AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00011
Edition Number	1
EudraCT Number	2011-005389-39

A Phase II, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multi-Centre Study to Assess the Efficacy and Safety of Two Staggered Dose Levels of Inhaled Once Daily AZD5423 or Twice Daily Budesonide for 12 Weeks in COPD Patients on a Background Therapy of Formoterol

Study dates:	First patient enrolled: 26 April 2012
	Last patient last visit: 29 April 2013
Phase of development:	Therapeutic exploratory (II)

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

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

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the efficacy of inhaled AZD5423 300 µg lung-deposited dose od compared with placebo in COPD patients	• Absolute change from baseline in pre dose FEV_1 • Relative change from baseline in pre-dose FEV_1 (supportive analysis) • Absolute change frombaseline in post-dose FEV_1 and pre- and post-dose FVC • Exacerbations
Secondary	Efficacy	To evaluate the efficacy of inhaled AZD5423 75 µg lung-deposited dose od versus placebo in COPD patients	• Absolute change from baseline in pre-dose FEV_1 • Relative change from baseline in pre-dose FEV_1 (supportive analysis) • Absolute change from baseline in post-dose FEV_1 and pre- and post-dose FVC • Exacerbations
	PRO		• eDiary variables (morning and evening: FEV_1 and PEF; night time awakenings, use of reliever medications, and BCSS), SGRQ-C, and BDI/TDI
	Efficacy	To evaluate the efficacy of inhaled AZD5423 compared with budesonide in COPD patients	• Absolute change from baseline in pre-dose FEV_1 • Relative change from baseline in pre-dose FEV_1 (supportive analysis) • Absolute change from baseline in post-dose FEV_1 and pre- and post-dose FVC • Exacerbations

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	PRO		• eDiary variables (morning and evening: FEV_1 and PEF; night time awakenings, use of reliever medications, and BCSS), SGRQ C, and BDI/TDI
	PD	To evaluate the effect on the HPA-axis of AZD5423	• Relative change from baseline in 24- hour plasma cortisol at Week 4 between AZD5423 75 µg od and budesonide 320 µg 2 doses bid • Relative change from baseline in 24 hour plasma cortisol at Week 12 between AZD5423 300 µg and budesonide 320 µg 2 doses bid
	Biomarker	To evaluate the effect on systemic inflammation	Relative change from baseline in pre-dose hsCRP
	PK	To assess the systemic exposure of AZD5423	C_{max}, t_{max}, AUC_{0-24}, AUC_{0-t}, CL/F, and C_{av}
Safety	Safety	To evaluate the tolerability and safety of AZD5423	AEs, SAEs, laboratory safety data, urinalysis, ECG, vital signs (blood pressure and pulse rate), and physical examination

The exploratory objectives are not included in the CSR synopsis.

AE Adverse Event; AUC_{0-24} Area Under the Plasma Concentration-Time Curve During a Dosing Interval; AUC_{0-t} Area under the plasma concentration-time curve from time 0 to time t; BCSS Breathlessness, Cough, and Sputum Scale; BDI Baseline Dyspnoea Index; C_{av} Average Plasma Concentration; C_{max} Maximum Plasma Concentration; CL/F Apparent Plasma Clearance; COPD Chronic Obstructive Pulmonary Disease; CSR Clinical Study Report; ECG Electrocardiogram; eDiary Electronic Diary; FEV_1 Forced Expiratory Volume in 1 Second; FVC Forced Vital Capacity; HPA-axis Hypothalamic-Pituitary-Adrenal axis; hsCRP High Sensitive C-Reactive Protein; od Once Daily; PD Pharmacodynamics; PEF Peak Expiratory Flow; PK Pharmacokinetics; PRO Patient Reported Outcome; SAE Serious Adverse Event; SGRQ-C St George's Respiratory Questionnaire for COPD Patients; TDI Transitional Dyspnoea Index; t_{max} Time to Maximum Plasma Concentration.

Study design

This was a multi-national, multi-centre Phase II study of a double-blind, placebo-controlled, randomised, parallel-group design with staggered dosing of AZD5423 in Chronic Obstructive Pulmonary Disease (COPD) patients, aged ≥40 years.

All patients who fulfilled the randomisation criteria were randomly assigned (in a ratio of 1:1:1) using an interactive web response system to a 12-week double-blind treatment to

receive any 1 of the following Investigational Products (IPs): 1) AZD5423 via Turbuhaler®[1] (75[2] µg lung-deposited dose once daily [od] for 4 weeks followed by 300[3] µg lung-deposited dose od for 8 weeks), 2) budesonide via Turbuhaler (320 µg [delivered dose], 2 doses twice daily [bid]), 3) placebo via Turbuhaler (2 doses bid), on a background therapy of formoterol 9 µg (delivered dose) bid.

Target subject population and sample size

Male and female patients aged ≥40 years, with a diagnosis of COPD for at least 1 year before Visit 1 (enrolment visit). Any females included were of non-childbearing potential. Patients were required to have a post-bronchodilator Forced Expiratory Volume in 1 second (FEV_1) of ≥40% and ≤80% of the predicted normal value, and a ≥10% increase of FEV_1 in response to bronchodilator.

A total of 315 patients were estimated to be needed to achieve 80% power for the primary comparison, AZD5423 300 µg od versus placebo with regards to change in pre-dose FEV_1, using a 2-sided test at 5% significance level. Patients were randomised in ratio 1:1:1 to the 3 treatment groups.

For the 24-hour plasma cortisol subgroup, assuming a 26% suppression of 24-hour plasma cortisol for AZD5423 300 µg lung-deposited dose od, a sample size of 99 evaluable patients (33 patients per treatment group) was expected to be sufficient. If instead, 29% suppression was assumed for AZD5423 300 µg lung-deposited dose od, a sample size of 150 evaluable patients (50 patients per treatment group) was needed. In same subgroup, 24-hour sampling for PK was also to be performed.

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

Two different doses of AZD5423 (powder form) were inhaled via Turbuhaler od in the morning. The lower dose of 75 µg lung-deposited dose od (batch number: 12-000398AZ), corresponding to 180 µg delivered dose, was inhaled during the first 4 weeks of treatment. This was followed by inhalation of the higher dose of 300 µg lung-deposited dose od (batch number: 12-000289AZ), corresponding to 800 µg delivered dose, for a further 8 weeks. Lung deposited dose is the predicted dose deposited in the lungs based on in vitro data for the inhaler and an assumed breathing pattern.

[1] Turbuhaler is a trademark of the AstraZeneca group of companies.

[2] AZD5423 75 µg lung-deposited dose od corresponds to 180 µg delivered dose. In the result section, data are presented as per the delivered dose.

[3] AZD5423 300 µg lung-deposited dose od corresponds to 800 µg delivered dose. In the result section, data are presented as per the delivered dose.

In the Clinical Study Report, all data in the result sections are presented as per delivered dose. The delivered dose was chosen since it could be measured and not estimated and since it has been used in other studies. The delivered dose stated above is a target delivered dose. The actual delivered doses had been assessed to be 196 µg and 912 µg, these doses were used in the Pharmacokinetic (PK) calculations.

Both active comparator and placebo were used in the study. Depending on randomisation, patients received budesonide 320 µg (delivered dose) 2 doses bid (batch number: 11-003373AZ) or placebo (batch number: 11-003374AZ). Both comparators were inhaled via Turbuhalers for 12 weeks of the study treatment on a background therapy of formoterol 9 µg bid (batch numbers: 12-000694AZ and 12-001716AZ).

Duration of treatment

The total study period per patient was about 17 to 23 weeks. The study included 4 periods; screening period (between enrolment on Visit 1 and confirmation of eligibility on Visit 2), 4 weeks run-in period (after Visit 2 until randomisation), 12 weeks of treatment period and 1 week of follow-up period.

Statistical methods

All hypothesis testing and confidence intervals were 2-sided at 5% significance level if not otherwise stated. Formal hypothesis testing was performed for the primary and the secondary analyses comparisons of 24-hour plasma cortisol suppression in a subgroup of patients using 2-sided tests at 5% significance level. In order to preserve the family wise type I error rate at 5%, testing of the primary and secondary endpoints of 24-hour plasma cortisol suppression was carried out in a sequential manner.

The sequence of the hypothesis testing of the primary and secondary endpoints was:

1. AZD5423 300 µg lung-deposited dose was superior to placebo with regard to change from baseline in average pre-dose FEV_1 at Week 8 to 12.

2. AZD5423 75 µg lung-deposited doses od were superior to budesonide 320 µg (delivered dose) 2 doses bid with regard to 24-hour plasma cortisol suppression after 4 weeks of dosing.

3. AZD5423 300 µg lung-deposited doses od were superior to budesonide 320 µg (delivered dose) 2 doses bid with regard to 24-hour plasma cortisol suppression after 12 weeks of dosing.

If statistical significance was not achieved at any point, the p-value for the subsequent endpoint could not be interpreted in terms of statistical significance. However, point estimates, 95% Confidence Intervals (CIs), and nominal p-values were to be presented for all comparisons even if they came after a point where formal hypothesis testing was not performed.

The primary analysis of comparison was the absolute change from baseline in pre-dose FEV_1 at Week 8 to 12 between AZD5423 300 μg and placebo, and was analysed using a baseline-adjusted analysis of covariance (ANCOVA) model, including treatment and country as factors and baseline FEV_1 as covariate. The results from ANCOVA models were presented as Least Square (LS) means estimates and 2-sided 95% CIs and p-values for mean changes from baseline between the treatments. In addition to the main analysis, a supporting analysis was performed on the relative change from baseline in pre-dose FEV_1. As sensitivity analysis, a Mixed Model Repeated Measure (MMRM) analysis was used to analyse absolute change from baseline in pre-dose FEV_1 to each time point, Weeks 8, 10, and 12.

Pharmacokinetics of AZD5423 was evaluated by non-compartmental analysis in a subgroup of patients and Pharmacokinetic (PK) variables were summarised by descriptive statistics.

The diary variables (COPD symptoms, use of reliever medication, FEV_1 and Peak Expiratory Flow [PEF] in the morning and evening, and night-time awakenings) were analysed as continuous data, comparing mean changes from baseline to the average of the double-blind treatment period between the treatments. Counts and percentage for categorical variables were presented.

The safety assessment was performed based on Adverse Events (AEs), laboratory safety data, urinalysis, Electrocardiogram (ECG), vital signs (blood pressure and pulse rate), and physical examination.

Subject population

A total of 482 patients were enrolled, of which 353 patients were randomised to the respective treatments at Visit 3. Of all the randomised patients, only 348 patients received at least1 dose of the IP (117 [98.3%], 116 [99.1%], and 115 [98.3%] patients received AZD5423, budesonide, and placebo, respectively). There were 5 patients who did not receive any treatment: 2 patients each from the AZD5423 and placebo groups were withdrawn due to study criteria not fulfilled and 1 patient from budesonide group was withdrawn due to patient's decision. A total of 31 patients (13 [10.9%] patients in AZD5423 group, 8 [6.8%] patients in budesonide group, and 10 [8.5%] patients in the placebo group) discontinued the study; the most common reason for discontinuation was AE (5 [4.2%] patients in AZD5423 group, 2 [1.7%] in budesonide group, and 5 [4.3%] patients in the placebo group).

Of the 353 patients randomised to receive treatment, 163 patients were part of the subgroup for the 24-hour plasma cortisol and 24-hour PK sampling.

The demographic and patient characteristics of the studied population were balanced across the treatment groups and generally consistent with the eligibility requirements, as stipulated in the Clinical Study Protocol.

Summary of efficacy results

The primary variable, pre-dose FEV_1 was measured using spirometry at the clinic visits (Visit 6 to 8 [Week 8 to 12]). The primary analysis was the absolute change from baseline in

pre-dose FEV_1 at Week 8 to 12 between AZD5423 800 µg delivered dose od and placebo. The result of primary analysis is presented in Table S2.

AZD5423 800 µg delivered dose od was not superior to placebo with regard to change from baseline in average pre-dose FEV_1 at Week 8 to12. There was no statistically significant difference observed in FEV_1 in patients receiving AZD5423 800 µg delivered dose od (LS Mean= -0.003; 95% CI= -0.06 to 0.06 and p-value=0.928).

The result of the sensitivity analysis was consistent with the result of the primary analysis.

Table S2 Absolute change from baseline in pre-dose FEV_1 (L) at Week 8 to 12 - ANCOVA (On Trt analysis set)

		Change from baseline	Difference between groups		
Group	**n**	**LS Mean(SE)**	**Estimate**	**95% CI**	**p-value**
AZD5423 800 ug od	109	-0.011(0.023)	-0.003	(-0.06,0.06)	0.928
Placebo	109	-0.008(0.023)			

Baseline defined as the last pre-dose value prior to 1st dose of randomised therapy.
The statistical model ANCOVA includes change from baseline to the average of Weeks 8 to 12 as outcome variable with treatment and country as a factor and baseline FEV_1 (pre-dose) value as covariate.
ANCOVA Analysis of Covariance; CI Confidence Interval; FEV_1 Forced Expiratory Volume in 1 Second; LS Mean Least Square Mean; n Number of Patients in a Category; od Once Daily; SE Standard Error; Trt Treatment.

A 12-week treatment with 2 staggered dose levels of AZD5423 (AZD5423 180 µg delivered dose od for the first 4 weeks and AZD5423 800 µg delivered dose od for the following 8 weeks), did not change lung function (pre-and post-dose FEV_1 and forced vital capacity); any of the eDiary variables (morning and evening: FEV_1 and PEF, night-time awakenings, use of reliever medications, and the scores of the breathlessness, cough, and sputum scale [BCSS]), and the number of exacerbations as compared with placebo and budesonide groups.

Overall, treatment with AZD5423 did not change the total SGRQ-C score compared with budesonide and placebo groups.

Summary of pharmacokinetic results

The median time to maximum plasma concentration was generally observed within 15 minutes post-dose for AZD5423 180 µg delivered dose od and 30 minutes post-dose for AZD5423 800 µg delivered dose od. At steady state, the geometric mean C_{max} was 0.761 nmol/L following 180 µg and 2.37 nmol/L following 800 µg od delivered doses of AZD5423. The geometric mean systemic exposure to AZD5423 during a dosing interval (Area Under the Plasma Concentration-Time Curve during a Dosing Interval [AUC_{0-24}]) was 4.26 nmol*h/L following AZD5423 180 µg and 12.1 nmol*h/L following AZD5423 800 µg delivered dose od. A high variability between patient was observed for the PK parameters. For AUC_{0-24} and Maximum plasma Concentration (C_{max}), Coefficient of Variation (CV%) ranging 79% to 194% were observed.

Following administration of AZD5423 via Turbuhaler, the dose increase expressed as delivered dose, was 4.7-fold. The corresponding increase expressed as the more relevant measure for lung deposition fine particle dose was 3.5-fold.

Geometric means (CV%) of the individual treatment ratios (800 µg/180 µg) of C_{max}, AUC_{0-t}, and AUC_{0-24} are 3.253 (136.4), 3.198 (117.6), and 3.287 (106.4), respectively, indicating dose proportionality in the studied dose range, expressed as fine particle doses (114 µg and 404 µg).

Summary of pharmacodynamic results

Effect of AZD5423 on the HPA-axis (24-hour plasma cortisol)

At Week 4, cortisol suppression was less when treated with AZD5423 180 µg delivered dose od compared to budesonide 320 µg (delivered dose) 2 doses bid (Geometric Mean Ratio [GMR]=1.14; 95% CI=0.98 to 1.33 and p-value=0.080), whereas the suppression was higher as compared with placebo (GMR=0.92; 95% CI=0.79 to 1.07 and p-value=0.267).

At Week 12, cortisol suppression was less when treated with AZD5423 800 µg delivered dose od compared to budesonide 320 µg (delivered dose) 2 doses bid (GMR=1.14; 95% CI=0.97 to 1.33 and p-value=0.110), whereas the suppression was higher as compared with placebo (GMR=0.84; 95% CI=0.72 to 0.98 and p-value=0.031).

Effect on systemic inflammation (Pre-dose hsCRP)

AZD5423 180 µg delivered dose od increased compared to budesonide 320 µg (delivered dose) 2 doses bid and placebo with regard to change from baseline in pre-dose High Sensitive C-Reactive Protein (hsCRP) at Week 4. Whereas, AZD5423 800 µg delivered dose od was no different compared to budesonide 320 µg (delivered dose) 2 doses bid and placebo at Week 12.

Summary of safety results

The overall safety results showed that there were no safety or tolerability concerns identified in this study. There were no imbalances between the treatment groups in exposure data. The mean duration of exposure observed was 79.4 days in the AZD5423 group, 81.7 days in the budesonide group, and 82 days in the placebo group.

There was no marked pattern of AEs following treatment with AZD5423, budesonide, or placebo. The frequency of AEs was similar between the treatment groups with only few AEs of severe intensity, and few AEs that were judged to be causally related to IP. The most commonly reported AEs by preferred term during the randomised treatment period were COPD and headache (5 [4.3%] and 5 [4.3%] patients, respectively) in patients receiving AZD5423; headache and COPD (7 [6.0%] and 5 [4.3%] patients, respectively) in patients receiving budesonide; headache, respiratory tract infection, and COPD (6 [5.2%], 5 [4.3%], and 5 [4.3%] patients, respectively) in patients receiving placebo.

There was 1 death reported in the AZD5423 group which was not causally related to the IP, as judged by the investigator. The overall safety results showed that there was no marked pattern of AEs following treatment with AZD5423, budesonide, or placebo. No safety concerns have been raised in this study in patients treated with AZD5423 with regard to changes in heart rate, haematology parameters, liver enzymes, osteocalcin, DHEAS, morning plasma cortisol, or oral status.