Clinical Study Report Synopsis	
Drug Substance	AZD8233
Study Code	D7990C00007
Edition Number	1.0
Date	01 June 2023
EudraCT Number	2021-003044-24
NCT Number	NCT05065463

A Single Dose, Non-randomised, Open-label, Parallel Group Study to Assess the Pharmacokinetics, PCSK9 Reduction, Safety, and Tolerability of AZD8233 in Participants with Severe Renal Impairment, End Stage Renal Disease and Healthy Participants as Controls

Study dates:
Early study termination decision date: 27 September 2022
First subject enrolled: 10 August 2022
Last subject last visit: 23 November 2022
The analyses presented in this report are based on a clinical data lock date of 27 March 2023

Phase of development:
Clinical pharmacology (I)

International Co-ordinating Investigator:
PPD, PhD, MD

Sponsor's Responsible Medical Officer:
PPD, MD
One Medimmune Way, 101 ORD – 2nd Floor, Area 2
Gaithersburg, MD 20878, USA

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

Study centre(s)

Originally this study was planned to be conducted in up to 4 centres in 1 to 2 countries. Of these, only 1 clinical site (Site 5701) in Poland was activated before early study termination.

Publications

No publication is planned for this study.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary Pharmacokinetics	
To assess the PK of AZD8233 full length ASOs in participants with severe renal impairment and ESRD compared to matched healthy control participants following single dose administration of [redacted] mg AZD8233.	Where possible, the PK parameters for AZD8233 full length ASOs will be derived from plasma and urine concentrations. • Plasma parameters: Cmax, AUCinf, AUClast, and AUC(0-24). • Urine parameters: CLR, Ae, and fe.
Primary Safety	
To evaluate the safety and tolerability of a [redacted] mg AZD8233 single dose in participants with severe renal impairment, ESRD and their healthy matched controls.	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECGs, and clinical laboratory evaluations including platelet count.
Secondary Efficacy	
To assess the effect of AZD8233 on % reduction in PCSK9 plasma levels from baseline over-time in participants with severe renal impairment and ESRD compared to their healthy matched controls.	• Percentage change from baseline in PCSK9 plasma levels.

Abbreviations: AE: adverse event; Ae: amount excreted in urine; ASO: antisense oligonucleotide; AUC(0-24): area under the concentration-time curve from time zero to 24 hours after dosing; AUCinf: area under the plasma concentration-time curve from time zero extrapolated to infinity; AUClast: area under the plasma concentration-curve from time zero to time of last quantifiable concentration; CLR: renal clearance; Cmax: observed maximum plasma concentration; ECG: electrocardiogram; ESRD: end-stage renal disease; fe: fraction unbound in plasma; PCSK9: proprotein convertase subtilisin/kexin type 9; PK: pharmacokinetics.

Note: The exploratory objectives defined in the protocol were not assessed and not presented in this synoptic clinical study report (CSR).

Study design

This was a Phase I, single dose, non-randomised, open-label, parallel group study designed to assess the pharmacokinetics (PK), pharmacodynamics (PD), and safety of AZD8233 in male and female participants with severe renal impairment and end-stage renal disease (ESRD) compared to matched healthy control participants. The study was planned to enrol 3 cohorts of participants:

- Cohort 1 was to include 8 participants with severe renal impairment (estimated glomerular filtration rate [eGFR]of ≥ 15 to < 30 mL/min/1.73 m^2).
  - Gender: At least 2 (each) male and female participants must be included.
- Cohort 2 was to include 8 healthy participants with normal renal function (eGFR of ≥ 90 mL/min/1.73 m^2) to serve as matched controls for Cohort 1 and Cohort 3. Participants in Cohort 2 must have matched participants in Cohort 1 with regard to:
  - Age: Healthy participants had to be at least 18 years old and no more than 10 years younger than the youngest participant in Cohort 1 or more than 10 years older than the oldest participant in Cohort 1.
  - Body mass index (BMI): Healthy participants had to have a BMI that was not more than 20% lower than the lowest BMI of participants in Cohort 1 or more than 20% higher than the highest BMI of participants in Cohort 1.
  - Gender: At least 2 (each) healthy male and female participants had to be included.
- Cohort 3 was to include 8 participants with ESRD on dialysis (eGFR of < 15 mL/min/1.73 m^2).
  - Gender: At least 2 (each) male and female participants had to be included.

The eGFR for each participant was based on serum creatinine and was derived using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, expressed as a single equation:

$GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

Scr: serum creatinine (mg/dL), κ:0.7 for females and 0.9 for males, α: -0.329 for females and -0.411 for males, min: indicates the minimum of Scr/κ or 1, max: indicates the maximum of Scr/κ or 1.

The study comprised:

- A Screening Period of maximum 21 days.
- A Treatment Period during which participants were resident at the clinical unit from Day -1 (the day before dosing with AZD8233 on Day 1) until at least 24 hours after dosing; discharged on the morning of Day 2.
- A Follow-up Period during which participants had to return to the clinical unit for 7 out-patient Follow-up Visits on Days 3, 7, 14, 28, 42, 56, and 90.

As the primary objectives of this study were to assess the PK and safety of AZD8233 full length antisense oligonucleotides (ASOs), the study was designed as open-label and non-randomised. The goal of including participants with impaired renal function was to determine if the PK of AZD8233 full length ASOs and proprotein convertase subtilisin/kexin

type 9 (PCSK9) reduction was altered to such an extent that the dosage had to be adjusted from the amount established in the confirmatory efficacy and safety trials.

The planned dose was CCI mg AZD8233, administered as a subcutaneous (SC) injection. The CCI mg dose was the mid dose (the other doses were CCI and CCI mg) which was investigated in the Phase IIb study in dyslipidaemia patients (Study D7990C00003), in which AZD8233 was administered once monthly as a SC injection. A dose of CCI mg once monthly was predicted to result in a PCSK9 reduction from baseline of around 90% over the dose interval and a low-density lipoprotein cholesterol (LDL-C) reduction from baseline of around 70% and was expected to be in the therapeutic range.

All the enrolled participants in this study belonged to Cohort 3 and had ESRD. No participants with severe renal impairment (Cohort 1) or healthy participants with normal renal function (Cohort 2) were recruited before early study termination.

Each enrolled participant received a single SC dose of CCI mg AZD8233 on Day 1 after haemodialysis. Pre-dose samples were collected after participants had fasted from midnight the day before. Participants were not allowed to consume water for 1 hour before and 1 hour after dosing. A meal was provided to the participants after dosing.

A participant was considered to have completed the study if he/she had completed all phases of the study including the last visit. The end of the study was defined as the date of the last visit of the last participant in the study.

The last participant completed the final Follow-up Visit on 23 November 2022.

Target subject population and sample size

Main inclusion criteria

Male or female participants had to be 18 to 80 years of age inclusive, at the time of signing the informed consent. For participants in Cohort 1 and Cohort 3, those who were on statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), beta-

blockers, diuretics or on any other cardio-renal relevant treatments, the dose of these concomitant medications had to be stable for at least 4 weeks prior to Screening (no dose adjustment within 4 weeks prior to Visit 1). Healthy participants with normal renal function in Cohort 2 had to have an eGFR of ≥ 90 mL/min/1.73 m^2 as determined at Screening (Visit 1) via the CKD-EPI formula. Participants in Cohort 3 with ESRD on dialysis had to have an eGFR of < 15 mL/min/1.73 m^2 and had to be on stable intermittent haemodialysis for at least 3 months prior to Screening (Visit 1). All participants had to have a body weight of at least 50 kg and BMI within the range ≥ 18 to ≤ 35 kg/m^2 (inclusive). Male participants had to use contraceptive means consistent with local regulations and female participants had to be of non-childbearing potential, non-lactating and had to have a negative pregnancy test at Screening (Visit 1).

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

Study intervention in this study included AZD8233 CCI mg/mL sterile solution for injection, administered as a single dose SC injection into abdomen region.

All participants received the study intervention from manufacturing batch number 0000595650. Packaging and labelling instructions are provided in the body of the synoptic clinical study report (CSR).

Duration of treatment

Single dose

Statistical methods

Due to limited data, no statistical models or summary tables were provided on the data from this study and only listings and some visualisation of data as figures have been performed.

Analyses sets

- Screened: all participants who signed the informed consent form (ICF).
- All dosed participant set: all participants who received the single dose of AZD8233.
- Pharmacokinetic analysis set (PKS): all participants who received the single dose of AZD8233 and who had no important protocol deviations thought to impact on the analysis of the PK data. The PK Scientist documented and included the reason(s) for exclusion of participants from the PKS, exclusion of any individual concentration timepoints from the calculation of the PK parameters or from the statistical analyses and corresponding figures and exclusion of individual PK parameters from the statistical analyses and corresponding figures.
- Safety analysis set (SAS): all participants who received the single dose of AZD8233 and for whom any safety post-dose data were available. Unless otherwise stated, the SAS was used for the presentation of all demographic and safety analyses.

Presentation and analysis of pharmacokinetic (PK) data

Due to the early termination of the study and limited data, PK parameters were derived and presented in listings but were not analysed with linear models. Urine PK parameters were presented for the PKS. Urine sample collection dates and times, urine volume, and plasma and urine concentrations were presented for the All dosed participant set.

Details of the originally planned presentation and analysis of PK data are included in the body of the synoptic CSR.

Presentation and analysis of pharmacodynamic (PD) data

Due to the early termination of the study and limited data, individual plasma PCSK9 and individual plasma LDL-C concentrations were presented in listings for the All dosed participant set. A graphic illustration was also provided for % reduction in PCSK9 over-time.

Details of the originally planned presentation and analysis of PD data are included in the body of the synoptic CSR.

Presentation and analysis of immunogenicity data

Individual anti-drug antibody (ADA) results and titres were listed by cohort, and reported ADA study status, time and date of sample collection were listed for all participants in the SAS.

Details of the originally planned presentation and analysis of immunogenicity data are included in the body of the synoptic CSR.

Presentation and analysis of safety and eligibility data

Data for adverse events (AEs), vital signs, clinical chemistry and haematology laboratory test results, urinalysis test results, weight, height, BMI, and electrocardiograms (ECGs) were presented in listings.

Any new or aggravated clinically relevant abnormal physical examination finding compared with the baseline assessment was reported as an AE. Clinical laboratory data were reported by individual laboratory listing (international system of units) and flagged out-of-range values for safety.

Due to the early termination of the study and the limited number of participants enrolled, no summary statistics were calculated, and safety data were presented by individual patient listings.

Details of the originally planned presentation and analysis of safety and eligibility data are included in the body of the synoptic CSR.

Study population

A total of 4 participants were screened for eligibility; of whom, 1 Participant (PPD) failed the Screening, and 3 participants were enrolled in the study and received the study intervention. All of the 3 participants were included in Cohort 3 (ESRD cohort), at one site in Poland.

Of the 3 enrolled and dosed participants, 1 Participant (PPD) had an early termination (discontinued the study) due to PPD . The other 2 Participants (PPD and PPD) completed the study.

Age of enrolled participants ranged from PPD years to PPD years and baseline BMI ranged from PPD to PPD kg/m^2. All participants were male and of White race. Participants' individual baseline eGFR ranged from 6 to 10 mL/min/1.73 m^2.

Summary of efficacy results

The effect of AZD8233 on % reduction in PCSK9 plasma levels from baseline over-time in participants with severe renal impairment and ESRD compared to their healthy matched controls was planned to be assessed as the secondary objective of this study.

Results of %PCSK9 reduction over-time are presented in the PD results section of this synopsis.

Summary of pharmacokinetic results

AZD8233full length ASOs concentrations declined in a biphasic manner, showing a rapid distribution phase and a protracted elimination phase. The terminal half-life associated with terminal slope of a semi-logarithmic concentration-time curve (t½λz) values ranged between 317 and 354 hours (approximately 13 to 15 days). The diagnostic parameters gave confidence in the quality of the t½λz estimate: the adjusted coefficient of correlation (Rsq adj) was > 0.8 and the percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve from the time of the last quantifiable concentration to infinity (%AUCextr) was < 3% for all 3 participants. The t½λz was estimated over an interval of 2.65* t½λz for 1 participant and > 3* t½λz for 2 participants.

The AUCinf values were 1800, 7310, and 2490 h*ng/mL, and Cmax values were 290, 1100, and 264 ng/mL for Participants PPD , PPD , and PPD , respectively. Participant PPD had systemic and peak exposure approximately 3 (or more) times higher compared to the other participants, whose exposures were similar to each other.

The apparent total body clearance of drug from plasma after extravascular administration (CL/F) value estimates were 27.8, 6.84, and 20.0 L/h for Participants PPD, PPD, and PPD respectively. The apparent total non-renal body clearance of drug from plasma after extravascular administration (CLNR/F) values were similar to CL/F; where calculable, and together with the urinary PK parameters, it confirms that the clearance of AZD8233 full length ASOs was predominantly non-renal. The apparent volume of distribution during the terminal phase after extravascular administration (Vz/F) value estimates were 12700 L, 3490 L, and 10200 L, respectively. The lowest CL/F and Vz/F values belonged to Participant PPD, who had the highest exposures.

The amount of full length ASOs excreted in urine was small and accounted for < 0.4% of the administered dose for the 2 participants for whom fe(0-last) was calculable. Most of the urinary excretion of full length AZD8233 ASOs occurred in the first collection period, which was available for all 3 participants. The fraction excreted between 0 and 8 hours post-dose (fe 0-8) estimates ranged between 0.0473% and 0.254%.

Due to the small sample size, and lack of control group with normal renal function, the data should be interpreted with caution.

Summary of pharmacodynamic results

A maximal decrease in PCSK9 was observed on Day 7 or Day 14 after administration of AZD8233 for the 3 participants. At subsequent timepoints, plasma PCSK9 concentrations started to increase over time.

In all 3 participants, individual post-dose LDL-C plasma concentrations showed a decrease from the pre-dose levels, starting at 48 hours after administration of the study intervention. On Day 14 post-dose or later, LDL-C plasma concentrations started to increase towards baseline levels.

Summary of immunogenicity results

The initial ADA test (Screening step) did not show presence of ADA (ADA-positive) at any timepoint for any of the study participants who were administered with a single dose of CCI mg AZD8233, hence no ADA confirmatory steps or titre determination were performed on the samples.

Summary of safety results

No AEs or serious adverse events (SAEs) were reported for participants after receiving the study intervention.

Some out-of-range results in laboratory findings were observed for the participants; however, none were considered clinically significant by the Investigator.

No clinically significant abnormalities in vital signs or ECG parameters were reported for study participants after administration of the study intervention.

Conclusion(s)

Efficacy conclusion:

A numerical reduction in percentage (%) change from baseline in PCSK9 plasma levels was observed in all 3 participants with ESRD.

Due to the limited data and lack of a cohort with normal renal function, no conclusion on impact of renal impairment or ESRD on PD response could be drawn.

PK conclusion:

AZD8233 full length ASOs appeared rapidly in the systemic circulation following SC administration, with tmax observed between 1.98 and 3.00 hours post-dose.

Following the initial rapid distribution phase, a slower elimination phase was observed with similar t½λz values in all 3 participants, ranging between approximately 13 and 15 days.

Clearance was predominantly non-renal with only < 0.4% of the dose recovered as full length ASOs in urine.

No comparison could be made between participants with ESRD and participants with normal renal function as only participants with ESRD were recruited.

Immunogenicity conclusion:

None of the participants had an ADA positive result after administration of a single dose of [redacted] mg AZD8233.

Safety conclusion:

During this study, no AEs or SAEs were reported for any of the participants. However, due to the limited data, no robust safety conclusion could be drawn.

Overall impact of coronavirus disease 2019 (COVID-19):

The coronavirus disease 2019 (COVID-19) pandemic was not considered to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of the results.