# A Single-Blind, Randomized, Placebo-Controlled 3-Part Study in Healthy Volunteers and Patients with Mild Asthma to Investigate the Safety, Tolerability and Pharmacokinetics of Inhaled AZD0449 Following Single and Multiple Ascending Doses and to Investigate the Anti-Inflammatory Effect of Inhaled AZD0449

**ClinicalTrials.gov Identifier: NCT03766399**

**Clinical Study Report Synopsis**

# 2 SYNOPSIS

| | | |
|---|---|---|
| **Title of Study:** | A Single-Blind, Randomized, Placebo-Controlled 3-Part Study in Healthy Volunteers and Patients with Mild Asthma to Investigate the Safety, Tolerability and Pharmacokinetics of Inhaled AZD0449 Following Single and Multiple Ascending Doses and to Investigate the Anti-Inflammatory Effect of Inhaled AZD0449 | |
| **Study Numbers:** | Parexel Study No.: CCI<br>Sponsor Study No.: D5371C00001 | |
| **Investigational Medicinal Product:** | Test Product: AZD0449<br>Reference Product: not applicable (tested vs placebo) | |
| **Indication Studied:** | Asthma | |
| **Development Phase:** | Phase I | |
| **Sponsor:** | AstraZeneca AB<br>151 85 Södertälje<br>Sweden | |
| **Chief Investigator:** | PPD Senior Clinical Research Physician | |
| **Lead Study Center:** | Parexel Early Phase Clinical Unit – London<br>PPD<br>Middlesex HA1 3UJ<br>UK | |
| **Publication:** | None | |
| **Study Duration:** | First subject first visit:<br>30 Nov 2018 | Last subject last visit:<br>24 Jun 2021 |

**Study Objectives:**

**Primary objectives:**

The primary objectives of the study and the corresponding outcome measures are presented in Table 2-1.

**Table 2-1 Primary Objectives and Outcome Measures**

| Primary Objectives | Outcome Measures |
|---|---|
| **Part 1a (SAD)** | |
| To assess the safety and tolerability of AZD0449 following inhaled administration of single ascending doses (SAD) to healthy volunteers. | Adverse events (AEs); vital signs (supine BP, pulse, respiratory rate and body temperature); 12-lead ECG; 12-lead dECG; telemetry; physical examination; laboratory assessments (hematology, biochemistry and urinalysis); spirometry and $SpO_2$ |
| **Part 1b (IV Cohorts)** | |
| To characterize the blood plasma PK of AZD0449 following intravenous administration of two single doses to healthy volunteers. | Where possible the following PK parameters were assessed: Cmax, tmax, λz, t½λz, AUC(0-24), AUClast, AUCinf, CL, Vz, AUC(0-24)/D, AUCinf/D, Cmax/D, tlast. |
| **Part 2a (Patients with Mild Asthma) and Part 2b (Healthy Volunteers)** | |
| To assess the safety and tolerability of AZD0449 following inhaled nebulized (Neb) administration of multiple ascending doses (MAD). | AEs; vital signs (supine BP, pulse, respiratory rate and body temperature); 12-lead ECG, 12-lead dECG; telemetry; physical examination; laboratory assessments (hematology, biochemistry and urinalysis); spirometry and $SpO_2$. |
| **Part 3a (Patients with Mild Asthma) and Part 3b (Healthy Volunteers)** | |
| To assess the safety and tolerability of AZD0449 following repeated inhaled administration using a DPI. | AEs; vital signs (supine BP, pulse, respiratory rate and body temperature); 12-lead ECG, 12-lead dECG; telemetry; physical examination; laboratory assessments (hematology, biochemistry and urinalysis); spirometry and $SpO_2$. |

**Secondary objectives:**

The secondary objectives of the study and the corresponding outcome measures are presented in Table 2-2.

**Table 2-2 Secondary Objectives and Outcome Measures**

| Secondary Objectives | Outcome Measures |
|---|---|
| **Part 1a (SAD)** | |
| To characterize the blood plasma PK of AZD0449 following inhaled administration of SAD of AZD0449. | Where possible the following PK parameters were assessed: Cmax, tmax, λz, t½λz, AUC(0-24), AUClast, AUCinf, CL/F, Vz/F, AUC(0-24)/D, AUCinf/D, Cmax/D, tlast. |
| **Part 1b (IV Cohorts)** | |
| To assess the safety and tolerability of AZD0449 following intravenous administration of two single doses to healthy volunteers. | AEs; vital signs (supine BP, pulse, respiratory rate and body temperature); 12-lead ECG, 12-lead dECG; telemetry; physical examination; laboratory assessments |

| | |
|---|---|
| | (hematology, biochemistry and urinalysis); spirometry and $SpO_2$. |
| **Part 2a (Patients with Mild Asthma) and Part 2b (Healthy Volunteers)** | |
| To characterize the blood plasma PK of AZD0449 following inhaled Neb administration of MAD. | Where possible the following PK parameters were assessed: Cmax, tmax, λz, t½λz, AUC(0-24), AUClast, AUCinf, CL/F, Vz/F, AUC(0-24)/D, AUCinf/D, Cmax/D, tlast. |
| To evaluate anti-inflammatory effect (Only Part 2a). | Change from baseline in 2 hours post-dose FeNO and FeNO AUC(0-12) to Day 12 and Follow-up. |
| **Part 3a (Patients with Mild Asthma) and Part 3b (Healthy Volunteers)** | |
| To characterize the blood plasma PK of AZD0449 following repeated inhaled administration using a DPI. | Where possible the following PK parameters were assessed: Cmax, tmax, λz, t½λz, AUC(0-24), AUClast, AUCinf, CL/F, Vz/F, AUC(0-24)/D, AUCinf/D, Cmax/D, tlast. |
| To evaluate anti-inflammatory effect (Only Part 3a). | Change from baseline in 2 hours post-dose FeNO and FeNO AUC(0-12) to Day 12 and Follow-up. |

**Exploratory objectives:**

The secondary objectives of the study and the corresponding outcome measures are presented in Table 2-3.

**Table 2-3 Exploratory Objectives and Outcome Measures**

| Exploratory Objectives | Outcome Measures |
|---|---|
| **Part 1a (SAD) and Part 1b (IV Cohorts)** | |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| | |
|---|---|
| CCI | |
| | |
| **Part 2a (Patients with Mild Asthma) and Part 2b (Healthy Volunteers)** | |
| CCI | |
| | |
| | |
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| | |
| | |
| | |

| | |
|---|---|
| CCI [redacted] | |
| **Part 3a (Patients with Mild Asthma) and Part 3b (Healthy Volunteers)** | |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

**Study Design:**

This was a Phase I, first in human study consisting of the following parts: Part 1a/b, Part 2a/b, and Part 3a/b.

Part 1a of the study was a randomized, single-blind, placebo-controlled, SAD, sequential group design study performed at a single clinical unit. This part of the study was planned to be conducted in up to 72 volunteers. Male and/or female healthy volunteers (non-childbearing potential), aged 18 to 55 years were included in this part of the study. Six inhaled dose levels of AZD0449 Neb suspension were planned to be investigated. Within each cohort, 6 volunteers were randomized to receive an inhaled dose of AZD0449 Neb suspension and 2 volunteers were randomized to receive inhaled placebo.

Part 1b, was open-label and consisted of two IV dose cohorts CCI [redacted]. This part of the study was planned to be conducted in 12 healthy volunteers. Six volunteers were selected for the first IV dose cohort in Part 1b (volunteers from Part 1a) and 6 healthy volunteers who had not previously participated in the study (naïve volunteers, including women of childbearing potential [WOCBP]) were selected for the second IV dose cohort.

Part 2a/b of the study was a randomized, single-blind, placebo-controlled, MAD, sequential group design study performed at 3 clinical units. Patients with mild asthma (Part 2a) and healthy volunteers (Part 2b) aged 18 to 55 years were included in this part of the study. This part of the study planned to recruit up to 56 subjects. Part 2a included cohorts 1 and 2, each comprised of 9 patients with mild asthma. Within each of these cohorts, 6 patients were randomized to receive AZD0449 Neb suspension and 3 patients were randomized to receive placebo. Part 2b consisted of 1 cohort of 8 healthy volunteers; 6 volunteers were randomized to receive AZD0449 Neb suspension and 2 volunteers were randomized to receive placebo.

Part 3a/b was a randomized, single-blind, placebo-controlled, DPI/PoM study. Part 3 was planned to be conducted in up to 36 patients with mild asthma (Part 3a) and 8 healthy volunteers (Part 3b). Part 3a consisted of 36 patients, aged 18 to 55 years, where 18 patients were randomized to AZD0449 DPI and 18 patients to placebo. Part 3b comprised 8 healthy volunteers, where 6 volunteers were randomized to AZD0449 DPI and 2 volunteers to placebo.

Study completion is defined as the last visit of the last subject for any protocol related activity.

The duration that each subject was involved in this is study is summarized in Table 2-4 below.

**Table 2-4 Expected Duration of the Study**

| | Screening | Treatment Period* | Safety Monitoring** Period | Follow-up | Total Duration |
|---|---|---|---|---|---|
| Part 1a | 28 days before dose | 1 day | 3 days | 6±1 days after dose | Up to 36 days |
| Part 1b (First IV cohort) | 28 days before dose | 1 day | 2 days | 6±1 days after dose | Up to 53 days |
| Part 1b (Second IV cohort) | 28 days before dose | 1 day | 2 days | 6±1 days after IV dose | Up to 36 days |
| Part 2a | 28 days before first dose | 12 days | 2 days | 10±1 days after last dose | Up to 52 days |
| Part 2b | 28 days before first dose | 12 days | 15 days | Not Applicable | Up to 55 days |
| Part 3a and Part 3b | 28 days before first dose | 12 days | 15 days | Not Applicable | Up to 55 days |

* This was a 12 day period with dosing on Day 1 and Day 3 to 12.

** Period of in-house monitoring from last dose until discharge from the unit. If permitted by local relevant regulatory authorities and considered feasible and safe to do so, the safety monitoring period for Part 2b, 3a, and 3b might be conducted as non-residential visits.

**Study Subjects:**

| **Included:** | **Randomized:** | **Completed Study:** |
|---|---|---|
| 125 subjects | Part 1a: 48 subjects (36 AZD0449/12 placebo).<br>Part 1b: 14 subjects (8 from Part 1a and 6 new subjects).<br>Part 2a: 18 subjects (12 AZD0449/6 placebo).<br>Part 2b: 9 subjects (7 AZD0449/2 placebo).<br>Part 3a: 36 subjects (18 AZD0449/18 placebo).<br>Part 3b: 8 subjects (6 AZD0449/2 placebo).<br>Total Randomized subjects: 125 subjects | In all 3 parts all randomized subjects completed the study. |

**Main Inclusion Criteria:**

Subjects who met the following criteria were considered eligible to participate in the study:

- Provision of signed and dated, written informed consent before any study specific procedures.
- For Part 1a/b, Part 2b and Part 3b - healthy male and female volunteers (for Part 1a and Part 1b first IV cohort, female volunteers must be of non-childbearing potential), aged 18 to 55 years with suitable veins for cannulation or repeated venipuncture.
- For Part 2a and Part 3a - male and female (including WOCBP) patients with mild asthma aged 18 to 55 years with suitable veins for cannulation or repeated venipuncture.
- For all parts, female patients were non-lactating and had a negative pregnancy test at the Screening Visit and on admission to the Clinical Unit.
- For healthy volunteers: had a BMI between 18 and 30 kg/$m^2$ inclusive and weighed at least 60 kg.
  For patients with mild asthma: had a BMI between 18 and 35 kg/$m^2$ inclusive and weighed at least 50 kg.
- Healthy volunteers had a FEV1 ≥80% of the predicted value regarding age, height, gender, and ethnicity at the Screening Visit.
- For patients with mild asthma (Part 2a and Part 3a):
  - Physician diagnosed (mild) asthma for at least 6 months prior to screening.
  - Lung function ≥70% predicted for FEV1 at the Screening Visit and at the 12 h time point on Day -1, in accordance with the ATS/ERS criteria.
  - Had a FeNO of ≥30 ppb at the Screening Visit and at the 12 h time point on Day -1.
- Male volunteers and their WOCBP partners were willing to use highly effective contraception measures and refrained from donating sperm or fathering a child from the first day of dosing until 3 months after the last dose of IMP.
- Female volunteers in Part 1b second IV cohort, Part 2a/b and Part 3a/b were willing to use highly effective contraception measures from the first day of dosing until 1 month after the last dose of IMP.
- Provision of signed, written, and dated informed consent for optional genetic research. If a volunteer declined to participate in the genetic component of the study, there was no penalty or loss of benefit to the volunteer. The volunteer was not excluded from other aspects of the study described in the CSP.

| **Investigational Medicinal Products:** | | | |
|---|---|---|---|
| **Formulations:** | **Strength/ Concentrations:** | **Batch/Manufacturing Lot Numbers:** | **Expiry Dates:** |
| Nebulizer suspension for inhalation | CCI | | |
| Nebulizer suspension for inhalation | CCI | | |
| Nebulizer suspension for inhalation | CCI | | |
| Solution for IV infusion | CCI | | |
| Inhalation powder for DPI | CCI | | |

DPI: Dry-powder inhaler; F Lot: Formulation Lot; IV: Intravenous; CCI P Lot: Packaging Lot

**Treatment Compliance:**

Dosing took place at the Clinical Unit. Subject compliance was assured by direct supervision and witnessing of IMP administration. Administration of IMP was recorded in DataLabs®.

**Criteria for Evaluation:**

**Safety Variables:**

See Table 2-1 for Primary Objectives and Outcome Measures and Table 2-2 for Secondary Objectives and Outcome Measures.

**Pharmacokinetic Parameters:**

See Table 2-1 for Primary Objectives and Outcome Measures and Table 2-2 for Secondary Objectives and Outcome Measures.

**Pharmacodynamic Parameters:**

See Table 2-1 for Primary Objectives and Outcome Measures and Table 2-2 for Secondary Objectives and Outcome Measures.

**Exploratory Variables:**

See Table 2-3 for Exploratory Objectives and Outcome Measures.

**Statistical Methods:**

**Determination of Sample Size:**

This was a Phase I study to investigate the safety and tolerability of a novel compound. The sample size was chosen to obtain reasonable evidence 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 had shown that the sample size being proposed was reasonable to accomplish the objectives of the study. Thus, no formal sample size calculation was done for Part 1 and the non-PoM cohorts in Part 2a/b and Part 3.

For Part 3a (PoM cohort):

- Endpoint: change from baseline in exhaled FeNO (log scale) while receiving multiple inhaled doses of AZD0449, in active and placebo arms.
- Treatment difference (Treatment – Placebo) of change from baseline of mean Log FeNO, equivalent to a 25% reduction of the ratio of geometric mean.

For Part 3a, assuming a log mean baseline FeNO level of 4.24 with SD of 0.38 (geometric coefficient of variation [GCV]=39.4%) and a correlation between baseline and last day of study data of 0.7, as suggested by previous studies, the required sample size for a 25% absolute reduction in the ratio of geometric means (a 0.288 reduction of the mean log FeNO levels) was 18 evaluable patients per arm using a one-sided test at 5% significance level.

The current design presented an opportunity to perform a sample size calculation at an interim analysis performed when approximately half the data from Part 3a was available. If the actual estimate of baseline FeNO SD was higher than expected, reaching SD=0.55, the sample size of the PoM cohort in Part 3a was planned to potentially be increased up to n=26 per arm. Should the variation be even higher, requiring adjustments beyond this, an amendment was to be submitted.

**Presentation and Analysis of Safety Data:**

All safety data (scheduled and unscheduled) were presented in the data listings. If not otherwise stated, continuous variables were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment, for each study part. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment and study part. All summaries were based on the safety analysis set unless otherwise stated.

**Presentation and Analysis of Pharmacokinetic Data:**

All reportable PK parameters were listed for AZD0449 and its CCI , as appropriate, for all subjects (Safety analysis set). A separate listing was provided for the diagnostic parameters.

Plasma PK parameters were summarized for the PK analysis set by analyte, treatment (dose level of AZD0449), study part, and study day using the following descriptive statistics:

- Cmax, AUC, AUC(0-12), AUC(0-24) and AUC(0-t) presented n, gmean, gmean+gSD, gmean-gSD, gCV(%), median, min and max.
- Cmax/D, AUC/D, AUC(0-t)/D and λz presented n, gmean, gCV%, mean, SD, median, min and max.
- t1/2λz, CL/F, CL, Vz/F, Vz, presented n, gmean, gCV%, mean, SD, median, min and max.
- tmax and tlast presented only n, median, min and max.
- diagnostic parameters (t upper, t lower, λzN, Rsq-adj and %AUCextr) were listed only and not summarized.

**Presentation and Analysis of Pharmacodynamic Data:**

Pharmacodynamic data were listed by subject and study day including absolute values and change from baseline. Summary tabulations as well as geometric mean for absolute values and changes from baseline were be presented by treatment (dose level of AZD0449, and pooled placebo), day and time-point for the full

analysis set and per protocol analysis set.

**Presentation and Analysis of Exploratory Data:**

CCI [redacted]

**Protocol Deviations:**

Overall, 104 subjects out of 125 subjects who participated in the study reported important protocol deviations. None of the reported deviations from the protocol had an effect on the interpretation of the study results or led to exclusion of any subject from the analysis populations.

**Safety Results:**

The primary and secondary objective of the study was to evaluate safety and tolerability of AZD0449 following inhaled Neb and IV administration of SAD in healthy volunteers (Part 1a/b), inhaled Neb administration of MAD in patients with mild asthma (Part 2a) and healthy volunteers (Part 2b), and following repeated inhaled administration using a DPI in patients with mild asthma (Part 3a) and in healthy volunteers (Part 3b).

The following conclusions apply across all the study parts, unless otherwise stated.

- There were no deaths and no SAEs reported. There was only one AE leading to study discontinuation reported in Part 2b of the study.
- The number of subjects with at least 1 AE was relatively low in all AZD0449 groups. In Part 1a and Part 3b of the study fewer subjects in the placebo group had at least 1 AE compared with pooled AZD0449 group. In Part 2a of the study percentage of subjects who had at least 1 AE was identical between the pooled AZD0449 group and the placebo group. In Part 2b and Part 3a of the study fewer subjects in the pooled AZD0449 group had at least 1 AE compared with placebo group.
- The highest number of AEs were reported in the SOCs of nervous system disorder, investigations, respiratory, thoracic, and mediastinal disorders, gastrointestinal disorders and general disorder, administration site conditions. The most frequently reported AE was headache. The incidence was higher in the pooled AZD0449 groups compared with the placebo groups.
- Fewer subjects in the pooled AZD0449 groups had at least 1 AE assessed as related to IMP compared with the placebo groups.
- The majority of subjects experienced AEs of mild intensity and some also experienced AEs of moderate intensity. There were no AEs of severe intensity.
- PPD healthy volunteer experienced herpes zoster after receiving a single dose of CCI AZD0449. It was treated with topical acyclovir. Herpes zoster has been included as a common adverse reaction for most of the orally administered JAK inhibitors. Therefore, it is considered as an important potential risk for AZD0449 and it will be kept under close surveillance.

**Pharmacokinetic Results:**

- When AZD0449 was administered as a single IV infusion (at 2 dose levels: CCI the median tmax occurred shortly before or at the end of infusion. The concentrations in plasma decreased in a biphasic manner and rapidly to concentrations below the LLOQ. The mean plasma CL, Vz, and t½λz for the 2 dose levels were 57 to 65 L/h, 232 to 248 L, and 2.5 to 3.4 hours, respectively.
- When a single AZD0449 nebulised dose was administered at increasing levels CCI the median tmax occurred shortly after the end of inhalation. The plasma concentrations increased proportionally with increasing dose and appeared to decline in a multiphasic manner for all dose levels. With increasing dose, a larger proportion of the PK curve was measurable (above LLOQ) and the mean t½λz for the highest dose was 84.3 hours (3.5 days).
- When AZD0449 was repeatedly administered on Day 1 and daily from Day 3 to Day 12 at increasing dose levels in the MAD study part (with nebulised inhaled suspension at CCI to mild asthmatics and at CCI to healthy volunteers) the single dose PK on Day 1 were similar to the PK in healthy volunteers in the SAD study part. Following repeated doses there was no accumulation in Cmax, but some accumulation in AUC. The t½λz following the last dose on Day 12 was followed and analysed the most thoroughly for the CCI dose level and was characterised up to 360 hours (15 days) post the last dose. The mean t½λz following the last dose on Day 12 was estimated to 160 hours (6.5 days).
- When AZD0449 was repeatedly administered on Day 1 and daily from Day 3 to Day 12 at the highest dose level CCI by DPI to mild asthmatics and healthy volunteers, the median tmax occurred at 1 to 2 hours post-dose, slightly later than that for the same dose level of nebulized suspension. Following repeated dosing there was some accumulation in Cmax and AUC. The plasma concentrations declined in a multiphasic manner and the mean t½λz following the last dose on Day 12 was estimated to be 124 and 133 hours (5.2 and 5.5 days) for mild asthmatics and healthy volunteers, respectively.
- CCI

**Pharmacodynamic Results:**

The anti-inflammatory effect of AZD0449, assessed by the change from baseline in 2 hours post-dose FeNO and FeNO AUC(0-12) to Day 12 and Follow-up in mild asthmatics, did not show any statistically significant change as compared to placebo.

**Discussion and Conclusion:**

- AZD0449 was well tolerated in all the three study parts with no deaths and no SAEs.
- The AZD0449 dose, administration route, and disease condition did not appear to elicit a specific safety profile. AZD0449 was well tolerated in all subjects.
- The systemic exposures of AZD0449 after inhaled administration up to the maximum dose of CCI was in general low (nM range) and well below the pre-defined safety limits.
- The plasma PK (Cmax and AUC) increased proportionally between dose-levels.
- The t½λz was long (5.2 to 6.5 days) following inhaled administration and possibly driven by slow absorption from the lung as confirmed by the short half-life (2.5 to 3.4 hours) after IV administration.
- There was no statistically significant reduction in FeNO in the AZD0449 group as compared to placebo in patients with mild asthma.

Version and Date of Report: Final Version, 09 March 2022

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