2 SYNOPSIS

Title of Study:	An Open-Label, Five-Period Study in Healthy Subjects to Investigate the Relative Bioavailability of AZD5055 Film-Coated Tablet versus AZD5055 Oral Suspension Formulation, the Absolute Oral Bioavailability of AZD5055 and to Evaluate the Effect of Food and Acid Reducing Agent on the Pharmacokinetics of AZD5055	
Study Numbers:	Parexel Study No.: Pxl 261992 Sponsor Study No.: D8960C00002	
Investigational Medicinal Products:	Test Product: AZD5055 Reference Product: Rabeprazole	
Indication Studied:	Idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs) associated with progressive fibrosis	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Ronald Goldwater, MD	
Study Center:	Parexel Early Phase Clinical Unit - Baltimore	
Publication:	None	
Study Duration:	First participant first visit: 02 Nov 2022	Last participant last visit: 09 Feb 2023

Study Objectives:

Primary Objectives:

- To estimate the relative bioavailability of AZD5055 film-coated tablet formulation versus AZD5055 oral suspension formulation.
- To estimate the absolute bioavailability of AZD5055 oral suspension and AZD5055 film-coated tablet formulation.
- To assess the effect of food on the pharmacokinetic (PK) parameters of AZD5055.
- To assess the effect of the acid reducing agent, rabeprazole, on the PK of AZD5055.
- To assess the effect of the acid reducing agent, rabeprazole, on the PK of AZD5055, when AZD5055 is administered with food.

Secondary Objective:

- To assess the safety following single oral and intravenous (IV) doses of AZD5055 in healthy participants.

Study Design:

This study was an open-label, five-period study in healthy participants (males and females of non-childbearing potential), performed at a single Clinical Unit.

All participants were partially randomized to 2 sequences. The randomization was 2:1 in favor of Treatment B.

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The study comprised of:

- A Screening Period of maximum 28 days.
- Five (5) periods during which participants participated from Day -1 of Period 1 to 72 hours after the AZD5055 dose in Period 5.
  - Period 1: On Day 1, the participants received either CCI mg AZD5055 as a 20-minute IV infusion (Treatment A) or AZD5055 CCI mg as oral suspension (Treatment B).
  - Period 2: On Day 1 (Study Day 4), the participants received CCI mg AZD5055 film-coated tablet (Treatment C).
  - Period 3: On Day 1 (Study Day 8) the participants received a standardized high-fat breakfast 30 minutes before CCI mg AZD5055 administered as film-coated tablet (Treatment D).
  - Period 4: On Study Day 10, 3 days prior to Day 1, rabeprazole was administered twice daily (BID). On Day 1 (Study Day 13), CCI mg AZD5055 film-coated tablet was administered together with rabeprazole and rabeprazole dosing continued BID (Treatment E).
  - Period 5: On Day 1 (Study Day 17) the participants received a low-fat breakfast 30 minutes before CCI mg AZD5055 film-coated tablet was administered together with rabeprazole. Rabeprazole was continued BID, and the last dose was on the evening of Study Day 18 (Treatment F).
- A Follow-up Visit, or telephone call, approximately 6 days after the last AZD5055 dose in Period 5.

There was a minimum washout of 3 days between the AZD5055 dose administration in Period 1 and Period 2 and a minimum washout of 4 days between AZD5055 doses administrations for subsequent study periods. Repeated PK sampling was performed pre-dose to 48 hours after dosing of AZD5055 of each period. Participants were discharged on Study Day 20 (Day 4 of Period 5), after all the samples were collected and all the assessments were performed.

Study Participants:

Planned for Inclusion:	Randomized:	Completed Study:	Completed Treatment:
18 participants	21 participants	21 participants	19 participants

Main Inclusion Criteria:

- Healthy male and female (of non-childbearing potential) participants aged 18 to 55 years, who had a body mass index (BMI) between 18 and 30 kg/m^2, inclusive.

Investigational and Auxiliary Medicinal Products:

Formulations:	Strength/Concentrations:	Batch/Manufacturing Lot Numbers:	Expiry Dates:
AZD5055 film-coated tablet	CCI mg	CCI CCI	CCI
AZD5055 oral suspension	CCI mg (CCI mg/mL)	CCI CCI	CCI
AZD5055 solution for infusion	CCI mg/mL	CCI CCI	CCI
Rabeprazole delayed-release tablet	20 mg	CCI	CCI

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Duration of Study:

Each participant participated in the study for approximately 8 weeks (including the Screening Period and the Follow-up Visit).

Treatment Compliance:

Dosing was performed at the Parexel Early Phase Clinical Unit. The administration of all investigational medicinal product (IMP) was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing of IMP administration. After administration, a check of the participant's mouth and hands was performed.

Criteria for Evaluation:

Pharmacokinetic Parameters:

Pharmacokinetic parameters of AZD5055 included, but not limited to, Cmax, AUCinf, and AUClast.

Safety Variables:

Safety endpoints included adverse events (AEs), clinical laboratory assessments (hematology, clinical chemistry, urinalysis, and urinary albumin:creatinine ratios), vital signs and peripheral oxygen saturation (SpO_2), standard 12-lead electrocardiogram, (ECG), telemetry, and physical examinations.

Statistical Methods:

Determination of Sample Size:

Approximately 18 healthy participants were enrolled to ensure that at least 15 participants completed the 5-period study.

It was expected that the proposed sample size would give adequate information on the effect of formulation and concomitant treatment on the exposure of AZD5055, while exposing as few participants as possible to study procedures.

Interpretation of the results were based on the estimated geometric mean ratio (GMR) and the associated 90% confidence interval (CI) between the combination of test and reference for AUC and Cmax.

Presentation and Analysis of Pharmacokinetic Data:

Plasma concentrations were listed for each participant at each actual sampling time and summarized by treatment and nominal sampling time, using the same descriptive statistics as for the PK parameters. Graphical presentations included individual and geometric mean time-concentration curves (actual sampling time for individual curves and nominal sampling time for mean curves) on linear and semi-logarithmic scale.

Pharmacokinetic variables and diagnostics of the PK analysis were listed, and PK variables were summarized by treatment using descriptive statistics (n, geometric mean, geometric coefficient of variation [gCV; %], arithmetic mean, arithmetic standard deviation [SD], minimum [min], median, and maximum [max]) for all variables except tmax, which were summarized using n, min, median, and max.

For the assessment of absolute and relative bioavailability of AZD5055 the following statistical comparisons were made on PK analysis set:

- AZD5055 film-coated tablet, fasted, C (test)/ AZD5055 oral suspension, fasted, B (reference).
- AZD5055 film-coated tablet, fasted, C (test)/ AZD5055 solution for infusion, A (reference).

The analyses were performed using a linear mixed-effects analysis of variance (ANOVA) model using the natural logarithm of Cmax, AUCinf, and AUClast as the response variables; sequence, period and treatment as

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fixed effect, and participant nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for Cmax, AUCinf, and AUClast were estimated and presented.

The result was transformed back to the original scale in order to give estimates of true */ geometric standard deviation (gSD) ratios and 90% CIs for these ratios. Additionally, the 90% CI for the difference was calculated and presented.

For the assessment of food effect and effect of acid reducing agents the following statistical comparisons were made on PK analysis set:

- AZD5055 film-coated tablet CCI mg, fed state, D (test)/ AZD5055 film-coated tablet CCI mg, overnight fasted state, C (reference).
- AZD5055 film-coated tablet fed, with rabeprazole, F (test)/ AZD5055 film-coated tablet overnight fasted, with rabeprazole, E (reference).
- AZD5055 film-coated tablet overnight fasted, with rabeprazole, E (test)/ AZD5055 film-coated tablet CCI mg, overnight fasted state, C (reference).
- AZD5055 film-coated tablet fed, with rabeprazole, F (test)/ AZD5055 film-coated tablet CCI mg, overnight fasted state, C (reference).

The effect of food and acid reducing agents on the PK of AZD5055 was assessed, using a linear mixed-effects ANOVA model with fixed effects for treatment, period, and sequence, and a random effect for participant within sequence. This analysis was performed using natural logarithmic transformed Cmax, AUClast, and AUCinf. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for Cmax, AUClast, and AUCinf were calculated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) were estimated and presented for treatment comparison (ie, AZD5055 under fed condition versus AZD5055 under fasted conditions).

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, SD, min, median, 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.

Protocol Deviations:

There were 2 participants with 2 important protocol deviations in Treatment Sequence ACDEF and 3 participants with 4 important protocol deviations in Treatment Sequence BCDEF.

None of the important protocol deviations are assumed to affect any of the pre-specified endpoints. Therefore, no participant with an important protocol deviation was excluded from any analysis set.

Pharmacokinetic Results:

- Absolute bioavailability of the film-coated tablet was approximately 66% and 64% based on AUCinf and AUClast. Cmax for the film-coated tablet was approximately 21% of the IV dose.
- Total systemic exposure to AZD5055 following dosing with the film-coated tablet was comparable to dosing with the oral suspension based on AUCinf and AUClast, however Cmax was approximately 35% lower.
- Exposure to AZD5055 based on Cmax, AUClast and AUCinf increased by between 22% and 32% when dosed in a fed state compared to fasted. However, when dosed with rabeprazole, food did not impact total

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systemic exposure to AZD5055, while it increased Cmax by approximately 17% compared to dosing with rabeprazole fasted.

- When dosed with rabeprazole in the fasted state there was no change in total systemic exposure (AUCinf and AUClast) compared to AZD5055 fasted alone, however Cmax was reduced by 32%.
- When dosed with rabeprazole in the fed state there was no change in total systemic exposure (AUCinf and AUClast) compared to AZD5055 fasted alone, however Cmax was reduced by 20%.

Safety Results:

- There were no deaths in this study. CCI [redacted] experienced an SAE in Period CCI [redacted] This SAE was assessed by the Investigator to be possibly related to the IMP (CCI [redacted]).
- CCI [redacted] experienced an AE CCI [redacted] events) leading to discontinuation of IMP after dosing in Period CCI [redacted] (CCI [redacted]).
- Overall, 11 (52.4%) participants experienced any AE (20 events) during the study. Five (23.8%) participants experience any AE (9 events) assessed by the Investigator to be possibly related to the IMP.
- In total, 8 (38.1%) participants reported at least 1 AE of Grade 1 intensity, and 4 (19.0%) participants reported at least 1 AE of Grade 2 intensity. No AEs Grade 3 or higher were reported.
- No clinically relevant trends were observed for laboratory parameters, vital signs, ECGs, or physical examination.
- The coronavirus disease 2019 (COVID-19) pandemic did not impact the overall safety results of this study.
- No major safety and tolerability concerns were identified in this study.

Discussion and Conclusions:

- Absolute bioavailability of the film-coated tablet was approximately 66% and 64% based on AUCinf and AUClast. Cmax for the film-coated tablet was approximately 21% of the IV dose.
- Total systemic exposure to AZD5055 following dosing with the film-coated tablet was comparable to dosing with the oral suspension based on AUCinf and AUClast, however Cmax was approximately 35% lower.
- Exposure to AZD5055 based on Cmax, AUClast and AUCinf increased by between 22% and 32% when dosed in a fed state compared to fasted. However, when dosed with rabeprazole, food did not impact total systemic exposure to AZD5055, while it increased Cmax by approximately 17% compared to dosing with rabeprazole fasted.
- When dosed with rabeprazole in the fasted state there was no change in total systemic exposure (AUCinf and AUClast) compared to AZD5055 fasted alone, however Cmax was reduced by 32%.
- When dosed with rabeprazole in the fed state there was no change in total systemic exposure (AUCinf and AUClast) compared to AZD5055 fasted alone, however Cmax was reduced by 20%.
- No major safety and tolerability concerns were identified in this study. Overall, the IMP was generally well-tolerated.

Version and Date of Report: Final, 22 June 2023

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