AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00005
Edition Number	1
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A Double-Blind, Double-Dummy, Randomised, Placebo-Controlled, 4-Way Crossover, Multi-Centre Phase II Study with Budesonide as an Active Control to Evaluate the Efficacy and Safety of 2 Doses of Inhaled AZD5423 Over 7 Days in Patients with Mild Allergic Asthma Challenged with an Inhaled Allergen

Study dates: First patient enrolled: 8 November 2010
Last patient last visit: 21 December 2011

Phase of development: Therapeutic exploratory (IIa)

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

Study centres

The study was conducted at 4 centres.

Publications

None.

Objectives and criteria for evaluation

The study objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective was to determine the efficacy of AZD5423 on allergen-induced responses in patients with mild allergic asthma.	**Primary variable** 1. Maximum % fall in FEV_1 3-7 h (LAR) post-allergen challenge. **Secondary variables** 1. Maximum % fall in FEV_1 0-3h (EAR) post-allergen challenge. 2. AUC for FEV_1 over 0-3 and 3-7 h post-allergen challenge. 3. Methacholine PC_{20} before and at 24 h post-allergen challenge. 4. Changes in sputum eosinophils (percentage and absolute numbers) at 7 h and 24 h post-allergen challenge.	Efficacy /PD
Secondary	**Secondary**	
To investigate the effects of AZD5423 by assessment of: 1. Sputum cells other than eosinophils at 7 hours and 24 hours post-allergen challenge (percentage and absolute numbers). 2. White blood cells (WBC) at 7 hours and 24 hours post allergen challenge; full differentials (percentage and absolute numbers). 3. Sputum cells after the 5th dose (percentage and absolute numbers). 4. WBC after the 5th dose; full differentials (percentage and absolute numbers). 5. Drug effects on HPA-axis and bone metabolism after the 7th dose; S-DHEAS and S-osteocalcin.	1. Neutrophils and lymphocytes (percentage and absolute numbers). 2. WBC; full differential (eosinophils, neutrophils, lymphocytes, monocytes, and basophils [percentage and absolute numbers]). 3. Eosinophils, neutrophils and lymphocytes after 5th dose (percentage and absolute number). 4. WBC; full differential (eosinophils, neutrophils, lymphocytes, monocytes, and basophils) (percentage and absolute numbers). 5. S-DHEAS and S-osteocalcin.	Efficacy /PD

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To evaluate the safety of 7 days repeated dosing with AZD5423 by assessment of the nature and incidence of AEs, clinical laboratory assessments (haematology, clinical chemistry, urinalysis), physical examination, pulse and blood pressure, ECG and spirometry.	AEs, clinical laboratory assessments (haematology, clinical chemistry, and urinalysis), physical examination, pulse and blood pressure, ECG and spirometry.	Safety
To investigate drug exposure of AZD5423 in patients with mild allergic asthma by assessment of plasma concentrations of AZD5423.	AZD5423 plasma concentrations at 1 hour and 8 hours after dose (Day 6), pre-dose concentrations on Day 1, Day 6, Day 7, and concentration immediately after dose on Day 5.	PK

Results from the exploratory analyses are not reported in the CSR.
Abbreviations:FEV_1 Forced Expiratory Volume in 1 second, EAR Early Allergic Response 0 to 3 h; PK Pharmacokinetic; PD Pharmacodynamic; LAR Late Allergic Response 3 to7 h; AUC Area Under Curve Concentration; HPA axis Hypothalamus-Pituitary-Adrenal axis; S-DHEAS Dehydroepiandrosterone Sulfate; S-osteocalcin Serum Osteocalcin.

Study design

This study was double-blind, double-dummy, randomised, placebo-controlled, 4-way cross-over design with budesonide as an active control to evaluate the efficacy of AZD5423 in patients with mild allergic asthma challenged with an inhaled allergen.

Target subject population and sample size

Target patient population for this study was patients with mild allergic asthma, who were not using regular asthma controller medication, and had confirmed late allergic response (LAR). For randomisation at Visit 3, patients had to have airway hyper-responsiveness equivalent to methacholine PC_{20} ≤16 mg/mL at Visit 2 and positive skin prick test to common aeroallergens at Visit 1 or 2. Another important criterion to be met by patients was that the patients had to have confirmed positive allergen induced early and late airway bronchoconstriction (≥20% fall in Forced Expiratory Volume in 1 second [FEV_1] for the Early Allergic Response [EAR] over 0 to 3 hours and ≥15% for the LAR over 3 to 7 hours).

Sample size was based on data from previously published allergen challenge and assuming an analysis on linear scale. Estimating the standard deviation of the differences to 16% and the mean minimum LAR in the placebo group to 25% in order to detect a 50% attenuation of the minimum LAR with 90% power and a 5% two-sided significance level, 20 patients were planned to be randomised. Of the 27 patients enrolled, 20 (74.1%) patients were randomised to receive a treatment sequence consisting of 4 different treatments in random order.

Investigational product and comparators: dosage, mode of administration and batch numbers

Investigational Product (IP): The IPs used in this study were 75 µg and 300 µg AZD5423 (predicted lung-deposited dose) administered once daily (od) as nebuliser suspension. A total of 4 batches were used for 75 µg and 300 µg AZD5423. Individual batch numbers and further information is included in the Clinical Study Report (CSR).

Comparator: The comparator drugs used in this study were:

- 200 µg budesonide metered dose administered via Pulmicort Turbuhaler® administered twice daily (bd).
- Placebo for AZD5423 was administered od, as nebuliser solution. Placebo for budesonide was administered bd, as dry powder for inhalation.

A total of 4 batches were used for 200 µg budesonide, placebo for budesonide, and placebo for AZD5243. Individual batch numbers and further information is included in the CSR.

Each patient received following 4 different treatments in random order for 7 consecutive days:

- AZD5423 75 µg od (predicted lung-deposited dose)+placebo for budesonide bd.
- AZD5423 300 µg od (predicted lung-deposited dose)+placebo for budesonide bd.
- Budesonide 200 µg bd (metered dose)+placebo for AZD5423 od.
- Placebo for AZD5423 od+placebo for budesonide bd.

All the investigational and comparator products were manufactured by AstraZeneca.

Reliever Medication: All patients were prescribed a short-acting β_2-agonist (SABA) and/or a short-acting anticholinergic drug to be used as reliever medication during the study period.

Duration of treatment

Patients were randomised to receive a treatment sequence consisting of 4 different treatments in random order for 7 consecutive days. Each treatment period was followed by a wash-out period of 2 to 3 weeks.

Statistical methods

Efficacy/PD analysis: The primary outcome variable for LAR was the maximum percent fall in FEV_1 over 3 to 7 hours (LAR). The pre-defined outcome variable for this was the minimum FEV_1 over 3 to 7 hours post-AC, as percentage of pre-AC FEV_1 value. AZD5423 (300 µg and 75 µg) was compared to placebo using a closed testing procedure as follows: first the highest dose of AZD5423 was compared to placebo; if this was statistically significant the lowest dose of AZD5423 was compared to placebo. Secondarily, budesonide was compared to placebo; the higher dose of AZD5423 was compared to the lower dose and finally AZD5423 was compared to budesonide. The statistical model used was Analysis of Variance (ANOVA) on the log transformed outcome variable with patient, treatment and period as factors and baseline FEV_1 (pre-treatment) as covariate. The analyses were performed using pharmacodynamic (PD) analysis set. All the other secondary PD variables such as maximum percentage fall in FEV_1 over 0 to 3 hours (EAR), average percentage fall in FEV_1 (AUC) based LAR and EAR, methacholine $PC_{20,}$ blood and sputum cells were analysed in the same

way as the primary variable using PD analysis set. The maximum and average (AUC) percentage fall in FEV_1 for EAR and LAR was analysed and presented as minimum and average percentage of FEV_1 remaining post-AC compared to pre-allergen challenge (pre-AC).

Pharmacokinetic (PK) analysis: The PK was evaluated by non-linear mixed effect modelling. The exposure (AUC) of AZD5423 in the patients was predicted. Plasma concentrations were summarised using descriptive statistics (geometric mean, coefficient of variation (CV [%]), min, median, and max) for each dose level.

Safety: Safety and tolerability data is described using descriptive statistics and qualitative analysis using safety analysis set.

Subject population

A total of 27 patients were enrolled from 4 centres in the AllerGen CIC group in Canada. Out of these patients, 20 (74.1%) patients were randomised to receive a treatment sequence consisting of 4 different treatments in random order. Of the 20 randomised patients, 18 (90%) patients completed the study and 2 (10%) patients were withdrawn from the study due to consumption of disallowed medications. A total of 19 patients completed each individual treatment period and 17 patients completed all 4 treatment periods according to assigned treatment sequence. The demographic and baseline characteristics of patients were in line with the inclusion and exclusion criteria as defined in the Clinical Study Protocol (CSP). However, 1 patient (E1002003) had not met an inclusion criterion for randomisation (ie, a fall in FEV_1 by $\geq$15 for LAR), yet this patient was included in the study. This patient was classified under important protocol deviation.

Summary of pharmacokinetic results

The daily exposure of AZD5423 measured as geometric mean (Coefficient of Variation [CV%]) of AUC during Days 5 to 7 was predicted to 1.77 nmol*h/L (26%) and 7.16 nmol*h/L (26%) at the 75 µg and 300 µg predicted lung-deposited dose level, respectively. No dose dependency in predicted AUC was indicated.

Summary of pharmacodynamic results

Primary variable of primary objective:

Maximum percentage fall in FEV_1: The primary outcome variable for LAR was the maximum percent fall in FEV_1 over 3 to 7 hours (LAR). The pre-defined outcome variable for this was the minimum FEV_1 over 3 to 7 hours post-AC, as percentage of pre-AC FEV_1 value. The result of primary analysis is presented in Table S2. The analysis demonstrated that a 6 day treatment with AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) showed a statistically significant attenuation of LAR in terms of maximum percentage fall in FEV_1 compared to placebo.

Table S2 Comparison of LAR; as minimum percentage of FEV_1 remaining 3 to 7 hours post-AC compared to pre-AC FEV_1 (PD analysis set)

Comparison	N	Geometric mean estimate	Ratio between groups Geometric mean ratio	95% CI	p-value
300ug AZD5423 vs Placebo	19 vs 19	91.31 vs 86.01	1.06	(1.00,1.12)	0.0339
75ug AZD5423 vs Placebo	19 vs 19	91.30 vs 86.01	1.06	(1.00,1.12)	0.0331
2x200ug budesonide vs Placebo	19 vs 19	87.47 vs 86.01	1.02	(0.96,1.08)	0.5555
300ug AZD5423 vs 75ug AZD5423	19 vs 19	91.31 vs 91.30	1.00	(0.95,1.06)	0.9972
300ug AZD5423 vs2x200ug budesonide	19 vs 19	91.31 vs 87.47	1.04	(0.99,1.10)	0.1205
75ug AZD5423 vs 2x200ug budesonide	19 vs 19	91.30 vs 87.47	1.04	(0.99,1.10)	0.1319

The statistical model was ANCOVA on the log transformed outcome variable with patient, treatment and period as factor, and baseline FEV_1 (pre-treatment) as covariate.

Abbreviations: ANCOVA Analysis of Covariance; FEV_1 Forced Expiratory Volume in 1 second, PD Pharmacodynamic; Pre-AC Pre-Allergen Challenge; Post-AC Post-Allergen Challenge.

Secondary variables of primary objective: The analyses of secondary variables of primary objective demonstrated following results:

Average (AUC) percentage fall in FEV_1: A 6 day treatment with AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) showed a statistically significant attenuation of LAR in terms of average percentage fall in FEV_1 compared to placebo. The Geometric Mean Ratio (GMR) of comparison between 300 µg AZD5423 vs placebo was 1.04 (95% CI 1.01, 1.08; p=0.0266). The GMR of comparison between 75 µg AZD5423 vs placebo was 1.04 (95% CI 1.00, 1.08; p=0.0301).

Early allergic response: A 6 day treatment with AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) did not show a statistically significant attenuation of EAR in terms of maximum and average percentage fall in FEV_1 compared to placebo.

Methacholine PC_{20}: The methacholine PC_{20} analyses demonstrated that a 7 day treatment with AZD5423 (300 µg od, predicted lung-deposited dose) showed a statistically significant attenuation of allergen induced airway hyper-responsiveness vs placebo as assessed by methacholine PC_{20}, 24 hours post-AC, as compared to baseline. The GMR of comparison between 300 µg AZD5423 vs placebo was 1.58 (95% CI 1.09, 2.29; p=0.0166).

Percentage of sputum eosinophils: Treatment with AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) statistically significantly attenuated the mean increase from baseline in percentage of sputum eosinophils at 7 hours (Day 6) and 24 hours (Day 7) post-AC compared to placebo. At Day 7 (24 hours post-AC), the differences in Least Square Mean (LSM) of comparison between 300 µg AZD5423 vs placebo was -5.04% (95% CI -8.43,

-1.65; p=0.0047). The differences in LSM of comparison between 75 µg AZD5423 vs placebo was -3.78% (95% CI-6.84, -0.71; p=0.0172). At Day 6 (7 hours post-AC), the differences in LSM of comparison between 300 µg AZD5423 vs placebo was -9.10% (95% CI -14.71, -3.50; p=0.0023). The differences in LSM of comparison between 75 µg AZD5423 vs placebo was -8.79% (95% CI -14.14, -3.43; p=0.0021).

Absolute values of sputum eosinophils: In line with the findings for percentage of the sputum eosinophils, treatment with AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) was associated with lower absolute count of sputum eosinophils at 7 hours (Day 6) and 24 hours (Day 7) post-AC compared to placebo.

Variables of secondary objectives:

Sputum cells other than eosinophils and blood cells: The analyses of variables for secondary objectives demonstrated that AZD5423 (300 µg and 75 µg, od, predicted lung-deposited dose) did not show a significant effect on sputum neutrophils and white blood cells on Day 5 (post-dose), and at 7 hours (post-dose, [Day 6]) and 24 hours (post-dose, [Day 7]) post-AC. The results of mean percentage and absolute values of sputum lymphocytes were inconclusive as only few lymphocytes were obtained in sputum samples of patients as measured on Day 5, Day 6, and Day 7.

S-DHEAS and S-Osteocalcin: A 7 day treatment with AZD5423 (300 µg od, predicted lung-deposited dose) did not show a statistically significant change in the concentrations of S-DHEAS and S-osteocalcin as compared to placebo.

Summary of pharmacogenetic results

Results of the pharmacogenetic analyses are not reported in this CSR synopsis.

Summary of safety result

The overall safety results (including AEs reported in active and wash-out/follow-up period) demonstrated that 7 days treatment with AZD5423 (75 µg and 300 µg, od, lung-deposited dose) was safe and well tolerated. No important differences in mean exposure time between the treatment periods were found. The mean duration of exposure was 7 days during active treatment periods (300 µg AZD5423, 75 µg AZD5423, and 2x200 µg budesonide) and 6.9 days for placebo treatment period.

No clinically important differences were seen between treatments periods with regards to number of patients with at least 1 AE. However, the lowest frequency of AEs was reported by patients during AZD5423 300 µg treatment period. There were no deaths, serious adverse events (SAEs), discontinuation of investigational product due to adverse events (DAEs) or other significant adverse events (OAEs) reported in this study. The most commonly reported AEs by preferred term during each treatment period were nasal congestion and oropharyngeal pain (2 [10%] patients each) during placebo; bronchitis (2 [10.5%] patients) during 2x200 µg budesonide; headache and oropharyngeal pain (2 [10.5%] patients each) during 75 µg AZD5423; drug eruption and helicobacter test positive reported by a single patient

(E1002001) during 300 µg AZD5423. Oropharyngeal pain was the only AE of severe intensity reported in this study by 1 patient (E1004005) during placebo treatment period. In total, 8 AEs considered causally related to the investigational product by the investigator were reported. Six of these events were reported by same patient E1003003. This patient reported dry mouth, dysphagia, and oropharyngeal pain after both 75 µg AZD5423 and 2x200 µg budesonide treatment periods. There were no clinically relevant safety findings noted in laboratory evaluations, vital signs, ECG, spirometry, and physical findings.