AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D3320C00002
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A 4-week, Double-Blind, Placebo-Controlled, Randomised, Parallel group, Multi-Centre, Phase IIa Study to Investigate the Tolerability and Safety of 100 mg Oral AZD2423 in Patients with Moderate to Severe COPD

Study dates: First patient enrolled: 11 October 2010
Last patient last visit: 08 March 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

This study involved 11 centres in 2 countries: 5 in Bulgaria and 6 in Slovakia.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and the 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 tolerability and safety of a 4-week oral treatment of AZD2423 100 mg in patients with moderate and severe COPD	Clinical chemistry, haematology, urinalysis, physical examination, vital signs, ECG, adverse events	Safety
Secondary	**Secondary**	
To evaluate the effects of AZD2423 compared to placebo in patients with COPD, as measured by lung function, symptoms, HRQL questionnaires and inflammatory mediators (CCL2 and SAA).	Lung function: • FEV_1, FVC, $FEF_{25-75\%}$, IC at clinic (pre-bronchodilator) • Morning and evening FEV_1 and PEF (daily at home) Symptoms and HRQL • Daily EXACT (evening) • Daily BCSS (evening) • Rescue medication (recorded daily morning and evening) • SGRQ-C at clinic COPD biomarker concentrations in blood including but not limited to CCL2 and SAA.	Efficacy
To investigate the pharmacokinetics of AZD2423 in patients with COPD	Population PK model parameter estimates, including exposures, derived from plasma concentrations of AZD2423	PK

Abbreviations: COPD Chronic Obstructive Pulmonary Disease; ECG Eclectrocardiogram; HRQL Health Related Quality of Life; CCL2 Chemokine Ligand for CCR2; SAA Serum Amyloid-A; FEV_1 Forced Expiratory Volume in 1 second; FVC Forced Vital Capacity; $FEF_{25-75\%}$, Forced Expiratory Flow between 25% to 75% of Vital Capacity; IC Inspiratory Capacity; PEF Peak Expiratory Flow; EXACT Exacerbations of Chronic pulmonary disease Tool; BCSS Breathlessness, Cough and Sputum Scale; SGRQ-C St George's Respiratory Questionnaire for COPD; PK Pharmacokinetic
Exploratory objectives will be reported separately from this CSR.

Study design

This was a multi-centre, randomised, double-blind, placebo-controlled, parallel group study.

Target subject population and sample size

Male and/or female patients of non-childbearing potential, aged between 40 to 80 years, with a clinical diagnosis of moderate to severe COPD (Global Initiative on Obstructive Lung Disease [GOLD] stage II-III) and the total COPD symptom score ≥2 per day for at least 7 of the last 14 days before Visit 2 (by totalling breathing, cough, and sputum scores from the BCSS diary) were included in this study.

Eighty patients were planned to be enrolled to achieve randomisation of 60 patients.

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

AZD2423 was supplied as 50 mg tablets with a matching placebo for oral administration. A total daily dose of 100 mg was taken by the patients. Both the active drug and the placebo were manufactured by AZ R&D Charnwood. Batch numbers for AZD2423 100 mg were 10-004767AZ and 10-005266AZ and that of placebo was 10-004661AZ.

Duration of treatment

Treatment duration was 4 weeks. Patients returned to the clinic 1-week after the last dose for a follow-up visit.

Statistical methods

The statistical evaluation was conducted by AstraZeneca Statistics and Programming, Mölndal, using SAS® software (Version 9.1).

The primary objective examined the safety variables by investigating the tolerability of a 4-week treatment with AZD2423 100 mg. No formal hypotheses based on statistical or numerical evaluations were associated with these variables, although informal comparisons were made between the treatment groups to determine whether there appeared to be any treatment-related effects: AEs, vital signs, 12-lead ECG, safety laboratory data (clinical chemistry, haematology, and urinalysis), physical examination and concomitant medication. Continuous variables were summarised by descriptive statistics, and categorical variables were summarised in frequency tables. Baseline was the last value prior to first dose. Laboratory results were graphically presented using box and shift plots.

Continuous efficacy endpoints were analysed by fitting an Analysis of Covariance (ANCOVA) to data, adjusting for treatment (as a factor with placebo as reference), country (as a factor), and baseline as a continuous covariate. As the study was exploratory in nature, a p-value of <0.1 was considered significant. A 2-sided 90% confidence interval (CI) for the treatment effect was constructed and its corresponding p-value. For variables with a skewed distribution, data were log-transformed prior to analysis or a non-parametric test (Wilcoxon rank sum) was used instead. No adjustment for multiplicity was applied.

The biomarker data were summarised (geometric mean and coefficient of variation [CV]), the ratio of post challenge means to baseline are included) and listed. The plots produced included: individual patient line plots and box plots both on logged data.

The PK of AZD2423 100 mg was analysed using non-linear mixed effects modelling.

All screening data (including medical and surgical history, etc) as well as drug compliance and exposure data were summarised and listed.

All concomitant medications reported at entry and recorded during the study were listed.

Subject population

The disposition of the patients in this study is summarised in Table S2.

Table S2 Patient disposition

	Number (%) of patients		
	Placebo	**AZD2423 100 mg**	**Total**
Patients enrolled[a]			74
Patients randomized	32 (100.0)	31 (100.0)	63 (100.0)
Patients who were not randomized			11
Eligibility criteria not fulfilled			11
Patients who received treatment	32 (100.0)	31 (100.0)	63 (100.0)
Patients who completed treatment	32 (100.0)	31 (100.0)	63 (100.0)
Patients who completed study	32 (100.0)	31 (100.0)	63 (100.0)

[a] Informed consent received

Seventy four (74) patients were enrolled, of which 63 patients were randomised and received investigational product: 31 in the AZD 2423 100 mg and 32 in the placebo group. All patients who were randomised, completed the study.

All the patients included in this study were White, aged between 44 and 78 years, with a mean age of 62.5 years and 60.6 years for the patients in AZD2423 100 mg and placebo groups, respectively. The study population consisted of COPD patients of whom 35 had moderate (GOLD class II), 27 had severe (GOLD class III), and 1 patient had very severe COPD (GOLD class IV).

The study population was well balanced across the treatment groups and appropriate for evaluation of the objectives.

Summary of efficacy results

There were no primary efficacy variables in this study. The primary objective of the study was safety and tolerability.

A 4- week treatment with AZD2423 100 mg did not change clinic lung function (FEV_1, FVC, $FEF_{25-75\%}$ and IC) and daily lung function (FEV_1, PEF), as compared to placebo.

Treatment with AZD2423 100 mg did not change the scores of the health related quality of life (HRQL) questionnaires (EXACT, BCSS and SGRQ-C) and the usage of daily reliever medication, as compared to placebo.

There was an increase in the blood levels of CCL2 within 1-week of treatment with AZD2423 100 mg. The CCL2 blood levels remained consistently increased over the 4-week treatment period, as compared to the placebo group which was constant over the study period. The blood CCL2 levels decreased after stopping AZD2423 treatment, but had not returned to baseline at the follow-up visit (approximately 1-week after the last dose).

Summary of pharmacokinetic results

In general, the PK in COPD patients was characterised by rapid absorption with time to reach maximum concentration (t_{max}) occurring at approximately 1 hour after dose for AZD2423 100 mg. The variability in exposure to AZD2423 observed in this study was intermediate. The model derived PK parameters in COPD patients were similar to previously observed PK parameters in healthy volunteers.

Summary of safety results

The number of patients who had at least 1 AE in any category is summarised in Table S3.

Table S3 Number (%) of patients who had at least 1 post-dose AE in any category (Safety analysis set)

	Number (%) of patients[a]	
	Placebo (N=32)	AZD2423 100 mg (N=31)
AE category		
Any AE	10 (31.3)	5 (16.1)
Any AE with outcome = death	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	2 (6.3)	0 (0.0)
Any AE leading to discontinuation of treatment	0 (0.0)	0 (0.0)
Any other significant AE[b]	0 (0.0)	0 (0.0)

Abbreviations AE Adverse event; SAE Serious adverse event

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as Other Significant AEs (OAEs).

At least 1post-dose AE was reported by a total of 15 patients across the treatment groups: 5 patients in the AZD2423 100 mg group as compared to 10 patients in the placebo group. A total of 19 AEs were reported: 8 in the AZD2423 100 mg group and 11 in the placebo group.

The most commonly reported AEs in the study were dry mouth (1 and 2 patients in the AZD2423 100 mg and placebo groups, respectively) and headache (1 and 2 patients in the AZD2423 100 mg and placebo groups, respectively). Most of the AEs were mild in intensity.

In the AZD2423 100 mg group, 2 patients reported 4 AEs which were considered by the investigator to be causally related: dry mouth (1), dysgeusia (1), nausea (1) and abdominal discomfort (1).

Two serious adverse events (SAEs), atrial flutter and atrial fibrillation, were reported in this study. The SAEs were reported by 2 patients in the placebo group. There were no deaths, discontinuation due to an AE (DAE) or other significant adverse events (OAE) reported in this study.

A reduction in monocytes count was observed in patients treated with AZD2423 100 mg during the treatment period as compared to placebo (observed after 1-week and sustained until 4-weeks of treatment).

There were no clinically significant changes in laboratory safety parameters or vital signs and ECG assessments for patients receiving AZD2423 100 mg.