2 SYNOPSIS

Title of Study:	A Randomized, 6-period, 6-treatment, Single-Dose, Crossover Study to Assess the Pharmacokinetics of AZD5462 Film-coated Tablet Formulation, to Assess the Relative Bioavailability of AZD5462 Film-coated Tablet Formulation vs Oral Solution, and to Assess the Influence of Food on the Pharmacokinetics of AZD5462 in Healthy Participants	
Study Numbers:	Parexel Study No.: CCI [redacted] Sponsor Study No.: D9090C00005	
Investigational Medicinal Product:	AZD5462	
Indication Studied:	Heart failure	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit – Baltimore	
Publication:	None	
Study Duration:	First participant first visit: 24 August 2022	Last participant last visit: 07 November 2022

Study Objectives:

Primary Objectives:

- To characterize the pharmacokinetics (PK) of a film-coated tablet of AZD5462 at 3 dose levels by assessment of AUCinf, AUClast, and Cmax of AZD5462.
- To evaluate the effect of a high-fat, high-calorie meal, in comparison to fasting conditions, on the PK of AZD5462 after a single oral dose at 2 dose levels by assessment of AUCinf, AUClast, and Cmax of AZD5462.
- To evaluate the relative bioavailability of the film-coated tablet vs oral solution formulation by assessment of AUCinf, AUClast, and Cmax of AZD5462.

Secondary Objectives:

- To further assess the safety and tolerability of single doses of AZD5462 in healthy participants.

Exploratory Objectives:

- CCI [redacted].

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Study Design:

This was an open-label, randomized, 6-period, 6-treatment, single-dose, crossover study in healthy participants, performed at a single study center. A total of 16 healthy male and female participants of non-childbearing potential were randomized in this study. Each participant received 6 single-dose treatments of AZD5462 across 6 treatment periods according to 1 of 4 treatment sequences (ADBCEF, BACDFE, CBDAEF, and DCABFE):

- Treatment A: CCI mg of AZD5462 film-coated tablet (CCI mg tablet; fasted state).
- Treatment B: CCI mg of AZD5462 film-coated tablet (CCI mg tablet; fed state).
- Treatment C: CCI mg of AZD5462 film-coated tablet CCI mg tablet; fasted state).
- Treatment D: CCI mg of AZD5462 oral solution (CCI mg/mL; fasted state).
- Treatment E: CCI mg of AZD5462 film-coated tablet (CCI mg tablet; fasted state).
- Treatment F: CCI mg of AZD5462 film-coated tablet (CCI mg tablet; fed state).

Treatments A, B, C, and D were administered during Periods 1 to 4, and Treatments E and F were administered during Periods 5 and 6.

There was a 2-day washout between Periods 1 and 2, Periods 3 and 4, and Periods 4 and 5 (ie, 48 hours [h] between the single doses of AZD5462). The duration of the washout was based on the estimated t1/2 of AZD5462, which was estimated to be approximately 5 h. The washout between Periods 2 and 3 was 3 days. After 48 h between the single doses of AZD5462, an additional day was included as buffer day, in consideration of participant's tolerance to the study procedures. The washout between Periods 5 and 6 was up to 5 days (ie, up to 120 h between the single doses of AZD5462) because AZD5462 at CCI mg could affect CYP3A4 activity via time-dependent inhibition and/or induction. Since pre-clinical data indicated that CYP3A4 plays an important role in the elimination of AZD5462, the washout period needed to be extended to ensure that the enzyme activity returned to baseline to avoid the risk of carry-over effects.

The study comprised:

- A Screening Period of maximum 28 days.
- Six Treatment Periods during which participants were residents at the study center from Day -1 until Day 17.
- A Follow-up Phone Call on Day 21 (± 1 day) to record adverse events (AEs) and concomitant medication.

Study Participants:

Planned for Inclusion:	Randomized:	Completed Study:
16 participants	16 participants	16 participants

Main Inclusion Criteria:

This study was conducted in healthy participants (male and female of non-childbearing potential), aged 18 to 55 years (inclusive), who had a body mass index (BMI) between 18 and 32 kg/m^2 (inclusive), and weighed at least 50 kg and no more than 105 kg (inclusive).

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Investigational Medicinal Product: AZD5462

Formulation(s):	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
Film-coated tablet	CCI [redacted] mg	CCI [redacted]	30 Apr 2023
Film-coated tablet	CCI [redacted] mg	CCI [redacted]	30 Apr 2023
Oral solution	CCI [redacted] mg/mL	CCI [redacted]	31 Jan 2024

Duration of Treatment:

Each participant was involved in the study for approximately 7 weeks (including the 28-day Screening Period).

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit. Compliance was assured by direct supervision and witnessing of AZD5462 administration. The administration of AZD5462 was recorded in ClinBase™.

Criteria for Evaluation:

Pharmacokinetic Parameters

- Primary PK parameters: AUCinf, AUClast, and Cmax of AZD5462
- Secondary PK parameters: tmax, t1/2λz, MRTinf, λz, CL/F, Vz/F, Vss/F, Clast, tlag of AZD5462.

Safety Variables

- Adverse events.
- Laboratory assessments (hematology and clinical biochemistry).
- Physical examination.
- Resting 12-lead electrocardiograms (ECGs).
- Vital signs.

Exploratory Variables:

- CCI [redacted].

Statistical Methods:

Determination of Sample Size:

Sixteen participants were randomized into 4 different sequences (ADBCEF, BACDFE, CBDAEF, and DCABFE).

It was expected that the proposed sample size would give adequate information on PK and food effect on the AZD5462 film-coated tablet, while exposing as few participants as possible to study procedures.

Based on an intra-subject coefficient of variation (CV) of 25%, 11 participants were expected to give a relative precision of 1.6 (ratio between the upper and lower limits of the confidence interval [CI]) with a probability of 80%. This corresponded to a 90% CI of 0.79 to 1.26 if the observed ratio was 1.00. The AZD5462 oral solution had an estimated intra-subject CV of 22% (AUC). The tablet formulation could display a somewhat higher intra-subject CV as compared with the oral solution; it was therefore estimated that 12 participants in the current study would provide an adequate precision of the PK parameters (AUC). To account for potential discontinuations, up to 16 participants were included in this study to ensure at least 12 participants at the end of the last treatment period.

Presentation and Analysis of Pharmacokinetic Data:

The PK analysis set consisted of all participants in the safety analysis set for whom at least one primary PK parameter for AZD5462 was calculated. To be included in the statistical analysis of food effect, relative bioavailability, and dose proportionality, the PK analysis set was limited to those who have at least one primary PK parameter for the treatments included in the respective analysis:

- Treatments A and B (CCI mg film-coated tablet – fasted and fed, respectively)
- Treatments C and D (CCI mg film-coated tablet and CCI mg oral solution – both fasted)
- Treatments E and F (CCI mg film-coated tablet – fasted and fed, respectively)
- Treatments A, C, and E (CCI mg, CCI mg, and CCI mg film-coated tablet – all fasted)

All PK concentration and parameter summaries, and statistical analyses were presented for the PK analysis set, unless otherwise specified. The available concentration data and PK parameter data for any participants excluded from the PK and/or statistical analysis were listed and presented in the individual figures of concentration versus time plots.

A listing of PK blood sample collection times (including nominal and actual sample times), derived sampling times and deviations outside the limits defined in the window allowance document (WAD) as well as concentrations at each nominal time point were provided.

Plasma concentrations and PK parameters were summarized by treatment using appropriate descriptive statistics. Tabulations were provided for AZD5462.

Diagnostic parameters were summarized for each analyte by treatment using appropriate descriptive statistics.

Nominal times were used to present the PK concentration summary tables and corresponding geometric mean concentration-time figures.

Data from participants excluded from the PK analysis set were included in the data listings, but not in the descriptive statistics or in the inferential statistics.

For the assessment of food effect, the ratios of AUCinf, AUClast, and Cmax of AZD5462 when dosed in the fed or fasted state at 2 dose levels (CCI mg and CCI mg) were calculated in each individual and summarized. For the assessment of relative bioavailability, the ratios of AUCinf, AUClast, and Cmax of AZD5462 when dosed as CCI mg film-coated tablet (Treatment C) vs CCI mg oral solution (Treatment D) were calculated in each individual and summarized. For tmax, only n, median, minimum, and maximum were presented.

Presentation and Analysis of Safety Data:

The analysis of the safety variables was based on the safety analysis set, which included all participants who received at least 1 dose of AZD5462 and for whom any safety post-dose data were available. All safety data

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(scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (number [n], mean, standard deviation [SD], minimum [min], median, and maximum [max]) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment/dose group. The analysis of the safety variables was based on the safety analysis set. Adverse events were summarized by Preferred Term and System Organ Class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of serious adverse events (SAEs) and adverse events leading to the discontinuation of IP (DAEs) were made and the number of participants who had any AEs, SAEs, DAEs, and AEs with severe intensity were summarized. Adverse events that occurred before dosing were reported separately. Tabulations and listings of data for vital signs, clinical laboratory tests, and ECGs (listing only) were presented.

Presentation and Analysis of Exploratory Data:

The pharmacodynamic (PD) analysis set consisted of all participants in the safety analysis and who had at least 1 pre-dose and 1 post-dose quantifiable measurement for CCI . All CCI and CCI concentration and parameter summaries, and statistical analyses were presented for the PD analysis set, unless otherwise specified. The available concentration data and PD parameter data for any subjects excluded from the PD and/or statistical analysis were listed and presented in the individual figures of concentration versus time plots.

Protocol Deviations:

Two participants had missing PK plasma samples for AZD5462 measurement on Day 8 at 1:00 post-dose. The impact of these missing samples on PK data analysis was considered not important.

None of the reported deviations from the protocol had an effect on the interpretation of the study results or led to exclusion of any participant from the analysis populations.

Pharmacokinetic Results:

Comparison of CCI , CCI , and CCI mg doses of AZD5462 film-coated tablet in the fasted state (Treatments A, C, and E) showed that AZD5462 was absorbed with median tmax occurring between 1.98 and 3.01 h. The terminal half-life for the film-coated tablet in fasted state ranged between 6.576 h and 16.46 h. The AUCinf, AUClast, and Cmax appeared to increase in a less than dose-proportional manner in the fasted state.

A food effect (high-fat meal) was not observed at the CCI mg dose level when comparing fasted (Treatment A) and fed (Treatment B) conditions, with the geometric least squared mean (GLSM) ratios being approximately equal to 1 for all primary PK parameters (1.174, 1.028, and 1.098 for AUCinf, AUClast, and Cmax, respectively). At the CCI mg dose level, exposure was higher in the fed state compared with the fasted state with GLSM ratios of 2.506, 2.549, and 2.558, for AUCinf, AUClast, and Cmax,respectively. Food intake also delayed tmax (from 2 h to 3.5 h) at the CCI mg dose level.

At the CCI mg dose level, the bioavailability of the film-coated tablet (Treatment C) was lower than that of the oral solution (Treatment D), with the GLSM ratios for, AUCinf, AUClast, and Cmax being 0.4024, 0.3730, and 0.09727, respectively.

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Pharmacodynamic Results:

- CCI [redacted]

Safety Results:

- There were no deaths or SAEs reported during the study.
- There were no AEs resulting in discontinuation of IP.
- None of the reported AEs were considered possibly related to IP by the Investigator.
- No clinically relevant trends were observed for laboratory results, vital signs, or ECG parameters over time.
- The COVID-19 pandemic did not impact the safety results of this study.
- Single doses of AZD5462 were generally well tolerated in the studied population and there were no safety concerns.

Discussion and Conclusion:

- Film-coated tablets of AZD5462 at CCI mg, CCI mg, and CCI mg dose levels administered in fasted state were absorbed with median tmax occurring between 1.98 and 3.01 h. The AUCinf, AUClast, and Cmax appeared to increase in a less than dose-proportional manner in the fasted state.
- Food effect (high-fat meal) was not observed at the CCI mg dose level. At the CCI mg dose level, food intake gave a 2.5-fold increase in exposure (AUCinf, AUClast, and Cmax) and a 1.5 h delay in tmax.
- The bioavailability of AZD5462 following administration of the film-coated tablet was lower than following administration of the oral solution (at CCI mg) with AUCinf, AUClast, and Cmax of the film-coated tablet being approximately 40%, 37%, and 9.7% of the respective parameter values for the oral solution.
- CCI [redacted]
- Single doses of AZD5462 were generally well tolerated in the studied population and there were no safety concerns.

Version and Date of Report: Final, dated 28 March 2023

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