A Single Dose, Non-Randomized, Open-Label, Parallel Group Study to Assess the Pharmacokinetics, Safety and Tolerability of AZD9977 in Participants with Renal Impairment

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2. SYNOPSIS

Study centres

The study was conducted at 6 study centres in the United States.

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

Objectives	Endpoints
Primary	
• To assess the PK of AZD9977 in participants with severe renal impairment compared with matched healthy control participants, and if necessary, unmatched participants with moderate and mild renal impairment, following single dose administration of AZD9977 CCI .	• PK parameters for AZD9977, derived from plasma and urine concentrations: • Plasma parameters: Cmax, AUC, AUC0-t, tmax, t1/2λz, λz , CL/F, CLNR/F, Vz/F, MRT • Urine parameters: CLR, Ae, fe.
Secondary	
• To evaluate the safety and tolerability of AZD9977 CCI single dose in participants with severe renal impairment and their healthy matched controls, and if necessary, unmatched participants with moderate and mild renal impairment. • To determine eGFR based on creatinine and cystatin C using CKD-EPI formula.	• Adverse events, vital signs (systolic and diastolic BP, pulse rate), 12-lead ECGs with QT intervals, physical examination, and laboratory assessments (hematology, clinical chemistry, and urinalysis). • Calculation of eGFR from serum creatinine and cystatin C.

Exploratory results are reported separately. Exploratory objectives and endpoints can be found in the CSR.

Ae: cumulative amount of unchanged drug excreted into the urine; AUC: area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC0-t: area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; BP: blood pressure; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CL/F: apparent total body clearance of drug from plasma after extravascular administration; CLNR/F: non-renal clearance of drug from plasma after oral administration (parent drug only); CLR: renal clearance of drug from plasma; Cmax: observed maximum plasma concentration; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; fe: fraction excreted unchanged in urine; λz: terminal elimination rate constant, estimated by log-linear least-squares regression of the terminal part of the concentration-time curve; MRT: mean residence time of the unchanged drug in the systemic circulation; PK: pharmacokinetic(s); QT: ECG interval measured from the onset of the QRS complex to the end of the T-wave; t1/2λz : half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax: time to reach peak or maximum observed concentration or response following drug administration; Vz/F: apparent volume of distribution during the terminal phase after extravascular administration (parent drug only).

Study design

This was a single dose, non-randomized, open-label, parallel group study to assess the pharmacokinetics (PK), safety and tolerability of AZD9977 in participants with severe renal impairment, and their healthy matched controls, following a single oral dose of CCI AZD9977. The study also assessed the estimated glomerular filtration rate (eGFR) of participants using the combined serum creatinine and cystatin C Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Control participants (Cohort 4) were matched to participants with severe renal impairment (Cohort 1) with respect to sex, age, and BMI. The age of participants in matched controls had to be no more than 10 years younger than the youngest participants, or more than 10 years older than the oldest participants with severe renal impairment (Cohort 1). The BMI of participants in matched controls had to be no more than 20% lower than the lowest BMI of participants, or more than 20% higher than the highest BMI of participants with severe renal impairment (Cohort 1). The matched control group had to include an equal number of male and female participants as in Cohort 1.

Participants came to the study Clinical Unit for a maximum of 7 visits, including:

- One Screening Visit within the Screening Period from Day -21 up to Day -3 (Visit 1).
- An active Treatment Period, where participants were admitted to the centre on the evening of Day -2 or on the morning of Day -1 and remained at the centre until Day 3 (Visit 2). Participants had the option to remain resident until all PK and other study procedures were completed on Day 7. This decision to extend residency were made at the discretion of the PI. Each participant received CCI AZD9977 orally under fasted conditions on Day 1.
- A PK sampling period, where PK samples were taken from Days 1 to 3 (Visit 2) at specific timepoints and when participants attended the centre for assessments on Days 4, 5, 6, 7 (Visits 3 to 6).
- A Follow-up Visit 14 days post-dose.

The study was planned to be conducted in up to 4 cohorts depending on participant's eGFR calculated by using the combined serum creatinine and cystatin C CKD-EPI equation:

- Cohort 1 – severe renal impairment (eGFR of < 30 mL/min/1.73m^2 not on dialysis).
- Cohort 2 – moderate renal impairment (eGFR of ≥ 30 to < 60 mL/min/1.73m^2).
- Cohort 3 – mild renal impairment (eGFR of ≥ 60 to < 90 mL/min/1.73m^2).
- Cohort 4 – healthy matched controls with Cohort 1 (eGFR of ≥ 90 mL/min/1.73m^2).

Target population and sample size

The study was planned to be conducted in male and female participants (non-childbearing potential) aged 18 to 80 years inclusive with mild to severe renal impairment (Cohort 1 to Cohort 3), and healthy matched participants (Cohort 4).

Approximately 36 participants were planned to be enrolled to the study, with up to 9 participants enrolled in each cohort (up to 4 cohorts) to achieve 8 evaluable participants per cohort (±1 participant was allowed in each cohort to aid recruitment). Following completion of Cohort 1 and Cohort 4, PK and safety data were reviewed, and a decision was to be made whether to study unmatched participants with moderate and mild renal impairment (Cohort 2 and Cohort 3, respectively). A mean plasma exposure (AUC) of > CCI higher in participants with severe renal impairment compared with matched controls was required to initiate Cohort 2 and Cohort 3.

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

Table S2 Study Treatment

Intervention Name	AZD9977
Supplier:	AstraZeneca
Batch/lot numbers:	Manufacturing Batch/lot No: CCI Labeled and Packaging Batch/lot No: CCI
Dose Formulation	Immediate release capsule
Unit Dose Strength	CCI
Dosage Level	CCI
Route of Administration	Oral
Use	Experimental
Packaging and Labelling	AZD9977 capsules were provided as open labeled bulk bottles. Each bottle CCI was labeled as required per country requirement.
Special handling requirements:	Provided in a separate document

Duration of treatment

Single dose.

Statistical methods

Presentation and analysis of pharmacokinetic data:

AZD9977 PK parameters was analyzed using a linear model following a natural logarithm transformation of AUC, AUC0-t, and Cmax with cohort as fixed effect. There was no repeated measure or random effect.

Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs; 2-sided 95%) for AUC, AUC0-t, and Cmax were estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) were estimated and presented in order to assess the PK of AZD9977 in participants with severe renal impairment compared with healthy control participants.

Presentation and analysis of safety and tolerability data:
Safety data were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by cohort and overall. The analysis of the safety variables was based on the safety analysis set, which included all participants who received the single dose of AZD9977.

Adverse events were coded using Medical Dictionary for Regulatory Affairs Activities (MedDRA) vocabulary and were summarized by preferred term (PT) and system organ class (SOC). Furthermore, listings of serious adverse events (SAEs), adverse events (AEs) that led to discontinuation of the investigational medicinal product (IMP), and AEs that led to withdrawal from the study were made and the number of participants who had any AE, SAEs, AEs that led to discontinuation of the IMP, withdrawal from the study, and AEs by intensity were summarized. The AEs that occurred before dosing were reported separately. Tabulations and listings of data for vital signs, clinical laboratory tests, and electrocardiograms (ECGs), were presented.

Study population

A total of 18 participants were assigned to the study cohorts (9 participants with severe renal impairment to Cohort 1, and 9 healthy participants to Cohort 4) and received the assigned treatment. Differences regarding demographic and baseline characteristics were observed between Cohort 1 and Cohort 4, however criteria for matching participants were fulfilled (see Study Design). Cohort 1 had a higher average age (60.3 years) compared to Cohort 4 (50.9 years). Both Cohort 1 and Cohort 4 had comparable mean BMI (27.8 and 29.6 kg/m^2 respectively) and were equally matched in terms of sex and ethnicity distribution.

Of the 18 participants enrolled, 17 participants completed the study. One participant in Cohort 1 experienced an AE of a fall that was mild in intensity and assessed as not related to the IMP, which led to the participant's withdrawal from the study before completion. The participant received the planned dose on Day 1 and experienced the fall just prior to the Follow-up Visit. The participant assessed it would be too difficult to attend the Follow-up Visit and withdrew consent. All collected samples were retained for analysis/future research, as consented by the participant.

The safety review meeting following completion of Cohort 1 and Cohort 4 indicated no evidence of safety concerns after a single dose of CCI of AZD9977 administered in healthy participants (Cohort 4) or participants with severely impaired renal function, not on dialysis, and eGFR <30 mL/min/1.73m^2 (Cohort 1). The PK data reviewed at the informal safety review and PK analysis (report dated 11 February 2022) supported not to further enroll participants with mild and moderate renal dysfunction per above criteria, therefore Cohort 2 and Cohort 3 were not initiated.

Summary of pharmacokinetic results

Systemic exposure to AZD9977 as measured by AUC was approximately CCI higher in participants with severe renal impairment when compared with healthy participants. The Cmax in participants with severe renal impairment was approximately CCI higher than observed for healthy participants.

Low to moderate between-participant variability (geometric mean coefficient of variation 23% to 26%) in Cmax and AUCs was observed for healthy participants, whereas moderate to high between-participant variability (geometric mean coefficient of variation 38% to 60%) was observed for participants with severe renal impairment.

The apparent clearance of AZD9977 in healthy participants was approximately CCI higher than that observed for participants with severe renal impairment, with an approximately CCI difference in renal clearance. The plot of apparent clearance vs eGFR shows a positive intercept on the y-axis, the non-renal CL at a theoretical eGFR of 0 indicating the presence of a non-renal or metabolic component to the clearance of AZD9977 even in participants with very low eGFR. Indeed, in both participants with severe renal impairment and in healthy participants, the non-renal clearance route plays the major role in elimination of AZD9977.

Summary of safety results

Adverse events:

In total, 3 (16.7%) participants experienced a total of 4 AEs after receiving treatment. No AEs leading to death and no SAEs were reported. Adverse events of the following PTs were reported: infusion site erythema, infusion site swelling, COVID-19, and a fall.

All of the reported AEs were of mild to moderate intensity and were reported as resolved before the End of Study Visit, except for the AE of a fall that led to the withdrawal of the participant from the study prior to Follow-up Visit, and COVID-19 AE which was not resolved at completion of study. None of the participants who received treatment experienced any AEs that were considered by the Investigator as related to the treatment.

Laboratory assessments:

No significant trends or shifts from baseline were observed in hematology and clinical chemistry parameters. No individually clinically important hematology and clinical chemistry abnormalities were observed for any of the participants in this study.

Vital signs:

No AEs based on vital sign measurements were reported in this study.

Electrocardiogram:

There were no notable differences in mean ECG values over time between cohorts and no clinically significant abnormal ECG results reported in either cohort. No consistent or clinically relevant changes from Baseline in ECG values were observed. Two (22.2%) participants from Cohort 1, and 3 (33.3%) participants from Cohort 4 had abnormal, non-clinically significant changes from Baseline in ECG values.

Conclusion(s)

- Systemic exposure to AZD9977 as measured by AUC was approximately CCI higher in participants with severe renal impairment when compared with healthy participants. The Cmax in participants with severe renal impairment was approximately CCI higher than observed for healthy participants.
- Low to moderate between-participant variability (geometric mean coefficient of variation 23% to 26%) in Cmax and AUCs was observed for healthy participants, whereas moderate to high between-participant variability (geometric mean coefficient of variation 38% to 60%) was observed for participants with severe renal impairment.
- The apparent clearance of AZD9977 in healthy participants was approximately CCI higher than that observed for participants with severe renal impairment, with an approximately CCI difference in renal clearance.
- AZD9977 administered as a CCI single dose was well tolerated in the studied population.
- All reported AEs were mild to moderate in severity and were assessed as not related to AZD9977.