AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5423
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An Open, Partly Randomised, Four-way Cross-over Study in Healthy Volunteers and in Patients with Mild Allergic Asthma to Investigate the Bioavailability and Basic Pharmacokinetics of a Single Dose of AZD5423 when Administered Intravenously, Orally, Inhaled via SPIRA Nebuliser or Inhaled via I-neb® AAD Systems

Study dates:	First subject enrolled: 18 April 2011 Last subject last visit: 5 October 2011
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic (PK)	To estimate the oral and pulmonary absolute bioavailability of AZD5423 for healthy volunteers and asthma patients	Pulmonary bioavailability ($F_{pulmonary}$) and absolute bioavailability after oral administration (F_{po})
	PK	To compare the systemic exposure between I-neb® AAD Systems and the SPIRA nebuliser	AUC and C_{max} of AZD5423
Secondary	PK	To compare the PK between healthy volunteers and asthma patients	AUC and C_{max} of AZD5423
	PK	To estimate the basic systemic PK parameters of AZD5423	C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{½\lambda z}$, MRT, CL, V_z, and V_{ss}
	Safety	To evaluate the safety and tolerability of AZD5423	Adverse events, physical examination, electrocardiogram (12-lead ECG and telemetry), vital signs (pulse rate and blood pressure), spirometry, and clinical laboratory assessments
Exploratory [a]	Pharmacogenetic	To collect and store optional DNA samples for possible future exploratory research into genes/genetic variation that may influence the response (PK, tolerability, and safety) to AZD5423	Not applicable

[a] Reported separate from the clinical study report.

AAD: Adaptive Aerosol Delivery; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last measurable concentration: CL: total clearance of drug from plasma; C_{max}: maximum plasma concentration; CSP: clinical study protocol; ECG: electrocardiogram; F_{po}: absolute bioavailability after oral administration; $F_{pulmonary}$: pulmonary bioavailability; MRT: mean residence time; PK: pharmacokinetic; $t_{½\lambda z}$: terminal plasma half-life; t_{max}: time to C_{max}; V_{ss}: volume of distribution at steady state; V_z: volume of distribution during terminal phase

Study design

The study was an open, partly randomised, four-way cross-over single dose study with the following administrations of AZD5423:

- Intravenous infusion (solution)
- Oral inhalation via SPIRA nebuliser (suspension)
- Oral inhalation via I-neb® (suspension)
- Oral administration (suspension)

In total, 4 single doses were administered on 4 separate occasions. There was a wash-out period of at least 2 weeks between the different treatments. The intravenous infusion was fixed as the first treatment and the oral administration was fixed as the last treatment. Subjects received the 2 oral inhalations in a randomised order. The randomisation scheme was produced by Quintiles using the global randomisation system (GRand) and the randomisation codes were assigned strictly sequentially as subjects became eligible for randomisation.

Target subject population and sample size

Six male healthy volunteers and 6 male patients with mild allergic asthma, aged 18 to 45 years (inclusive), weight between 50 and 100 kg (inclusive), and body mass index between 18 and 30 kg/m^2 (inclusive).

Asthmatic patients had to have an asthma diagnosis according to the Global Initiative for Asthma (GINA) guidelines, a history of episodic wheeze and shortness of breath, forced expiratory volume at 1 second (FEV_1) of ≥70% of the predicted normal value, and a positive skin prick test to a panel of relevant common aeroallergens.

The study was descriptive, thus no power calculations were performed. Twelve (12) randomised subjects (6 healthy volunteers + 6 asthmatic patients) were considered sufficient to get reliable estimates of the PK parameters, and the relative bioavailability between the different formulations.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

AZD5423 solution for injection (10 µg/mL) administered as an intravenous infusion at a rate of 1 mL per minute for approximately 25 minutes (corresponding to a total dose of 250 µg AZD5423). Batch number: 11-000720AZ.

AZD5423 nebuliser suspension (2.2 mg/g) inhaled via a SPIRA nebuliser using 2 seconds nebulising time/breath and a pre-determined number of breaths to deliver a dose of 450 µg (corresponding to a predicted lung-deposited dose of approximately 300 µg). Batch number: 10-005217AZ. Administration of the investigational product including the inhalation

procedure was to be performed according to detailed separate instructions. The subjects were to practice the inhalation technique at screening and at Visits 3 and 4, before the dose was to be inhaled.

AZD5423 nebuliser suspension (1.6 mg/g) inhaled via an I-neb® AAD Systems using a medication chamber volume of 0.25 mL to deliver a dose of 420 µg (corresponding to a predicted lung-deposited dose of approximately 300 µg). Batch numbers: 11-002067AZ, 11-001819AZ, 10-004483AZ. The practice and inhalation procedure were to be performed according to detailed instructions provided separately. In order to ensure that the subjects were able to perform inhalation according to the instructions and to achieve reproducibility in inhalation techniques, inhalation techniques were to be practiced with the I-neb® filled with saline after admission to the study centre at Visits 3 and 4 before investigational product administration. In error, subjects practiced inhalation techniques with an empty I-neb® device instead of the I-neb® filled with saline.

AZD5423 nebuliser suspension (for oral use) (0.54 mg/g), 2.2 g administered orally (corresponding to a total dose of 1200 µg AZD5423). Batch number: 10-005216AZ.

Duration of treatment

The duration of the study was approximately 11 weeks and consisted of 6 visits. Visit 1, screening, took place within 28 days before Visit 2. Visits 2 to 5 (Periods 1 to 4) were the treatment visits. Visit 6, follow-up, took place at least 2 weeks after the last investigational product administration and consisted of a post-study medical examination and safety laboratory sampling.

The treatment visits consisted of 3 study days (Day 1 [investigational product administration], Day 2 [24 hours postdose assessments], and Day 3 [48 hours postdose assessments]). Subjects were resident in the study centre from the evening of Day -1 until discharge on Day 3 after the 48 hour postdose assessments were performed. Subjects returned to the study centre for PK blood sampling at the specified time points until 96 hours postdose.

Statistical methods

Summaries of the data were produced using standard summary statistics. For continuous variables, these statistics included the arithmetic or geometric mean, standard deviation (SD) or coefficient of variation (CV) (%), median, minimum, and maximum.

For categorical data, statistics consisted of frequencies and associated percentages. The denominator for the calculation of the percentages in each category was generally the total number of subjects with data recorded.

Unless otherwise stated and with the exception of PK data, measures of location (mean, median, minimum, and maximum) were analysed with full precision and reported to the same degree of precision as the raw data. Measures of spread (SD) were analysed with full precision and reported to 1 further degree of precision. Percentage frequencies were generally presented to the nearest integer.

All PK parameters were analysed with full precision. Pharmacokinetic parameters directly derived from source data were presented with the same precision as the source data. Other parameters were presented with the same precision as the source data exhibiting the lowest precision.

Subject population

All subjects were male, aged 18 to 42 years, with weight from 67.1 to 95.2 kg and body mass index (BMI) from 20.5 to 28.4 kg/m^2, as stipulated in the inclusion criteria. The mean age, weight and BMI values were similar for healthy volunteers and asthmatic patients. The asthmatic patients had a mean FEV_1 of 3.89 L and the healthy volunteers had a mean FEV_1 of 4.05 L. One subject was withdrawn from the study after receiving only the intravenous infusion due to a protocol deviation. The subject was replaced and a total of 12 subjects completed the study (ie, received all 4 treatments).

Summary of pharmacokinetic results

Administration of 250 µg intravenous, 450 µg SPIRA, 420 µg I-neb®, and 1200 µg oral AZD5423 did not result in similar systemic exposures. The order of AZD5423 exposure parameters (C_{max}, AUC, $AUC_{(0-t)}$) was intravenous>SPIRA>I-neb> oral. No significant differences were observed in exposure parameters between healthy volunteers and patients with mild allergic asthma for any of the 4 treatments.

The geometric mean of $t_{½\lambda z}$, CL, and V_z, and V_{ss} in healthy volunteers and patients with mild allergic asthma were similar upon intravenous administration

In healthy volunteers, the geometric mean total absolute bioavailability of AZD5423 following inhalation via I-neb®, inhalation via SPIRA and following oral administration was 23.8%, 42.5 %, and 3.16% respectively. In asthma patients, the geometric mean total absolute bioavailability following inhalation via I-neb®, inhalation via SPIRA and following oral administration in asthma patients was 25.6%, 48.5%, and 3.27% respectively. In both the healthy volunteers as well as patients with mild asthma, with both the SPIRA and I-neb® systems the pulmonary bioavailability was almost equal to the total absolute bioavailability with a low fraction (<3%) of the dose being delivered by the oral route.

The peak and total exposure (C_{max} and AUC) of AZD5423 was about 2-fold greater following inhalation with SPIRA as compared to I-neb® in both healthy volunteers as well as patients with mild allergic asthma. Since there were no marked differences in the PK of AZD5423 between healthy volunteers and patients with mild allergic asthma, a combined analysis was performed (pooling the data from healthy volunteers and asthma patients) which displayed a similar 2-fold difference in the AZD5423 exposure parameters with SPIRA as compared to I-neb®.

Summary of safety results

No deaths, serious adverse events (SAEs), or discontinuations due to AEs (DAEs) were reported. All AEs reported were mild in intensity.

The highest number of subjects reported at least 1 AE after receiving the inhalation via SPIRA (6 subjects [50%]: 1 healthy volunteer and 5 asthmatic patients). After all 4 treatments, the number of asthmatic patients who reported AEs was higher than the number of healthy volunteers.

Overall, the most frequently reported AEs were headache (1 healthy volunteer and 1 asthmatic patient, inhalation via SPIRA: 1 healthy volunteer and 2 asthmatic patients, and oral administration: 1 asthmatic patient) and dizziness (inhalation via SPIRA: 1 asthmatic patient, and inhalation via I-neb®: 1 asthmatic patient).

The only AEs reported by healthy volunteers were nausea and headache.

No clinically relevant differences were noted for the clinical chemistry, haematology, or urinalysis variables. No clinically relevant differences were noted for vital signs or spirometry variables. No clinically significant ECGs were reported.