Clinical Study Report

1 TITLE PAGE

A Double-blind, Randomized, Placebo-controlled Study in Healthy Volunteers to Investigate the Safety, Tolerability and Pharmacokinetics of oral AZD5055 following Single and Multiple Ascending Doses

Investigational Medicinal Product:	Study Drug:	AZD5055
Indication Studied:	Idiopathic pulmonary fibrosis and other interstitial lung diseases with progressive fibrosis	
Parexel Study Number:	CCI [redacted]	
Sponsor Study Number:	D8960C00001	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Investigator Name and Address:	PPD [redacted] Parexel Early Phase Clinical Unit - Baltimore Harbor Hospital 3001 South Hanover St. Baltimore, MD 21225 United States of America	
Study Duration:	18 Nov 2021 (first subject first visit) to 31 Mar 2023 (last subject last visit)	
Version and Date of Report:	Final dated 18 Aug 2023	

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Title of Study:	A Double-blind, Randomized, Placebo-controlled Study in Healthy Volunteers to Investigate the Safety, Tolerability and Pharmacokinetics of oral AZD5055 following Single and Multiple Ascending Doses	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D8960C00001	
Investigational Medicinal Products:	Study Drug: AZD5055	
Indication Studied:	Idiopathic pulmonary fibrosis and other interstitial lung diseases with progressive fibrosis	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit - Baltimore	
Publication:	None	
Study Duration:	First subject first visit: 18 Nov 2021	Last subject last visit: 31 Mar 2023

Study Objective(s):

Primary objective(s):

- **Part 1: SAD (Single Ascending Dose)**
  To assess the safety and tolerability of AZD5055 following oral administration of single ascending doses to healthy subjects.
- **Part 2: MAD (Multiple Ascending Dose)**
  To assess the safety and tolerability of AZD5055 following oral administration of multiple ascending doses to healthy subjects.

Secondary objective(s):

- **Part 1: SAD**
  To characterize the PK of AZD5055 following oral administration of single ascending doses to healthy subjects.
- **Part 2: MAD**
  To characterize the PK of AZD5055 following oral administration of multiple ascending doses to healthy subjects.

Exploratory objective(s):

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- **Part 2: MAD**
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Study Design:

This was a double-blind, randomized, placebo-controlled Phase I FIH study, in healthy male and healthy female subjects of non-childbearing potential, conducted at a single study centre. The study consisted of 2 parts, Part 1 was a single ascending dose (SAD) study and Part 2 was a multiple ascending dose (MAD) study.

Part 1- SAD study

In Part 1 of the study, the SAD part, 3 dose levels of AZD5055 were investigated in 3 cohorts. Each cohort included 8 subjects. Within each cohort, 6 subjects were randomized to receive AZD5055, and 2 subjects were randomized to receive placebo.

The Part 1 study comprised of the following:

- A Screening Period of a maximum of 6 weeks.
- A Treatment Period during which subjects were resident at the Clinical Unit from 1 day before Investigational medicinal product (IMP) administration (Day -1) until at least 72 hours after IMP administration (Day 4). Subjects received a single oral dose of AZD5055 or placebo on Day 1. Subjects were discharged after all samples were collected and assessments were performed on Day 4.
- A Follow-up Visit within 6 ± 1 day after the IMP dose.

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Part 2- MAD study

In Part 2 of the study, the MAD part, 3 dose levels of AZD5055 were investigated in 3 cohorts. In each cohort, 9 subjects were randomized to receive AZD5055, and 3 subjects were randomized to receive placebo. Naive subjects ie, those who did not participate in Part 1 of this study, were included in Part 2 of the study. One subject in Cohort 1 who was randomized to receive AZD5055, did not receive IMP treatment and withdrew from the study due to headache.

The Part 2 study comprised of the following:

- A Screening Period of a maximum of 6 weeks.
- A Treatment Period during which subjects were resident at the Clinical Unit from 1 day before IMP administration (Day -1) until at least 72 hours after the last dose given on Day 16 (Day 19). Subjects were dosed for a total of 15 days and received a single once daily morning dose of AZD5055 or placebo on Day 1 and on Days 3 through Day 16, with no dosing on Day 2. Subjects were discharged on Day 19 at least 72 hours after the last IMP dose, after all the samples were collected and all assessments were performed.
- A Follow-up Visit within 6 ± 1 day after the last IMP dose.
- An additional Follow-up Visit within 29 ± 2 days after the last IMP dose.

Study Subjects: This includes only the subjects who received the correct dose of IMP.

Planned for Inclusion:	**Randomized:**	**Completed Study:**
Part 1: 24 subjects Part 2: 30 subjects	Part 1: 24 subjects Part 2: 36 subjects	Part 1: 24 subjects Part 2: 30 subjects

Main Inclusion Criteria:

The study was conducted in healthy male and healthy female subjects of non-childbearing potential with suitable veins for cannulation or repeated venipuncture. The subjects had a body mass index between 18 and 30 kg/m^2 (inclusive) and weighed at least 50 kg. Also, the subjects were aged 18 to 55 years inclusive for men and women in Part 1 and only men in Part 2. For female subjects in Part 2, the age range was 18 to 49 years inclusive.

Investigational Medicinal Product(s):

	AZD5055	**Placebo**
Supplier	AstraZeneca AB, R&D Gothenburg	AstraZeneca AB, R&D Gothenburg
Type	Drug	Drug
Dose formulation	CCI	CCI
Unit dose strength	CCI mg/mL, and CCI mg/mL	Not applicable
Dosage levels	Part 1 (SAD): CCI mg, CCI mg, CCI mg, CCI mg Part 2 (MAD): CCI mg, CCI mg, CCI mg	Not applicable
Dosing frequency	Part 1: Single dose on Day 1 Part 2: Once daily dose from Day 1 to Day 16. No dosing on Day 2.	Part 1: Single dose on Day 1 Part 2: Once daily dose from Day 1 to Day 16. No dosing on Day 2.
Route of administration	Oral	Oral
Use	Intervention	Placebo-comparator

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	AZD5055	**Placebo**
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and labeling	Study Intervention was provided in glass vials. Each vial was labeled per United States of America (USA) requirement.	Study Intervention was provided in glass vials. Each vial was labeled per USA requirement.
Special handling requirements	Was provided in a separate document.	Handled in the same way as the AZD5055.
Availability of the IMP	The IMP was shipped when approval was in place.	The IMP was shipped when approval was in place.
Batch/Manufacturing Lot Number	**1st Shipment:** AZD5055 CCI mg/mL: CCI ; CCI CCI AZD5055 CCI mg/mL: CCI ; CCI CCI **2nd Shipment:** AZD5055 CCI mg/mL: CCI CCI AZD5055 CCI mg/mL: CCI CCI	CCI CCI
Expiry Date	**1st Shipment:** 31 July 2022 **2nd Shipment:** 31 July 2023	31 May 2024

Duration of Treatment:

For Part 1 of the study, each subject was involved in the study for up to approximately 8 weeks. For Part 2 of the study, each subject was involved in the study for up to approximately 13 weeks.

Treatment Compliance:

Dosing took place at the Parexel EPCU. Compliance was assured by direct supervision and witnessing of IMP administration. The administration of all IMPs was recorded in ClinBase™.

Criteria for Evaluation:

Safety Variables:

Safety endpoints included adverse events; vital signs (supine blood pressure, pulse, respiratory rate, and body temperature); 12-lead ECG, 12-lead dECG, telemetry, physical examinations, clinical laboratory assessments (hematology, clinical chemistry [including serum creatinine and creatine phosphokinase], urinalysis [including protein and albumin : creatinine ratios], and cardiac biomarkers [including cardiac Troponin T (cTNT), cardiac Troponin I; (cTNI), and B type natriuretic peptide]), and peripheral oxygen saturation (SpO_2).

Pharmacokinetic Parameters:

- Primary PK parameters: Cmax, AUCinf, and AUClast.
- Secondary PK parameters: including but not limited to tmax, AUC (0-12) or AUC (0-24) (the one not being the primary parameter), t½λz, MRTinf, CL/F, Vz/F, Rac, TCP, Ae(t1-t2), fe (t1-t2), and CLR.

Pharmacodynamic Parameters:

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Statistical Methods:

Determination of Sample Size:

The sample sizes for Part 1 and Part 2 of the study were chosen to obtain an adequate assessment of safety and tolerability without exposing undue numbers of subjects to the compound at this phase of clinical development. Previous experience in Phase I studies showed that the sample sizes proposed for Part 1 and Part 2 of the study were adequate to accomplish the objectives of the study.

To enable an adequate analysis of the PK and safety of AZD5055, 8 evaluable subjects in the AZD5055 treatment arm were selected in Part 2 (MAD) Cohorts 1, 2 and 3. Eight evaluable subjects in the placebo arm were selected in Part 2 (MAD) Cohort.

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, standard deviation, min, median, max) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment (both Parts 1 and 2).

The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarized by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities vocabulary. Furthermore, listings of serious adverse events (SAEs) and adverse events leading to the discontinuation of IMP (DAEs) were made and the number of subjects who had any adverse events (AEs), SAEs, DAEs and AEs with severe intensity were summarized. Adverse events that occur before dosing were reported separately.

Tabulations and listings of data for ECG, vital signs, AEs, and clinical laboratory tests, measurements were presented.

Presentation and Analysis of Pharmacokinetic Data:

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability, PK, and PD data was summarized descriptively by treatment/dose /study day separately using appropriate descriptive statistics including tables, listings, and graphs, as appropriate.

Preliminary dose proportionality of AZD5055 after single dose (Day 1) in Part 1 and 2 and multiple dose (Day 16) in Part 2 was assessed graphically and was analyzed using the power model approach with the logarithm of PK parameters (AUC and Cmax on Day 1) and (AUC(0-τ) and Cmax on Day 16) as the dependent variable and the logarithm of the dose as the independent variable.

For data collected in Part 2, the time dependency of the PK was evaluated by comparing AUC(0-τ) (Day 16) with AUC (Day 1) and accumulation was evaluated by comparing AUC(0-τ) (Day 16) with AUC(0-τ) (Day 1) and Cmax (Day 16) with Cmax (Day 1).

A linear mixed-effect analysis of variance model using the logarithm of the above PK parameters as the response variable and treatment, day, and treatment by day interaction as fixed effects. Day was treated as a repeated effect within subject.

Presentation and Analysis of Exploratory Data:

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Protocol Deviations:

A total of 11 important protocol deviations were reported in 8 subjects.

In Part of the study, 2 subjects had missing PK urine measurements, 1 subject had vomited within 2 hours of IMP administration, and 1 subject had another protocol deviation related to urine sample collection. From these subjects, one subject was excluded from the PK analysis set (descriptive and inferential statistics) due to vomiting within 2 hours of IMP administration (at/before 2 times median tmax)

In Part 2 of the study, 4 subjects had time window deviations for PK plasma processing, 2 subjects had missing dECG measurements, and 1 subject had a time window deviation for PK urine processing reported. One subject was excluded from the PK analysis set as no PK sample was available, and one subject was excluded from the PD set as no PD sample was available.

None of the reported deviations from the protocol influenced the interpretation of the study results.

Pharmacokinetic Results:

- AZD5055 was rapidly absorbed (median tmax of 1.00 to 1.51 hours; individual values ranging from 0.30 to 4.02 hours) following dosing with CCI of single ascending doses of CCI mg AZD5055. AZD5055 exposure increased approximately proportionally over the tested dose range of CCI mg after single and multiple dose administrations. A similar range of medians and a similar range of tmax of 1.00 to 1.30 hours was observed after multiple daily doses of CCI mg AZD5055.
- The AZD5055 concentrations declined in a bi-phasic manner with geometric mean terminal half-life values ranging 9.7 to 11.4 hours after single administration and ranging 12.2 to 17.2 hours after multiple daily administration of AZD5055.
- Between subjects, variability in the peak and extent of exposure (Cmax and AUCs) was low (<25%) to moderate (>25%, <40%) respectively.
- The temporal change in systemic exposure was expected to be minimal, with geometric mean ratio ranging between 133% and 160%. Little to moderate accumulation of AZD5055 was observed following repeat daily administration, with geometric mean accumulation for Cmax and AUC ranging between 108% to 193%.
- Renal clearance of AZD5055 (geometric mean ranging between 0.2 and 0.7 L/h) accounted for a small share of AZD5055 total clearance (geometric mean ranging between 18.3 and 30.6 L/h).
- Less than 2.3% of the dose administered was recovered unchanged (as AZD5055) in urine.

Pharmacodynamic Results:

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Safety Results:

Part 1 (SAD study)

Single ascending doses of AZD5055 (CCI mg) administered to subjects, were well tolerated and there were no safety concerns observed.

These conclusions are based on the following treatment emergent adverse event results:

- There were no SAEs, deaths, or AEs leading to discontinuation of IMP or withdrawal from the study.
- Overall, 4 (22.2%) subjects across all AZD5055 doses and 1 (16.7%) subject in the pooled placebo group experienced at least one AE.
- There were no notable trends for AEs by SOC or PT. All AEs across all AZD5055 doses were reported only once.

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- Overall, 3 (16.7%) subjects across all AZD5055 doses and none in the pooled placebo group had at least one AE considered possibly related to IMP as assessed by the Investigator. These AEs include dizziness, ventricular tachycardia, wheezing, upper abdominal pain, vomiting, and nausea.
- All AEs were of Grade 1 (mild) intensity and recovered/resolved by the end of the study.
- No clinically relevant trends were observed for clinical laboratory results, vital signs, physical examinations, and ECGs.

Part 2 (MAD study)

Multiple ascending doses of AZD5055 (CCI, and CCI mg) administered to subjects, were well tolerated and there were no major safety concerns observed.

These conclusions are based on the following treatment emergent adverse event results:

- There were no SAEs and deaths.
- There were 3 AEs leading to discontinuation of IMP.
  - Two subjects who received the CCI mg AZD5055 dose experienced an AE of ventricular tachycardia/non-sustained ventricular tachycardia of Grade 2 (moderate) intensity, which were both considered to be possibly related to the IMP as assessed by the Investigator.
  - One subject who received the CCI mg AZD5055 dose experienced an AE of coronavirus infection of Grade 1 (mild) intensity, which was not considered to be possibly related to the IMP as assessed by the Investigator.
- Overall, 21 (80.8%) subjects across all AZD5055 doses and 5 (55.6%) subjects in the pooled placebo group experienced at least one AE.
- There were no notable trends for AEs by SOC or PT.
- The majority of the AEs 16 (61.5%) were of Grade 1 (mild) intensity and there were 5 (19.2%) subjects (across all AZD5055 doses) with an AE of Grade 2 (moderate) intensity. All AEs recovered/resolved by the end of the study.
- A total of 7 (26.9%) AEs across all AZD5055 doses and none in pooled placebo group were considered possibly related to IMP treatment as assessed by the Investigator. These AEs included dysgeusia (1 [3.8%]), headache (3 [11.5]), photophobia (1 [3.8%]), ventricular tachycardia (2 [7.7%]), and breath odour (1 [3.8%]).
- No clinically relevant trends were observed for clinical laboratory results, vital signs, physical examinations, and ECGs.

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Discussion and Conclusion:

Safety

AZD5055 at all doses administered was well tolerated in healthy subjects and there were no major safety concerns observed.

Pharmacokinetics

AZD5055 was rapidly absorbed following dosing with CCI of single ascending doses of [redacted] to CCI mg AZD5055. AZD5055 exposure increased approximately proportionally over the tested dose range of CCI mg after single and multiple dose administrations. A similar range of medians and a similar range of tmax of 1.00 to 1.30 hours was observed after multiple daily doses of CCI mg AZD5055.

The AZD5055 concentrations declined in a bi-phasic manner with geometric mean terminal half-life values ranging 9.7 to 11.4 hours after single administration and ranging 12.2 to 17.2 hours after multiple daily administration of AZD5055.

Between subjects, variability in the peak and extent of exposure (Cmax and AUCs) was low (<25%) to moderate (>25%, <40%) respectively.

The temporal change in systemic exposure was expected to be minimal. Little to moderate accumulation of AZD5055 was observed following repeat daily administration.

Renal clearance of AZD5055 accounted for a small share of AZD5055 total clearance.

Less than 2.3% of the dose administered was recovered unchanged (as AZD5055) in urine.

Pharmacodynamics (Exploratory Objective)

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Version and Date of Report: 1.0 dated 18 Aug 2023

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