Clinical Study Report	
Drug Substance	AZD8233
Study Code	D7990C00006 (Part A)
Edition Number	2.0
Date	08 February 2023
NCT Number	NCT04823611

A Phase I and II Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of AZD8233 Following a Multiple Subcutaneous Dose Administration in Japanese Participants with Dyslipidaemia (HAYATE) - Part A -

Study dates: First participant enrolled: 20 January 2021
Last participant last visit: 18 August 2021
The analyses presented in this report are based on a clinical data lock date of 06 April 2022.

Phase of development: Parts A and C: Clinical pharmacology (I)
Part B: Therapeutic exploratory (II)

International Co-ordinating Investigator: Not applicable.

Sponsor's Responsible Medical Officer: PPD

This study was performed in compliance with ICH Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study Centres

Part A of this study was performed at 2 sites in Japan.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand Description/Endpoints
Primary	
To assess the safety and tolerability of AZD8233 following SC administration of multiple doses.	Adverse events, vital signs, ECG, cardiac telemetry, injection site reaction examination and clinical laboratory evaluations including platelet count.
Secondary	
To characterise the PK of AZD8233 following SC administration of multiple doses.	Plasma parameters (t_{lag}, t_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}48)}$, AUC, AUCτ, C_{trough}, CL/F, Vz/F, $t_{1/2}$, MRT); urine parameters (Ae, Fe, CLR).
To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.	Absolute change from baseline in log-transformed PCSK9 in plasma. Percent change from baseline in PCSK9 in plasma.
To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.	Percent change in levels of LDL-C in serum.
To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.	Levels of other lipid parameters, including: • TC • HDL-C • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Triglycerides
Exploratory	
To collect and store plasma and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies), and tolerability related to AZD8233 treatment or cardiometabolic diseases.	The biomarkers to be analysed may include but are not limited to Apo CIII (3), ANGPTL3, ANGPTL4, ANGPTL8, and ProC3. The results will not form part of this CSR.
To collect and analyse samples for exploration of anti-drug immunogenicity.	ADAs.

ADA = antidrug antibody; Ae = amount excreted in urine; ANGPLT3 = angioprotein-like protein 3; ANGPLT4 = angioprotein-like protein 4; ANGPLT8 = angioprotein-like protein 8; apoB = apolipoprotein B; apoCIII (3) = apolipoprotein CIII (3); AUC = area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-last})}$ = area under the plasma concentration-time curve from time zero to time last value above the limit of quantification; $AUC_{(0\text{-}24)}$ = area under the plasma conversation-time curve from time zero to 24 hours after dosing; $AUC_{(0\text{-}48)}$ = area under the plasma conversation-time curve from time zero to 48 hours after dosing; AUCτ = area under the plasma concentration-time curve from time during the dosing interval; CLR = renal clearance; CL/F =apparent total body clearance of drug from plasma after extravascular administration; C_{max} = observed maximum plasma concentration; CSR= clinical study report; C_{trough} = trough plasma concentration; ECG = electrocardiogram; Fe = fraction excreted unchanged in urine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MRT = mean residence time of the unchanged drug in the systemic circulation; PCSK9 = proprotein convertase subtilisin/kexin 9; PD = pharmacodynamics; PK = pharmacokinetics; ProC3 = propepticde of type III collagen; SC = subcutaneous; $t_{1/2}$ = terminal half life; t_{max} = time to reach peak maximum or maximum observed concentration or response following drug administration; t_{lag} = time delay between drug administration and the first observed concentration in plasma; TC = total cholesterol; VLDL-C = very low-density lipoprotein cholesterol; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration.

Study Design

This was a randomised, blinded, multidose Phase I/II study. The study consisted of three distinct parts:

- Part A – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.
- Part B – a randomised, double-blind, placebo-controlled, dose ranging Phase II study.
- Part C – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.

Only information pertaining to Part A of the study is presented here.

Part A of the study comprised of:

- A Screening Period which started ≤ 28 days before the randomisation visit and ended on Day −4.
- A Treatment Period that lasted 58 days (up to Visit 9).
- A Follow-up Period which included Visit 10 to Visit 17 (Weeks 2, 4, 6, 8, 10, 12, 14, and 16 after last dose of study treatment).

Participants were randomised across the two treatment arms, AZD8233 CCI and placebo, in the ratio 8:3 for the Treatment Period. Participants were dosed on Days 1, 8, 29, and 57.

The study was single-blind with regards to treatment (AZD8233 or placebo). AZD8233 and placebo were matched in appearance. Participants that were randomised to placebo received the same volume of injection as that of those randomised to receive AZD8233.

After the Treatment Period, participants continued in a Follow-up Period of 14 weeks (up to 16 weeks after the last dose).

Target Population and Sample Size

The study was conducted in male or female participants between 20 and 60 years old (inclusive) with documented dyslipidaemia.

Approximately 11 participants were planned to be randomised to Part A of the study, in an 8:3 ratio across the two treatment arms; AZD8233 CCI or placebo.

Due to the exploratory nature of the study, the sample size was not based on formal statistical considerations. Eight Japanese participants on active treatment was considered to be sufficient to confirm a tendency for safety, PK, and PD data.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Participants in the AZD8233 CCI treatment group received CCI of AZD8233 through subcutaneous administration of an AZD8233 CCI solution for injection. The AZD8233 solution for injection batch number was L014633.

Participants in the placebo treatment group received placebo through subcutaneous administration of a matched placebo solution for injection. The placebo batch number was L014625.

Duration of Treatment

The total study duration was approximately 28 weeks (a 28-day screening period, 58-day treatment period, and a 16 week follow-up period).

Statistical Methods

No formal statistical hypotheses were set for Part A of this study. Data were interpreted through descriptive statistics only.

Study population

A total of 11 participants were randomised and received study treatment: 8 participants in the AZD8233CCI treatment group and 3 participants in the placebo treatment group.

Demographics, participant characteristics, and baseline disease characteristics were generally balanced between the AZD8233 and placebo treatment groups. The minor differences observed were not expected to adversely affect the interpretation of the study results.

All 11 participants completed the study: 2 participants (25%) in the AZD8233 CCI treatment group discontinued treatment due to AEs. The remaining 9 participants

(6 participants [75.0%] in the AZD8233 CCI treatment group and 3 participants [100.0%] in the placebo treatment group) completed all study treatment.

No important protocol deviations were reported during the study.

Summary of efficacy results

At Visit 11 (4 weeks post last dose of study treatment), in the AZD8233 CCI treatment group, there was a mean decrease observed in PCSK9, LDL-C, and the majority of the other lipid parameters.

At Visit 11, in the AZD8233 CCI treatment group, an absolute mean change from baseline of −334.15 µg/L (SD=59.969) was observed in PCSK9; this corresponded to a percent change of −94.19% (SD=1.651%). Based on the log-transformed data, there was a relative change of 0.056 in PCSK9, which was equivalent to a relative reduction of 94.44%. In the placebo treatment group, there was an absolute mean change from baseline of 81.07 µg/L (SD=94.535); this corresponded to a percent change of 24.64% (SD=28.514%).

At Visit 11, in the AZD8233 CCI treatment group, an absolute mean change from baseline of −1.990 mmol/L (SD=0.4990) was observed in LDL-C by the Friedewald formula; this corresponded to a percent change of −78.48% (SD=13.789%). In the placebo treatment group, there was an absolute mean change from baseline of 0.289 mmol/L (SD=0.6066); this corresponded to a percent change of 18.64% (SD=33.475%). Similar LDL-C results were obtained using the Martin-Hopkins calculation and the direct method for measuring LDL-C.

At Visit 11, in the AZD8233 CCI treatment group, a mean percent change (reduction) from baseline in the following other lipid parameters was observed: TC −44.74% (SD=11.651%), non-HDL-C −68.65% (SD=11.825%), VLDL-C −24.67% (SD=25.027%), ApoA1 −1.12% (SD=9.644%), ApoB −62.56% (SD=14.093%), Lp(a) −56.94% (SD=14.838%), triglycerides −24.44% (SD=27.622%). A mean percent change (increase) from baseline was observed in HDL-C of 5.85% (SD=8.917%). In the placebo treatment group, there was an upward trend in all the other lipid parameters throughout the study period.

Summary of pharmacokinetic results

AZD8233 and AZD8233 full length ASOs appeared rapidly in plasma with median t_{max} values of 2.00 to 2.25 hours across both analytes and study days. At early time points the AZD8233 full length ASOs concentration versus time profiles mirrored that of the parent AZD8233, but at slightly higher concentrations. At later time points AZD8233 full length ASOs were the only quantifiable species in plasma.

The full length ASOs had a biphasic plasma concentration versus time profile with a geometric mean terminal $t_{1/2}$ of 23.4 days. Clearance of AZD8233 full length ASOs was

predominantly non-renal with less than 0.5% of the dose excreted as full length ASOs in urine during the first 24 hours. There appeared to be no accumulation in AZD8233 and full length ASOs (AUC and C_{max}) exposure following multiple AZD8233 monthly doses.

Inter-participant variability in AZD8233 and AZD8233 full length ASO plasma exposure was high and moderate, respectively.

Summary of pharmacokinetic/pharmacodynamic relationships

After the end of treatment, throughout the follow-up period, the PCSK9 levels slowly increased. This slow increase in PCSK9 levels is consistent with the long terminal half-life of AZD8233 full length ASOs observed in plasma.

Summary of immunogenicity results

Three participants (37.5%) in the AZD8233 CCI treatment group developed treatment induced ADAs and no participants in the placebo treatment group had a positive ADA result during the study.

Summary of safety results

The median duration of exposure was 57 days in both treatment groups.

Overall, 6 participants (75.0%) in the AZD8233 CCI treatment group and 2 participants (66.7%) in the placebo treatment group reported adverse events (AEs). There were no SAEs, injection site reactions, or AEs with the outcome of death reported during the study. All AEs were mild in intensity; those reported in the AZD8233 CCI treatment group were considered as possible related to the study treatment.

Two participants (25.0%) in the AZD8233 treatment group experienced AEs (hepatic function abnormal) that led to discontinuation of study treatment.

There were no clinically notable trends in haematology parameters, including platelets and coagulation, or urinalysis parameters. There was no indication of renal impairment/renal toxicity. One participant (12.5%) in the AZD8233 CCI treatment group had an ALT $\geq 3 \times$ ULN and $< 5 \times$ ULN.

Conclusions

- Subcutaneous administration of repeated (monthly) doses of AZD8233 CCI was well tolerated in Japanese participants with dyslipidaemia apart from mild to moderate increases in ALT. The reported AEs and other safety results did not raise any new safety concerns.
- The majority of AEs reported were hepatobiliary disorders – hepatic function abnormal (reported in 7 participants in total). Two participants (25.0%) in the AZD8233 CCI treatment group were discontinued from study treatment due to these AEs.

- Administration of AZD8233 resulted in a decrease in PCSK9, LDL-C, and the majority of other lipid parameters (TC, non-HDL-C, VLDL-C, ApoA1, ApoB, Lp(a), and triglycerides). HDL-C levels increased throughout the study.
- Three participants (37.5%) in the AZD8233 CCI treatment group developed treatment induced ADAs; no participants in the placebo treatment group had positive ADA results. There were no ADA safety related concerns raised.
- There appeared to be no accumulation in AZD8233 and full length ASOs exposure (AUC and C_{max}) following multiple monthly doses of CCI AZD8233.

Clinical Study Report	
Drug Substance	AZD8233
Study Code	D7990C00006 (Part B)
Edition Number	1.0
Date	16 February 2023
NCT Number	NCT04823611

A Phase 1 and 2 Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of AZD8233 Following a Multiple Subcutaneous Dose Administration in Japanese Participants with Dyslipidemia (HAYATE) - Part B -

Study dates:	First participant enrolled:10 Aug 2021 Last participant last visit:07 Mar 2022 The analyses presented in this report are based on a clinical data lock date of 18 May 2022.
Phase of development:	Parts A and C: Clinical pharmacology (I) Part B: Therapeutic exploratory (II)
International Co-ordinating Investigator:	Not applicable
Sponsor's Responsible Medical Officer:	PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study sites

Part B of this study was performed at 6 sites in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Objectives and Endpoints in Part B

Objectives	Estimand description/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 serum.
Secondary	
To assess the effect of different doses of AZD8233 on PCSK9 versus placebo.	Absolute change from baseline in log-transformed PCSK9 in plasma. Percent change from baseline in PCSK9 in plasma.
To assess the effect of different doses of AZD8233 on LDL-C versus placebo.	Percent change in levels of LDL-C in serum.
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 • RLP-C
To evaluate the PK of AZD8233.	Population PK parameters. [a]
To evaluate the immunogenicity of AZD8233.	Development of ADA and ADA titre (if participants were 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, injection site reactions, and clinical laboratory evaluations, including platelet count.

Table S1 Objectives and Endpoints in Part B

Objectives	Estimand description/Endpoints
Exploratory	
To collect and store blood (plasma) and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies) and tolerability related to AZD8233 treatment or cardiometabolic diseases.	Evaluation of changes in biomarkers. 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 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.

[a] Plasma concentrations were evaluated descriptively in place of population PK parameters (see SAP Section 4.2.5.2).

ADA = anti-drug antibody; AE = adverse event; ApoA1 = Apolipoproteins A1; ApoB = apolipoprotein B; CSR = clinical study report; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type-9; PD = pharmacodynamics; PK = pharmacokinetics; RLP-C = remnant lipoprotein cholesterol; TC = Total cholesterol; VLDL-C = Very-low-density lipoprotein cholesterol.

Study design

This was a randomised, blinded, multidose Phase I/II study. The study consisted of three distinct parts (only information pertaining to Part B of the study is presented in this report):

- Part A – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.
- Part B – a randomised, double-blind, placebo-controlled, dose-ranging Phase II study.
- Part C – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.

In Part B, participants were randomised to 3 different treatment groups (AZD8233 CCI , AZD8233 CCI , and placebo) in a 1:1:1 ratio for a 12-week treatment period. Participants were dosed subcutaneously (SC) on Day 1, Day 29, and Day 57.

The screening period started within 28 days before the randomisation visit and ended on Day −4. After the 12-week treatment period was completed, participants continued in a follow-up period of 12 weeks (up to 16 weeks after the last dose).

Eligible participants attended 7 visits during the treatment period and 7 additional visits during the follow-up period.

Target population and sample size

The study was conducted in male or female participants between 20 and 75 years old (inclusive) with documented dyslipidaemia.

Approximately 60 participants were planned to be randomised to Part B of the study. The actual number of participants randomised in Part B was 65.

A complete description and justification of the methods used to determine the planned sample size, together with their derivations or the reference source, is provided in Section 9.2 of the clinical study protocol (CSP).

Investigational product and comparator: dosage, mode of administration and batch numbers

Participants in AZD8233 CCI treatment group received AZD8233 CCI via SC administration of an AZD8233 CCI solution for injection. Batch number: L014629.

Participants in AZD8233 CCI treatment group received CCI AZD8233 via SC administration of an AZD8233 CCI solution for injection. Batch number: L014626.

Participants in the placebo treatment group received placebo through SC administration of a matched placebo solution for injection. Batch number: L014625.

Duration of treatment

Participants were to be dosed on Day 1, Day 29, and Day 57, and were followed up for 12 weeks after the 12-week treatment period.

Statistical methods

Efficacy analyses were summarised based on the Full Analysis Set.

Primary endpoint

A mixed model with repeated measures (MMRM) was fitted using the log-transformed low-density lipoprotein cholesterol (LDL-C) data. The model included the log-transformed LDL-C baseline value as a covariate and time point (visit number), treatment, and the interaction between time point and treatment were included as factors.

Secondary endpoints

The absolute change from baseline in the log-transformed proprotein convertase subtilisin kexin type 9 (PCSK9) was fitted using the mixed model for repeated measures as described for the primary endpoint, such that the model included the log-transformed baseline value as a covariate, time point (visit number), treatment, and the interaction between time point and

treatment as factors. The percent change from baseline in PCSK9 was analysed using the same model as described without log-transformation.

The LDL-C secondary endpoint (the percent change in LDL-C) was also analysed using the statistical model described for the primary endpoint. The LDL-C secondary endpoint was also summarised by visit and treatment group using descriptive statistics (arithmetic mean, standard deviation [SD], minimum, median, maximum).

The other secondary endpoint lipid parameters (change from baseline and percent change from baseline) were summarised by visit and treatment group using descriptive statistics (arithmetic mean, SD, minimum, median, maximum). An MMRM on percent change from baseline to Week 12 was also presented for each other lipid parameter.

The pharmacokinetic (PK) evaluation was carried out for all participants in the PK Analysis Set. Plasma concentrations of AZD8233 full lengths antisense oligonucleotides (ASOs) were summarised by each analysis visit and scheduled time using descriptive statistics, reporting the number of non-missing observations, number below the lower limit of quantification (LLOQ), arithmetic mean, SD, geometric mean, geometric coefficient of variation (CV%), min, median and max.

Anti-drug antibody (ADA) endpoints were analysed based on the Safety Analysis Set. The number and percentage of participants with a positive result were tabulated for: any time in study, baseline, any time post baseline, and by treatment group and study visit. Anti-drug antibody titre was summarised descriptively as a continuous variable, only for ADA positive tests, with median, interquartile range, minimum, and maximum, at each visit. All immunogenicity parameters were also reported in a listing for the Safety Analysis Set.

Study population

A total of 65 participants were enrolled in the study and randomised in a 1:1:1 ratio to receive AZD8233 CCI (22 participants), AZD8233 CCI (22 participants), or placebo (21 participants).

Overall, 64 participants (98.5%) completed study treatment. One participant (4.5%) in the AZD8233 CCI treatment group discontinued treatment due to a pre-treatment SAE; the SAE started before the first dose of study treatment, and the participant was discontinued after the first dose of study treatment was administered. One participant (4.8%) in the placebo treatment group experienced an important protocol deviation (IPD) related to an out-of-range heart rate at inclusion.

The mean age of the study participants was 62.3 years (range: 50 to 73 years). Slightly more than half of participants were male (37 [56.9%] male to 28 [43.1%] female participants).

Participant demographics, characteristics, and baseline disease characteristics were generally balanced between the treatment groups.

Mean treatment compliance in the study was 99.0%; 100% in both AZD8233 CCI and placebo treatment groups, and 97.0% in the AZD8233 CCI treatment group due to the 1 participant who discontinued from study treatment.

Summary of efficacy results

LDL-C (Friedewald formula with reflex PUC/beta-Quantification)

Greater changes from baseline in log-transformed LDL-C at Week 12 were achieved for both AZD8233 treatment groups compared with the placebo treatment group. These changes were statistically significant in favour of the AZD8233 treatment groups ($p < 0.001$). At Week 12, relative changes from baseline in LDL-C were −80.2% and −54.2% in the AZD8233 CCI and AZD8233 CCI treatment groups respectively, versus −4.7% for the placebo treatment group.

The sensitivity analysis of the primary endpoint and analysis of LDL-C without log-transformation yielded consistent results.

PCSK9

Greater changes from baseline in log-transformed PCSK9 at Week 12 were achieved for both AZD8233 treatment groups compared with the placebo treatment group. These changes were statistically significant in favour of the AZD8233 treatment groups ($p < 0.001$). At Week 12, relative changes from baseline in PCSK9 were −93.4% and −70.4% in the AZD8233 CCI and AZD8233 CCI treatment groups respectively, versus −12.6% for the placebo treatment group.

Other lipid parameters

For most of the other lipid parameters (TC, non-HDL-C, VLDL-C, ApoB, Lp(a), triglycerides, and RLP-C), reductions from baseline were observed in both the AZD8233 CCI and AZD8233 CCI treatment groups. The reductions from baseline in these lipid parameters were dose-dependent and were maintained up to Week 12. Increases from baseline in HDL-C and ApoA1 were observed in all treatment groups.

Immunogenicity

In total, 6 participants (4 participants [18.2%] in the AZD8233 CCI treatment group and 2 participants [9.1%] in the AZD8233 CCI treatment group) developed treatment-emergent ADAs.

No AEs of hypersensitivity, anaphylactic or flu-like reactions or injection site reactions were reported among the ADA positive participants. There was no indication that the presence of ADAs influenced the efficacy/pharmacodynamic results or had a clear impact on PK results.

Summary of pharmacokinetic results

AZD8233 full length ASO plasma concentrations were higher in the AZD8233 CCI treatment group than in the AZD8233 CCI treatment group; this was consistent with a proportional increase in relation to dose. A slight increase in mean trough concentrations of AZD8233 in plasma was observed over time (Day 29, Day 57, and Day 85); the increase between Day 57 and 85 was minor, indicating that close to steady state conditions had been achieved after 12 weeks of once monthly dosing.

Summary of safety results

AZD8233 was well-tolerated, and the TEAEs reported were balanced between the treatment groups. There were no TESAEs, TEAEs with the outcome of death, or TEAEs that resulted in discontinuation from the study. All TEAEs reported were mild in intensity.

Three participants (2 participants [9.1%] in the AZD8233 CCI treatment group and 1 participant [4.5%] in the AZD8233 CCI treatment group) experienced TEAEs that were assessed by the Investigator as related to the IP: mild injection site reactions in both AZD8233 groups, and mild ventricular extrasystoles in the AZD8233 CCI treatment group.

No safety findings of concern were observed in participants with treatment-emergent ADA responses.

There were no sustained decreases in platelet count observed in any participant, and no incidents of platelets $< 150 \times 10^9$/L were reported as TEAEs. There was no indication of renal impairment/renal toxicity. There were no clear changes in complement activation in any of the treatment groups. Small increases from baseline in liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed on an individual level in all treatment groups (AZD8233 and placebo). There were no instances of ALT or AST $> 3 \times$ ULN, or instances of TBL $\geq 2 \times$ ULN and none of these incidences of fluctuations in liver enzymes were reported as TEAEs.

There were no safety concerns with the vital signs and electrocardiogram (ECG) data.

Conclusions

- AZD8233 demonstrated a dose-dependent reduction in LDL-C, PCSK9, and the majority of the other lipid parameters by Week 12 in Japanese participants with dyslipidaemia.
- AZD8233 was well tolerated in the AZD8233 CCI and AZD8233 CCI treatment groups; all TEAEs reported were mild in intensity and balanced between the treatment groups.

Clinical Study Report	
Drug Substance	AZD8233
Study Code	D7990C00006 (Part C)
Edition Number	1.0
Date	14 June 2023
NCT Number	NCT04823611

A Phase I and II Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of AZD8233 Following a Multiple Subcutaneous Dose Administration in Japanese Participants with Dyslipidaemia (HAYATE) - Part C -

Study dates:	First participant enrolled: 18 February 2022 Last participant last visit: 10 September 2022 The analyses presented in this report are based on a clinical data lock date of 25 November 2022
Phase of development:	Parts A and C: Clinical pharmacology (I) Part B: Therapeutic exploratory (II)
International Co-ordinating Investigator:	Not applicable
Sponsor's Responsible Medical Officer	PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centres

Part C of this study was performed at 2 sites in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
To assess the safety and tolerability of AZD8233 following SC administration of multiple doses.	Adverse events, vital signs, ECG, cardiac telemetry, injection site reaction examination, and clinical laboratory evaluations including platelet count.
Secondary	
To characterise the PK of AZD8233 following SC administration of multiple doses.	Plasma parameters (t_{last}, t_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}48)}$, AUC, AUCτ, C_{trough}, CL/F, Vz/F, $t_{1/2}$, MRT); urine parameters (Ae, Fe, CLR).
To assess the effect of AZD8233 on levels of PCSK9 following SC administration of multiple doses.	Absolute change from baseline in log-transformed PCSK9 in plasma. Percent change from baseline in PCSK9 in plasma.
To assess the effect of AZD8233 on levels of LDL-C following SC administration of multiple doses.	Percent change in levels of LDL-C in serum.
To assess the effects of AZD8233 on other lipid parameters following SC administration of multiple doses.	Levels of other lipid parameters, including: • TC • HDL-C • Non-HDL-C • VLDL-C • ApoA1 • ApoB • Lp(a) • Triglycerides
Exploratory	
To collect and store plasma and urine samples for potential future exploratory research aimed at exploring biomarkers involved in PK, PD, safety (including antiplatelet antibodies), and tolerability related to AZD8233 treatment or cardiometabolic diseases.	The biomarkers to be analysed may include but are not limited to ApoCIII (3), ANGPTL3, ANGPTL4, ANGPTL8, and ProC3. The results will not form part of this CSR.
To collect and analyse samples for exploration of anti-drug immunogenicity.	ADAs.

ADA = anti-drug antibody; Ae = amount excreted in urine; ANGPLT3 = angioprotein-like protein 3; ANGPLT4 = angioprotein-like protein 4; ANGPLT8 = angioprotein-like protein 8; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoCIII (3) = apolipoprotein CIII (3); AUC = area under the plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}last)}$ = area under the plasma concentration-time curve from time zero to time last value above the limit of quantification; $AUC_{(0\text{-}24)}$ = area under the plasma conversation-time curve from time zero to 24 hours after dosing; $AUC_{(0\text{-}48)}$ = area under the plasma conversation-time curve from time zero to 48 hours after dosing; AUCτ = area under the plasma concentration-time curve from time during the dosing interval; CL_R = renal clearance; CL/F =apparent total body clearance of drug from plasma after extravascular administration; C_{max} = observed maximum plasma concentration; CSR= clinical study report; C_{trough} = trough plasma concentration; ECG = electrocardiogram; Fe = fraction excreted unchanged in urine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); MRT = mean residence time of the unchanged drug in the systemic circulation; PCSK9 = proprotein convertase subtilisin/kexin 9; PD = pharmacodynamics; PK = pharmacokinetics; ProC3 = propepticde of type III collagen; SC = subcutaneous; $t_{1/2}$ = terminal half-life; t_{max} = time to reach peak maximum or maximum observed concentration or response following drug administration; t_{lag} = time delay between drug administration and the first observed concentration in plasma; TC = total cholesterol; VLDL-C = very low-density lipoprotein cholesterol; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration.

Study design

This was a randomised, blinded, multidose Phase I/II study. The study consisted of three distinct parts:

- Part A – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.
- Part B – a randomised, double-blind, placebo-controlled, dose ranging Phase II study.
- Part C – a randomised, single-blind (blinding of study participants and sites), placebo-controlled, multiple dose Phase I study.

Only information pertaining to Part C of the study is presented here.
Part C of the study comprised of:

- A screening period which started ≤ 28 days before the randomisation visit and ended on Day −4.
- A treatment period that lasted 58 days (up to Visit 9).
- A follow-up period which included Visit 10 to Visit 17 (Weeks 2, 4, 6, 8, 10, 12, 14, and 16 after last dose of study treatment).

Participants were randomised across the two treatment arms, AZD8233 CCI and placebo, in the ratio 8:3 for the treatment period. Participants were dosed on Days 1, 29, and 57.
Part C of the study was single-blind with regards to treatment (AZD8233 or placebo). AZD8233 and placebo were matched in appearance. Participants who were randomised to placebo received the same volume of injection as that of those randomised to receive AZD8233.
After the treatment period, participants continued in a follow-up period of 14 weeks (up to 16 weeks after the last dose).

Target population and sample size

The study was conducted in male or female participants between 20 and 60 years old (inclusive) with documented dyslipidaemia.

Approximately 11 participants were planned to be randomised to Part C of the study, in an 8:3 ratio across the two treatment arms; AZD8233 CCI or placebo.

Due to the exploratory nature of Part C of this study, the sample size was not based on formal statistical considerations. Eight Japanese participants on active study treatment were considered to be sufficient to confirm a tendency for safety, pharmacokinetic (PK), and pharmacodynamic (PD) data.

Investigational product and comparator: dosage, mode of administration and batch numbers

Participants in the AZD8233 CCI treatment group received CCI of AZD8233 through subcutaneous (SC) administration of an AZD8233 CCI solution for injection. The AZD8233 solution for injection batch number was L014633.

Participants in the placebo treatment group received placebo through SC administration of a matched placebo solution for injection. The placebo batch number was L014625.

Duration of treatment

The total study duration was approximately 28 weeks (a 28-day screening period, 58-day treatment period, and a 16-week follow-up period).

Statistical methods

No formal statistical hypotheses were set for Part C of this study. Data were interpreted through descriptive statistics only.

Study population

A total of 11 participants were randomised and received study treatment: 8 participants in the AZD8233 CCI treatment group and 3 participants in the placebo treatment group.

Demographics, participant characteristics, and baseline disease characteristics were generally balanced between the AZD8233 and placebo treatment groups. The minor differences observed were not expected to adversely impact the interpretation of study results.

No participant discontinued study treatment; all 11 participants completed the study. No important protocol deviations were reported during the study.

Summary of efficacy results

At Visit 11 (4 weeks post last dose of study treatment), in the AZD8233 CCI treatment group, there was a mean decrease observed in proprotein convertase subtilisin/kexin type 9 (PCSK9), low-density lipoprotein cholesterol (LDL-C), and the majority of the other lipid parameters.

At Visit 11 (4 weeks post last dose of study treatment), there was a larger change from baseline observed in PCSK9 and LDL-C in the AZD8233 CCI treatment group (−92.95% [SD = 3.634%] and −73.76% [SD = 9.241%], respectively) when compared to the placebo treatment group (−16.22% [SD = 26.937%] and 8.47% [SD = 9.309%], respectively).

Based on the log-transformed data at Visit 11, there was a relative change from baseline of 0.063 in PCSK9 in the AZD8233 CCI treatment group, which was equivalent to a relative change of −93.7%. In the placebo group, there was a relative change from baseline of 0.807 in PCSK9 in the placebo treatment group, which was equivalent to −19.3%.

At Visit 11 (4 weeks post last dose of study treatment), there were differences in the changes from baseline observed in TC, non-HDL-C, ApoB and Lp(a) between the AZD8233 CCI treatment group (−42.15% [SD = 7.350%], −65.43% [SD = 6.783%], −60.36% [SD = 6.631%], −58.61% [SD = 18.592%], respectively) when compared with the placebo treatment group (7.97% [SD = 6.442], 5.53% [SD = 10.942%], 6.00% [SD = 9.361], −21.53% [SD = 12.700%], respectively). It was noted that TC, non-HDL-C, and ApoB were all increased from baseline in the placebo group at Visit 11, whereas Lp(a) had decreased. The decrease from baseline in Lp(a) was larger in the AZD8233 CCI treatment group compared with the placebo treatment group at Visit 11.

At Visit 11 (4 weeks post last dose of study treatment), there was overlap between the AZD8233 CCI and placebo treatment groups in the HDL-C, VLDL-C, ApoA1, and triglycerides data; this overlap in data was also observed at all other study visits. AZD8233 had no discernible effect on these lipid parameters compared to placebo.

Summary of pharmacokinetic results

AZD8233 and AZD8233 full length antisense oligonucleotides (ASOs) appeared rapidly in plasma with median t_{max} values of 1.765 and 2.000 (AZD8233 on Day 1 and Day 57, respectively), and 2.250 and 1.750 hours (AZD8233 full length ASOs on Day 1 and Day 57, respectively). At early time points, the AZD8233 full length ASOs concentration versus time profiles mirrored that of the parent AZD8233, but at slightly higher concentrations. At later time points, AZD8233 full length ASOs were the only quantifiable species in plasma.

The full length ASOs had a biphasic plasma concentration versus time profile with a geometric mean terminal $t_{1/2}$ of approximately 27 days as estimated after the last dose. Clearance of AZD8233 full length ASOs was predominantly non-renal with less than 0.5% of the dose excreted as full length ASOs in urine during the first 24 hours. There appeared to be no accumulation in AZD8233 and full length ASOs (AUC and C_{max}) plasma exposure following repeated monthly dosing with AZD8233.

A slight increase in mean trough concentrations of AZD8233 full length ASOs in plasma was observed over time (Day 29, Day 57, and Day 85); the increase between Day 57 and 85 was minor, indicating that close to steady state conditions had been achieved after 12 weeks of one monthly dosing.

Interparticipant variability in AZD8233 and AZD8233 full length ASO plasma exposure was moderate and moderate to high, respectively.

Summary of pharmacokinetic/pharmacodynamic relationships

After the end of treatment, throughout the follow-up period, the PCSK9 levels slowly increased towards baseline. This slow increase in PCSK9 levels was consistent with the long terminal half-life of AZD8233 full length ASOs observed in plasma.

Summary of immunogenicity results

No study participant developed anti-drug antibodies (ADAs).

Summary of safety results

All participants were exposed to study treatment for 57 days.

Overall, 2 (25.0%) participants in the AZD8233 CCI treatment group and 1 (33.3%) participant in the placebo treatment group reported adverse events (AEs). There were no injection site reactions, serious AEs, or AEs with the outcome of death. All AEs were mild in intensity and considered not related to the study treatment.

There were no clinically notable trends in haematology, including platelets and coagulation, clinical chemistry, or urinalysis parameters. There was no indication of renal impairment/renal toxicity.

Conclusions

- Subcutaneous administration of repeated (monthly) doses of AZD8233 CCI was well tolerated in Japanese participants with dyslipidaemia. The reported AEs and other safety results did not raise any new safety concerns.
- Administration of AZD8233 resulted in a decrease in PCSK9, LDL-C, TC, non-HDL-C, and ApoB at Visit 11 (4 weeks post last dose of study treatment) when compared to placebo.
  - Lp(a) decreased from baseline in both treatment groups at Visit 11, with the larger decrease observed in the AZD8233 CCI treatment group.
  - AZD8233 had no discernible effect on HDL-C, VLDL-C, ApoA1, or triglycerides when compared to placebo.
- AZD8233 was rapidly absorbed to the systemic circulation. After reaching C_{max}, the plasma profile showed the ASO characteristic biphasic decline in plasma concentrations with a long terminal half-life estimated to 27 days, supporting the once monthly dosing regimen.
- There appeared to be no accumulation in AZD8233 and full length ASOs plasma exposure (AUC and C_{max}) following multiple monthly doses of CCI AZD8233.