Clinical Study Report Synopsis	
Drug Substance	AZD4831
Study Code	D6580C00009
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A Single Dose, Non-Randomised, Open-Label, Parallel Group Study to Assess the Pharmacokinetics, Safety and Tolerability of AZD4831 in Participants with Severe Renal Impairment and Healthy Volunteers

Study dates: First subject enrolled: 21 January 2022
Last subject last visit: 04 March 2022
The analyses presented in this report are based on a clinical data lock date of 23 May 2022

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents. Due to incorrectly labelled boxes, participants were administered with CCI investigational product instead of the planned CCI. The CCI tablet was released per standard requirement.

Study centre(s)

The study was conducted at a single study centre in Bulgaria.

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 PK of a single dose of CCI AZD4831 in participants with severe renal impairment compared with that in matched healthy participants	• Plasma PK parameters: Cmax, tmax, t1/2 λz, CL/F, CLNR/F, Vz/F, AUClast, and AUCinf • Urine PK parameters: CLR
Secondary	
• To evaluate the safety and tolerability of a single oral dose administration of CCI AZD4831 in participants with severe renal impairment and matched healthy participants	• Adverse events, serious adverse events, AEoSIs of skin reactions including maculopapular rash • Vital signs (systolic and diastolic BP, and pulse rate) • 12-Lead ECG • Laboratory assessments (haematology, clinical chemistry, and urinalysis)

AEoSI: adverse event of special interest; AUCinf: area under the plasma concentration-time curve from time zero to infinity; AUClast: area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; BP: blood pressure; CL/F: apparent total body clearance of drug from plasma after extravascular administration; CLNR/F: apparent total non-renal body clearance of drug from plasma after extravascular administration; CLR: renal clearance of drug from plasma; Cmax: maximum observed plasma concentration; ECG: electrocardiogram; PK: pharmacokinetic(s); t1/2 λz : half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax: time to reach maximum observed plasma concentration; Vz/F: apparent volume of distribution during the terminal phase after extravascular administration.

Study design

This was a single dose, open-label, non-randomised, parallel group study to compare AZD4831 pharmacokinetic (PK) parameters between participants with severe renal impairment and group-matched healthy participants following a single dose administration.

The study comprised of the following study periods:

- Screening period for maximum 21 days: participants were screened for eligibility.
- Treatment period of 3 days: participants were admitted to the study centre in the evening of Day -1, received a single oral dose of AZD4831 (Day 1), and were discharged after at least 24 hours post-dose (Day 2).

- Follow-up period of 13 ± 2 days: participants attended 5 visits at the study centre on Days 3, 5, 8, 11, and 15.

Participants received CCI instead of the planned CCI oral dose of AZD4831 under fasted conditions on Day 1 of the treatment period. When plasma samples for the participants in another study (D6580C00012) were analysed, only half the expected concentration of AZD4831 was found. An investigation showed that due to incorrectly labelled boxes, CCI was administered instead of the planned CCI in this study (D6580C00009) as well. It was considered that there was no risk to participant safety as a lower dose was administered. Data from this study were analysed for the scientific value this data can provide.

Participants were involved in the study for approximately 2 weeks after dosing and up to approximately 38 days after screening.

Target population and sample size

Participants with severe renal impairment and healthy participants, male or female of non-childbearing potential, aged between 18 to 80 years (inclusive), with a body weight of at least 50 kg and a body mass index (BMI) within the range of ≥18 to ≤35 kg/m^2 were eligible for inclusion in this study.

Approximately 20 participants were planned to be enrolled into 2 cohorts as follows:

- Cohort 1: 10 participants with severe renal impairment (estimated glomerular filtration rate [eGFR] ≥ 15 to < 30 mL/min/1.73 m^2) as assessed at screening.
- Cohort 2: 10 matched (in age, BMI, and sex) healthy participants with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) as assessed at screening.

Ten participants per cohort was believed to achieve 8 evaluable participants in each cohort. No formal calculation of sample size was deemed necessary for this study. Based on previous experience, 8 evaluable participants per cohort, ie, 8 participants with severe renal impairment participants (Cohort 1) and 8 healthy participants (Cohort 2) were considered appropriate to obtain adequate data to achieve the primary objective.

Investigational product: dosage, mode of administration and batch numbers

Each participant received a single oral dose of CCI AZD4831 as a tablet (Batch number CCI).

Duration of treatment

Single dose.

Statistical methods

Presentation and analysis of pharmacokinetic data

All AZD4831 PK concentration and parameter summaries, and statistical analysis was presented for the PK analysis set, unless otherwise specified. The PK parameters were analysed using a linear model, using the natural logarithm of AUClast, AUCinf, and Cmax as the response variables, and the cohorts as fixed effect, assuming equal variance in the 2 cohorts. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUClast, AUCinf, and Cmax was estimated and presented by cohort. Also, ratios of geometric means together with CIs (2-sided 90%) was estimated and presented for comparison between renally impaired and healthy participants.

Regression analysis of PK parameter versus renal function (eGFR) were performed with renal function as independent variable and CL/F as dependent variable. Calculations for eGFR based on serum creatinine alone and on serum creatinine and serum cystatin C was used for this analysis. The eGFR value at screening (baseline value) derived from serum creatinine was used to report categorical PK parameters.

Presentation and analysis of safety and eligibility data

Safety data (scheduled and unscheduled) was presented in data listings. Continuous variables were summarised by cohort using descriptive statistics (number of participants in analysis [n], mean, standard deviation, minimum, median, and maximum). Categorical variables were summarised in frequency tables (frequency and proportion) by cohort. The analysis of the safety variables was based on the safety analysis set.

Adverse events (AEs) were summarised by preferred term (PT) and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. All AEs and serious adverse events (SAEs) were listed and the number of participants who had any AE, SAE, adverse event of special interest (AEoSI), AE that led to withdrawal, and AEs with severe intensity were summarised. Any AEs that occurred before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, electrocardiograms (ECGs), and eGFR were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared with the baseline assessments, was reported as an AE. Data were summarised for the observed values at each scheduled assessment, and as absolute and percentage change from baseline. Clinical laboratory data were reported in Système International (SI) units in the Clinical Study Report. Out-of-range values for safety laboratory data were flagged in individual listings as well as summarised descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, programme, or laboratory ranges).

Study population

	Severely renally impaired n (%)	Healthy volunteers n (%)	Total n (%)
Participants screened			21
Screen failures			1
Judgement by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements			1
Participants started treatment	10 (100.0)	10 (100.0)	20 (100.0)
Participants completed study	10 (100.0)	10 (100.0)	20 (100.0)
Participants withdrawn from study	0	0	0
Due to COVID-19 pandemic	0	0	0

COVID-19: Coronavirus Disease 2019; N: number of participants in each cohort; n: number of participants in the category.

PPD

The healthy participants were group-matched with the participants with severe renal impairment with regard to sex, BMI, and age (participants in the healthy volunteer cohort were not aged more than 10 years younger or older than the youngest and oldest participants, respectively, the BMI was not more or less than 20% above or below the highest and lowest BMI values, respectively, and an equal number or men and women were enrolled). All participants were White and of not Hispanic or Latino ethnicity and an equal number of males and females were enrolled in each cohort.

Summary of pharmacokinetic results

Following single CCI oral dose administration, AZD4831 was rapidly absorbed and reached median tmax at 2.00 hours and 1.75 hours post-dose in participants with severe renal impairment and healthy volunteers respectively. After Cmax, plasma concentrations declined in a biphasic manner. Apparent clearance was approximately halved in participants with severe renal impairment versus healthy volunteers. Non-renal clearance was similar between the 2 groups. Inter-subject variability, based upon geometric CV% was moderate (25% to 40%) for AUCinf and AUClast and high (> 40%) Cmax for the participants with severe renal impairment and was moderate for AUCinf and high for AUClast and Cmax for healthy volunteers.

Ae(0-last) and fe(0-last) were lower in participants with severe renal impairment. Geometric mean fe(0-last) was 3.285% and 17.30% in participants with severe renal impairment and healthy volunteers, respectively, and the ranges did not overlap.

Renal clearance was reduced in participants with severe renal impairment versus healthy volunteers, with geometric mean values of 2.310 L/h and 14.19 L/h, respectively. There was some correlation between eGFR and CL/F.

AUCinf and AUClast were increased 2.197 (90% CI 1.620, 2.981) and 2.140-fold (90% CI 1.627, 2.814) in participants with severe renal impairment compared to healthy volunteers. Cmax was similar between participants with severe renal impairment and healthy volunteers.

Summary of safety results

All participants received a single dose of CCI AZD4831 on Day 1 of the study, instead of the planned CCI (see Study design), and completed the study. There were no deaths, SAEs, AEoSI of skin reactions, or AEs that lead to discontinuation in the study. CCI

No clinically significant trends or shifts from baseline were reported for laboratory results, vital signs, or ECGs. Abnormal results were reported for participants with severe renal impairment, including increased creatinine, cystatin C, and urea and abnormal urinalysis, as was expected in patients with renal impairment. Other abnormal results reported were not clinically significant and most normalised on subsequent visits.

Conclusion(s)

- AUCinf and AUClast were increased by 2.197 and 2.140-fold respectively in participants with severe renal impairment (with eGFR ≥ 15 to < 30mL/min/1.73^2 and not on dialysis) compared to healthy volunteers.
- Cmax was similar between the 2 cohorts. The GLSM ratio was 1.192 and the 90% CI spanned unity.
- Half-life was increased by 2.6-fold in the participants with severe renal impairment. The geometric mean estimate was 131.5 hours versus 50.05 hours in the healthy volunteers.
- Apparent total clearance was reduced by 2-fold in participants with severe renal impairment compared to healthy volunteers from 26.28 L/h (healthy) to 11.96 L/h (severe renal impairment).
- Non-renal clearance and Vz/F were similar between the 2 cohorts.
- Apparent total clearance showed a positive correlation with eGFR.
- Inter-subject variability in peak and systemic exposure was moderate (25% to 40%) to high (> 40%) in both cohorts.

- Administration of AZD4831 as a CCI single dose did not results in safety concerns and was considered safe in both participants with severe renal impairment and healthy volunteers.