AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D3320C00001
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A Single-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Phase IIa Study to Investigate the Effects of 100 mg AZD2423 as an oral tablet in Subjects with Mild COPD Following Segmental Endobronchial LPS Instillation. Eudract number 2010-020141-26

Study dates: First subject enrolled: 01 October 2010
Last subject last visit: 28 July 2011

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the effect of a 11 day oral treatment of AZD2423 100 mg on the influx of monocytes into BAL fluid following segmental LPS challenge in subjects with mild COPD	Absolute monocyte count in BAL	Efficacy
Secondary	**Secondary**	
To evaluate the effects of AZD2423 on monocyte infiltration, general inflammation and inflammatory phenotype in endobronchial biopsies	Inflammatory cell infiltrate and inflammatory phenotype in biopsies	Efficacy
To investigate the effect of AZD2423 on inflammatory cells and mediators in the blood and BAL fluid	Leucocyte differentials in BAL COPD biomarker concentrations in BAL (TNF-α, MCP-1, IL-1β, IL-6, IL-8, RANTES, SP-D and CC16) COPD biomarker concentrations in blood (SAA, MCP-1, IL-1β, IL-6, IL-8, TNF-α, SP-D and CC16) Cell differentials (including monocytes) in blood	Efficacy
To explore the pharmacokinetics of AZD2423 in subjects with COPD	AZD2423 concentration in plasma assessed by: • Maximum plasma concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the plasma concentration-time curve at steady state from zero to 24 h ($AUC_{(0-24)}$) • Area under the plasma concentration-time curve at steady state from zero to 8 h ($AUC_{(0-8)}$)	Pharmaco-kinetic (PK)
To investigate the safety and tolerability of AZD2423 in subjects with COPD	Adverse events, haematology, clinical chemistry (including standard CRP), coagulation panel, urinalysis, vital signs, 12-lead ECG, physical examination, spirometry (FEV_1, FVC pre-bronchodilator), body temperature and weight	Safety

BAL Bronchoalveolar lavage; CC16 Clara cell protein; CRP C-Reactive protein; FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity; IL-1β Interleukin 1β, IL-6 Interleukin 6; IL-8 Interleukin 8; MCP-1 Ligand for CCR2b receptor, also known as CCL2; RANTES A member of the IL-8 interleukin cytokine family; SAA Serum Amyloid-A; SP-D Surfactant Protein D; TNF-α Tumour necrosis factor-alpha

Study design

This was a single-centre, randomised, double-blind, placebo-controlled, parallel group, Phase IIa study to investigate the effects of AZD2423 following segmental endobronchial LPS instillation in patients diagnosed with GOLD Stage I Chronic Obstructive Pulmonary Disease (COPD).

Target subject population and sample size

The target population was male and/or female subjects of non-childbearing potential, aged ≥40 years of age, with a clinical diagnosis of mild COPD (GOLD stage I). Patients had to have FEV_1 ≥80% of the predicted normal value and FEV_1/FVC <70% post-bronchodilator at Visit 1.

It was planned to randomise approximately 44 patients to achieve at least 36 patients completing the study (18 per treatment group). This was considered sufficient to detect a difference of 40% between the 2 treatments for the monocytes in BAL fluid following segmental LPS challenge; assuming a coefficient of variation of 50%, it would be possible to demonstrate an effect at a 5% level one-sided test with power 80%.

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

Details of the investigational product are presented in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number
AZD2423	50 mg tablet 2 tablets taken orally once daily (100 mg)	AZ R&D Charnwood	D1000076	10-003900AZ 10-005266AZ 11-000173AZ
Placebo	Tablet to match 50 mg AZD2423 active tablet 2 tablets taken orally once daily	AZ R&D Charnwood	D1000225	10-004415AZ 10-004661AZ 10-005777AZ

Duration of treatment

Patients received an oral dose of 100 mg AZD2423 (2 x 50 mg tablets) once daily, for a period of 11 to 13 days.

Statistical methods

To evaluate the effect of AZD2423 compared to placebo on the primary endpoint, post-LPS monocyte count in BAL, an analysis of covariance (ANCOVA) was fitted to data with log (post-LPS monocyte count in BAL) as a response variable, log (pre-LPS monocyte count in BAL) as a continuous covariate, and treatment as a factor with 2 levels (placebo as reference).

As a sensitivity analysis, the same ANCOVA was fitted to the data but without the pre-LPS monocyte count in BAL as a covariate.

As the study was exploratory in nature, a p-value (2-sided) of <0.1 was considered significant. A 2-sided 90% confidence interval was constructed for the treatment difference and p-values given. The focus of this study was to estimate the treatment effect and as such no adjustments for multiple comparisons were performed.

The efficacy analysis set comprised all subjects randomised into the study, who had received at least one dose of study medication and had at least baseline and one piece of post challenge efficacy data. The safety analysis set included all subjects who received at least one dose of AZD2423/placebo and for whom post-dose safety data were available. Both analysis sets were analysed according to the treatment the patients actually received. In addition, a PK analysis set was defined after finalisation of the protocol. This analysis set was based on all subjects who received AZD2423 with adequate sampling and treatment compliance, and included all evaluable PK data appropriate for the evaluation of interest (with no major protocol deviations or violations thought to significantly affect the PK of the drug).

Subject population

The patient disposition and analysis sets are presented in Table S3.

Table S3 Patient disposition and analysis sets

	Number (%) of patients		
	Placebo	**AZD2423 100 mg**	**Total**
Patients enrolled[a]			71
Patients randomised	22 (100.0)	22 (100.0)	44 (100.0)
Patients who received treatment	22 (100.0)	22 (100.0)	44 (100.0)
Patients who completed treatment and study	19 (86.4)	21 (95.5)	40 (90.9)
Patients who discontinued treatment and study	3 (13.6)	1 (4.5)	4 (9.1)
Adverse event	1 (4.5)	1 (4.5)	2 (4.5)
Development of study-specific withdrawal criteria	1 (4.5)	0 (0.0)	1 (2.3)
Subject decision	1 (4.5)	0 (0.0)	1 (2.3)
Patients included in efficacy analysis set	19 (86.4)	20 (90.9)	39 (88.6)
Patients included in safety analysis set	22 (100.0)	22 (100.0)	44 (100.0)
Patients included in PK analysis set	0 (0)	22 (100.0)	22 (50.0)

[a] Informed consent received.

All patients had mild COPD (GOLD stage I). The mean age of patients in the study was 52.9 years. All patients were White. There was an imbalance in gender between the 2 treatment groups, with only 9% of patients in the AZD2423 group being female, compared to 41% in the placebo group.

Overall, the patient characteristics represented a COPD population as intended for this study.

Summary of efficacy results

A summary of the monocyte counts in BAL (the primary variable) at Visits 4 and 5 is provided in Table S4, and the analysis of the post-challenge data (adjusted for pre-challenge) is presented in Table S5.

Table S4 Summary of monocyte count (x10^4 cells/mL) in bronchoalveolar lavage (Efficacy analysis set)

Treatment	Visit	N	Gmean	CV (%)	Mean	SD	Median
Placebo	4	18	18	236.3	53	130.6	19
	5 LPS	19	511	166.3	779	614.5	544
	5 Saline	19	28	163.2	53	69.1	20
AZD2423	4	20	20	167.8	30	30.8	21
	5 LPS	20	415	118.8	548	327.4	523
	5 Saline	20	32	172.9	48	36.4	53

Table S5 Analysis of post-LPS monocyte count in bronchoalveolar lavage (Visit 5), adjusting for pre-challenge (Efficacy analysis set)

	Placebo			AZD2423 100mg			Ratio of AZD2423 to Placebo			
Variable	N	LSMean	(SE)	N	LSMean	(SE)	LSMean	(SE)	90% CI	P-value
Monocytes (x10^4 cells/mL)	19	514.4	1.284	20	398	1.276	0.773	1.418	(0.429, 1.397)	0.4677

Adjustment is made for Visit 4, Day 10 pre-challenge. The log-transformed biomarker data are analysed using analysis of covariance, using log(pre-challenge) as covariates. Estimates and ratios are then back-transformed. A ratio less than 1 represents a reduction due to AZD2423.

The ratio of the post-challenge monocyte count in BAL between the AZD2423 and placebo treatment groups was 0.773, indicating a 23% reduction due to AZD2423, although not statistically significant (p=0.4677). No treatment effect was detected in the analysis of monocyte counts at pre-challenge Visit 4.

In general, with the exception of CCL2, there was no effect of AZD2423 100 mg compared to placebo on any of the secondary variables measured: endobronchial biopsy biomarkers, inflammatory cell differentials and COPD biomarkers in blood or BAL fluid. There was an increase in CCL2 levels in blood and BAL in both the AZD2423 and placebo groups following LPS challenge, with the increase being greater in the AZD2423 group.

Summary of pharmacokinetic results

In total, 22 patients provided plasma samples and 21 patients were included in the evaluation of PK at Visit 4.

In general, the PK was characterised by rapid absorption with a median t_{max} at 0.3 hours after dosing. The geometric mean C_{max} was 229 nmol/L and the highest individual plasma concentration of AZD2423 observed was 655 nmol/L. It was not possible to calculate $AUC_{(0-24)}$ using actual data, since the extrapolated area (and thus the uncertainty) was too high; $AUC_{(0-24)}$ was therefore calculated using the pre-dose sample at steady state as 24 hours.

The geometric mean $AUC_{(0-24)}$ was 1454 nmol*h/L and the highest individual value was 2259 nmol*h/L. The C_{min} values indicated that steady state had been reached at Visit 4. The variability in exposure in terms of C_{max} and $AUC_{(0-24)}$ was intermediate to high with CV of 50% and 26%, respectively.

Based on previous studies with AZD2423, the exposure obtained after a 100 mg dose in the present study was as expected.

Summary of safety results

There were no deaths during the study. Three patients in the placebo group reported SAEs during the study (haemoptysis, hypoxia, procedural pain). The AE of procedural pain led to discontinuation of the investigational product for that patient. There was also one AE that led to discontinuation of the investigational product in a patient in the AZD2423 group (myocardial ischaemia). There were no other significant AEs.

In the AZD2423 group, 12 patients reported 31 AEs compared with the placebo group where 20 patients reported 37 AEs. AEs occurred most frequently in the 'respiratory, thoracic and mediastinal disorders' SOC (7 patients [31.8%] in the AZD2423 group and 9 patients [40.9%] in the placebo group). Cough was the most frequently reported AE (6 patients [27.3%] in the AZD2423 group and 3 patients [13.6%] in the placebo group). Eight patients reported AEs in the 'gastrointestinal disorders' SOC – 5 patients (22.7%) in the AZD2423 group and 3 (13.6%) in the placebo group. Within this SOC, diarrhoea was the most commonly reported AE (3 patients [13.6%] in each group). The majority of AEs were mild or moderate in intensity. Six patients reported severe AEs: 5 patients (23%) in the placebo group (AEs of: COPD, circulatory collapse, gingival infection, haemoptysis, nausea, procedural pain, vomiting) and one patient (5%) in the AZD2423 group (dry mouth). Adverse events were considered by the Investigator to be causally related in a total of 9 patients (5 patients [23%] in the AZD2423 group and 4 patients [18%] in the placebo group).

With the exception of CRP levels, which increased in both treatment groups during the study, there were no clinically significant changes in any laboratory values over time and no individual clinically important abnormalities.

There were no notable changes in vital signs or ECG over time, no notable differences between the treatment groups, and no individual clinically important abnormalities.

Conclusion(s)