Clinical Study Report Synopsis	
Drug Substance	AZD8233
Study Code	D7990C00003
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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

Study dates: First subject enrolled: 28 October 2020
Last subject last visit: 20 July 2021

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: PPD

Sponsor's Responsible Medical Officer: PPD

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

The study was conducted at study centres in the United States of America (USA) and Europe. A total of 19 study centres in 3 countries (Denmark, Slovakia, and the USA) enrolled participants.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

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	• Percent 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
	  • Remnant 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

Objectives	**Endpoints**
Safety	
• To assess the safety and tolerability of AZD8233	• Safety and tolerability were evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations including platelet count
Tertiary/Exploratory	
Reported in this CSR	
• To assess lipoprotein profile following SC administration of AZD8233	• Lipoprotein profile, including particle size and number
Not reported in this CSR	
• 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 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

ADA = anti-drug antibody; AE = adverse event; ApoA1 = apolipoprotein 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); non-HDL-C = non high density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SC = subcutaneous(ly); TC = total cholesterol; VLDL C = very low-density lipoprotein cholesterol

Study design

This was a randomised, parallel, double-blind, placebo-controlled, dose-ranging, Phase 2b study to evaluate the efficacy, safety and tolerability of AZD8233 in participants with dyslipidaemia (characterised by elevated low-density lipoprotein cholesterol [LDL-C] levels). The study was conducted across multiple sites and aimed to enrol approximately 108 participants with dyslipidaemia. Eligible participants were randomised in a 1:1:1:1 ratio between AZD8233 CCI , AZD8233 CCI , AZD8233 CCI , or matching placebo.

All randomised participants received a subcutaneous (SC) injection of study intervention on Days 1, 8, 29, and 57. Participants attended 7 visits during the treatment period and 7 additional visits during the safety follow-up period. From randomization, every second visit was planned to be a site visit and the visits in-between could have been home visits. Home visits were optional; however, no home visits were performed during the study.

After the treatment period, participants continued in a safety follow-up period of 12 weeks (up to 16 weeks post last dose).

Target subject population and sample size

Participants between 18 to 75 years of age, inclusive at the time of signing the informed consent form with fasting LDL-C ≥ 70 mg/dL, but < 190 mg/dL at screening. Participants must have also had fasting triglycerides < 400 mg/dL at screening and been receiving moderate- or high-intensity statin therapy as defined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on blood cholesterol management, or according to local guidelines.

The study was conducted across multiple sites and aimed to enrol approximately 108 participants so that at least 80 evaluable participants completed treatment up until and including Week 12.

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

- AZD8233 CCI – solution for SC injection (batch 71188.1/1)
- AZD8233 CCI – solution for SC injection (batch 71188.2/1)
- AZD8233 CCI – solution for SC injection (batch 71188.3/1, 71188.2/1, and 71188.7/1)
- Placebo matched to AZD8233 – solution for SC injection (batch 71188.4/1 and 71188.8/1)

Duration of treatment

Participants were randomised to either AZD8233 CCI , CCI , CCI , or placebo and received treatment on Days 1, 8, 29, and 57. Participants were followed up for 12 weeks after the treatment period.

Statistical methods

The primary objective of this study was to compare absolute change from baseline in log-transformed LDL-C across different dose levels of AZD8233.

The key secondary objective of this study was to compare absolute change form baseline in log-transformed proprotein convertase subtilisin/kexin type 9 (PCSK9) across different dose levels of AZD8233.

Both log-transformed LDL-C and log-transformed PCSK9 were analysed by fitting a mixed model for repeated measures to the data with baseline as covariate and treatment, time (visit), and interaction between treatment and time as factors.

For the efficacy analyses, participants were analysed according to the treatment to which they were randomised. Participants were analysed with respect to the intention-to-treat principle

using the full analysis set, which contains data from each participant who received at least one dose of placebo or AZD8233.

Safety and tolerability were evaluated; adverse events (AEs), vital signs, electrocardiograms (ECGs), and clinical laboratory evaluations were presented with descriptive statistics.

Study population

- A total of 210 participants were enrolled into the study from 19 centres in 3 countries (Denmark, Slovakia and the United States of America). Of these 210 participants, 119 were randomised in a 1:1:1:1 ratio to receive either AZD8233 CCI (29 participants); AZD8233 CCI (30 participants); AZD8233 CCI (30 participants); or placebo (30 participants).
- A total of 104 (87.4%) participants completed study intervention and 114 (95.8%) completed the study.
- Participants had a median age of 64.0 years (range: 40 to 75 years), 52.1% were male, 47.9% were female, and the majority were White (92.4%).
- The study population recruited was representative of the target population, and demographic characteristics were generally balanced across the treatment groups.
- The medical history reported was generally typical for this patient population.
- All participants used allowed concomitant medications; no participants used disallowed concomitant medication.
- The majority of participants (99.2%) used concomitant 3-hydroxy-3-methyl-glutarylcoenzyme A (HMG-CoA) reductase inhibitors during the study.
- Treatment compliance was high and similar across the treatment groups.
- Important protocol deviations reported during the study did not raise any concerns regarding the overall conduct or quality of the study.

Summary of efficacy results

Efficacy:

- Greater changes from baseline in log-transformed LDL-C at Week 12 were achieved for all AZD8233 groups compared with placebo. These changes were statistically significant in favour of the AZD8233 groups ($p<0.001$). At Week 12, relative changes from baseline in LDL-C were 79.4%, 73.0%, and 39.4% in the AZD8233 CCI, CCI, and CCI groups, respectively, compared with 2.2% in the placebo group.
- Greater changes from baseline in log-transformed PCSK9 at Week 12 were achieved for all AZD8233 groups compared with placebo. These changes were statistically significant in favour of the AZD8233 groups ($p<0.001$). At Week 12, relative changes from baseline in PCSK9 were 94.0%, 89.0%, and 58.0% in the AZD8233 CCI, CCI, and CCI groups, respectively, compared with 5.0% in the placebo group.
- Clinically meaningful reductions in LDL-C were observed 1 week after first dose for the CCI and CCI groups; all AZD8233 groups maintained clinically meaningful reductions until Week 14 (6 weeks after last dose) before returning to near baseline values by Week 24.

- Dose-dependent and statistically significant reductions from baseline at Week 12 were observed for all AZD8233 groups compared with placebo for total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), and apolipoprotein B (ApoB), while a slight increase was observed for apolipoprotein A1 (ApoA1). Reductions from baseline in ApoB were generally consistent with those achieved for LDL-C.
- For all efficacy parameters, a dose-dependent trend in improvement from baseline was observed.

Summary of pharmacokinetic results

- Across the AZD8233 treatment groups, mean plasma concentrations of AZD8233 full length antisense oligonucleotides (ASO) were similar at Week 8 and Week 12 (4 weeks after previous dose) indicating that steady state had been reached at that time.

Summary of immunogenicity results

- A total of 14 participants were ADA positive at baseline and/or post baseline during the study (4 [13.8%] CCI ; 5 [16.7%] CCI ; 4 [13.3%] CCI ; and 1 [3.3%] placebo). Of these, 10 participants had treatment-emergent anti-drug antibodies (ADAs) (4 each in the AZD8233 CCI and CCI groups and 2 in the AZD8233 CCI group). For all participants, ADA titres were generally low, except for 1 participant in the AZD8233 CCI group.
- For participants that developed treatment-emergent ADAs during the study, no impact on the efficacy of AZD8233 in relation to LDL-C and PCSK9 reduction or clear effect on AZD8233 full-length ASO plasma concentrations were observed.

Summary of safety results

- The exposure to study intervention was generally balanced across the treatment groups.
- AZD8233 was well tolerated in the CCI and CCI groups. In the AZD8233 CCI group, mild to moderate increases in alanine aminotransferase (ALT) were observed.
- Overall, a higher proportion of participants in the AZD8233 groups (52 [58.4%]) experienced AEs compared with the placebo group (12 [40.0%]), with the highest frequency in the AZD8233 CCI dose group (20 [69.0%]).
- The majority of AEs were mild to moderate in intensity. Severe AEs were reported in 7 (7.9%) participants, all in the AZD8233 groups.
- Four participants experienced serious adverse events (SAEs), all reported in the AZD8233 groups. No deaths were reported. Seven participants discontinued the investigational product due to AEs (6 in the AZD8233 groups and 1 in placebo group).
- Nine participants, all in the AZD8233 groups, reported injection site reactions of mild intensity, which led to discontinuation of the investigational product for 1 participant in the CCI group.
- A total of 10 participants in the AZD8233 groups had treatment-emergent ADAs. No ADA-related safety concerns were observed.
- No clinically significant trends in clinical laboratory results (including platelets), vital signs, or ECGs were observed, except in the AZD8233 CCI group where transient and

mild to moderate ALT increases were observed. Four participants experienced ALT increases between 3 × upper limit of normal (ULN) and < 6 × ULN, of which 2 were discontinued from the investigational product.

Conclusion(s)

- AZD8233 demonstrated a statistically significant and dose-dependent reduction in LDL-C and PCSK9 levels by Week 12 in participants with dyslipidaemia, with corresponding reductions in non-HDL-C and ApoB levels.
- AZD8233 showed a dose-dependent trend of improvement for the majority of efficacy parameters evaluated.
- AZD8233 was well tolerated in the CCI and CCI groups. In the AZD8233 CCI group, mild to moderate increases in ALT were observed.