Statistical Analysis Plan	
Study Code	D7990C00003
Edition Number	V4.0
Date	11/08/2021

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CS	Compound symmetry covariance structures
CSP	Clinical study protocol
CSR	Clinical study report
CTMS	Clinical trial management system
CV	Coefficient of variation
D	Day
dLDL-C	Direct low-density lipoprotein cholesterol
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	Early discontinuation visit
EXP	Exponent
GGT	Gamma glutamyl transferase
HbA1c	Haemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HLT	High level term
HR	Heart rate
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
IDRP	Integrated data review plan
IP	Investigational product
IPD	Important protocol deviation
IRT	Interactive Response Technology
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
Lsmean	Least squared mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NHP	Non-compliance handling plan

PCSK9	Proprotein convertase subtilisin/kexin type-9
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
QRS	QRS wave
QT	QT wave
QTcF	Corrected QT Interval using Fridericia's Formula
REML	Restricted maximum likelihood
RR	Respiratory rate
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study data tabulation model
SE	Standard error
SI	International system of units
SMQ	Standardized MedDRA queries
SOC	System organ class
SP(POW)	Power spatial covariance structures
TBL	Total bilirubin
TC	Total cholesterol
TE-ADA	treatment emergent ADA
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
UNS	Unscheduled
URC	Unblinding review committee team
VLDL-C	Very-low-density lipoprotein cholesterol
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

AMENDMENT HISTORY

Version number	Date	Brief description of change
V1.0	18/11/2020	N/A
V2.0	09/04/2021	Minor amendment: added the IPD list, not available at the time of V1.0; reviewed some sections about external data, not available at the time of V1.0; added correlation analysis on LDL-c and additional figures for ADA parameters as per sponsor late request. All the other minor changes are reported in section 8.1.2.
V3.0	22/06/2021	Minor amendment: added "+1" in the calculation of durations for ADA measurements
V4.0	10/08/2021	Minor amendment: Rephrased the description of ADA boxplots

1 STUDY DETAILS

1.1 Study objectives

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

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

Two analyses are planned for this study:

- A primary analysis after the treatment period,
- A complete analysis after the final follow-up (after final database lock).

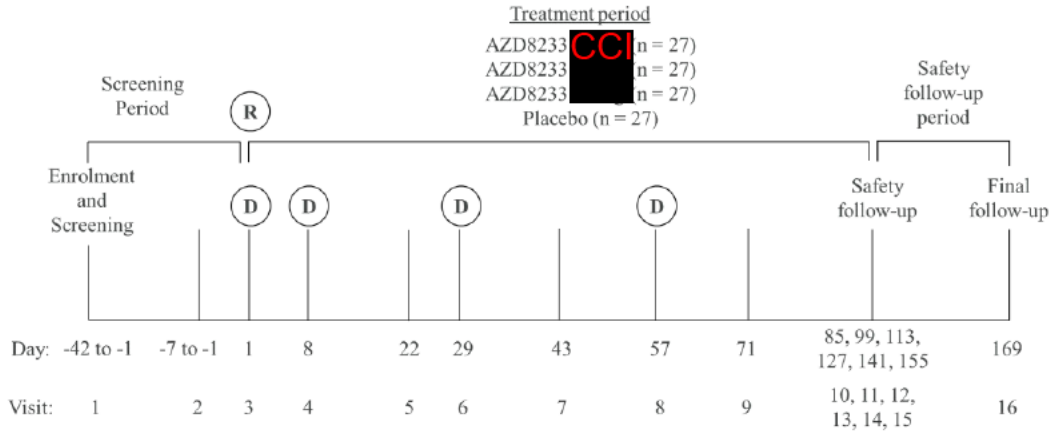
The two analyses will have the same scope, except for lipoprotein profile which will be included only in the complete analysis, as described in sections 2, 3 and 4. With the aim to maintain the blinding the primary analysis will be performed by an independent unblinded team. The purpose of the primary analysis is to help inform further clinical development; no changes will be made to this study unless a safety signal is observed. This analysis will not have any impact on the overall type-1 error because no changes will be made to the trial based on the outcome of the analysis (all efficacy data is already collected at the point of the primary analysis, no changes to the efficacy model will be made). The primary analysis will be done when all patients still in study have completed the treatment period (visit 10). Additional details will be given in the primary analysis charter and the Unblinded Review Committee (URC) charters (i.e. data cut-off rules, data cleaning, nomination of the unblinded biometrics team and the URC and the operational procedures used to protect the blinding).

1.2 Study design

This is a randomized, parallel, double-blind, placebo-controlled, dose-ranging Phase 2b study in approximately 108 participants with dyslipidaemia. The study will be conducted in up to 25 sites in up to 4 countries.

The screening period starts up to 42 days before the randomization visit and ends on Day -1. Eligible participants will attend 7 visits during the treatment period and 7 additional visits during the safety follow up period. Eligible participants are randomized across four different treatment arms in a 1:1:1:1 ratio stratified by region (North America vs Europe) for a 12-week treatment period. The planned treatment arms are AZD8233 CCI SC, AZD8233 CCI SC, AZD8233 CCI SC, and Placebo SC on Days 1, 8, 29, and 57.

Figure 1 Study Design



Note: All visits include blood and urine sample collection as well as safety assessment.
D = dosing day; R = randomization

Note: All visits include blood and urine sample collection as well as safety assessment, except for Visit 2, which includes only blood sample collection.

D = dosing day; R = randomization

Subjects who discontinue the treatment but not the study, should perform the EDV at the next scheduled visit and then go to the following scheduled visits exactly as subjects who are still on-treatment, for a total of 3 months.

The table below shows all procedures to be conducted at the scheduled visits.

Table 1 Schedule of assessment

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

Table 1 Schedule of assessment

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

Table 1 Schedule of assessment

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

Table 1 Schedule of assessment

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

Table 1 Schedule of assessment

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

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

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

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

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

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

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

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

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

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

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

[i] PK sampling to be performed at Visits 4 (D8), 6 (D29), 7 (D43), 8 (D57), 9 (D71), 10 (D85), 12 (D113) and 14 (D141) and final follow-up visit/EDV. Schedule of sampling for Visits 4 (D8), 6 (D29), 8 (D57) are shown below.

Visit 4 (Day 8; Loading dose): pre-dose
Visit 6 (Day 29; Dose 3): pre-dose
Visit 8 (Day 57; Final dose): pre-dose

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

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

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

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

1.3 Number of subjects

Approximately 108 participants will be randomly assigned to study intervention such that at least 80 evaluable participants complete the study. Any participant who receives at least one dose of study intervention is considered evaluable and is included in the full analysis set. Participants are randomly assigned to study treatment in a ratio of 1:1:1:1.

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

2 ANALYSIS SETS

2.1 Definition of analysis sets

All analysis sets are reported in the table below.

Table 2 Populations for Analysis

Population/Analysis set	Description
All enrolled subjects	All participants who sign the ICF.
All randomized subjects	All participants who were randomized. Participants will be analysed according to the treatment to which they were randomized.
Full analysis set	All randomized participants who received at least one dose of IP, in accordance with the intention to treat principle. Participants will be included in the analysis according to the treatment to which they were randomized. This is the primary analysis set.
Safety analysis set	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment and for whom any post-dose data are available. Participants will be analysed according to the treatment which they actually received. If a participant received study intervention from the wrong kit for only part of the treatment duration and then switched to another, the associated treatment group for that participant will be the treatment group that participant was randomized to.
ADA analysis set	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment and had at least one ADA assessment available. Participants will be included in the analysis according to the treatment to which they were randomized.
PK analysis set	All participants in the full analysis set who have at least one PK sample post dose. A patient will be considered as having at least one PK sample post dose if he has at least one plasma concentration that is not below LLOQ after the first dose. Subjects will be analysed according to the treatment which they actually received. However, only samples taken on patients planned to receive active

	treatment are analysed. Thus, patients planned to receive placebo but who finally received active treatment will not have any result available.

2.2 Violations and deviations

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

- All IPDs included in the category 1 - Inclusion Criteria Deviations (Subject who did not meet the below criteria. Those who entered the study even though they did not satisfy the entry criteria. If Screen failure, then this is not PD);
- All IPDs included in the category 2 - Exclusion Criteria Deviations (Enrolled, even though subject fulfilled the below criteria. Those who entered the study even though they did not satisfy the entry criteria. If Screen failure, then this is not PD);
- All IPDs included in the category 3 - Discontinuation Criteria for study product met but patient not withdrawn from study treatment.
- All IPDs included in the category 5 - Investigational Product (IP) Deviation, with the except of the IPD 5.02 - Subjects who were randomised but did not receive IP which is not considered relevant.
- All IPDs included in the category 6 - Excluded Medications taken.

3 BASELINE, EFFICACY AND SAFETY EVALUATION

3.1 General principles

3.1.1 Handling of missing data

Missing data are not replaced unless otherwise specified for the statistical models. Only date of first and last dose of IP, AE start and end date and concomitant medications end date are imputed. Imputation rules are reported below.

3.1.1.1 Imputation of date of first dose of IP

Date and time of first dose of IP are mandatory eCRF fields recorded in the treatment log. No Imputations are expected. In the rare cases of missing date, the date of first dose of IP will be imputed if all the following criteria are met:

- There is at least one injection (including lot number) recorded in the eCRF treatment log
- The first recorded injection has a missing or partial missing date

If that is the case, the date of first dose of IP is imputed with the date of eCRF visit Day 1. Completely missing time and time where only hour is missing is imputed to 00:00. If only minutes are missing, then it will be imputed to HH:00.

3.1.1.2 Imputation of date of last dose of IP

Date and time of last dose of IP are mandatory eCRF fields recorded in the treatment log. No Imputations are expected. In the rare cases of missing date, the date of last dose of IP is imputed if all the following criteria are met:

- There is at least one injection (including lot number) recorded in the eCRF treatment log
- The last recorded dose has a missing or partial missing date

If that is the case, the date of last dose of IP is imputed with the date in which the subject ended the treatment phase recorded in the end of treatment eCRF.

3.1.1.3 Imputation of AE end date

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

- If the AE is ongoing, the end date is stated to missing.
- If the AE is not ongoing, and if only the day is missing: Assume the last day of the collected month.
- If the AE is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

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

3.1.1.4 Imputation of AE start date

Before to proceed with the AE start date imputation, the first dose of IP 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 IP, assume 01-MMM-YYYY. If the month and year are the same as the first dose of IP month and year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date is prior to the first dose of IP, then assume the end date.

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

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

3.1.1.5 Imputation of concomitant medications and concomitant procedures end date

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

- If the concomitant medication is ongoing, the end date is set to missing.
- If the concomitant medication / procedure is not ongoing, and if only the day is missing: Assume the last day of the collected month.
- If the concomitant medication / procedure is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed date is after the end of study date or the date of death, the concomitant medication / procedure end date is set to the earliest date between the end of study date and the date of death.

3.1.1.6 Imputation of concomitant medication and concomitant procedures start date

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

3.1.2 Analysis visit windows

For the purpose of the statistical analysis all parameters, except the adverse event, concomitant medication / procedure, medical history, protocol deviations and other non-compliances reported in the CTMS and some demographic data (sex, ethic group and race) are allocated to the analysis visit as reported in the tables below. The allocation to visit windows is performed after the imputation of date of first and last doses of IP as in section 3.1.1. Measurements with missing or partially missing dates cannot be imputed to any analysis visit.

Table 3 Analysis visit windows

Analysis visit (AVISIT)	Scheduled visit day	Visit Window (Days)	Days of flexibility used to build the visit window
Baseline	D-42 to D1	<=1[a]	
Day 1	1	1[b]	
Week 1	8	6 – 10	2
Week 3	22	19 – 25	3
Week 4	29	26 – 32	3
Week 6	43	39 – 47	4
Week 8	57	53 – 61	4
Week 10	71	67 – 75	4
Week 12	85	80 – 87	5 - 2

Table 3 Analysis visit windows

Analysis visit (AVISIT)	Scheduled visit day	Visit Window (Days)	Days of flexibility used to build the visit window
Week 14	99	92 – 106	7
Week 16	113	107 – 120	7
Week 18	127	121 – 134	7
Week 20	141	135 – 148	7
Week 22	155	149 – 162	7
Week 24	169	163 – 176	7

[a] Includes all measurements collected before or on day 1 prior to first dose of IP. If the measurement is collected on day 1 but it cannot be determined if it was done before or after the first dose of IP (due to missing time and/or planned time point), then it will be considered as collected after the first dose of IP. For height, weight, BMI and Age if the measurement is collected/derived on day 1, it is always considered as collected before the first dose of IP.

[b] Includes all measurements collected at day 1 on or after the first dose of IP.

After having assigned the visit windows as described above, if there are measurements which have not yet the analysis visit assigned, they are labelled as reported in the table below.

Table 4 Analysis visit windows for unscheduled visits

Analysis visit (AVISIT)	Visit Window (Days)
UNS 1	2 – 5
UNS 2	11 – 18
UNS 3	NA
UNS 4	33 – 38
UNS 5	48 – 52
UNS 6	62 – 66
UNS 7	76 – 79
UNS 8	88 – 91
UNS 9	>=177

The unscheduled visits will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in the unscheduled visits that occur between visit Day 29 and Day 43, then these unscheduled visits will be numbered UNS 4.1 and UNS 4.2 in the order they occurred. The unscheduled visits are not summarized in tables but only presented in listing.

For the purpose of the statistical analysis:

- the baseline value used for statistical analyses is the last available value among those in the baseline analysis visit window. If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements is taken. If there are several categorical values corresponding to the worst case, then the last measurement registered in eCRF will be taken.
- all the other post baseline visit values: If more than one measurement falls in the same visit window but in different days, the nearest to the scheduled visit day is taken. If several measurements are collected within the same distance from the scheduled study day, the data of the earlier visit after the scheduled study day within that window is used. If several measurements are collected during the selected day (selected timepoint within the day for PK), the average (for numeric values)/worst (for categorical values) of the measurements is taken. If there are several categorical values corresponding to the worst case, then the last measurement registered in eCRF will be taken. For coagulation parameters and complement activation panel if the selected day is a dosing day (except Day 1), two timepoints within the day need to be considered (pre-dose and 2h post-dose).

Averages are calculated after LLOQ replacement as reported in the following sections.

3.1.3 Study phase windows

For the purpose of the statistical analysis adverse events, immunogenicity data, LDL-C, PCSK9, other lipid parameters, lipoprotein profile, laboratory evaluations, vital sign and ECG are allocated to the study phase in which they are collected as reported below. The allocation to the study phases is performed after the imputation of date of first and last doses of IP as in section 3.1.1. The allocation of the AEs to the study phases is performed after the imputation of AE start and AE end dates as reported in section 3.1.1.

Table 5 Study phases

Study phase	Phase Window for Analysis (Days)
Pre-treatment	before first dose of study IP (day <1[a])
On-treatment	> day 1[b] to the end of study date

[a] Includes all measurements collected before first dose of IP. If the measurement is collected on day 1 it cannot be determined if it was done before or after the first dose of IP (due to missing time and/or planned time point), then it will be considered as collected after first dose of IP.

[b] Includes all measurements collected on the day of first dose of IP, at the time of IP intake and after.

3.2 Baseline assessments and other subject-specific characteristics

Demographic and subject characteristics, medical history and nicotine and alcohol use are collected pre-treatment as per section 1.2.

3.2.1 Demographic and subject characteristics

Demographic and subject characteristics include age, age group (<50; >=50 -<65; >=65), sex, race, ethnic group, country, region, height (cm), weight (kg), body mass index (BMI) (kg/m2). Age is the age at screening as reported in the eCRF, BMI (kg/m2) is calculated as: weight (kg) / [(height (cm)/100)]^2.

Height, weight and BMI are allocated to the concerning analysis visits as per section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit. Only baseline values are included in the demographic and subject characteristics.

3.2.2 Medical history and prior procedures

The eCRF collects any relevant medical histories and prior procedures. Medical history and prior procedures are coded in MedDRA version 23.0 or higher.

The procedures are classified as prior as below:

The imputation method described in section 3.1.1.5 is used in case the procedure end date is partially missing. The imputation method described in section 3.1.1.1 is used in case the first dose of IP date and time are missing or partially missing.

After the end date imputation, the procedures will be classified as either prior or concomitant (but not both) according to the end date. Prior procedure is defined as any procedure with an end date prior to the first dose of IP (exclusive). Concomitant procedure is defined as any procedure with an end date on or after the first dose of study drug. Procedures with completely missing end date are classified as concomitant.

3.2.3 Nicotine and alcohol use

Nicotine and alcohol use (never-current-former) are collected at screening.

3.3 Efficacy, safety and exploratory variables

The primary efficacy endpoint of the study is

1. the change from baseline in log-transformed dLDL-C compared with placebo descriptively for all visits and within a statistical model at the week 12.

The secondary efficacy endpoints of the study are:

2. the change from baseline in log transformed PCSK9 compared with placebo descriptively for all visits and within a statistical model at the week 12
3. the percent change from baseline in dLDL-C compared with placebo descriptively for all visits and within a statistical model at the week 12.
4. Correlation of LDL-C Friedewald and LDL-C Martin-Hopkins with dLDL-C
5. Level of other lipid parameters compared with placebo descriptively for all visits and within a statistical model at the week 12. Other lipid parameters include:
   - TC
   - HDL-C
   - Non-HDL-C
   - VLDL-C
   - ApoA1
   - ApoB

- Lp(a)
- Triglycerides
- Remnants cholesterol

6. PK parameters (to be reported in a separate report)
7. Development of ADA and immunogenicity titre during the on-treatment and follow-up analysis phases

The safety endpoints of the study are:

8. AE
9. Vital signs
10. ECG
11. Safety clinical laboratory parameters

The exploratory endpoint of the study is:

12. Lipoprotein profile

Efficacy, safety, and exploratory endpoints are collected as reported in section 1.2.

3.3.1 Primary endpoint

3.3.1.1 Change from baseline in log-transformed dLDL-C

dLDL-C is assessed in a central laboratory. LDL-C is assigned to the analysis visits and analysis phase as described in section 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase. dLDL-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.

After the LLOQ replacement, change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. The relative change from baseline is calculated back transforming the change from baseline of the log-transformed variable.

3.3.2 Secondary efficacy endpoints

3.3.2.1 Change from baseline in natural logarithm transformed PCSK9

PCSK9 is assessed in a central laboratory. PCSK9 is assigned to the analysis visits and analysis phases as described in sections 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase. PCSK9 below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. The relative

change from baseline is calculated back transforming the change from baseline of the log-transformed variable. Percent change from baseline is also calculated as the visit value minus the baseline value divided by the baseline value *100.

3.3.2.2 Percent change from baseline in LDL-C

dLDL-C is assessed in a central laboratory. dLDL-C is assigned to the analysis visits and analysis phases as described in sections 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase. dLDL-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.

After the LLOQ replacement, percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value *100.

3.3.2.3 LDL-C Friedewald and LDL-C Martin-Hopkins

LDL-C Friedewald and LDL-C Martin-Hopkins are also derived in a central laboratory. LDL-C Friedewald and LDL-C Martin-Hopkins are assigned to the analysis visits and analysis phase as described in section 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase.

3.3.2.4 Level of other lipid parameters

Other lipid parameters include:

- TC
- HDL-C
- Non-HDL-C
- VLDL-C
- ApoA1
- ApoB
- Lp(a)
- Triglycerides
- Remnants cholesterol

Lipid parameters are assessed in a central laboratory. Lipid parameters are assigned to the analysis visits and analysis phases as described in sections 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase. Lipid parameters below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline of the log-transformed variable is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm. The relative change from baseline is calculated back transforming the change from baseline of the log-transformed variable. Percent change from baseline is also calculated for all variables as the visit value minus the baseline value divided by the baseline value *100.

3.3.2.5 Pharmacokinetic parameters

PK concentrations are tested in a central external laboratory as per scheduled timepoints.

PK concentrations are assigned to the analysis visits as described in section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit. PK concentrations below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ.

PK parameters are not derived and analysed within this SAP. Details on pharmacokinetic parameters are provided in an additional bioanalytical report prepared by a dedicated pharmacometrics support group at AstraZeneca.

3.3.2.6 Immunogenicity

Immunogenicity parameters are:

- ADA
- Immunogenicity titre

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

All these parameters are assigned to the analysis visits and to the analysis phases as described in section 3.1.2 and in section 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase. ADA confirmed positive results with titre lower than the MRD (<50) will be replaced with titre =50 for the statistical analysis.

The study day of ADA measurement is calculated as the date of the ADA sample collection – the date of first IP +1 for ADA sample collected on or after the day of first IP and as the date of the ADA sample collection – the date of first IP for ADA sample collected before the day of first IP.

3.3.3 Safety endpoint

3.3.3.1 Adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered. SAEs will be collected from time of signature of informed consent, throughout the treatment period

and including the follow-up period. All non-serious AEs will be recorded from time of first dose of IP, throughout the treatment period and including the follow-up period. Adverse events (AEs) will be coded with MedDRA version 23.0 or higher. For any additional details on AE reporting please refer to the study protocol.

After start and end date imputation as per section 3.1.1 the AEs are assigned to the study phases described in section 3.1.3, based on the AE start date and time as follows:

If both the start date and start time of an AE are known, then:

- If the AE start datetime is before the first dose of IP datetime, then the AE is assigned to the pre-treatment phase.
- If the AE start datetime is on or after the first dose of IP datetime, then the AE is assigned to the on-treatment phase,

If only the start date of an AE is known, and the start time of the AE is unknown, then:

- If the AE start date is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE start date is on or after the first dose of IP date then the AE is assigned to the on-treatment phase,

If the start date of an AE is completely missing, the AE is assigned as follow:

- If the AE end date is known and is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE end date is completely missing or if the AE end date is on or after the first dose of IP date no assignation can be done.

All the AE in the on-treatment phase are considered TEAEs.

The study day of AE is calculated as the start date of the AE – date of first IP +1 for AE started on or after the day of first IP and as start date of the AE – date of first IP for AE started before the day of first IP. Imputed dates should not be used. If one of the dates is missing or partially missing, the study day of the start of the AE is set to missing.

The duration of AE is calculated as the end date of the AE – start date of the AE +1. Duration is calculated for complete dates only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

3.3.3.2 Safety clinical laboratory parameters

Safety clinical laboratory tests are performed in a central clinical laboratory.

Safety clinical laboratory tests are:

Haematology

- White blood cell (WBC) count
- Red blood cell (RBC) count

- Haemoglobin (Hb)
- Haematocrit (HCT)
- Mean-corpuscular volume (MCV)
- Mean corpuscular haemoglobin concentration (MCHC)
- Neutrophils absolute count
- Lymphocytes absolute count
- Monocytes absolute count
- Eosinophils absolute count
- Basophils absolute count
- Platelets absolute count
- Reticulocytes absolute count

Coagulation parameters

- Prothrombin time
- Activated partial thromboplastin time (aPTT)
- International normalized ratio (INR)

Clinical chemistry

- Sodium
- Potassium
- Blood urea nitrogen (BUN)
- Creatinine
- Calcium
- Phosphate
- Creatine kinase (CK)
- Direct bilirubin
- alkaline phosphatase (ALP)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- gamma glutamyl transferase (GGT)
- Total bilirubin (TBL)
- Glutamate dehydrogenase (GLDH)
- Bicarbonate
- Uric acid
- FSH (women only)
- LH (women only)

Urinalysis

- pH (quantitative)
- Specific gravity (quantitative)
- Glucose (qualitative)
- Blood (qualitative)
- Colour (qualitative)
- Protein (qualitative)
- Appearance (qualitative)
- Nitrites (qualitative)
- Ketones (qualitative)
- Leukocytes (qualitative)

- Urobilinogen (qualitative)
- Microscopic panel (if positive for blood, nitrites or protein):

    - Sediment, Leucocytes
    - Sediment, Erythrocytes
    - White Blood Cell Clumps
    - Epithelial Cells, Tubular
    - Epithelial Cells, Squamos
    - Epithelial Cells, Transitional
    - Red Blood Cell Clumps
    - Sediment, Hyaline Casts
    - Sediment, Granular Casts
    - Sediment, Leucocyte Casts
    - Sediment, Erythrocyte Casts
    - Sediment, Epithelial Casts
    - Sediment, Fatty Casts
    - Sediment, Cell casts
    - Broad Casts
    - Sediment, Waxy Casts
    - Sediment, Triple Phosph Cryst.
    - Sediment, Calcium Ox. Cryst.
    - Sediment, Calcium Phosphate
    - Sediment, Calcium carbonate Cryst
    - Sediment, Uric Acid Cryst.
    - Amorphous Crystals
    - Sediment, Leucine Cryst.
    - Sediment, Cystine Cryst.
    - Sediment, Tyrosine Cryst.
    - Sediment, Ammonium Urate Crystals
    - Sediment, Bilirubin Cryst.
    - Sediment, Bacteria
    - Yeast, Budding
    - Sediment, Trichomonas
    - Yeast Hyphae
    - Oval Fat Body
    - Fat
    - Sperm
    - Sediment, Mucus

Urine renal safety biomarkers

- Albumin
- Total protein
- Creatinine
- Urine protein to creatinine ratio (UPCR)
- Urine albumin to creatinine ratio (UACR)
- Estimated glomerular filtration rate (eGFR; by CKD-EPI formula)

Other Laboratory Assessments

- Complement activation panel (C3a, Bb, C5a)

- hs-CRP

Safety clinical laboratory parameters are assigned to the analysis visits and the study phases as described in section 3.1.2 and section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

Safety clinical laboratory results below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline to each post-baseline visit for safety clinical laboratory results is defined as the post-baseline visit value minus the baseline visit value; percent change from baseline to each post-baseline visit for platelet count is defined as the post-baseline visit value minus the baseline visit value divided by the baseline visit value *100.

After the LLOQ replacement, Safety clinical laboratory results except urine renal safety biomarkers and other laboratory assessments 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.

After the LLOQ replacement, AST, ALT and TBL are also classified as below:

AST and ALT:

- <3xULN (or below the LLOQ)
- ≥3 - <5xULN
- ≥5 - < 8xULN
- ≥8xULN

TBL:

- <1 xULN (or below the LLOQ)
- ≥1 - <2xULN
- ≥2xULN

Occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN are reported as SAE (Potential Hy´s law) as described in the study protocol.

3.3.3.3 Vital signs

Vital signs include:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Temperature (C)

Vital signs parameters are assigned to the analysis visits and analysis phases as described in sections 3.1.2 and 3.1.3. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit / analysis phase.

Change from baseline is defined as the post-baseline visit value minus the baseline value.

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), and high (if value is above the normal reference range) according to the normal reference ranges:

Table 6 Vital signs normal reference ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 160 mmHg
Diastolic blood pressure	50 -90 mmHg
Heart rate	50 - 100 bpm
Temperature	<=37ºC

3.3.3.4 Weight and BMI

BMI (kg/m2) is calculated as: weight (kg) / [(height (cm)/100)]^2. Weight (kg) and BMI (kg/m2) are assigned to analysis visits as described in section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit. Change from baseline is defined as the post-baseline visit value minus the baseline value.

3.3.3.5 ECG

ECG parameters includes the following:

- RR (msec)
- PR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)
- HR (beats/min)
- Overall evaluation (normal, abnormal). If abnormal also reason and clinically significance is collected

For each participant, RR, PR, QRS and QT will be calculated as follow: the mean value of all measurements will be taken provided that at least 2 measurements are present (and at least 3 consecutive beats were analysable in each ECG) or else, the averaged value at the corresponding target time point will be set to missing. QTcF will be calculated as QTcF=QT*RR^-1/3, where the QT interval is in milliseconds and the RR interval is in seconds. Heart rate will be calculated, based on the RR interval as HR=60/RR interval, where the RR interval is in seconds. Calculation of derived parameters will be performed after averaging of QT and RR data. Results from these calculations will be reported in the eCRF together with the overall evaluation.

ECG parameters are assigned to analysis visits and study phases as described in section 3.1.2 and section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

ECG last observation on treatment is defined as last available value among those in the on-treatment analysis phase.

Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, ECG values will be 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) according to the below normal reference ranges:

Table 7 ECG normal reference ranges

Parameter	Normal Reference Ranges
RR	600 -1200 msec
PR	120 – 200 msec
QRS	80 – 120 msec
QT	350 – 430 msec
QTcF	320 – 470 msec
Heart rate	50 – 100 beats/min

QTcF intervals are classified also as:

- >=450 msec
- >=480 msec
- >=500 msec

QTcF increases respect to baseline are classified as:

- >=30 msec
- >=60 msec
- >=90 msec

3.3.4 Exploratory endpoints

3.3.4.1 Lipoprotein profile

Lipoprotein profile parameters are:

- VLDL Subclass >200 nm-Trigl.
- VLDL, Large-Trigl.
- VLDL, Medium-Trigl.
- VLDL, Small-Trigl.
- Low Density Lipoprotein Particle Conc.

- Intermed.Dens. Lipoprot. 25+/-2 nm-Chol*
- Low Density Lipoprotein, Large-Chol.
- Low Density Lipoprotein, Small-Chol.
- HDL Particles
- High Density Lipoprotein, Large-Chol*
- Medium HDL
- High Density Lipoprotein, Small-Chol*
- Very Low Density Lipoprotein, Mean
- Low Density Lipoprotein, Mean
- High Density Lipoprotein, Mean
- Triglycerides
- VLDL-Triglycerides
- HDL-Cholesterol Direct*
- Lipoprotein Insulin Resistance Score
- Apolipoprotein A-I
- Apolipoprotein B
- Non-HDL-Cholesterol

Lipoprotein parameters are assessed in a central laboratory and assigned to the analysis visits and analysis phases as described in section 3.1.2 and 3.1.3. Measurements with missing or partial missing dates are not assigned to any analysis visit / analysis phase.

Change from baseline is calculated as the visit value minus the baseline value.

3.4 Exposure and treatment compliance

As per study protocol, subjects start the subcutaneous injections of the study IP at day 1. Then the subjects will be subcutaneously dosed also on Days 8, 29, and 57. Subcutaneous injections should primarily be performed on site. Dosing visits may be undertaken as home visits. If participants are dosed at home, they will receive the study intervention directly from the nurse.

The date, and time if applicable, of dose administered in the clinic and at home, as well as the anatomical location of the injection site, will be recorded in the eCRF.

3.4.1 Exposure

Exposure (days) is calculated only for subjects in the full analysis set as the total number of days on study drug. Exposure is calculated as the study drug dose last date minus study drug dose first date plus one as reported in the eCRF study treatment log page. If any of the first or last dates are missing or partially missing, then imputed dates will not be used, and study drug exposure is set to missing.

3.4.2 Compliance

Overall compliance to the IP is calculated only for subjects in the full analysis set.

The percent compliance is defined as the total number of vials consumed divided by the total number of vials that should have been taken where, total number of vials consumed will be calculated as number of kits recorded in the IRT system, number of vials that should have been

taken is calculated as the number of the scheduled dispensation visits (even if not done) before the end of the study.

No replacement of missing data is used. Therefore, if one of the above factors is missing then compliance will be missing.

Compliance is also categorized as:

- < 80%
- ≥ 80% to < 120%
- ≥ 120%

3.5 Concomitant medications and procedures

Subjects can undergo concomitant medications or procedure deemed necessary to provide adequate supportive care except for those medications identified as restricted and prohibited as listed in the study protocol and detailed (coding and indication wherever applicable) in the in the IDRP.

The eCRF collects concomitant medications and procedures. The WHO-DD March 2019 B3 Global or higher is used to classify medications. MedDRA version 23.0 or higher is used to classify procedures.

Medications and procedures are classified as concomitant as below:

The imputation method described in section 3.1.1.5 is used in case the medication / procedure end date is partially missing. The imputation method described in section 3.1.1.1 is used in case the first dose of IP date and time are missing or partially missing.

After the end date imputation, the medications and the procedures will be classified as either prior or concomitant (but not both) according to the end date. Prior medication or procedure is defined as any medication / procedure with an end date prior to the first dose of study drug (exclusive). Concomitant medication / procedure is defined as any medication / procedure with an end date on or after the first dose of study drug, or any medication / procedure that is ongoing at the end of the study. Medications and procedures with completely missing end date are classified as concomitant.

Prohibited concomitant medications are confirmed and flagged by the study physician in accordance with the study protocol.

4 ANALYSIS METHODS

All analyses method described in this section will be applicable to both the analyses, primary and final.

4.1 General principles

Unless otherwise specified, for continuous variables, descriptive statistics will include the number of subjects (n), mean, SD, median, minimum and maximum. For log-normal variables also the Geometric mean and Geometric CV will be used.

For categorical variables the number and percentages of subjects by categories will be tabulated. Percentages will be calculated based on the number of subjects with no missing data, i.e., will add up to 100%. Categories with count of zero will be not displayed.

Unscheduled analysis visits will not be used in descriptive statistics. Unscheduled analysis visits will only be reported in listings and used where explicitly needed.

For continuous variables, descriptive statistics will be summarized for the observed values, and where specified, also for changes from baseline and relative or percent change from baseline.

Changes from baseline, in certain categorical variables will be summarized using shift tables. The number and percent of subjects within each treatment group will be generated for each category post-baseline by baseline category.

If not otherwise specified, all the analyses will include the post IP-discontinuation data for those subjects who discontinue from study treatments but are still followed up for their scheduled visits.

The following statistical models will be used:

4.1.1 MMRM assuming a log-normal distribution

An MMRM will be fitted on log-transformed change from baseline. Log-transformed change from baseline is calculated as the visit value in natural logarithm minus the baseline value in natural logarithm.

The visit statistically tested within the MMRM model is week 12 (day 85). All previous available data on scheduled visits will be used in the model. Fixed factors of the model will be treatment, visit and treatment*visit interaction. The natural log-transformed baseline value of the outcome variable will be used as a covariate. Visits within subjects will be considered as repeated measurements.

Comparisons derived from the model will be:

- AZD8233 CCI versus placebo,
- AZD8233 CCI versus placebo
- AZD8233 CCI versus placebo
- AZD8233 CCI versus AZD8233 CCI
- AZD8233 CCI versus AZD8233 CCI
- AZD8233 CCI versus AZD8233 CCI

The REML approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 5% will be used for the comparisons and for the t-type confidence interval calculation.

The model will be fitted with an unstructured covariance structure and the Kenward-Roger correction applied to obtain the degrees of freedom.

In case the model will not converge for any reason, the following hierarchical model fitting procedure will be adopted:

1. The MMRM will be fitted using a SP(POW) covariance structure; Visit will be expressed as scheduled visit days to accomplish the variance-covariance matrix estimation.
2. The MMRM will be fitted using a CS covariance structure
3. An ANCOVA model will be used

The reportable results from the model will be:

- The LSmean and their 95% CI for each group for the log-transformed change from baseline
- Back transformed LSmean for each group, which correspond to the estimated relative change from baseline; back transformed LSmean is derived as [EXP(LSmean)].
- 95% CI of the back transformed LSmean for each group; 95% CI of the back transformed LSmeans is derived as [EXP(lower limit of the 95% CI of the LSmean)]; [EXP(upper limit of the 95% CI of the LSmean)].
- The geometric mean ratio between active groups and the control group; the ratio is calculated as EXP(of the LSmean of the difference)
- The 95% CI of the geometric mean ratio; the 95% CI of the ratio is calculated as [EXP(Lower limit of the 95% CI of the LSmean of the difference)]; [EXP(Upper limit of the 95% CI of the LSmean of the difference)].
- P-value of the geometric mean ratio

4.1.2 MMRM assuming a normal distribution

An MMRM will be fitted on percent change from baseline. Percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value *100.

The visit statistically tested within the MMRM is week 12 (day 85). All previous available data on scheduled visits will be used in the model. Fixed factors of the model will be treatment, visit and treatment*visit interaction. The baseline value of the outcome variable will be used as a covariate. Visits within subjects will be considered as repeated measurements.

Comparisons derived from the model will be:

- AZD8233 CCI versus placebo,
- AZD8233 CCI versus placebo
- AZD8233 CCI versus placebo
- AZD8233 CCI versus AZD8233 CCI
- AZD8233 CCI versus AZD8233 CCI
- AZD8233 CCI versus AZD8233 CCI

The REML approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 5% will be used for the comparisons and for the t-type confidence interval calculation.

The model will be fitted with an unstructured covariance structure and the Kenward-Roger correction applied to obtain the degrees of freedom.

In case the model will not converge for any reason, the following hierarchical model fitting procedure will be adopted:

1. The MMRM will be fitted using a SP(POW) covariance structure; Visit will be expressed as scheduled visit days to accomplish the variance-covariance matrix estimation.
2. The MMRM will be fitted using a CS covariance structure.
3. An ANCOVA model will be used.

The reportable results from the model will be:

- The LSmean and their 95% CI for each group for the percent change from baseline
- The LSmean of the difference between active groups and the control group
- The 95% CI of the LSmean of the difference
- P-value of the LSmean of the difference

4.1.3 Sensitivity analysis 1

The sensitivity analysis 1 will consist of repeating the MMRM assuming a log-normal distribution including only subjects who have completed the treatment period as per protocol and who have no relevant IPDs. Subjects who have completed the treatment period as per protocol are the subjects who reached week 12 and received all four scheduled doses of IP; subjects who received wrong dose of IP or wrong treatment will be excluded. Further, relevant IPDs are defined in section 2.2.

4.1.4 Sensitivity analysis 2

The sensitivity analysis 2 will consist of repeating MMRM assuming a log-normal distribution (without any back-up strategy) using the pattern-mixture model with control-based pattern imputation (reference 1). To implement this approach, we firstly use MCMC to impute non monotone MAR missing data for subjects who have completed the treatment period as per protocol (reached week 12 and received all four doses of IP). Then we use the resulting dataset to sequentially impute missing data at each visit using a monotone regression approach. Sequential imputation will be done in two ways:

- considering only placebo group for the estimations of missing data for placebo patients and for active subjects at visits for which the previous scheduled dose of IP is missing or not as per protocol (wrong dose of IP or a wrong treatment);
- considering only the relevant active group for the estimations of missing data for active subjects at visits for which the previous scheduled dose of IP was taken as scheduled.

The results from each imputation set will be combined using Rubin's formulas

4.2 Analysis of variables

4.2.1 Disposition of subjects

Subject dispositions (number and percentage of subjects enrolled, subjects randomized, subjects who received at least one dose of study IP, subjects who completed the treatment and subjects who completed the study) will be presented in a summary table for each treatment group and overall. A listing including all standardized disposition terms will also be provided for all discontinued subjects. Both, the table and the listing will be based on all enrolled subjects.

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

The number of subjects belonging to each analysis population will be presented in a separate summary table for each treatment group. The table will be based on all enrolled subjects. Listings of all subjects excluded from the full analysis set and from the safety analysis set will also be provided. The listings will include reason for exclusion from respective population and will be based on all enrolled subjects.

Randomization code and actual kit are also listed.

4.2.2 Important protocol deviations

The number and percentage of subjects with at least one IPD will be summarized following the NHP categories, for each treatment group and overall, for the full analysis set. All the IPDs as reported in the CTMS (pre-treatment and on treatment) will be included in the table. All IPDs will also be listed for all subjects included in the full analysis set.

4.2.3 Baseline assessment and other subject-specific characteristics

4.2.3.1 Demographic and subject-specific characteristics

All demographic and subject-specific characteristics reported in section 3.2.1 will be presented in summary tables for each treatment group and overall; Age, height, weight and BMI will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; all the other demographic and subject-specific characteristics will be summarized as categorical variables with the number and percentages of subjects by categories. Only the baseline measurement for height, weight and BMI will be considered in these tables. Baseline and post-baseline definitions are detailed in section 3.1.2. All demographic and subject-specific characteristics will also be provided in listings. The tables and the listings will be based on the full analysis set.

Recruitment by region country and centre will also be summarized.

4.2.3.2 Medical history

Any relevant medical histories and prior procedures as described in section 3.2.2 will be presented in summary tables as number and percentages of subjects by SOC and PT for each treatment group and overall. Subjects with multiple medical histories in the same SOC/PT will

be counted only once in that SOC/PT. Subjects with medical histories in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT. The table will be based on the full analysis set.

4.2.3.3 Nicotine and alcohol use

Nicotine and alcohol use as described in section 3.2.3 will be presented in summary table as number and percentages of subjects for each treatment group and overall for the full analysis set.

4.2.4 Primary / Secondary efficacy endpoints

4.2.4.1 Change from baseline in log-transformed LDL-C and percent change from baseline in LDL-C

dLDL-C is described in section 3.3.1.1 and in section 3.3.2.2. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the full analysis set and presented for each treatment group.

dLDL-C will be summarized descriptively as a continuous log-normal variable at each analysis visit and for relative change and percent change from baseline. Observed values will also be presented in figure with geometric mean and 95% CI by visit. Percent changes from baseline will be presented in figure with mean and 95% CI by visit.

An MMRM assuming a log-normal distribution as described in section 4.1 on log-transformed change from baseline to week 12 will be presented.

Additionally, as secondary objective, an MMRM assuming a normal distribution as described in section 4.1 on percent change from baseline to week 12 will be presented.

Sensitivity analyses 1 and2 as per section 4.1 will also be produced.

Finally, dLDL-C will also be reported in a listing.

The correlation of LDL-C Friedewald and LDL-C Martin-Hopkins towards dLDL-C will also be estimated. The correlations are estimated using the mixed model approach, considering the two measurement as random effect in the model, and visits within subject as repeated measurements. Data are log-transformed to fulfil normal distribution criteria. Bland-Altman scatter plot on log-transformed data will also be shown.

4.2.5 Secondary efficacy endpoints

4.2.5.1 Change from baseline in log transformed PCSK9

PCSK9 is described in section 3.3.2.1. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the full analysis set and presented for each treatment group.

PCSK9 will be summarized descriptively as a continuous log-normal variable at each analysis visit and for relative change and percent change from baseline. Observed values will also be presented in figure with geometric mean and 95% CI by visit. Percent changes from baseline will be presented in figure with mean and 95% CI by visit.

An MMRM assuming a log-normal distribution as described in section 4.1 on log-transformed change from baseline to week 12 will be presented.

Finally, PCSK9 will also be reported in a listing.

4.2.5.2 Level of other lipid parameters

The other lipid parameters are listed and described in section 3.3.2.4.Baseline and post baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the full analysis set and presented for each treatment group.

All lipid parameters will be summarized descriptively as continuous log-normal variables at each analysis visit and for relative change and percent change from baseline.

An MMRM assuming a normal distribution as described in section 4.1 on percent change from baseline to week 12 will also be presented.

Percent changes from baseline will be presented in figure with mean and 95% CI by visit.

All other lipid parameters will also be reported in a listing.

4.2.5.3 Pharmacokinetic parameters

The analysis will be based on the PK analysis set.

Plasma concentrations will be summarized descriptively as a continuous log-normal variable at each analysis visit and scheduled time. The geometric mean +/- the geometric standard deviation will be also reported together with the number of samples below the limit of quantification. The geometric mean +/- the geometric standard deviation is calculated as the exp(mean(variable in log) +/- SD(variable in log)). Plasma concentrations will also be listed for all subjects in the PK analysis set. Listings of all subjects excluded from the PK analysis set will also be provided. The listing will be based on all enrolled subjects.

PK parameters are not derived and analysed within this SAP. Derivations and results of the pharmacokinetic analyses are provided in an additional bioanalytical report prepared by a dedicated pharmacometrics support group at AstraZeneca.

4.2.5.4 Immunogenicity

The analysis will be based on the ADA analysis set.

Immunogenicity parameters are described in section 3.3.2.5. Baseline and post-baseline definitions are detailed in section 3.1.2. Immunogenicity parameters tables and listings will be based on the ADA analysis set and presented for each treatment group.

ADA will be summarized as categorical variables with the number and percentages with a positive result at the specific visit. Immunogenicity titre will be summarized descriptively as a continuous variable, only for ADA positive tests, with median, interquartile range, minimum, and maximum, at each analysis visit.

ADA will also be summarized including the following:

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

Post baseline coincide with the on-treatment phase as described in section 3.1.3.

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

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

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

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

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

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

The median of maximum titres is calculated based on the maximum titre for each ADA positive subject within each treatment group (including both baseline and post-baseline measurements).

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

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

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

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

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

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

4.2.6 Safety endpoints

4.2.6.1 Adverse events

After having assigned the AEs to the corresponding study phase as described in section 3.3.3.1, the AEs will be summarized for each treatment group. The AEs tables will be based on the safety analysis set. Summary tables will include AEs in the on-treatment phase as described in section 3.1.3.

Summary tables are listed below.

An overview table containing:

- Number and percentage of subjects with any AEs
- Number and percentage of subjects with any AEs with outcome of death
- Number and percentage of subjects with any SAEs
- Number and percentage of subjects with any AEs leading to discontinuation / interruption / reduction of IP
- Number and percentage of subjects with any AEs leading to withdrawal from study

An overview table by ADA category containing:

- Number and percentage of subjects with any AEs
- Number and percentage of subjects with any AEs with outcome of death
- Number and percentage of subjects with any SAEs
- Number and percentage of subjects with any AEs leading to discontinuation of IP

The following summary tables will be presented by SOC and PT:

- The number and percentage of subjects with any AEs
- The number of AEs
- The number and percentage of subjects with AEs with outcome of death
- The number and percentage of subjects with SAEs
- The number of SAEs
- The number and percentage of subjects with AEs leading to discontinuation.

The following summary tables will be presented by PT:

- The number and percentage of subjects with most common AEs (frequency of >5%)
- The number and percentage of subjects with any AEs by maximum reported intensity
- The number and percentage of subjects with any AEs and investigator's causality assessment. If a subject has multiple events in the same PT, the event with the strongest relationship will be counted.

Where number of subjects with AEs are summarized by SOC and/or PT , subjects with multiple events in the same SOC/PT are counted only once in that SOC/PT. Subjects with events in more than 1 SOC/PT are counted once in each of those SOCs/PTs.

Additionally, the following tables will be presented:

- the number of subjects with serious adverse events, by seriousness criteria
- number and percentage of subjects with non-serious AEs occurring with a frequency > 5.0% in any treatment group for each SOC and PT. This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the CSR. It will be delivered at the same time as the CSR outputs.
- the number of subjects with injection site reactions by HLT and PT
- the number of subjects with bleedings by SMQ and PT

A list of key subject information for subjects with AEs with outcome of death, subjects with SAEs, and subjects with AEs leading to discontinuation of IP will be provided. The durations reported in these tables, will be derived only for fully completed dates as below:

- Time from first dose of IP to AE (in days) will be calculated as the AE start date minus date of first dose of IP +1.
- Time from first dose to death (in days) will be calculated as the date of death minus date of first dose of IP +1.
- The same approach will be used for deriving time from start of treatment to AE becoming serious or discontinuation.
- Time from last dose prior to AE start and last dose prior to death (in days) will be calculates as the date of death minus the date of last dose prior to AE/death +1.

All the AEs will also be listed for all subjects included in the safety analysis set. AEs among ADA positive and ADA negative subjects will also be listed. A subject is considered ADA

negative if collected samples are tested negative at all timepoints, including baseline and post-baseline. Regarding ADA positive categories in section 4.2.5.4 are included.

4.2.6.2 Safety clinical laboratory parameters

Safety clinical laboratory parameters are described in section 3.3.3.2. Baseline and post-baseline definitions are detailed in section 3.1.2.

Safety clinical laboratory parameters including haematology, coagulation, clinical chemistry, urine renal safety biomarkers, other laboratory assessments and urinalysis quantitative parameters except for the microscopic panel will be summarized in SI units as continuous variables at each visit and for change from baseline; additionally, platelet count will be summarized with percent change from baseline. Shifts from baseline to maximum and minimum value during the on-treatment phase will also be presented for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters except for the microscopic panel.

Shifts from baseline to maximum value during the on-treatment phase will be presented for urinalysis qualitative parameters, except for the microscopic panel.

All laboratory data for haematology, coagulation, clinical chemistry, urine renal safety biomarkers, other laboratory assessments and urinalysis will also be presented in listings.

In addition to the tables above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria and a list of key subject information for subjects with potential Hy's law will be presented. Potential Hy's law is defined as AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in ALP. For potential Hy's law 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. Same list is presented for subjects with potential Hy's law adverse event as reported in the eCRF.

Subjects with platelet count <150 (10^9/L) or percent decrease from baseline greater than 30% will be also summarized and listed including all platelet count measurements. Individual plots of observed data over time and spaghetti plots on percent change from baseline will be also represented.

All tables and listings for laboratory data will be based on the safety analysis set and presented for each treatment group.

4.2.6.3 Vital signs

Vital signs parameters are described in section 3.3.3.3. Baseline and post-baseline definitions are detailed in section 3.1.2. Vital signs will be summarized descriptively as continuous variables at each visit and timepoint within visit and for change from baseline. Vital signs will

also be presented in listing. Vital signs tables and listings will be based on the safety analysis set and presented for each treatment group.

4.2.6.4 Weight and BMI

Weight and BMI are described in section 3.3.3.4. Baseline and post-baseline definitions are detailed in section 3.1.2. Weight and BMI will be presented in listing based on the safety analysis set.

4.2.6.5 ECG

ECG parameters are described in section 3.3.3.55. Baseline and post-baseline definitions are detailed in section 3.1.2. ECG parameters (except for the overall evaluation) will be summarized in SI units as continuous variables, at each visit and for change from baseline. Number and percentage of subjects within each QTcF intervals classes at any time during the on-treatment phase will also be reported together with number and percentage of subjects within QTcF increase classes at any time during the on-treatment phase. Overall evaluation will be analysed as shift from baseline to last value in the on-treatment phase. ECG parameters will also be listed. Overall evaluation will be listed for subjects with clinically significant abnormalities. ECG tables and listings will be based on the safety analysis set and presented for each treatment group.

4.2.7 Exploratory endpoints

4.2.7.1 Lipoprotein profile

Lipoprotein profile parameters are listed and described in section 3.3.4.1. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be produced only for the complete analysis after the final follow-up (after final database lock). They will be based on the full analysis set and presented for each treatment group.

Lipoprotein profile parameters will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, maximum, at each analysis visit and for change from baseline.

Lipoprotein profile parameters will also be reported in a listing.

4.2.8 Treatment compliance

Exposure and compliance are calculated as described in section 3.4.

4.2.8.1 Exposure

The exposure will be presented in a summary table for each treatment group. The table will be based on the full analysis set. Exposure will also be listed for the full analysis set.

4.2.8.2 Compliance

Overall compliance will be presented in a summary table for each treatment group and overall. The overall compliance will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum.

Compliance will also be listed together with the exposure. Both, the table and the listing will be based on the full analysis set.

4.2.9 Concomitant medications

Concomitant medications and procedures are defined in section 3.5. The number and percentage of subjects with at least one allowed concomitant medication and the number and percentage of subjects by ATC level 4 (therapeutic subgroup) and product name will be provided using the full analysis set.

The number and percentage of subjects with at least one disallowed concomitant medication and the number and percentage of subjects by ATC level 4 (therapeutic subgroup) and product name will be provided using the full analysis set.

The concomitant procedures will be presented in summary tables as number and percentages of subjects by SOC and PT for each treatment group and overall. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT. The table will be based on the full analysis set.

5 INTERIM ANALYSES

No interim analysis planned for this study.

6 CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is based on study protocol D7990C00003 v2.0 dated 16Dec2020. Any further amendment of the study protocol which can have an impact on the SAP will lead to an amendment of this document. Changes of analysis from protocol D7990C00003 v2.0 dated 16Dec2020 are listed here below:

Section 3 - Objectives and endpoints

Even if not specified in the protocol, two analyses are planned for this study:

- A primary analysis after the treatment period,
- A complete analysis after the final follow-up (after final database lock).

As per additional FDA request, analysis of percent change with MMRM for all lipid parameters added.

Section 4.2.6.1 Adverse event

Protocol stated that “Injection site reactions will be considered an AE of special interest and will be listed separately. Listing of injection site reactions will include information about size,

colour and itching status…" however this information is not collected in eCRF so this listing cannot be produced.

Section 8.2.3 – Electrocardiograms

Protocol stated that "ECG results will be listed by treatment and dose level of AZD8233 for each participant and time point and will include all individual and averaged values of PR, RR, QRS, QT interval, and the derived values of QTcF and HR (RR)". The investigators are supposed to report in the eCRF only 1 result for each parameter (average for PR, RR, QRS, QT and derived from averages for QTcF and HR). Due to this, only list of averaged values as reported in eCRF can be done.

Section 9.4 - Statistical analysis

Protocol stated that "Estimation of the treatment effect will be done for each visit after baseline", however only estimation at visit week 12 are reported in the statistical outputs.

Protocol stated that "All treatment arms will be compared with each other", however only selected comparisons are reported in the statistical outputs.

7 REFERENCES

1 "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures", PharmaSUG2011 - Paper SP04, Authors: Bohdana Ratitch, Quintiles, Montreal, Quebec, Canada and Michael O'Kelly, Quintiles, Dublin, Ireland

8 APPENDIX

8.1 Appendix 1 Changes made to the SAP after initial sign-off

8.1.1 Version 1.0

NA

8.1.2 Version 2.0

Added the relevant IPD list in section 2.2 and in section 4.1.3.

Changed the analysis phase, section 3.1.3, consequently change on AE analysis phase allocation rules, section 3.3.3.1 and consequently deleted sensitivity analysis 3 on on-treatment data, section 4.1.5.

Specified that AE duration is calculated as per AZ standard (xxENDTC – xxSTDTC; If ADURN >= 0 then ADURN = ADURN+1).

Specified derivation of ADA positive measurements in section 3.3.2.5.

Deleted lipoprotein profile and added ADA tables at primary analysis, section 1.1.

Added Coagulation parameters 2h post dose as per CSP v2.0 in the Schedule of assessment: (table 1 in section 1.2) and in the analysis visit windows derivation section 3.1.2.

Added the correlation of LDL-C Friedewald and LDL-C Martin-Hopkins towards dLDL-C calculation as secondary objective in section 3.3.2.2 and 4.2.4.

Added the definition of ADA negative in section 4.2.6.1.

Urinalysis micro panel parameters updated as per laboratory data transfer specifications in section 3.3.3.2.

Added +1 in the calculation of durations for tables S14, S18 and S20 in section 4.2.6.

Changed imputation of last dose of IP because there was a typo referring to drug accountability form which is not used in this study, section 3.1.1.2.

Added detail on maintaining the blinding at primary analysis in section 1.1.

Updated Lipoprotein profile section based on available DTS in sections 3.3.4.1 and 4.2.7.1.

Updated primary analysis and complete analysis name and details in section 1.1.

Added figure for complete analysis only in the ADA section.

8.1.3 Version 3.0

Typo in table 1. Added footnotes

Added +1 in the calculation of durations for ADA measurements in section 4.2.5.4

8.1.4 Version 4.0

Rephrased the description of box-plots in section 4.2.5.4 because was not cristal clear from the text. No change in the content but only in the description.