2 SYNOPSIS

Title of Study:	A Randomised, Single-dose, Open-label, Single-centre, Crossover Study to Assess the Relative Bioavailability and Safety of Different Formulations of AZD5718 in Fasted and Fed State in Healthy Volunteers	
Study Numbers:	PAREXEL Study No.: PXL254135 Sponsor Study No.: D7551C00003	
Investigational Medicinal Products:	Test Product: AZD5718 Reference Product: Not Applicable	
Indication Studied:	Chronic Kidney Disease	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Centre:	PAREXEL Early Phase Clinical Unit - London	
Publication:	None	
Study Duration:	First subject first visit: 01 Feb 2021	Last subject last visit: 25 Mar 2021

Study Objective(s):

Primary objective(s):

1. To evaluate the relative bioavailability of a tentative Phase III formulation of AZD5718, compared to the formulation used in the Phase IIb clinical study, in healthy volunteers.
2. To evaluate the impact of food on the exposure of the tentative Phase III formulation of AZD5718 in healthy volunteers.

Secondary objective(s):

1. To further assess the safety and tolerability of single doses of AZD5718 in healthy volunteers.

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Study Design:

This study was a randomised, open-label, 3-period, 3-treatment, single-dose, crossover study in healthy subjects performed at a single study centre. The study comprised of:

- A 28-day screening period.
- Three treatment periods during which subjects were resident at the Clinical Unit from the day before dosing with investigational medicinal product (IMP; Day -1) until at least 48 hours after dosing (Day 3); with discharge on the morning of Day 3 of each treatment period after all the assessments were completed.
- A 7-day washout period between treatment periods.
- Final visit within 5 to 7 days after the last dose.

The Clinical Unit called the subjects in between treatment periods to confirm attendance at the following treatment period. Eligibility checks including SARS-CoV-2 testing (RT-PCR) was done before re-admittance to the Clinical Unit.

Subjects received single doses of AZD5718 on 3 occasions under fasted and fed conditions. Two different formulations were given in a randomised order:

- Treatment A (Test Formulation): AZD5718 CCI [redacted], fasted.
- Treatment B (Test Formulation): AZD5718 CCI [redacted], fed.
- Treatment C (Reference Formulation): AZD5718 CCI [redacted], fasted.

When dosed in a fasting state, subjects received IMP following an overnight fast of at least 10 hours. When dosed in a fed state, IMP was administered 30 minutes after starting to eat the standard Food and Drug Administration (FDA) high-fat breakfast.

Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
16 subjects	16 subjects	16 subjects

Main Inclusion Criteria:

This study was to be conducted in healthy subjects (males and females of non-childbearing potential), 18 to 55 years of age, with a body mass index (BMI) between 18.5 and 30 kg/m^2 (inclusive), and weigh between 50 and 100 kg (inclusive).

Investigational Medicinal Product(s):

Formulation(s):	CCI [redacted]	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
AZD5718 Test Formulation; CCI [redacted]	CCI [redacted]	CCI [redacted] CCI [redacted]	30 Jun 2021
AZD5718 Reference Formulation; CCI [redacted]	CCI [redacted]	CCI [redacted] CCI [redacted]	31 Jan 2023

Duration of Treatment:

Each subject received a single dose of IMP on 3 separate occasions, over a period of approximately 2 months.

Treatment Compliance:

All dosing took place at the Clinical Unit under direct supervision where Clinical Unit staff checked the subject's mouth and hands following IMP administration.

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Criteria for Evaluation:

Pharmacokinetic Parameters:

Relative bioavailability of the Test Formulation in a fasted state (Treatment A) compared to the Reference Formulation in a fasted state (Treatment C) using the following primary pharmacokinetic (PK) parameters:

- AUCinf, AUClast, Cmax, and C24.

Relative bioavailability of the Test Formulation in a fed state (Treatment B) versus the Test Formulation in a fasted state (Treatment A) using the following primary PK parameters:

- AUCinf, AUClast, Cmax, and C24.

Pharmacokinetic parameters were assessed for AZD5718 on plasma concentrations:

- Primary PK parameters: AUCinf, AUClast, Cmax, and C24.
- Secondary PK parameters: tmax, λz, t1/2λz, CL/F, and Vz/F.

Safety Variables:

- Adverse events (AEs).
- Laboratory assessments (haematology, clinical chemistry, coagulation, and urinalysis).
- Physical examinations.
- 12-Lead electrocardiograms (ECGs).
- Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and oral body temperature).

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Statistical Methods:

Determination of Sample Size:

The number of subjects was based on the desire to gain adequate information on the primary endpoints while exposing as few subjects as possible to study procedures.

Interpretation of the results was based on the size of the treatment ratio and associated 90% confidence interval (CI). It was estimated that 12 subjects would provide a CI within 0.8 to 1.25 with a probability of 80% if the calculated treatment ratio is 1.0 based on an intra-subject coefficient of variation (CV) of 25% (AUC) for AZD5718.

A total of 16 subjects were randomised to 6 sequences (ABC, ACB, BAC, BCA, CAB, CBA), to ensure at least 12 evaluable subjects completed the study at the end of the last treatment period.

Presentation and Analysis of Pharmacokinetic Data:

The plasma AZD5718 concentrations and the PK parameters were listed and presented in tabular and graphical form as appropriate according to the most recent version of the AstraZeneca CCI Table, Figure, or Listing (TFL) standards, which included applicable descriptive statistics, as well as final TFL shells of this study that define handling of individual concentrations below the lower limit of quantification for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (number, mean, standard deviation, min, median, max) by treatment. Categorical variables were summarised in frequency tables (frequency and proportion) by treatment. The analyses of the safety variables were based on the safety analysis set. Adverse events were summarised by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs leading to the discontinuation of the IMP (DAEs) were made and the number of subjects who had any AEs, SAEs, DAEs and AEs with severe intensity were summarised. Adverse events were summarized by maximum reported intensity for each treatment arm. Tabulations and listings of data for vital signs, clinical laboratory tests, ECGs (listings only), were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment would have been reported as an AE. Data were summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined. Clinical laboratory data were reported in Système International units. Out-of-range values for safety laboratory were flagged in individual listings as well as summarised descriptively using agreed reference ranges (eg, laboratory ranges).

Protocol Deviations:

No important protocol deviations were reported during the study.

Pharmacokinetic Results:

The relative bioavailability of AZD5718 CCI Test Formulation was similar to that of the Reference Formulation for AUClast, AUCinf, Cmax and C24.

Administration of AZD5718 CCI Test Formulation after a high fat meal resulted in 17%, 17%, and 31% lower AUClast, AUCinf, and Cmax, respectively, than that in fasted state. Corresponding C24 was 18% higher in fed compared to fasted state.

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Safety Results:

There were no SAEs, DAEs, or AEs that resulted in death reported during the study. In total, 7 subjects (43.8%) reported 13 AEs. All AEs were reported by a single subject each, except for headache, reported by 1 subject after receiving Treatment B and 1 subject after receiving Treatment C. All the reported AEs were mild in intensity. All reported AEs, except for 1 AE of dry skin (reported by 1 subject after receiving Treatment C) were resolved before the end of the study. The AE of dry skin was not considered related to the IMP. Only 1 AE of abdominal pain, which was mild in intensity, was considered likely related to the IMP and resolved on the same day without intervention.

Discussion and Conclusion:

- The relative bioavailability of AZD5718 CCI Test Formulation was similar to that of the Reference Formulation for AUClast, AUCinf, Cmax, and C24.
- Administration of AZD5718 CCI Test Formulation after a high fat meal resulted in 17%, 17%, and 31% lower AUClast, AUCinf, and Cmax, respectively, than in the fasted state. Corresponding C24 was 18% higher in fed compared to fasted state.
- AZD5718 was well tolerated in healthy male subjects and there were no safety concerns observed.

Version and Date of Report: Version 1.0, 07 September 2021

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.