2 SYNOPSIS

Title of Study:	A Single-blind, Randomised, Placebo-controlled 3-Part Study in Healthy Volunteers and Patients with Mild Asthma to Investigate the Safety, Tolerability, and Pharmacokinetics of Inhaled AZD4604 Following Single and Multiple Ascending Doses and to Investigate the Anti-inflammatory Effect of Inhaled AZD4604	
Study Numbers:	Parexel Study No.: PXL 252435 Sponsor Study No.: D8210C00001	
Study Intervention:	AZD4604	
Indication Studied:	Mild asthma	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Chief Investigator:	Pablo Forte Soto, MD, MSc, PhD	
Study Centres:	This study was conducted at 3 different centres in the UK.	
Publication:	None	
Study Duration:	First participant first visit: 20 September 2021	Last participant last visit: 24 January 2023

Study Objectives:

Primary objectives:

- **Part 1a**
  To assess the safety and tolerability of AZD4604 following inhaled administration of single ascending doses to healthy volunteers.
- **Part 1b**
  To characterise the plasma pharmacokinetics (PK) of AZD4604 following intravenous (IV) and per os (PO – oral) administration of a single dose to healthy volunteers.
- **Part 2**
  To assess the safety and tolerability of AZD4604 following inhaled administration of multiple ascending doses to healthy volunteers.
- **Part 3**
  To assess the safety and tolerability of AZD4604 following inhaled dry powder inhaler (DPI) administration of multiple ascending doses to patients with mild asthma.

Secondary objectives:

- **Part 1a**
  To characterise the plasma PK of AZD4604 following inhaled administration of single ascending doses of AZD4604.
- **Part 1b**
  To assess the safety and tolerability of AZD4604 following IV and PO administration of a single dose to healthy volunteers.

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To assess renal clearance of AZD4604 following IV administration of a single dose to healthy volunteers.

- **Part 2**
  To characterise the plasma PK of AZD4604 following inhaled administration of multiple ascending doses to healthy volunteers.
  To evaluate the effect of AZD4604 on cough severity in healthy volunteers when compared with placebo.
- **Part 3**
  To characterise the plasma PK of AZD4604 following inhaled DPI administration of multiple ascending doses to patients with asthma.
  To evaluate the effect of AZD4604 on cough severity in patients with mild asthma.
  To evaluate anti-inflammatory effect in patients with mild asthma.

Exploratory objectives:

- **Part 1a and Part 3**
  To evaluate CCI .

Other exploratory objectives will be reported outside of the clinical study report (CSR).

Study Design:

This was a first-in-human (FIH) clinical study which assessed the safety and tolerability, as well as the single- and multiple-dose PK, of inhaled AZD4604 in healthy volunteers, as well as the safety, tolerability, and pharmacodynamics (PD) in patients with mild asthma. The study consisted of 4 parts:

- Part 1a: Single ascending dose (SAD) in healthy subjects,
- Part 1b: IV or PO dose in healthy subjects,
- Part 2: Multiple ascending dose (MAD) in healthy subjects, and
- Part 3: Multiple doses in patients with mild asthma and proof of mechanism (PoM).

After completion of the Part 3 Cohorts 1 and 2, a Safety Review Committee (SRC) meeting was to be held to establish a dose-level for a further PoM cohort. However, the study was terminated early as after reviewing the positive PD data (fractional exhaled nitric oxide [FeNO] levels) in asthmatic patients on active treatment, it was concluded that proof of mechanism had been observed and there was no need for a separate PoM cohort of patients with mild asthma.

Part 1a

Part 1a of the study was a randomised, single-blind, placebo-controlled, SAD, sequential group design study. Seven inhaled dose-levels of AZD4604 were planned to be investigated in cohorts of 8 healthy subjects, with 6 healthy subjects randomly assigned to inhaled AZD4604 and 2 healthy subjects randomly assigned to inhaled placebo in each cohort. Depending on emerging safety and PK data, up to 3 additional cohorts within the pre-specified dose range could have been added at the discretion of the Sponsor if the planned dosing steps appeared to be inappropriate.

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All cohorts were preceded by a sentinel cohort of 2 healthy subjects (1 subject received AZD4604, and one subject received placebo).

Part 1a comprised of:

- A Screening Visit within 28 days before dosing.
- A Treatment Period (Day -1 to Day 7, in the Study Centre) with a single inhaled dose of AZD4604 or corresponding placebo on Day 1. Although the anticipated systemic exposure and risk for potential adverse systemic effects were considered to be low for AZD4604, healthy subjects remained resident at the site for an additional 6 days of monitoring, which was predicted to allow sufficient time for near-complete washout (estimated time for > 97% of the dose to have been eliminated) of any target engagement from the lungs. Subjects were discharged after all samples had been collected and all extended safety monitoring and assessments had been performed on Day 7. Depending on the emerging data, the length of the stay at the Study Centre, timing, and number of assessments and/or blood and urine samples could have been adjusted, and the collection period could have been extended.
- A Final Assessment on day of discharge.

Part 1b

In Part 1b, AZD4604 was administered as a single IV or PO dose to healthy subjects in order to compare the PK between IV, PO, and inhaled administration.

Part 1b could have been initiated at any point after agreement of the SRC following Cohort 4 in Part 1a.

Part 1b was open-labelled and consisted of 2 dose cohorts, IV and PO, with 6 healthy subjects in each. It followed a 2-stage design so that healthy subjects from Part 1a who received AZD4604 could be selected for the IV or PO cohort in Part 1b. If Part 1b could not be completed with 12 healthy volunteers from Part 1a, or if some of the data were considered not evaluable, up to 12 additional naïve healthy volunteers could have been enrolled. Healthy volunteers from Part 1a were re-screened for eligibility and 4 naïve healthy volunteers were enrolled.

The IV and PO cohorts were each preceded by a sentinel healthy subject.

Part 1b comprised of:

- A washout period of at least 2 weeks before IV or PO dosing in Part 1b for the healthy subjects who received inhaled dosing in Part 1a. All healthy subjects had a Screening Visit within 28 days of dosing.
- A Treatment Period (Day -1 to Day 3, in the Study Centre) with a single IV or PO dose of AZD4604 on Day 1. Healthy subjects were discharged from the Study Centre after all samples had been collected and assessments had been performed on Day 3.
- A Follow-up Visit within 6 ± 1 day after dosing.

Part 2

Part 2 of the study was a randomised, single blind, placebo-controlled, MAD, sequential group design. This part of the study was to be conducted in up to 32 healthy subjects. The doses administered ([redacted] mg, [redacted] mg, and [redacted] mg) did not exceed the pre-specified maximum dose of [redacted] mg twice daily (BID).

The first MAD cohort could have been initiated after 4 cohorts in the Part 1a SAD study had been completed, provided that the predicted exposures in the MAD did not exceed the studied exposures in the completed SAD cohorts.

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AZD4604 was administered BID in a standard MAD sequential group design, ie, each healthy subject received AZD4604 over 7 days and the dose was increased stepwise between cohorts. Three inhaled dose-levels of AZD4604 were planned to be investigated in 3 cohorts. Each cohort comprised of 8 healthy subjects, with 6 healthy subjects randomly assigned to inhaled AZD4604 and 2 healthy subjects randomly assigned to inhaled placebo. Depending on emerging safety and PK data, one additional cohort within the pre-specified dose and exposure range could also have been added at the discretion of the Sponsor.

Each cohort was preceded by a sentinel cohort of 2 healthy subjects (one subject received AZD4604, and one subject received placebo).

Part 2 comprised of:

- A Screening Visit within 28 days before first dosing.
- A Treatment Period (Day -1 to Day 12 in the Study Centre) with BID inhaled doses of AZD4604 or placebo on Day 1 to Day 6 (12 hour [± 30 min] intervals between doses), and a single inhaled dose on Day 7. Although the anticipated systemic exposure and risk for potential adverse systemic effects were considered to be low for AZD4604, healthy subjects remained resident at the site for an additional 6 days of monitoring, which was predicted to allow sufficient time for near-complete washout (estimated time for > 97% of the dose to have been eliminated) of any target engagement from the lungs. Healthy subjects remained in the Study Centre for the duration of the Treatment Period and were discharged on Day 13, 6 days after administration of the last dose, once all samples had been collected and assessments had been performed. Depending on the emerging data, the length of stay at the Study Centre, timing, and number of assessments and/or blood and urine samples could have been adjusted, and the collection period could have been extended.
- A Final Assessment on day of discharge.

Based on interim safety and PK data reviewed from Part 2 Cohort 2, the SRC decided that Part 2 Cohort 3, would receive [redacted] mg BID of AZD4604 DPI instead of the planned dose of [redacted] mg BID of AZD4604 DPI.

Part 3

Part 3 of the study was a randomised, single blind, placebo-controlled, multiple-dose, PK and PD study, with twice daily non-residential visits during the Treatment Period. This part of the study was to be conducted in at least 45 patients with mild asthma, 16 patients in Cohorts 1 and 2 and at least 29 patients in the further PoM cohort. However, the study was terminated early after completion of Cohorts 1 and 2 as reviewing the positive PD data (FeNO levels) in asthmatic patients on active treatment confirmed that there was no need to have a separate PoM cohort. Two dose-levels ([redacted] mg and [redacted] mg) of AZD4604 were administered as per the maximum dose in healthy volunteer cohorts. Each cohort comprised of 8 patients, with 6 patients randomly assigned to inhaled AZD4604 and 2 patients randomly assigned to inhaled placebo.

The dose-levels in Part 3 were based on the PK and safety data reviewed during the SRC meetings in Part 2 (MAD). Any dose-level used in Part 3 was equal to or lower than the dose-levels assessed in Part 2.

Part 3, Cohort 1 could have been initiated at any point after the SRC meeting for Part 2, Cohort 2 if this was supported by the PK and safety data. Part 3, Cohort 2 could have been initiated at any point after the SRC meeting for Part 2, Cohort 3 if this was supported by the PK and safety data.

AZD4604 was administered BID to each patient over 10 days.

After completion of Part 3, Cohorts 1 and 2, an SRC meeting was held, and the safety, PK, and PD data were reviewed to establish a dose-level for a further PoM cohort. Twenty-nine additional patients with mild asthma were planned to be enrolled in the PoM cohort, with the aim of enabling the evaluation of a statistically

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significant effect of AZD4604 on FeNO. However, the study was terminated early upon review of the positive PD data (FeNO levels) in asthmatic patients on active treatment, as it was concluded that PoM had been achieved and that there was no need for further cohorts with participants with mild asthma.

Part 3 comprised of:

- A Screening Visit within 42 days before first dosing.
- A Treatment Period (Day -3 to Day 15 as daily, non-residential visits) with BID inhaled doses of AZD4604 or placebo on Day 1 to Day 9 (12-hour intervals between doses), and a single inhaled dose on Day 10. Dosing took place at the clinical site and patients visited the site twice daily on Day 1 to Day 9. The anticipated systemic exposure and risk for potential adverse systemic effects were considered to be low for AZD4604, therefore, patients were not required to be resident at the site during the Treatment Period.
- A Final Assessment (Day 16) on the last day of the Treatment Period.

Study Subjects:

Planned for Inclusion:	**Randomised:**	**Completed Study:**
Part 1a: 80 healthy subjects	Part 1a: 57 healthy subjects	Part 1a: 56 healthy subjects
Part 1b: 12 healthy subjects	Part 1b: 12 healthy subjects	Part 1b: 12 healthy subjects
Part 2: 32 healthy subjects	Part 2: 24 healthy subjects	Part 2: 24 healthy subjects
Part 3: 45 patients with mild asthma	Part 3: 18 patients with mild asthma	Part 3: 16 patients with mild asthma

Main Inclusion Criteria:

Part 1a, Part 1b, and Part 2

These parts of the study were conducted in healthy male and female subjects (including females of childbearing potential) aged 18 to 55 years 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 60 kg.

Part 3

This part of the study was conducted in mild asthma male and female patients (including females of childbearing potential) aged 18 to 65 years with suitable veins for cannulation or repeated venipuncture. The patients had a body mass index between 18 and 35 kg/m^2 (inclusive) and weighed at least 60 kg. In addition, patients had a lung function ≥ 70% predicted for FEV_1 at the Screening Visit and the pre-morning dose on Day -1, in accordance with the American Thoracic Society/European Respiratory Society criteria and a FeNO of ≥ 40 ppb at the Screening Visit and at the corresponding clock time of pre-morning dose on Day -3.

Investigational Medicinal Product(s):

AZD4604 for inhalation via DPI	
Supplier:	AstraZeneca AB, R & D Gothenburg
Formulation:	AZD4604 inhalation powder
Strength/Concentrations:	CCI mg, CCI mg, and CCI mg

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Dose:	Dose range Part 1a: CCI mg to CCI mg daily dose Dose range Part 2: CCI mg to CCI mg daily dose Dose range Part 3: CCI mg to CCI mg daily dose
Route of administration:	Inhalation
Specific device for drug administration:	SD3FL version of Genuair
Regimen:	Part 1a: Single ascending dose Part 2: BID multiple ascending doses Part 3: BID doses
Type:	Integral device
Batch/Manufacturing Lot number:	CCI mg: CCI CCI mg: CCI CCI mg: CCI
Expiry date:	CCI mg: 30 April 2023 CCI mg: 31 August 2023 CCI mg: 31 August 2023
Placebo for AZD4604 for inhalation via DPI	
Supplier:	AstraZeneca AB, R & D Gothenburg
Formulation:	Placebo for AZD4604 inhalation powder
Dose:	N/A
Route of administration:	Inhalation
Specific device for drug administration:	SD3FL version of Genuair
Regimen:	Part 1a: single ascending dose Part 2: BID multiple ascending doses Part 3: BID doses
Type:	Integral device
Batch/Manufacturing Lot number:	CCI
Expiry date:	31 March 2024

AZD4604 for intravenous administration	
Supplier:	AstraZeneca AB, R & D Gothenburg
Formulation:	AZD4604 solution for infusion
Strength/Concentrations:	CCI mg/mL
Packaging unit:	Type I glass vials
Dose:	CCI mg
Route of administration:	Intravenous
Specific device for drug administration:	Infusion pump set
Regimen:	Part 1b: single dose
Type:	Drug
Batch/Manufacturing Lot number:	CCI
Expiry date:	February 2023
AZD4604 for oral administration	
Supplier:	AstraZeneca AB, R & D Gothenburg
Formulation:	AZD4604 solution for infusion (for oral administration)
Strength/Concentrations:	CCI mg/mL
Packaging unit:	Type I glass vials
Dose:	CCI mg
Route of administration:	Oral
Regimen:	Part 1b: single dose
Type:	Drug
Batch/Manufacturing Lot number:	CCI
Expiry date:	February 2023
Duration of Treatment: Part 1a: In all dosing cohorts, each subject received a single inhaled dose of AZD4604 or placebo on Day 1. Part 1b: Each subject received either a single IV dose of AZD4604 (Cohort 1) or a single oral dose of AZD4604 (Cohort 2) on Day 1. Part 2: In all dosing cohorts, each subject received inhaled doses of AZD4604 or placebo BID on Day 1 to Day 6 (12-hour [± 30 min] intervals between doses), and a single inhaled dose of AZD4604 or placebo on Day 7. Part 3: In all dosing cohorts, each patient received inhaled doses of AZD4604 or placebo BID on Day 1 to Day 9 (12-hour intervals between doses), and a single inhaled dose of AZD4604 or placebo on Day 10. For Part 1a of the study, each subject was involved in the study for up to approximately 35 days. For Part 1b of the study, each subject was involved in the study for up to approximately 36 days. For Part 2 of the study, each subject was involved in the study for up to approximately 41 days. For Part 3 of the study, each patient was involved in the study for up to 58 days.	
Treatment Compliance: Dosing took place at the Study Centre. The administration of all study interventions were recorded in the electronic data capture system. Compliance was assured by direct supervision and witnessing of study	

intervention administration. In addition, bioanalysis of the plasma sample collected 1 hour after start of dose administration from all presumed placebo treated subjects was used to confirm lack of AZD4604 in the plasma.

Criteria for Evaluation:

Safety Variables:

Part 1a

Safety outcome measures included adverse events (AEs), vital signs (supine blood pressure [BP], pulse, respiratory rate and body temperature), 12-lead electrocardiogram (ECG), 12-lead digital ECG (dECG), telemetry, physical examination, laboratory assessments (haematology, clinical chemistry, and urinalysis), spirometry, end-tidal carbon dioxide ($ETCO_2$), capillary blood gas, and peripheral capillary oxygen saturation (SpO_2).

Part 1b

Safety outcome measures included AEs, vital signs (supine BP, pulse, respiratory rate and body temperature), 12-lead ECG, 12-lead dECG, telemetry, physical examination, laboratory assessments (haematology, clinical chemistry, and urinalysis), and $ETCO_2$.

Part 2

Safety outcome measures included AEs, vital signs (supine BP, pulse, respiratory rate and body temperature), 12-lead ECG, 12-lead dECG, telemetry, physical examination, laboratory assessments (haematology, clinical chemistry, and urinalysis), spirometry, SpO_2, and cough severity self-assessment.

Part 3

AEs, vital signs (supine BP, pulse, respiratory rate and body temperature), 12-lead ECG, 12-lead dECG, telemetry, physical examination, laboratory assessments (haematology, clinical chemistry, and urinalysis), spirometry, SpO2, and cough severity self-assessment.

Pharmacokinetic Parameters:

Part 1a

PK concentrations and PK parameters: Cmax, tmax, λz, t½λz, AUC(0 12), AUC(0 24), AUClast, AUCinf, CL/F, Vz/F, AUClast/D, AUCinf/D, Cmax/D, and tlast

Part 1b

PK concentrations and PK parameters: Cmax, tmax, λz, t½λz, AUC(0-12), AUC(0-24), AUClast, AUCinf, CL/F, CL (IV cohort), Vz/F, Vz (IV cohort), AUClast/D, AUCinf/D, Cmax/D, and tlast

Where possible the following PK parameters were assessed: CLR, fe(t1-t2), Ae(t1-t2).

Part 2

PK concentrations and PK parameters: Cmax, tmax, λz, t½λz, AUC(0 24), AUCτ, AUClast, CL/F, Vz/F, AUClast/D, AUCτ/D, Cmax/D, Rac AUC, Rac Cmax, and tlast

Part 3

PK concentrations and PK parameters such as: Cmax, AUCτ and AUC

Pharmacodynamic Parameters:

- Change from baseline in 2 hours post-morning dose FeNO levels on Days 1 to 10
- Change from baseline in pre-morning dose (Days 1 to 9 and 10) and pre-evening dose FeNO levels on Days 1 to 9

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 has 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 non-PoM cohorts (Parts 1a, 1b, and MAD cohorts in Part 2 and Part 3).

For PoM Cohort

Assuming a log mean baseline FeNO level of approximately 4.5 (~ 90-95 ppb) with geometric coefficient of variation of 46% (~SD = 45 ppb), 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 CCI in the ratio of geometric means (a CCI) was CCI evaluable subjects in the active arm and CCI in placebo arm, 2:1 randomisation.

The study design presented an opportunity to perform a sample size calculation at an IA taking place when around 50% the data from the PoM cohort was available (from around 18 subjects). If the actual estimate of baseline FeNO SD was higher than expected, reaching GCV of 60%, the sample size of the PoM cohort would have been potentially increased.

Should the variation be even higher, requiring adjustments beyond this, an amendment would have been submitted.

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 (n, mean, SD, min, median, max) by dose group. Categorical variables were summarised in frequency tables (frequency and proportion) by dose group. The analysis of the safety variables was based on the safety analysis set.

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

Tabulations and listings of data for vital signs, clinical laboratory tests, 12 lead safety ECGs (listings only), dECGs, spirometry, $ETCO_2$, capillary blood gas (listings only), and SpO_2 were presented (where applicable to study parts). The visual analogue scale (VAS) (0 to 100) was treated as a continuous variable and summarised and analysed accordingly. Individual readout for VAS was provided in listings. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was 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 the units provided by the clinical laboratory for the SRC meeting, and in Système International units in the CSR.

Out of range values for safety laboratory tests were flagged in individual listings as well as summarised descriptively using agreed reference ranges (eg, laboratory ranges).

Presentation and Analysis of Pharmacokinetic Data:

All PK parameters (including diagnostic parameters) were summarised for AZD4604 by study part, PK Day/Visit, and dose group using appropriate descriptive statistics, based on the PK Analysis Set.

The AZD4604 plasma concentrations for each scheduled time point were listed and summarised using appropriate descriptive statistics by study part, PK Day/Visit, and dose group, based on the PK analysis set.

For the IV cohort, urine PK concentration and volume/weight data were listed by collection interval and not summarised.

All PK parameters (including diagnostic parameters) were listed and summarised using appropriate descriptive statistics by study part, PK Day/Visit, and dose group, based on the PK Analysis Set.

Figures for the geometric mean concentration-time data were presented for all study parts by PK sampling Day/Visit and dose groups on both a linear and semi-logarithmic scale, based on the PK analysis set.

Individual concentration-time data were graphically presented on linear and semi-logarithmic scales, for the PK Analysis Set. For Part 2 and Part 3, each individual's plot included both the single and multiple-dose PK profiles for Part 2 and multiple-dose PK profiles for Part 3. Combined individual plasma concentration versus actual times were plotted on both the linear and semi-logarithmic scale for all subjects in the PK Analysis Set. Plots were grouped by dose-level.

Presentation and Analysis of Pharmacodynamic Data:

The PD analysis set consisted of all patients in the safety analysis set who received AZD4604 with baseline FeNO assessment and who had at least one morning pre-dose, at least one 2-hour post-morning dose or at least one evening pre-dose assessment, with no important protocol deviations thought to impact on the analysis of the PD data.

The date and time that the samples were collected and assessment for FeNO was performed, were listed. Change from baseline in 2 hours post-dose FeNO (Days 1 to 10), change from baseline in pre-morning dose (Days 1 to 9 and 10) and pre-evening dose (Days 1 to 9) and change from baseline to the final Follow-up Visit were also calculated and listed. The baseline for FeNO analysis was the average FeNO measurement on Day -2 and Day -1 corresponding to the analysed endpoint. Modelling was performed on both absolute and percentage scale.

Summaries of FeNO values by time point were provided and change from baseline in 2 hours post-dose FeNO at Day 10, change from baseline in pre-morning dose and pre-evening dose and change from baseline to the final Follow-up Visit were also calculated, listed and summarised by treatment (dose-level of AZD4604 and pooled placebo). Listings were based on the safety analysis set and summaries were provided based on the PD analysis set.

The analysed data could have had negative values for the change from baseline, which made it impossible to calculate the logarithm of this value. Therefore, the change from the baseline was replaced by the relative change from baseline. In addition, visit covariate was added to the analysis to include the effect of individual visits on the model results and to make it consistent with the interaction term.

The cough VAS was summarised as a continuous variable at baseline dosing days. Statistical analysis consisted of a mixed effect model of repeated measures model for change form baseline, with baseline as covariate, and fixed effect for treatment and random effect for subject. As Cough VAS questionnaire values were collected for each treatment day, visit and treatment-by-visit interaction covariates were added to include the effect of individual visits. Cough VAS was visually presented as a trend plot with days on the x-axis and change form baseline on the y-axis with associated 90% confidence interval (CI).

The same approach was applied for the pre-morning dose and pre-evening dose.

CCI

CCI

CCI [redacted]

Protocol Deviations:

There were no COVID-19-related important protocol deviations reported for any of the participants.

In Part 1a, 2 important protocol deviations were reported:

- One subject in Part 1a, who rolled over into Part 1b, signed the Part 1b informed consent form (ICF) but the Investigator did not sign and date the COVID ICF that was to be signed before or along with the main ICF.
- One subject met one of the exclusion criteria (Exclusion Criterion no 22; Protocol Amendment 3).

In Part 3, 7 important protocol deviations were reported:

- Spirometry for a patient randomised to receive AZD4604 CCI mg (DPI) was not performed at Screening.
- One patient randomised to receive AZD4604 CCI mg (DPI) was not dosed in the morning of Day 8 in relation to Day 1 dosing (-60 to +60 min).
- Spirometry for a patient randomised to receive placebo was not performed on Day 15.
- Spirometry for a patient randomised to receive AZD4604 CCI mg (DPI) was not performed Day 15.
- The Day 3 morning PK sample for a patient randomised to receive AZD4604 CC mg (DPI) was labelled as a duplicate despite one of the samples belonging to another patient randomised to receive AZD4604 CC mg (DPI). The site was unable to determine which sample belonged to which patient. Deviations were reported for each patient.
- The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of a patient randomised to receive AZD4604 CC mg (DPI) started to increase during Day 2 of the Treatment Period. The highest values of ALT and AST were reached at Day 10 (above 3.6 and 3.3 upper limit of normal, respectively). The levels of AST and ALT began to decrease thereafter. These changes were noted by the clinical team but were not considered clinically significant at the time. Therefore, no action was taken until later when it was noticed by the clinical research associate during the remote monitoring visit.

There were no important protocol deviations reported for Part 1b and Part 2.

The reported deviations from the protocol did not have an effect on the interpretation of the study results nor did it lead to the exclusion of the participants from the analysis populations.

Safety Results:

No major safety or tolerability concerns were identified in the study in doses up to the highest dose given (CC mg). However, after reviewing interim safety and PK data (taking into consideration predicted Cmax and AUC values for the planned doses), the SRC recommended the following dose changes in order to avoid meeting any PK stopping criteria:

- Part 1a Cohort 7: Planned dose of CCI mg was changed to CC mg.
- Part 2 Cohort 3: Planned dose CC mg was changed to CCI mg.
- Part 3 Cohort 2: Planned dose CC mg was changed to CCI mg.

There were no deaths or SAEs reported during the study.

Three subjects (2 receiving single dose CCI mg AZD4604 and one placebo) experienced hypoventilation and increases in pCO2, but none of the individuals fulfilled the stopping criteria of respiratory acidosis (pCO2 > 6 kPa, pH < 7.35). These conditions were considered mild in nature.

One subject who was administered AZD4604 CCI mg in Part 1a tested SARS-CoV-2 positive and was withdrawn from the study.

One patient who was administered AZD4604 [redacted] mg in Part 3 tested SARS-CoV-2 positive and was withdrawn from the study.

Overall, all reported AEs were considered by the Investigator to be mild or moderate in intensity, except for an AE of syncope experience by one subject in Part 1a that was considered by the Investigator to be of severe intensity, as well as 2 AEs of ALT increase and AST increase, experienced by one patient in Part 3 that were considered by the SRC to be of severe intensity.

No medically important trends for changes were observed for any of the laboratory parameters or vital signs across cohorts. Although there were other fluctuations in laboratory parameters from baseline and some of these were outside of the normal range, none of these met the limits for clinical significance.

There were no clinically significant observations for the 12-lead ECGs and dECGs.

There was one clinically significant observation noted from the telemetry data. An asystole of 4.5 sec occurred during blood sampling with associated transient dizziness caused by a vasovagal reaction; reported for a subject in Part 2.

The COVID-19 pandemic did not impact the safety results of this study. Participants who were exposed to COVID-19 after exposure to AZD4604 did not suffer significant AEs.

Pharmacokinetic Results:

AZD4604 was rapidly absorbed following single and multiple inhaled doses of AZD4604, with median tmax ranging from 0.07 to 0.14 hours post-dose in healthy volunteers (Parts 1a and 2) and patients with mild asthma (Part 3).

Single ascending doses of CCI mg AZD4604 DPI (Part 1a) showed consistent t½λz across the dose range, with geometric mean values ranging from 28.6 to 31.0 hours. Similar geometric mean t½λz values were determined following multiple BID dosing in healthy volunteers (range: 37.2 to 39.0 hours) and in patients (36.9 and 44.7 hours) in Parts 2 and 3, respectively.

At CCI mg DPI AZD4604 in Part 1a, the concentration-time profiles CCI CCI

Accumulation of plasma AZD4604 following multiple dosing was similar in healthy volunteers and patients, ranging from 3.89- to 4.69-fold increases in AUCτ and 1.56- to 2.83-fold increases in Cmax.

Steady state was achieved after approximately 6 days of multiple BID dosing based on trough concentrations.

Exposure to inhaled AZD4604 increased in an approximately dose-proportional manner following single and multiple DPI doses of AZD4604 in healthy volunteers (Parts 1a and 2) based on Cmax, AUCinf or AUCτ. Dose proportionality in patients was inconclusive due to the limited data available.

In general, patients appeared to show lower exposure to AZD4604 compared to healthy volunteers receiving the same dose: geometric mean Cmax were generally 27 to 35% lower and geometric mean AUCτ was 7 to 26% lower in patients.

Following CCI mg IV dosing, AZD4604 plasma concentration peaked around the end of the 20-minute infusion (median tmax at 0.33 hours post-dose). Absorption of AZD4604 from oral administration of 1 mg AZD4604 was steady, with detectable plasma concentrations at ~30 minutes after dosing and a median tmax of 4.51 hours post-dose.

The rate of AZD4604 elimination from plasma was consistent between IV, oral and inhalation dosing based on geometric mean t½λz values (CCI CCI).

The estimated probable oral bioavailability of AZD4604 based on geometric mean AUCinf values was CCI %. The inhaled bioavailability of AZD4604 based on AUCinf for 3 subjects that received both inhaled and IV doses were CCI and CCI %. However, this is based on very limited data.

Renal excretion as AZD4604 was low following a single IV dose of CCI mg AZD4604, based on fe(0-48) of CCI % and CLR of CCI L/h.

Between-subject variability in exposure to AZD4604 based on geometric CV ranged from 20.1 to 79.0% for Cmax and 13.0 to 45.1% for AUC(0-24) following single DPI dosing. Following IV and oral dosing, geometric CV was 42.9 and 44.1% for Cmax, respectively, and 17.4 and 38.1% for AUC(0-24), respectively.

Higher between-subject variability from the first inhaled dose of AZD4604 was observed compared to multiple dosing in Parts 2 and 3: single dose geometric CV were 56.3 to 80.7% for Cmax and 20.1 to 37.1% for AUCτ; multiple-dose geometric CV were 16.4 to 30.8% for Cmax and 10.3 to 25.7% for AUCτ.

Pharmacodynamic Results:

When compared with placebo, both AZD4604 [redacted] mg and AZD4604 [redacted] mg showed significant changes from baseline for relative FeNO levels 2 hours post-morning dose on Days 1 to 10 (p-value = [redacted]).

Similarly, when compared with placebo, changes from baseline in pre-morning dose (Days 1 to 9 and 10) and pre-evening dose FeNO levels on Days 1 to 9 were highly significant (p-value [redacted]).

[redacted]

Discussion and Conclusion:

Safety and Tolerability

AZD4604 administered as single ascending inhaled doses was found to have a good safety profile and was generally well tolerated in healthy male and female subjects. No major safety or tolerability concerns were identified in the study in doses up to the highest dose given ([redacted] mg). Pre-specified study stopping criteria were not met (Part 1a).

Overall, AZD4604 was well tolerated by healthy subjects after administration of a single dose of [redacted] mg IV and [redacted] mg PO (Part 1b).

AZD4604 administered as multiple ascending inhaled doses was found to have a good safety profile and was generally well tolerated in healthy male and female subjects. No major safety or tolerability concerns were identified in the study in doses up to the highest dose given ([redacted] mg BID). Pre-specified study stopping criteria were not met (Part 2).

AZD4604 administered as [redacted] mg and [redacted] mg multiple inhaled doses (BID) was found to have a good safety profile and was generally well tolerated in patients with mild asthma. No major safety or tolerability concerns were identified in the study (Part 3).

Although cough was reported as an AE for several subjects, the results of the cough VAS were not clinically significant (Part 2 and Part 3).

Pharmacokinetics

AZD4604 was rapidly absorbed following single and multiple inhaled doses of AZD4604, with median tmax ranging from 0.07 to 0.14 hours post-dose in healthy volunteers and patients with mild asthma. Oral absorption of AZD4604 was considerably slower with median tmax of 4.51 hours post-dose.

The rate of AZD4604 elimination from plasma was consistent between IV, oral and inhalation dosing based on geometric mean t½λz values ([redacted]).

Exposure to inhaled AZD4604 increased in an approximately dose-proportional manner following single and multiple DPI doses of AZD4604 in healthy volunteers based on Cmax, AUCinf or AUCτ.

Steady state was achieved after approximately 6 days of multiple BID dosing based on trough concentrations.

Accumulation in systemic AZD4604 following multiple dosing was similar in healthy volunteers and patients, ranging from 3.89- to 4.69-fold increases in AUCτ and 1.56- to 2.83-fold increases in Cmax.

The estimated probable oral bioavailability of AZD4604 based on geometric mean AUCinf values was 36.0%. The inhaled bioavailability of AZD4604 based on AUCinf was 81.0 to 90.7%. These estimates of oral and inhaled bioavailability should be considered with caution as they were based on inter-subject calculations and limited data, respectively.

Renal excretion of AZD4604 from IV dosing was low based on fe(0-48) of 8.25% and CLR of 1.77 L/h.

Higher between-subject variability from the first inhaled dose of AZD4604 was observed compared to multiple dosing, likely due to improved inhalation technique over time.

Pharmacodynamics

Change from baseline FeNO results after administration of CCI mg and CCI mg (DPI) BID indicated a significant anti-inflammatory effect in the airways of patients with mild asthma (Part 3).

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Version and Date of Report: Final 1.0, dated 04 December 2023

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