AE end date
      - If yes, re-impute the end of study date (or the date of death if end of study date is missing and the participant is known to have died)
  - Both the day and the month are missing:
    - Impute 31-DEC of year of collection
    - Check whether end of study date or date of death is earlier than imputed AE end date
      - If yes, re-impute the end of study date (or the date of death if end of study date is missing and the participant is known to have died)
  - Only month is missing
    - Apply the same rules as in case of missing month and day.

Imputation of AE start date

Before proceeding with the AE start date imputation, the first dose of study treatment and the AE end date are imputed as described in the previous section.

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

Partial dates are imputed as described below:

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

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

Imputation of concomitant medications and concomitant procedures end date

The imputation of dates is used to decide if a medication or procedure is concomitant. The imputed dates should not be used to calculate durations.

Completely missing end dates or dates for which the year is missing are not imputed. Partial missing concomitant medication end dates are handled as below:

- CM is ongoing
    - Set the end date as missing.
- CM is not ongoing
    - Only the day is missing: impute last day of the month of data collection.
        - Check whether end of study date or date of death is earlier than imputed CM end date
            - If yes, re-impute the end of study date (or the date of death if end of study date is missing and the participant is known to have died)
    - Both the day and the month are missing:
        - Impute 31-DEC of year of collection
        - Check whether end of study date or date of death is earlier than imputed CM end date
            - If yes, re-impute the end of study date (or the date of death if end of study date is missing and the participant is known to have died)
    - Only month is missing
        - Apply the same rules as in case of missing month and day.

Imputation of concomitant medication and concomitant procedures start date

Both completely missing and partially missing start dates are not imputed.

3.3.2 Visit Window

3.3.2.1 Analysis Visit Windows

For the purpose of the statistical analysis, all parameters presented by visit are allocated to the analysis visit as reported in Table 5 below. The allocation to visit windows is performed after the imputation of date of first and last doses of study treatment as in Section 3.3.1.6. Measurements not done or with missing or partially missing dates will not be imputed to any analysis visit.

The visit closest to the scheduled visit day will be mapped to the visit window, irrespective of whether it is scheduled and unscheduled. If there are multiple measurements in the same analysis visit window, they will all be mapped to the same analysis visit window and the one closest to the scheduled visit day will be included in the analysis.

Scheduled visits are defined in 1.2. Schedule of Activities section of the CSP.

A summary of the analysis visit windows for scheduled visits is provided in Table 5.

Table 5 – Analysis Window of Scheduled Visits

Analysis visit	Targeted visit day	Analysis visit windows (days)
Screening	D -21 to D -1	Up to D -1
Day 1	D1	D1
Week 1	D8	D5-D11
Week 2	D15	D12-D18
Week 4	D29	D24-D34
Week 8	D57	D52-D62
Week 12	D85	D80-D90
Week 14	D99	D94-D104

Early discontinuation visits (EDV) are mapped based on their time of occurrence to scheduled or unscheduled visit windows, and are not automatically mapped to Visit 8 as presented in CSP Section 1.2. Schedule of Activities.

3.3.2.2 Special cases

More than one measurement falls in the same visit window:

- PK measurements are mapped to the nominal visits
- One measurement falls on the scheduled visit day: the measurement on the scheduled visit date is used.
- No measurements fall on the scheduled visit day:

  The time-interval between the scheduled visit day and the day of the measurement is to be considered.

  - Different intervals: the nearest to the scheduled visit day is taken.
  - Same intervals: the first measurement after the scheduled visit day is to be considered.
  - Several measurements are collected during the same day the following is taken into consideration:
    - PK: selected timepoint within the day.
    - Numeric values: the average of measurement values.
    - Categorical values: clinically worst value.

3.3.2.3 Handling of Unscheduled Visits

Both unscheduled and scheduled visits are considered when assigning the visit windows as described in Section 3.3.2.1. If there are measurements that have not yet been assigned to an analysis window, they are labelled as described in Table 6 below.

Table 6 – Analysis Windows for Unscheduled Visits

Analysis visit	Analysis visit windows (days)
(UNS) Week 0	D2-D4

(UNS) Week 3	D19-D23
(UNS) Week 5	D35-D39
(UNS) Week 6	D40-D46
(UNS) Week 7	D47-D51
(UNS) Week 9	D63-D67
(UNS) Week 10	D68-D74
(UNS) Week 11	D75-D79
(UNS) Week 13	D91-D93
(UNS) Week 15+	From D105

UNS= unscheduled visit

The unscheduled visits falling into the same window will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in the unscheduled visit window that occur between visit Day 65 and Day 67, then these unscheduled visits will be numbered (UNS) Week 9.1 and (UNS) Week 9.2 in the order they occurred.

For measurements on a specific parameter that are not planned to be taken within a scheduled visit window according to the Schedule of Activities in the CSP but have been taken, a corresponding unscheduled visit will be created (e.g., An ApoA1 value measured at D8 will be mapped to (UNS) Week 1).

3.3.3 Multiplicity/Multiple Comparisons

Adjustment for multiple comparisons against placebo will be applied to the primary endpoint as listed in Table 8. To strongly control the familywise error rate at the 0.05 level (2-sided) for the primary endpoint, a hierarchical testing strategy (closed testing procedure) will be employed. The alpha expenditure will be allocated to test the null hypotheses as detailed in Table 7.

Table 7 – Order of Hierarchical Testing to Control Type I Error

Order	Null hypothesis	Alternative hypothesis
H1	$\mu_{\text{AZD0780 30 mg}} = \mu_{\text{placebo}}$	$\mu_{\text{AZD0780 30 mg}} \neq \mu_{\text{placebo}}$
H2	$\mu_{\text{AZD0780 10 mg}} = \mu_{\text{placebo}}$	$\mu_{\text{AZD0780 10 mg}} \neq \mu_{\text{placebo}}$
H3	$\mu_{\text{AZD0780 3 mg}} = \mu_{\text{placebo}}$	$\mu_{\text{AZD0780 3 mg}} \neq \mu_{\text{placebo}}$

H4	$\mu_{AZD0780\ 1\ mg} = \mu_{placebo}$	$\mu_{AZD0780\ 1\ mg} \neq \mu_{placebo}$

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

H1 will be tested first using the full test mass alpha. If H1 is rejected, then the full test mass will be recycled to test H2. If H2 is rejected, then H3 will be tested with full alpha, and if H3 is rejected, H4 will be further tested with full alpha. For all other comparisons, no multiplicity adjustment will be applied.

3.3.4 Handling of Protocol Deviations in Study Analysis

Important Protocol Deviations are detailed in the current, approved Protocol Deviation Plan.

Categories of IPDs:

1. Inclusion Criteria Deviations
2. Exclusion Criteria Deviations
3. Discontinuation Criteria for study product met but participant not withdrawn from study treatment
4. Discontinuation Criteria for overall study withdrawal met but participant not withdrawn from study
5. Investigational Product (IP) Deviation
6. Excluded Medications taken
7. Deviations related to study procedure
8. Other Important Protocol Deviations

IPDs will not be used to exclude any participant from any analysis set described in this SAP, unless otherwise specified. Please refer to Section 3.3.1.4 for definition of ICEs and the associated handling strategies. A list of all protocol deviations will be reviewed and documented by the study team physician, clinical pharmacology scientist (if relevant) and statistician prior to clinical data lock.

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, disease characteristics, medical history, prior and concomitant medication, and study treatment compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

For disposition and completion status, the following definitions will apply:

- Subjects enrolled will be defined as a subject who signed the informed consent of the study.
- Subjects not randomised have consented to participate in the clinical study but are not subsequently randomly assigned to study intervention.
- Subjects randomised will be defined as a subject who has been randomised to a treatment group.
- Subjects randomised, not treated will be defined as a randomised subject who has not received any study treatment.
- Subjects who started treatment will be defined as a randomised subject who has received at least one dose of study treatment.
- Subjects who completed treatment will be defined as a subject who started treatment and has not permanently prematurely discontinued study treatment during the study. A subject who dies during participation without having permanently discontinued study treatment prior to date of death, will be considered to have completed treatment.
- Subjects who discontinued treatment will be defined as a subject who started treatment and has permanently prematurely discontinued study treatment for reasons other than death. The reasons for discontinuation as collected on the EOT eCRF will be presented. For reason collected as other, the specify field will be presented in listings but not in the disposition table.
- Subjects who completed study will be defined as a subject who has not withdrawn consent, has not been lost to follow-up and has not died.
- Subjects withdrawn from study will be defined as a subject who has withdrawn consent, has 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 study completion status will be summarised overall and by planned treatment group (if applicable) for all enrolled subjects. Number of participants in each category will be presented, when applicable, percentages will also be presented. Disposition of enrolled participants will be presented in a listing, alongside age, sex assigned at birth, ethnicity, and race.

Participant recruitment will be summarized by region, country, and site. Region is defined in Appendix B (Section 7.2)

In case of global and local *vis major* events, number and percentage of affected participants in the randomized population will be summarized overall and by treatment group as defined in Section 3.3.

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 presented by number and percentage (if applicable) of participants in each analysis set defined in Section 3.2, by treatment group and overall. The reason for exclusion from an analysis set will be tabulated and listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Deviations from the protocol will be assessed as important or non-important by blinded members of the study team before clinical data lock and unblinding based on the latest approved version of the Protocol Deviation Plan.

4.1.3.2 Presentation

Important Protocol Deviations (IPDs) will be summarized for the FAS. Number and percentage of participants with at least one IPD in any of the IPD categories, as well as by category, will be presented by treatment group and overall.

Details about the IPDs, start and end date of the IPDs will be listed by participant.

4.1.4 Demographics

4.1.4.1 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, Multiple, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Region and country

4.1.4.2 Presentation

Demographics will be summarised for participants in the FAS, by treatment group and overall.

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

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline participant characteristics includes:

- Weight (kg)
- Height (cm)
- BMI (kg/m2)
- BMI group:
    - 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 (≥ 30 kg/m^2).

BMI will be automatically calculated in the EDC as weight (kg)/[height (m)]^2 based on weight and height of the participant collected at baseline.

4.1.5.2 Presentation

Baseline participant characteristics will be presented descriptively for each treatment group and overall for the FAS. Height, weight, and BMI will be presented as continuous variables with descriptive statistics. BMI will also be presented categorically by BMI group.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics will be presented:

- Background lipid lowering statin therapy at baseline
- Non-prohibited background lipid lowering non-statin therapy at baseline
- The following parameters (from blood sample) at baseline:
    - Direct LDL-C
    - LDL-C (Friedewald method)
    - Total cholesterol
    - HDL-C
    - Triglycerides
    - Non-HDL-C
    - VLDL-C
    - ApoA1
    - ApoB
    - Lp(a)
    - Remnant cholesterol
    - hsCRP
    - PCSK9
- Renal function based on eGFR at screening
    - $45 \leq$ eGFR <60
    - $60 \leq$ eGFR <90
    - eGFR ≥ 90
- Glycaemic control at baseline
    - HbA1c

4.1.6.2 Presentation

Disease characteristics will be summarised for each treatment group and overall for the FAS.

Background therapy and renal function based on eGFR will be characterized by categorical summary, and blood and glycaemic control parameters will be presented as continuous variables with descriptive statistics as defined in Section 3.3.1.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history will be coded according to MedDRA version 26.0 or higher.

4.1.7.2 Presentation

Categorical summary of medical history will be presented in summary tables as number and percentages of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall for the FAS. Participants are only counted once per SOC and PT regardless of the number of occurrences within each category. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. PT will be presented nested within the relevant SOC and sorted by international order of SOC and alphabetically by PT.

Medical history will be presented overall and by the age groups specified in Section 4.1.4.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior medications are those taken prior to study treatment with a stop date prior to the first dose of the study treatment.

Concomitant medications (CM) are either ongoing or those with a stop date on or after the date of the first dose of study treatment, and must have started prior to or during treatment so there is at least one day in common with the study treatment.

Prohibited concomitant medications are defined in Section 5. and 6.9 of the CSP, and are listed in the latest approved version of the Prohibited Medication Memo. All other concomitant medications are classified as allowed.

Prior and concomitant medications will be coded according to WHODrug.

4.1.8.2 Presentation

Categorical summary of prior and concomitant medications will be presented.

Prior and concomitant medications will be summarized by ATC classification and generic drug name for each treatment group and overall for the FAS. Participants 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.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Percent compliance to treatment will be calculated for each participant based on tablet count as: the number of tablets taken (dispensed minus returned), divided by the number of tablets expected to have been taken, multiplied by one hundred. The number of tablets expected to have been taken is defined as 1 tablet/bottle (3 tablets in total) multiplied by 'date of last dose minus date of first dose plus one'. If the number of tablets dispensed, or the number of tablets returned, is missing for at least one observation for a participant, compliance is not calculated for that participant.

4.1.9.2 Presentation

Compliance (%) will be summarised as a continuous and categorical variable for each treatment group and overall for the FAS.

The compliance categories to be presented are the following:

1. <80% compliance
2. 80%-120% compliance
3. >120% compliance

4.2 Endpoint Analyses

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

Table 8 - Objectives, Endpoints and Estimand attributes

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "ideal" scenarios in which intercurrent events would not occur					
Primary analysis of	Percent change from baseline of direct LDL-C at Week 12	FAS	See details in Table 3.	Difference in mean percent change from	4.2.1

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
the primary endpoint				baseline to Week 12 between treatment groups (LSMD from MMRM model without explicit imputation).	
Objective 2a: To evaluate the effect of different doses of AZD0780 on LDL-C versus placebo in "real-world" conditions					
Primary analysis of the secondary endpoint	Percent change from baseline of direct LDL-C at Week 12	FAS	See details in Table 3.	Difference in mean percent change from baseline to Week 12 between treatment groups (LSMD from MMRM model with multiple imputation).	4.2.2
Objective 2b: To assess the PK of AZD0780					
Primary analysis of the secondary endpoint	AZD0780 plasma concentrations summarized by sampling timepoints	PK analysis set		Summary statistics presented by sampling timepoints.	4.4
Objective 2c: To evaluate the effects of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "ideal" scenarios in which intercurrent events would not occur					
Primary analysis of the secondary endpoint	Percent change from baseline at Week 12 in: • Total cholesterol • HDL-C • Triglycerides	FAS	See details in Table 3.	Difference in mean percent change from baseline to Week 12 between treatment groups (LSMD from	4.2.3

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	• Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Remnant cholesterol • hsCRP			MMRM model without explicit imputation).	
Objective 2d: To evaluate the effects of AZD0780 on other lipid parameters and inflammatory markers versus placebo in "real-world" conditions					
Primary analysis of the secondary endpoint	Percent change from baseline at Week 12 in: • Total cholesterol • HDL-C • Triglycerides • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Remnant cholesterol • hsCRP	FAS	See details in Table 3.	Difference in mean percent change from baseline to Week 12 between treatment groups (LSMD from MMRM model with multiple imputation).	4.2.4
Objective 3: To assess the safety and tolerability of AZD0780					
Safety and tolerability	Safety and tolerability will be assessed in terms of AEs, vital signs, ECG, and clinical laboratory evaluations	SAS	See details in Table 3.	Descriptive statistics	4.6.2 4.6.3 4.6.4 4.6.5 4.6.6
Objective 4: *Exploratory objectives*					
Exploratory analysis	To assess baseline PCSK9 levels	NA	NA	NA	Results of baseline PCSK9

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
					levels may be reported outside of the CSR.
Exploratory analysis	To collect and store plasma, serum, and urine samples for potential future exploratory biomarkers involved in PK, PD, safety and tolerability related to AZD0780 treatment and/or cardiometabolic diseases	NA	NA	NA	Results of potential future exploratory biomarkers may be reported outside of the CSR
Exploratory analysis	***Optional:*** To store DNA from blood samples according to each country's local and ethical procedures for future exploratory research into genetic variations that may influence AZD0780 treatment	NA	NA	NA	Results of possible future genetic research may be reported outside of the CSR

AE = adverse event; ApoA1 = apolipoprotein A-1; ApoB = apolipoprotein B-100; CSR = Clinical Study Report; DNA= Deoxyribonucleic acid; ECG = electrocardiogram; FAS = Full Analysis Set; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low- density lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSMD = Least Square Mean Difference; MMRM = Mixed Model for Repeated Measures; NA = Not Applicable; PCSK9 = Proprotein Convertase Subtilisin/Kexin Type 9; PD = Pharmacodynamic; PK = pharmacokinetic(s); SAS = Safety Analysis Set; VLDL-C = very-low-density lipoprotein cholesterol.

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary efficacy endpoint is percent change from baseline to Week 12 in direct LDL-C. The clinical question of interest is:

What is the difference in means of percent change in LDL-C from baseline to Week 12 in participants with dyslipidemia treated with AZD0780 vs placebo in the hypothetical condition that all participants could adhere to study intervention and non-prohibited

background lipid lowering statin and non-statin therapy, prohibited medications affecting lipid parameters were not available, regardless of whether additional treatment is used, where participants cannot die.

The primary estimand attributes are defined as:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia, defined by the inclusion and exclusion criteria. Implemented using FAS.
- Endpoint: Percent change in direct LDL-C from baseline at Week 12.
- Population-level summary measure: Difference in means of percent change in direct LDL-C from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The hypothetical strategy will be used for premature and permanent discontinuation of study treatment; change in background lipid lowering statin therapy; initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy and intake of prohibited medications affecting lipid parameters. Efficacy assessments obtained after these will not be included in the analysis. Initiation or changes in other concomitant or prohibited medication will be handled with treatment policy strategy. Deaths will be handled with a hypothetical strategy.

4.2.1.2 Derivations

Direct LDL-C below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

Percent change from baseline is derived as:

$$\frac{(y_{V_j} - y_{BL})}{y_{BL}} * 100$$

where

- y_{V_j} represents the efficacy measurement at Visit *j*, and
    - *j* refers to the visit number, specifically 3,4,5,6,7 (i.e., the visits included in the analysis),
        - In case of treatment discontinuation ICE, *j* includes all visits up to and including the date of treatment discontinuation.

- For every other ICE handled with the hypothetical strategy, *j* refers to the last visit before the first ICE occurrence handled with the hypothetical strategy, as detailed in Section 3.3.1.4.

- y_{BL} is the efficacy measurement at Baseline.

4.2.1.3 Handling of Dropouts and Missing Data

Missing baseline measurements

Missing baseline values will not be imputed.

Non-monotone missing data

Non-monotone missing data means that observations exist after the time point with the missing data.

Non-monotone missing data will not be explicitly imputed.

Monotone missing data

Monotone missing data are defined on a participant level as missing data that constitutes the end of participant follow-up.

Monotone missing data will be assumed to be Missing at Random (MAR) and will not be explicitly imputed.

4.2.1.4 Primary Analysis of Primary Endpoint

The summary measure for the primary endpoint will be the difference in least squares mean of percent change from baseline of direct LDL-C at Week 12. The primary endpoint will be analysed using a MMRM on the FAS. Percent change from baseline in direct LDL-C at each post-baseline visit will be used as the dependent variable. The model will include the fixed effects of baseline direct LDL-C, treatment group, visit, and treatment-by-visit interaction, and the random effect (random intercept) of participant. The Restricted Maximum Likelihood estimation approach will be used with a compound symmetry covariance structure for repeated measures.

In case of non-converge, an ANCOVA model will be run. The model will include the fixed effects of baseline direct LDL-C and treatment group as covariates. In this model, the dependent variable will be the percent change in direct LDL-C from baseline to Week 12.

The results will be summarized by the difference in least squares means, 95% confidence interval, and p-value.

The hierarchical testing strategy will be employed to strongly control the familywise error rate at the 0.05 level (2-sided), as described in Section 3.3.3.

The primary endpoint will also be characterized by descriptive statistics (as defined in Section 3.3.1) at each scheduled visit and visualized with line plot.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

No sensitivity analysis is planned for the primary estimand.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The supplementary analysis of the primary endpoint using the primary estimand will be conducted by replacing the direct LDL-C with the LDL-C derived from the Friedewald equation with reflex ultracentrifugation using the analysis model specified in Section 4.2.1.4.

4.2.1.7 Subgroup Analyses

The primary endpoint will also be assessed based on the intensity of the statin background therapy at baseline. Both descriptive and inferential statistics will be presented.

Additionally, the subgroup analysis will be conducted based on Ezetimibe use at baseline (categorized as 'Yes' and 'No') and direct LDL-C levels at baseline (categorized as <2.6 mmol/L, >=2.6 mmol/L to <=3.9 mmol/L, and >3.9 mmol/L).

The statistical model described in Section 4.2.1.4 will be applied to each subgroup separately.

If the number of participants is too small within a subgroup, the subgroup categories may be redefined prior to unblinding of the study.

4.2.2 Secondary Endpoint: Percent change from baseline of LDL-C at Week 12

4.2.2.1 Definition

The clinical question that this estimand aims to answer is the following:

What is the difference in means of percent change in LDL-C from baseline to Week 12 in participants with dyslipidemia treated with AZD0780 vs placebo, regardless of study treatment adherence, changes in background lipid lowering statin therapy, initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy and use of allowed and prohibited concomitant medications, where participants cannot die?

The estimand is described by the following attributes:

- Treatment: AZD0780 or placebo.

- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia, defined by the inclusion and exclusion criteria. Implemented using the FAS.
- Endpoint: Percent change in direct LDL-C from baseline at Week 12
- Population-level summary measure: Difference in means of percent change in direct LDL-C from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The treatment policy strategy will be used for all ICEs except death in this analysis. With this strategy, efficacy assessments are used for treatment effect estimation regardless of the occurrence of ICEs. In case of death, the hypothetical strategy will be applied.

4.2.2.2 Derivations

Direct LDL-C below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

The dependent variable is percent change from baseline to Week 12 in LDL-C. Values taken into consideration in the statistical analysis are derived as:

$$\frac{(y_{V_j} - y_{BL})}{y_{BL}} * 100$$

where

- y_{V_j} represents the efficacy measurement at Visit j, and
  - j refers to the visit number up to the last completed visit, which can take any value from the set of {3, 4, 5, 6, 7}
- y_{BL} is the efficacy measurement at Baseline.

4.2.2.3 Handling of Dropouts and Missing Data

Monotone missing values will be imputed using different methods depending on whether they occurred prior to or after any of the ICEs described in the CSP (i.e., ICE 1, 2, 3, 4(a) described in Table 3). Details on the imputation algorithm is outlined in Appendix A Missing data handling: MI-RD and placebo-washout imputation.

4.2.2.4 Primary Analysis of Secondary Endpoint

The secondary endpoint will be analysed using a MMRM based on the FAS, missing data will be imputed prior to fitting the model, as described in Section 4.2.2.3

The analysis model is specified in Section 4.2.1.4.

The secondary endpoint will also be characterized by descriptive statistics (as defined in Section 3.3.1) at each scheduled visit and visualized with line plot.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

4.2.2.5.1 Sensitivity analysis 1: Analysis with multiple imputation under the MNAR assumption for all monotone missing data

A sensitivity analysis that does not distinguish between the imputation approach in Step 2, Appendix 7.1 Table 12 for monotone missing data occurring prior to or after any of the ICEs described in the CSP will be conducted. In this sensitivity analysis all monotone missing data will be imputed under the MNAR assumption according to MI-RD or – if MI-RD is not feasible – the placebo washout methodology.

4.2.2.5.2 Sensitivity analysis 2: Analysis without explicit missing data imputation

A sensitivity analysis that does not explicitly impute missing data will also be conducted. In this sensitivity analysis, the analysis method will be the same as the main analysis described in 4.2.2.4 except that missing data will not be explicitly imputed prior to model fitting.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

The supplementary analysis of the secondary endpoint using the primary estimand will be conducted by replacing the direct LDL-C with the LDL-C derived from the Friedewald equation with reflex ultracentrifugation using the analysis model specified in Section 4.2.2.4.

4.2.2.7 Subgroup Analyses

The subgroup analysis described in Section 4.2.1.7 will be conducted for this secondary endpoint as well.

4.2.3 Secondary Endpoint: Percent change from baseline of lipid parameters and inflammatory markers at Week 12 (hypothetical strategy for ICEs defined in the CSP)

The following lipid and inflammatory parameters will be analysed as secondary endpoints using same model as described in Section 4.2.1.4:

- Non-HDL-C
- VLDL-C
- ApoA1
- ApoB
- Total cholesterol
- HDL-C

- Triglycerides
- Lp(a)
- Remnant cholesterol
- hsCRP

4.2.3.1 Definition

The clinical question of interest is:

What is the difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 in participants with dyslipidemia treated with AZD0780 vs placebo in the hypothetical condition that all participants could adhere to study intervention and non-prohibited background lipid lowering statin and non-statin therapy, prohibited medications affecting lipid parameters were not available, regardless of whether additional treatment is used, and participants cannot die.

The estimands are described by the following attributes:

- Treatment: AZD0780 or placebo.
- Population: Male and female participants of non-childbearing potential, 18 to 75 years of age with dyslipidemia, defined by the inclusion and exclusion criteria. Implemented using the FAS.
- Endpoint: Percent change in other lipid parameters and inflammatory markers from baseline to Week 12.
- Population-level summary measure: Difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 between AZD0780 and placebo.
- Handling of intercurrent event: The hypothetical strategy will be used for premature and permanent discontinuation of study treatment; change in background lipid lowering statin therapy; initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy and intake of prohibited medications affecting lipid parameters. Efficacy assessments obtained after these will not be included in the analysis. Initiation or changes in other concomitant medication will be handled with treatment policy strategy. Deaths will be handled with the hypothetical strategy.

4.2.3.2 Derivations

Percent change from baseline at Week 12 will be derived according to the specifications in Section 4.2.1.2.

4.2.3.3 Handling of Dropouts and Missing Data

Considerations about missing data is detailed in Section 4.2.1.3.

4.2.3.4 Primary Analysis of Secondary Endpoint

The secondary endpoint will be analysed using a MMRM based on the FAS, in alignment with the primary analysis strategy as described in Section 3.3.1.4.

The analysis model is specified in Section 4.2.1.4. Multiplicity adjustment defined in Section 3.3.3 will not be applied to these endpoints.

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint

Not Applicable.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint

Not Applicable.

4.2.3.7 Subgroup Analyses

A subgroup analysis may be conducted to assess the impact of baseline lipoprotein(a) [Lp(a)] levels on the treatment effect on Lp(a). The analysis will stratify participant based on their baseline Lp(a) values, as below:

- Lp(a) < 50 mg/dL
- Lp(a) ≥ 50 mg/dL

The primary analysis described in Section 4.2.3.4 will be applied separately to each Lp(a) subgroup. If the number of participants is too small within a subgroup, the subgroup categories may be refined prior to unblinding of the study.

4.2.4 Secondary Endpoint: Percent change from baseline of lipid parameters and inflammatory markers at Week 12 (treatment policy strategy for ICEs defined in the CSP)

The lipid and inflammatory endpoints are detailed in Section 4.2.3.

4.2.4.1 Definition

The clinical question of interest is:

What is the difference in means of percent change in other lipid parameters and inflammatory markers from baseline to Week 12 in participants with dyslipidemia treated with AZD0780 vs placebo, regardless of study treatment adherence, changes in background lipid lowering statin therapy, initiation, change or discontinuation in non-prohibited background lipid lowering non-statin therapy and use of allowed and prohibited concomitant medications, where participants cannot die?

The estimands are described by the following attributes:

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

4.2.4.2 Derivations

Percent change from baseline at Week 12 will be derived according to the specifications in Section 4.2.2.2.

4.2.4.3 Handling of Dropouts and Missing Data

Please refer to the approach described in Section 4.2.2.3.

4.2.4.4 Primary Analysis of Secondary Endpoint

The secondary endpoint will be analysed using a MMRM based on the FAS, in alignment with the secondary analysis strategy as described in Section 3.3.1.4.

The analysis model is specified in Section 4.2.1.4. Multiplicity adjustment defined in Section 3.3.3 will not be applied to these endpoints.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint

Not Applicable.

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

Not Applicable.

4.2.4.7 Subgroup Analyses

The subgroup analysis described in Section 4.2.3.7 will be conducted for this endpoint as well.

4.2.5 Exploratory Endpoint

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

4.3 Pharmacodynamic Endpoint(s) (if not already covered as endpoint variables)

Not Applicable.

4.4 Pharmacokinetics

Plasma concentration data of AZD0780 will be summarized by treatment group for each sampling timepoint using number of measurements below LLOQ, arithmetic mean and SD, geometric mean and CV, minimum, median and maximum.

The geometric mean of plasma concentrations versus time will be plotted by dose in a line plot both on the linear and on the log-linear scale.

If data permit a population PK (popPK) model may be developed, possibly with the support of PK data from other studies, using nonlinear mixed effects regression analysis in NONMEM. Exposure/response modeling may also be performed to characterize the relationships between AZD0780 exposure and measures of efficacy (eg LDL-C) and safety. PopPK and Exposure/response analysis will use all available data including data corresponding to both on and off treatment (eg missed doses).

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

4.4.1 Derivation

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as NQ (Not Quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant TFLs.

Individual concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. If more details are collected regarding the reasons for missing concentrations, the comment text will be displayed.

Concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.

- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the geometric mean, the gSD, geometric mean ± gSD and geometric CV will be set to Not Calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The geometric mean, minimum, median and maximum will be reported as NQ and the geometric CV, gSD and geometric mean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).
- Three observations > LLOQ are required as a minimum for a plasma concentration to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC. One observation > LLOQ is presented as maximum with the other summary statistics as NC.

4.5 Immunogenicity

Not Applicable.

4.6 Safety Analyses

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

Tables are provided for the SAS unless otherwise specified, for baseline, on-treatment and on-study periods as defined in Section 3.3.1.3.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure data will be presented for the on-treatment period.

Duration of exposure will be presented for all strength of AZD0780, AZD0780 Total, Placebo and Total.

Exposure measured as amount administered will be presented for all strength of AZD0780, and AZD0780 Total.

Duration of exposure is calculated for participants in the SAS as the total number of days on study treatment and it is calculated as:

Duration of exposure (days) = min(Last day of study treatment + 10, Last study visit) - first day of study treatment + 1

Last study treatment administration will be extracted from the EXL form, while the first dose administration is derived from the earliest administered dose collected on the EXL form. If any of the first or last dates are missing or partially missing, then imputed dates will not be used and study treatment exposure is set to missing.

Cumulative exposure is also computed using the following duration (days) categories:

- ≥ 14 days
- ≥ 28 days
- ≥ 56 days
- ≥ 84 days

These categories are cumulative, and participants will be included in all categories that apply to them.

Exposure as measured by amount administered will be calculated from the data collected on the DA form as:

$$m\ (AZD0780)\ [mg] = \sum_{i=P_1}^{P_{Last\ dispensing\ period}} ((n(tablet\ dispensed)_{Bottle\ A} - n(tablet\ returned)_{Bottle\ A}) * dose(tablet)_{Bottle\ A}) + ((n(tablet\ dispensed)_{Bottle\ B} - n(tablet\ returned)_{Bottle\ B}) * dose(tablet)_{Bottle\ B}) + ((n(tablet\ dispensed)_{Bottle\ C} - n(tablet\ returned)_{Bottle\ C}) * dose(tablet)_{Bottle\ C})$$

Where,

- $m\ (AZD0780)[mg]$ – exposure to AZD0780 as measured by amount administered in milligrams
- $n(tablet\ dispensed)_z$ – number of tablets dispensed in z at the beginning of given dispensing period
  - z: $\{Bottle\ A, Bottle\ B, Bottle\ C\}$
- $n(tablet\ returned)_z$ – number of tablets returned in z at the end of given dispensing period
  - z: $\{Bottle\ A, Bottle\ B, Bottle\ C\}$
- $dose(tablet)_z$ – dose of the tablet in z in a given day

  - z: $\{Bottle\ A, Bottle\ B, Bottle\ C\}$
- P_x – dispensing period

4.6.1.2 Presentation

The duration of exposure and exposure as measured by amount administered will be summarized using descriptive statistics according to the group defined in Section 4.6.1.1. Duration of exposure will also be presented categorically by using the cumulative categories as described above. Exposure over time will be presented in a figure, with one line for each treatment group.

A listing with individual exposure to study treatment will be presented.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

The Medical Dictionary for Regulatory Activities (MedDRA) (latest version) is used to code the AEs. AEs are graded according to their intensity (Mild, Moderate, Severe) and they will be classified by MedDRA system organ class (SOC) and MedDRA preferred term (PT).

For rules on missing or partial dates, see Section 3.3.1. AEs with a missing start time (or where time is not collected) which occur on the same day as first study treatment administration are reported as on-treatment.

The following definitions and principles are to be followed:

Any AE

Defined as participants with at least one reported AE with an onset date within the analysis periods defined in Section 3.3.1.3.

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 participant. The start date of the AE determines the analysis period, irrespective of date of death.

AEs Leading to Discontinuation of study treatment

Defined as an AE with action taken study treatment reported as drug withdrawn. The start date of the AE determines the analysis period, irrespective of date of discontinuation of study treatment.

AEs Leading to Interruption of study treatment

Defined as an AE with action taken study treatment reported as drug interrupted. The start date of the AE determines the analysis period, irrespective of date of interruption of study treatment.

AEs Leading to Withdrawal of the Participant from the Study

Defined as an AE with action taken as Participant Withdrawn from Study. The onset date of the AE determines the analysis period, irrespective of date of withdrawal.

SAEs

Defined as participants with at least one reported serious AE, irrespective of outcome, with an onset date within the defined analysis period. The onset date of the premeditating AE determines whether the SAE belongs to the analysis period, irrespective of the date the AE becomes serious.

AEs Possibly Related to study treatment

Defined as an AE that is reported as "reasonable possibility of a causal relationship between the study treatment and the AE". If this causality evaluation is missing, it will be counted as an AE possibly related to study treatment.

4.6.2.2 Presentation

Treatment groups will be presented according to Table 2.

AEs are counted once for each participant for calculating percentages of participants experiencing AE. In addition, if the same AE occurs multiple times within a particular participant, the highest intensity and level of relationship observed are reported. For tables by MedDRA SOC and MedDRA PT, participants with multiple AEs are counted once for each SOC/PT.

The durations reported in the listings, will be derived only for fully completed dates as below:

- Time from first dose of study treatment to AE (in days) will be calculated as the AE start date minus date of first dose of study treatment +1. Time from first dose to death and AE becoming serious will be calculated with the corresponding formula.
- Time from (last dose prior to AE start) and (last dose prior to death) will be calculated as the (date of death or AE start date) minus the (date of last dose of study treatment prior to AE) and death, respectively, +1.

The following summary table will be presented on participant-level:

- Number of participants with any AE
- Number of participants with any AE considered related to study treatment
- Number of participants with any SAE with outcome of death
- Number of participants with any SAE
- Number of participants with any AE leading to discontinuation of study treatment
- Number of participants with any AE leading to interruption of study treatment
- Number of participants with any AE leading to withdrawal of participant from the study

The following summary tables will be presented by SOC and PT on participant-level:

- AEs
- AEs that are possibly related to study treatment
- SAEs
- SAEs with outcome of death
- SAEs that are possibly related to study treatment
- AEs leading to discontinuation of study treatment
- AEs by maximum intensity on the preferred term level.

The following summary tables will be presented by PT:

- AEs sorted by decreasing frequency of PT, based on the actual treatment arm "AZD0780 30 mg"

A list of key participant information for participants with SAEs with outcome of death, participants with SAEs, participants with AEs leading to discontinuation of study treatment will be provided. A listing of all AEs will also be provided.

A table with non-serious adverse events occurring in more than 5% of participants will be reported.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Table 9 – Blood Sample Safety Variables

Haematology/Haemostasis	**Clinical Chemistry**

• Blood
  ○ Haematocrit
  ○ Hb (g/L)
  ○ Leukocyte count
  ○ Leukocyte differential count (absolute count)
  ○ MCV (fL)
  ○ MCH (pg)
  ○ MCHC (g/L)
  ○ Platelet count
  ○ RBC
  ○ Reticulocyte absolute count
  ○ Coagulation
  ○ HbA1C
	• Plasma/Serum
	  ○ Albumin (g/L)
	  ○ ALP (ukat/L)
	  ○ ALT (ukat/L)
	  ○ AST (µmol/L)
	  ○ Bilirubin, total (µmol/L)
	  ○ Bicarbonate (mmol/L)
	  ○ Blood urea nitrogen
	  ○ Creatinine (µmol/L)
	  ○ GGT (ukat/L)
	  ○ High sensitivity CRP (mg/L)
	  ○ Potassium (mmol/L)
	  ○ Sodium (mmol/L)
	  ○ Total Protein (g/L)
	• eGRF (mL/min/1.73m^2)

ALP = alkaline phosphatase; ALT = alanine aminotransferase/transaminase; AST = aspartate aminotransferase/transaminase; CRP = C-reactive protein; eGFR: Glomerular Filtration Rate; GGT = gamma glutamyl transpeptidase; Hb = haemoglobin; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell.

LLOQ and ULOQ

Laboratory parameters below the lower limit of quantification (LLOQ) for which the exact value cannot be determined, will be replaced with the LLOQ/sqrt(2) value. Similarly, laboratory test results above the upper limit of quantification (ULOQ) for which the exact value cannot be determined, will be replaced with the ULOQ value. After the LLOQ/ULOQ replacement, change from baseline to each post-baseline visit is defined as the post-baseline visit value minus the baseline value. After the LLOQ/ULOQ replacement, safety clinical laboratory results are also classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on the reference range indicator. Tables will utilize the LLOQ/ULOQ replacement. However, listings will display the original LLOQ/ULOQ inequality (e.g., "< x" and "> x").

Abnormalities in Laboratory Parameters

Treatment emergent abnormalities are defined as abnormalities that manifested after the first administration of study treatment.

The predefined criteria for a parameter abnormality are based on reference ranges from the central lab and defined as >ULN or <LLN, where applicable. In addition, the following definitions of abnormalities (non-mutually exclusive) will be used for specific parameters listed below:

- Platelet count: < 50, < 75, < 100, < 150 x 10^9/L, and > 30% decrease from baseline
- 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
- ALP: > 2 x ULN, > 3 x ULN
- Total Bilirubin (TBL): > 2 x ULN, > 5 x ULN, > 8 x ULN
- eGFR: ≥ 25% decrease, ≥ 50% decrease and ≥ 75% decrease
- Creatinine: ≥ 1.5 x baseline, ≥ 2 x baseline and ≥ 3 x baseline

Potential Hy's Law

Potential Hy's law is defined as AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN at any point during the study, following the start of study intervention irrespective of an increase in ALP. The elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Shift Tables

Shift tables will be presented for the following parameters according to unique thresholds:

For ALT and AST:

- ≤ 1 x ULN
- > 1 x ULN and ≤ 3 x ULN
- > 3 x ULN and ≤ 5 x ULN
- > 5 x ULN and ≤ 10 x ULN
- > 10 x ULN and ≤ 20 x ULN
- > 20 x ULN

Bilirubin, total will be categorised into:

- ≤ 2 x ULN
- >2 x ULN and ≤ 5 x ULN
- >5 x ULN and ≤ 8 x ULN
- >8 x ULN

ALP will be categorised into:

- ≤ 2 x ULN
- >2 x ULN and ≤3 x ULN
- >3 x ULN

Platelet absolute count will be categorised into:

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

Categories for parameters that are not listed above will be defined according to the mutually exclusive thresholds based on central laboratory ranges (when applicable):

- < LLN
- ≥ LLN and ≤ ULN
- > ULN

Risk differences between active treatment groups and Placebo and 95% confidence intervals of the risk difference will be calculated according to the following formulas:

$$\delta_{Trt-Placebo} = \pi_{Trt} - \pi_{Placebo}$$

$$Var(\delta_{Trt-Placebo}) = Var(\pi_{Trt}) + Var(\pi_{Placebo})$$

$$CL_{Trt-Placebo}: \delta_{Trt-Placebo} \pm 1.96 * \sqrt{Var(\delta_{Trt-Placebo})}$$

Where:

- Trt: All strength of AZD0780 as presented in Table 2 and AZD0780 Total
- $\delta_{Trt-Placebo}$ −Difference between treatment group and Placebo
- π − Proportion of subjects with given blood abnormalities in each treatment group
- $Var()$ – Variance of a given parameter
- CL− 95% confidence limits

4.6.3.2 Presentations

All laboratory data will be presented for the on-treatment and on-study periods using international system of units and presented as detailed in Table 2.

Clinical laboratory parameters will be presented by scheduled visit, separately for haematology and chemistry 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 from baseline will be presented using descriptive statistics for all scheduled assessments after baseline.

The number of participants with treatment-emergent laboratory parameter abnormalities will be presented categorically in frequency tables, according to the categories defined in Section 4.6.3.1. Risk differences between active treatment groups and Placebo will be presented with 95% CI.

Key subject information will be separately listed for participants with haematology abnormalities, chemistry abnormalities, or potential Hy's law. Additionally, individual chemistry laboratory measurements and individual haematology laboratory measurements will be listed.

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

A descriptive table for maximum ALT and AST versus maximum total bilirubin for the on-treatment and on-study analysis periods will be shown.

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

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urinalysis will be done according to the schedule of activities in the CSP (Table 1). The parameters included in the scope of the analysis are specified in the list below:

Table 10 – Renal Safety Variables

Qualitative	Quantitative
• Urobilinogen • Erythrocytes • Glucose	• pH • Specific gravity • Albumin/Creatinine (ratio)

• Ketones • Leukocytes esterase • Nitrites • Protein	

Abnormalities in Urinalysis Parameters

Treatment emergent abnormalities are defined as abnormalities that manifested after the first administration of study treatment.

For quantitative parameters, participants with treatment emergent urinalysis abnormalities will be categorized according to mutually exclusive thresholds based on central laboratory ranges: < LLN, > ULN.

In addition, abnormalities in 'albumin/creatinine' (ratio) will be defined as ≥ 300 mg/g.

Shift Tables

Shift tables will be presented for all parameters according to thresholds described below.

For qualitative parameters, the values will be reported using ordered categorical values, where 'Negative' represents the absence of abnormality, and increasing levels (Trace, +, ++, +++, ++++) indicate progressively worsening of abnormality.

For quantitative parameters, the categories will be defined according to the mutually exclusive thresholds based on central laboratory ranges (when applicable):

- < LLN
- ≥ LLN and ≤ ULN
- > ULN

4.6.4.2 Presentations

Treatment emergent urinalysis abnormalities by predefined criteria will be presented in a frequency table. Risk differences between active treatment groups and Placebo will be presented, alongside 95% confidence intervals of the risk difference according to the definitions in Section 4.6.3.1.

Shift tables will present changes from baseline to the maximum (for quantitative parameters) or the worst (for qualitative parameters) on-treatment and on-study values, using the standard categories and classifications described in 4.6.4.1.

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

4.6.5 Vital Signs

4.6.5.1 Definitions and Derivations

The following vital signs will be measured:

- Body weight (kg)
- Body temperature (degrees Celsius)
- Heart (pulse) rate (bpm)
- Respiratory rate (1/min)
- Oxygen saturation (SpO_2)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)

Vital signs will be collected at the visits indicated in the SoA (see CSP).

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range or limit), and high (if value is above the normal reference range or limit) according to the normal reference values given in Table 11 below. Based on the categories presented in Table 11 variables may have 2-level classification and 3-level classification.

Systolic and diastolic blood pressure will be measured in triplicates and the mean of the three measurements will be collected in the EDC and used in the subsequent analyses.

Table 11 - Vital Signs Normal Reference Ranges

Parameter	Normal reference range
Systolic blood pressure	< 140 mmHg
Diastolic blood pressure	< 90 mmHg
Heart (pulse) rate	50-100 bpm
Body temperature	≤ 37°C
Oxygen saturation	≥ 95%
Respiratory rate	12-20 per minute

Abnormalities in Vital Signs

Treatment emergent abnormalities are defined as abnormalities that manifested after the first administration of study treatment.

The presence of the abnormalities will be determined based on the following criteria (at any time during treatment/study, as applicable):

1. Systolic blood pressure
    a. Maximum value is > 40 mmHg increase from baseline
    b. Maximum value is > 180 mmHg
    c. Maximum value is ≥ 140 mmHg with ≥ 20 mmHg increase from baseline
    d. Maximum value is ≥ 160 mmHg with ≥ 30 mmHg increase from baseline
    e. Maximum value is ≥ 180 mmHg with ≥ 40 mmHg increase from baseline
    f. For change from baseline to mean value
        i. > 10 mmHg
        ii. > 20 mmHg
        iii. > 30 mmHg
        iv. > 40 mmHg
2. Diastolic blood pressure
    a. Maximum value is > 20 mmHg increase from baseline
    b. Maximum value is > 100 mmHg
    c. Maximum value is ≥ 90 mmHg with ≥ 10 mmHg increase from baseline
    d. Maximum value is ≥ 100 mmHg with ≥ 20 mmHg increase from baseline
    e. For change from baseline to mean value
        i. > 10 mmHg
        ii. > 20 mmHg
        iii. > 30 mmHg
        iv. > 40 mmHg
3. Heart rate

a. Maximum value is > 100 beats/min with > 20 beats/min increase from baseline

b. Minimum value is < 50 beats/min with > 20 beats/min decrease from baseline

c. Minimum value is < 60 beats/min with > 20 beats/min decrease from baseline

Shift Tables

Shift tables will be presented for all parameters based on the following thresholds:

1. Diastolic Blood Pressure (DBP):
   - Normal (<90 mmHg)
   - High (≥90 mmHg)
2. Systolic Blood Pressure (SBP):
   - Normal (<140 mmHg)
   - High (≥140 mmHg)
3. Heart (Pulse) Rate:
   - Low (<50 bpm)
   - Normal (50-100 bpm)
   - High (>100 bpm)
4. Body Temperature:
   - Normal (≤37°C)
   - High (>37°C)
5. Oxygen Saturation:
   - Low (<95%)
   - Normal (≥95%)
6. Respiratory Rate:

- Low (<12 breaths/min)
- Normal (12-20 breaths/min)
- High (>20 breaths/min)

4.6.5.2 Presentations

Observed values and change from baseline in vital signs will be summarised by the treatment group and visit with descriptive statistics.

A figure with mean change from baseline over time by treatment group will be presented.

Shift tables from baseline to maximum on-treatment and on-study value (excluding Oxygen Saturation, because shift to maximum is not relevant), from baseline to minimum on-treatment and on-study value will be presented for each treatment group and AZD0780 Total.

Treatment emergent vital signs abnormalities will be reported as defined in Section 4.6.5.1.

Risk differences between active treatment groups and Placebo will be presented, alongside 95% confidence intervals of the risk difference according to the definitions in Section 4.6.3.1.

The key subject information about the treatment emergent vital signs abnormalities will also be listed. Additionally, individual vital signs data will be listed.

4.6.6 Electrocardiogram

4.6.6.1 Definitions and Derivations

At visits specified in the Schedule of activities (CSP), 12-lead ECG will be obtained in triplicates, using the study site's own ECG machines. The following variables will be collected: PR interval, RR interval, QRS duration, QT and QTcF intervals, and heart rate. All ECG parameters will be measured in triplicates and the mean value will be entered to the EDC system and will be used in subsequent calculations. Additionally, an overall evaluation of ECG results will also be performed.

Abnormalities in ECG

Treatment emergent abnormalities in QTcF at any visit will be summarised using following criteria:

- QTcF value above specific ms at any time:
  - > 450 and ≤ 480 (ms)
  - > 480 and ≤ 500 (ms)
  - > 500 (ms)

- QTcF increase from baseline by more than specific ms at any time:
  - > 30 and ≤ 60 (ms)
  - > 60 (ms)
- QTcF value above specific ms and QTcF increase from baseline by more than specific ms at any time:
  - Value > 450 and ≤ 500 (ms) and increase > 30 and ≤ 60 (ms)
  - Value > 500 (ms) and increase > 60 (ms)
  - Value > 450 and ≤ 500 (ms) and increase > 60 (ms)
  - Value > 500 (ms) and increase > 30 and ≤ 60 (ms)

Shift Tables

Shift tables will be presented for ECG parameters according to the following categories: "normal", “borderline”, "abnormal, not clinically significant", and "abnormal, clinically significant".

4.6.6.2 Presentations

Descriptive statistics per visit and change from baseline will be presented for all parameters.

Treatment emergent electrocardiogram abnormalities by predefined criteria (Section 4.6.6.1) will be presented.

ECG overall assessment (report by "normal", “borderline”, "abnormal, not clinically significant", and "abnormal, clinically significant") at baseline versus the last value on-treatment and on-study will be presented. Shift table from baseline to worst on-treatment and on-study value will also be presented. Key subject information about treatment emergent ECG abnormalities will be listed. Additionally, measurements of individual ECG data and abnormalities in ECG will be presented in the listings.

4.6.7 Other Safety Assessments

Not Applicable.

5 INTERIM ANALYSIS

An interim analysis with the purpose of informing further development of the clinical programme, including but not limited to dose selection for Phase 3 may be conducted when at least 175 randomized participants have completed 12 weeks of treatment. The unblinded team would consist of members responsible for the unblinded analysis conduct and members of the Unblinded Review Committee (URC). The URC would review the results of interim analysis. Details will be described in a separate URC charter.

6 REFERENCES

D7960C00006 (AZD0780) Clinical Study Protocol Version 3.0

PhUSE guidance

http://www.phusewiki.org/wiki/index.php?title=Imputing_Partial_Dates

7 APPENDIX

7.1 Appendix A Missing data handling: MI-RD and placebo-washout imputation

For post-baseline missing values on secondary endpoints used to assess Objective 2a and 2d (Table 8), a distinction in the imputation will be made between non-monotone and monotone missing data.

The steps of the imputation algorithm are described in Table 12.

Table 12 - MMRM 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 the baseline value of the respective secondary endpoint, along with all scheduled post-baseline assessments for that endpoint, organized in chronological order. In this step, 1000 imputation datasets will be generated using the seed 230612, 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 values prior to the first occurrence of any of the intercurrent events described in the CSP for the respective secondary endpoint, assuming missing at random, using the MAR statement. For each of the 1000 imputed datasets, impute all monotone missing values after the first occurrence of any of the intercurrent events described in the CSP for the respective secondary endpoint sequentially using the pattern mixture model assuming missing data are missing not at random (MNAR) with the seed 2306121. 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, participants are categorised either as on-treatment (= participant for whom Time t is during the on-treatment period), or as treatment discontinuers (= participant for whom Time t is outside the on-treatment period). Values after death ICE will not be imputed. 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. Participants who had missing data imputed at previous timepoints will contribute to the imputation for the current timepoint.
Step 3	Fit MMRM or ANCOVA models	Fit the pre-specified MMRM 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. If the MMRM model cannot be fitted due to convergence issues, use the ANCOVA model in this step.
Step 4	Pool MMRM or 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. In case in the pooling step zero between imputation variabilities are encountered when using the MMRM model, ANCOVA model may be considered.

This MI-RD approach described in Step 2 in Table 12 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, monotone missing data until Week 12 in the placebo group will be replaced based on participants in the same group using standard MI and assuming missing at random, including baseline value and observations between baseline and Week 12 in the imputation model. Missing values in the active treatment group after first occurrence of any of the intercurrent events described in the CSP will be replaced by washout multiple imputation. For the sensitivity analysis described in Section 4.2.2.5.1, all monotone missing values would be imputed with placebo washout if MI-RD is not feasible.

In washout multiple imputation, monotone missing 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., 2306121). For the imputation of monotone missing data, seed 102010 will be used for the placebo group and seed 201020 will be used for the AZD0780 group.

7.2 Appendix B Region definition

Region	Country
Asia	Japan
Europe	Czech Republic
	Denmark
	Hungary
	Slovakia
	Spain
North America	Canada
	United States of America