Clinical Study Report Synopsis	
Drug Substance	AZD8233
Study Code	D7990C00004
Edition Number	1.0
Date	08 February 2023
EudraCT Number	2020-005845-18
NCT Number	NCT04964557

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

Study dates: First subject enrolled: 07 July 2021
Last subject last visit: 15 July 2022

Phase of development: Therapeutic exploratory (Phase 2b)

International Co-ordinating Investigator: [redacted]s

Sponsor's Responsible Medical Officer: [redacted] FESC
AstraZeneca, SE-431 83 Gothenburg, Sweden

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

Study centres

The study was conducted at a total of 66 study centres in 8 countries: Czech Republic (10 centres), Denmark (8 centres), Hungary (4 centres), Netherlands (6 centres), Poland (8 centres), Slovakia (7 centres), Spain (7 centres), and United States (16 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives	Endpoints
Primary Safety	
To assess the safety and tolerability of AZD8233 as compared with placebo in subjects with hyperlipidaemia receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical laboratory evaluations, including platelet count
Primary Efficacy	
To assess the effect of AZD8233 versus placebo on serum LDL-C at the end of Week 28 compared with baseline, in subjects with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The relative change in serum LDL-C from baseline to the end of Week 28
Secondary Efficacy	
To assess the effect of AZD8233 versus placebo on plasma PCSK9 at the end of Week 28 compared with baseline, in subjects with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator	The relative change in PCSK9 from baseline to the end of Week 28
Secondary PK	
To evaluate the PK of AZD8233	Model population PK parameters to be reported in a separate report
Secondary Immunogenicity	
To evaluate the immunogenicity of AZD8233	Development of ADA and titre (if subjects are ADA positive) during treatment and follow-up

ADA,anti-drug antibodies; AE, adverse event; ECG, electrocardiogram; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type-9; PK, pharmacokinetics.

Study design

SOLANO was a randomised, parallel, double-blind, placebo-controlled Phase 2b study to evaluate the safety and tolerability of AZD8233 compared with placebo. The study was carried out across 66 clinical sites in 8 countries.

Subjects with hyperlipidaemia were randomly assigned to AZD8233 CCI or matching placebo in a 1:1 ratio using Interactive Response Technology (IRT)/ randomisation and trial supply management (RTSM), and treated SC, Q4W for 28 weeks. The effect of AZD8233 on concentrations of low-density lipoprotein cholesterol (LDL-C) in serum was also evaluated. The aim was that, of the subjects randomised to AZD8233 doses, at least 150 should complete the 28 weeks of planned treatment.

Target population and sample size

Subjects between 18 to 75 years of age inclusive, at the time of signing the informed consent form with fasting low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL (≥ 1.8 mmol/L), but < 190 mg/dL (< 4.9 mmol/L) at screening, with fasting triglycerides < 400 mg/dL (< 4.52 mmol/L) at screening and receiving a stable dose (≥ 3 months) of maximally tolerated statin and/or ezetimibe therapy as defined by the investigator for that subject at screening, were eligible to be included in the study. Subjects were to be male, or female of non-childbearing potential.

The study was conducted across multiple sites and aimed to randomise approximately 376 participants.

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

- AZD8233 CCI – solution for subcutaneous (SC) injection (batch number: CCI)
- Placebo matched to AZD8233 – solution for SC injection (batch number: CCI)

Duration of treatment

Subjects were randomised to either AZD8233 CCI or placebo and received treatment on Days CCI and CCI. The study was divided into a planned treatment period of 28 weeks followed by a safety follow-up of 12 weeks, giving a total study participation time of 40 weeks.

Statistical methods

Safety Analysis

The primary safety objective of this study was to evaluate safety and tolerability of AZD8233 versus placebo in terms of adverse events (AEs), vital signs, electrocardiogram (ECG), and clinical laboratory evaluations, including platelet count. Safety analyses were performed using the safety analysis set, which included subjects who took at least one dose of investigational product (IP).

Efficacy Analysis

The effect of AZD8233 on primary and secondary efficacy variables was assessed under a treatment policy estimand, and all subjects who were randomly assigned to study intervention

were included in the analysis. An ANCOVA model was used with relative change from baseline to end of Week 28 in LDL-C and PCSK9, respectively, as response variables. Treatment group and baseline value were included as covariates in the model.

Pharmacokinetic Analysis

The AZD8233 full length antisense oligonucleotide (ASO) concentrations in plasma were summarised by descriptive statistics by sampling time point and listed on individual level based on the pharmacokinetic (PK) analysis set. Concentrations were analysed on a natural logarithmic scale and then back-transformed to the original scale.

Immunogenicity Analysis

Number and percentage of subjects in each anti-drug antibodies (ADA) response category were tabulated by treatment group and in total, with corresponding summary statistics (minimum, Q1, median, Q3, maximum) for ADA titre when applicable.

Study population

- A total of 411 subjects were randomised to either AZD8233 or placebo treatment group at 66 study centres in Czech Republic, Denmark, Hungary, Netherlands, Poland, Slovakia, Spain and the United States of America.
- Overall, 362 (88.3%) subjects completed the study treatment and 397 (96.6%) subjects completed the study. Thirty-one (15.1%) subjects in AZD8233 group and 17 (8.3%) subjects in placebo group, discontinued the study treatment. The most frequent reasons for discontinuation of IP were adverse event and subject decision.
- The most frequently reported important protocol deviations (IPDs) overall were deviations to study procedure and exclusion criteria deviations.
- The demographic characteristics were generally balanced between the two treatment groups. The mean age of the subjects was 62.3 years, approximately half of the subjects randomised were male, and more than 95% were White.
- Concomitant medications of class 3-hydroxy-3-methyl-glutarylcoenzyme (HMG-CoA) reductase inhibitors were used by the majority of subjects (362 subjects; 88.1%). Concomitant medications that were disallowed were used by 26 (6.3%) subjects with similar incidence in both the treatment groups.
- Overall, the reported concomitant medications were as expected for the subject population enrolled in the study (in terms of baseline demographics and underlying disease), and were aligned with the reported baseline medical conditions of the randomised subjects.
- Treatment compliance was high in both treatment groups.

Summary of efficacy results

- There was a statistically significant difference in mean relative change in LDL-C and Proprotein convertase subtilisin/kexin type 9 (PCSK9) at the end of Week 28 (Day 197) in AZD8233 group as compared to placebo group.

- At 28 weeks, the relative change in LDL-C was -56.7% (95% CI: -60.8%, -52.7%) in the AZD8233 group, compared to 5.6% (95% CI: 1.5%, 9.6%) in the placebo group, with an absolute difference in least squares (LS) means of -62.3% (95% CI: -68.0%, -56.6%; $p < 0.001$).
- At 28 weeks, the relative change in PCSK9 was -77.5% (95% CI: -81.1%, -74.0%) in the AZD8233 group, compared to -0.8% (95% CI: -4.3%, 2.6%) in the placebo group, with an absolute difference in LS means of -76.7% (-81.7%, -71.7%, $p < 0.001$).

Summary of pharmacokinetic results

A slight increase in geometric mean pre-dose concentrations (Ctrough) of AZD8233 was observed over the treatment period. The inter-subject variability (geometric mean CV) in pre-dose concentrations was high and increased over time.

Summary of immunogenicity results

- A total of 53 subjects were ADA positive during the study, with higher incidence in AZD8233 treatment group (48/204 subjects; 23.5%) as compared to placebo group (5/202 subjects; 2.5%). Of these, 45 subjects had treatment emergent ADA positive response (44/204 subjects [21.6%] in AZD8233 group and 1/202 subjects [0.5%] in placebo group).
- The treatment effect of AZD8233 in terms of LDL-C and PCSK9 reduction was similar in subjects with ADA positive response as compared to subjects with ADA negative response.
- In subjects with ADA positive response on Day 141 and Day 197, respectively, the median AZD8233 concentration were higher compared to subjects with ADA negative response at each of those visits.

Summary of safety results

- A total of 173 (83.6%) subjects in AZD8233 group and 186 (91.6%) subjects in placebo group were exposed to the study intervention for at least 28 weeks.
- There were 141 (68.1%) and 127 (62.6%) subjects with any AE in the AZD8233 and the placebo group respectively.
- Most commonly reported AEs occurring in ≥ 5% of subjects in AZD8233 or placebo were: Coronavirus disease 2019 (COVID-19) (33 [15.9%] subjects in AZD8233 group and 36 [17.7%] subjects in placebo group), injection site reactions (22 [10.6%] subjects in AZD8233 group and 5 [2.5%] subjects in placebo group), diabetes mellitus inadequate control (18 [8.7%] subjects in AZD8233 group and 14 [6.9%] subjects in placebo group) and hypertension (11 [5.3%] subjects in AZD8233 group and 13 [6.4%] subjects in placebo group).
- Serious adverse events were reported in 18 (8.7%) subjects in the AZD8233 group and in 12 (5.9%) subjects in the placebo group. The most common serious adverse event (SAE) by system organ class (SOC) was cardiac disorders (5 [2.4%] subjects in the AZD8233 group compared to 3 [1.5%] subjects in the placebo group.

- Three (1.4%) subjects in the AZD8233 group and none in the placebo group reported SAEs of fatal outcome. None were considered as possibly related to IP by the investigator.
- Moderate or severe AEs were reported in 60 (29.0%) subjects in the AZD8233 group and 49 (24.1%) subjects in the placebo group. Severe AEs were reported in 15 (7.2%) subjects in the AZD8233 group and 7 (3.4%) subjects in the placebo group.
- Adverse events leading to discontinuation of IP were reported in 12 (5.8%) subjects in the AZD8233 group and for 5 (2.5%) subjects in the placebo group. Cardiac disorders were the most common reason (SOC) for discontinuation of IP, with 3 subjects discontinued in the AZD8233 group and 2 in the placebo group.
- Injection site reaction (ISR) was the most frequently reported investigator-assessed possibly related AE on-study (19 [9.2%] subjects in AZD8233 group and 5 [2.5%] subjects in placebo group). There was an imbalance in ISRs in the two treatment groups, 22 (10.6%) subjects in AZD8233 group and 5 (2.5%) subjects in placebo group reported AEs related to ISRs; none of these were SAEs or resulted in discontinuation of IP. The predominant symptoms associated with ISRs included erythema, pruritus, pain, discolouration and swelling. The most common location of occurrence of ISRs was the abdominal region.
- A total of 44 subjects in the AZD8233 treatment group had treatment emergent ADAs. No ADA-related safety concerns were observed.
- There were no SAEs associated with hypersensitivity. None of the hypersensitivity events were of severe maximum intensity in either group.
- SOLANO results show that AZD8233 had no overall numerical or clinically significant effect on platelet count. No levels below $< 50 \times 10^9$/L were recorded. The lowest platelet count was 72×10^9/L, in a subject who had increased levels above 75×10^9/L on follow-up testing. Platelet percentage drops of 30% or more from baseline were balanced between AZD8233 and placebo. There were no clinically meaningful differences in mean activated partial thromboplastin time (aPTT pre- and post-dosing), suggesting that administration of AZD8233 had no effect on coagulation. There were no bleeding events with a fatal outcome; 2 bleeding events in the AZD8233 group (coagulation time prolonged and haemothorax) were categorized as SAEs of severe intensity.
- A total of 7 subjects (5 in AZD8233 group and 2 in placebo group) had treatment emergent Alanine aminotransferase (ALT) increases $> 3 \times$ upper limit normal (ULN) and of these, 5 subjects (3 in AZD8233 and 2 in placebo) had increases $> 5 \times$ ULN. Of these 7 subjects, 3 subjects discontinued IP due to the subject's decision (all in AZD8233) and 4 remained on treatment. No subjects treated with AZD8233 had treatment emergent increases in ALT $> 10 \times$ ULN during the on-study period and no cases of Hy's Law were reported.

Conclusion

- AZD8233 was safe and generally well tolerated with no cases of treatment emergent platelet counts $< 50 \times 10^9$/L.
- The primary efficacy objective was met. AZD8233 demonstrated statistically significant reduction in LDL-C levels at end of Week 28.