AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1236
Study Code	D4260C00003
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A 6-Week Double-Blind, Placebo-controlled, Randomised, Parallel Group Phase IIa Study to Assess the Tolerability/Safety and Efficacy of AZD1236 as an Oral Tablet in Patients with Moderate to Severe COPD

Study dates: First subject enrolled: 8 September 2008
Last subject last visit: 10 March 2009

Phase of development: Therapeutic exploratory (IIa)

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

Study centre(s)

The study was performed at 14 centres in Germany, Finland, Slovakia, Hungary and Bulgaria.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective was to investigate the tolerability and safety of AZD1236, as an oral tablet, in chronic obstructive pulmonary disease (COPD) patients by assessment of incidence and nature of adverse events (AEs) and vital signs and laboratory safety assessments.	AEs, vital signs, electrocardiogram (ECG) and laboratory safety assessments.	Safety
Secondary	**Secondary**	
The secondary objectives of the study were to evaluate the effects of AZD1236 as an oral tablet in COPD patients as compared with placebo on: lung function, functional capacity, BODE index, health status assessed by clinical COPD questionnaire (CCQ) and diary variables, selected biomarkers in blood and urine, and systemic exposure of AZD1236.	Lung function: FEV_1, FVC, $FEF_{25-75\%}$, VC and IC	Efficacy
	Functional capacity by 6MWT including assessment of dyspnoea and fatigue using the Borg scale.	
	BODE index.	
	Health status assessment by CCQ.	
	Diary variables: lung function assessed by PEF, COPD symptoms (breathlessness, cough, chest tightness and night-time awakenings) and rescue medication.	
	Blood cells and soluble inflammatory markers in blood including leukocyte differential cell count, hs-CRP, serum Amyloid-A Protein, desmosine, TNF-α, IL-8, IL-6, IL-1β. 24-hour urinary desmosine and creatinine excretion.	Pharmaco-dynamics
	Plasma concentrations of AZD1236.	Pharmaco-kinetics

6MWT 6-minute walk test. AE Adverse event. BODE A composite variable of; body mass index (B), airway obstruction as assessed by FEV1 (O), dyspnoea as assessed by the Modified Medical Research Council dyspnoea scale (D), exercise capacity as assessed by 6MWT (E). CCQ Clinical COPD Questionnaire. COPD Chronic obstructive pulmonary disease. ECG Electrocardiogram. $FEF_{25-75\%}$ The mean forced expiratory volume flow between 25% and 75% of the FVC. FEV_1 Forced expiratory volume in one second. FVC Forced vital capacity. hs-CRP High-sensitivity C-reactive protein. IC Inspiratory capacity. MMRC Modified Medical Research Council. PEF Peak expiratory flow. TNF-α Tumour necrosis factor-alpha. VC Vital capacity.

Study design

This was a double-blind, placebo-controlled, randomised, parallel group multi-centre study assessing the tolerability/safety and efficacy of AZD1236. Patients who used oral steroids had a 4-week wash-out. All patients entered a 2-week run-in. After randomisation, patients received 75 mg AZD1236 twice daily (bid) or placebo for 6 weeks. Treatment with inhaled glucocorticosteroids (GCS), ipratropium bromide and short-acting rescue/reliever medication as required was allowed during the study. A follow-up visit was performed 1 week after the last treatment day.

Target subject population and sample size

Eligible patients were men or women, not of childbearing potential, aged 40 years or above with moderate to severe chronic obstructive pulmonary disease (COPD). The COPD was defined as having post-bronchodilator forced expiratory volume in 1 second (FEV_1) between 30% to 80% of predicted normal (PN) value and a post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.

The target sample size for this study (approximately 60 randomised patients) was considered a reasonable minimal size for a safety and tolerability study.

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

AZD1236 3 x 25 mg bid (oral tablet, batch number 08-000003AZ) and placebo (oral tablet, batch number 08-000004AZ) matching AZD1236.

Duration of treatment

Randomised patients received 75 mg AZD1236 bid or placebo during 6 weeks.

Statistical methods

Only 1 population is described, consisting of all patients who received at least 1 dose of the investigational product after randomisation and who had any post randomisation data.

Safety and tolerability data were described using descriptive statistics. For efficacy variables (and laboratory assessments) the change (or ratio) from baseline to end-of-treatment was analysed using standard analysis of variance techniques, with treatment as a factor and baseline as covariate. When appropriate, a multiplicative model was used ie, data log-transformed before analysis and results presented on the original scale after exponentiation.

Subject population

A total of 120 patients were enrolled and 74 patients were randomised to treatment. Approximately 10% of patients discontinued prematurely, the majority due to adverse events (AEs). The proportion of patients who discontinued was similar in both treatment groups.

Table S2 Disposition of Patients

	AZD1236	Placebo	All
Enrolled patients			**120**
Not randomised	-	-	**46**
Eligibility criteria not fulfilled	-	-	**38**
Patient not willing to continue study	-	-	**5**
Other reasons(s)	-	-	**3**
Randomised	35	39	**74**
Discontinued	3	4	**7**
Eligibility criteria not fulfilled	0	1	**1**
Adverse event	3	2	**5**
Patient not willing to continue study	0	1	**1**
Completers	32	35	**67**

The 2 treatment groups were generally well balanced in terms of demographic data. The placebo group appeared to have a slightly more severe COPD in terms of FEV_1, FEV_1 (% PN) and breathlessness score but these differences were not considered clinically important.

Table S3 Summary of demographic data and disease under study

		AZD1236 n=35	Placebo n=39	All n=74
Sex	Male, n (%)	24 (69)	27 (69)	**51 (69)**
	Female, n (%)	11 (31)	12 (31)	**23 (31)**
Age (years)	Mean	61.7	61.7	**61.7**
	Range	48 to 76	46 to 77	**46 to 77**
Race	White, n (%)	35 (100)	39 (100)	**74 (100)**
BMI (kg/m^2)	Mean	28.1	27.1	**27.6**
	Range	20 to 41	19 to 36	**19 to 41**
Time since diagnosis (years)	Median	5.7	6.1	**6**
	Range	0 to 27	1 to 33	**0 to 33**
Smoking status	Previous, n (%)	20 (57)	16 (41)	**36 (49)**
	Habitual, n (%)	15 (43)	23 (59)	**38 (51)**

Table S3 Summary of demographic data and disease under study

		AZD1236 n=35	Placebo n=39	All n=74
Time since discontinuing smoking (years)	Median	6.3	9.9	**8.1**
	Range	0 to 29	0 to 29	**0 to 29**
Pack years	Median	34	36	**35**
	Range	10 to 93	15 to 200	**10 to 200**
Inhaled GCS at entry	N	21	25	**46**
	Mean dose (μg)	668.6	768.8	**723.0**
	Dose range (μg)	160 to 1000	320 to 1000	**160 to 1000**
FEV_1 (L)	Mean	1.439	1.307	**1.369**
	Range	0.54 to 2.94	0.57 to 2.52	**0.54 to 2.94**
FEV_1 (% PN)	Mean	49.3	44.6	**46.8**
	Range	23 to 91	24 to 76	**23 to 91**
Reversibility (%)	Mean	13.2	16.1	**14.7**
	Range	-7 to 58	-7 to 67	**-7 to 67**
FEV_1 (% VC)	Mean	48.3	46.7	**47.4**
	Range	32 to 76	24 to 71	**24 to 76**
Number of rescue medications[a]	Mean	3.45	3.89	**3.68**
	Range	0.0 to 7.9	0.0 to 10.2	**0.0 to 10.2**
Breathlessness score	Mean	1.66	2.02	**1.85**
	Range	0.7 to 3.0	0.7 to 3.6	**0.7 to 3.6**

[a] Mean number of rescue medications per 24 hours.
BMI Body Mass Index; FEV_1 Forced expiratory volume in 1 second; GCS Glucocorticosteroid; PN Predicted normal; VC Vital capacity.

Summary of efficacy results

Lung Function

There was no indication of improved lung function (FEV_1, FVC, VC, IC, $FEF_{25-75\%}$) after 6 weeks treatment with AZD1236 compared with placebo.

Other Clinical Data

Only 1 variable, the clinical COPD questionnaire (CCQ) Functional domain, demonstrated a statistically significant difference in favour of AZD1236 (p=0.02 1-sided). There was a trend towards statistical significance for CCQ total score (p=0.07 1-sided) for AZD1236 compared with placebo. For 6MWT, MMRC dyspnoea, BODE total score and dyspnoea and fatigue measured on the Borg scale there were no statistically significant differences between the treatment groups and changes were minimal in the AZD1236 group compared with placebo.

Diary Card Data

The statistical analysis on morning peak expiratory flow (PEF) data from the last 4 weeks of treatment indicated a group difference of approximately 6 L/min in favour of placebo. However, there was not sufficient evidence of a real effect on PEF in the morning (90% CI -17.9, 5.60, p=0.385). During the evening, the difference in PEF was negligible; there were small changes in both treatment groups after baseline.

The COPD symptoms scores appeared to decrease slightly more in the placebo group than in the AZD1236 group. The use of rescue medication was similar in both treatment groups.

Summary of pharmacodynamic results

There was no evidence of any effect of AZD1236 on any of the blood and urine biomarkers.

Summary of pharmacokinetic results

The exposure, measured as area under the plasma concentration-time curve (AUC), was estimated to be 77.3 μM*h (relative standard deviation 28%) during a 12-hour interval at steady state. Assuming negligible circadian rhythm in PK, the 24-hour AUC was estimated to be 155 μM*h.

One patient was excluded from the PK analyses because 5 out of 6 of his values were below the limit of quantification.

Summary of safety results

The number of patients experiencing AEs was well balanced between the 2 groups. The actual number of AEs reported was slightly higher with AZD1236 compared with placebo but this difference was accounted for primarily by mild AEs. One patient in the AZD1236 group had a serious adverse event (SAE) and 5 patients were withdrawn as a result of an AE. Ten AEs were considered by the investigator to be causally related to investigational product (6 with AZD1236 and 4 with placebo). No individual AE was assessed as causally related to investigational product for more than 1 patient.

Table S4 Number (%) of patients who had an adverse event in any category, and number of adverse events by category

	AZD1236 n=35	Placebo n=39	All n=74
Number (%) of patients who had an AE in each category[a]			
Any AEs	13 (37%)	17 (44%)	**30 (41%)**
SAEs	1 (3%)	0	**1 (1%)**
DAEs[b]	3 (9%)	2 (5%)	**5 (7%)**
Total number of AEs[c]			
Any AEs	28	21	**49**
Causally related AEs[d]	6	4	**10**
SAEs	1	0	**1**
DAEs[b]	6	3	**9**

[a] Patients with multiple events in the same category are counted once in each category.
[b] Discontinuation of investigational product/from study due to AEs.
[c] Multiple events with the same preferred term are counted once for each patient and category.
[d] As assessed by the investigator.
AE Adverse event; DAE Premature discontinuation of treatment with investigational product due to an adverse event; SAE Serious adverse event.

AEs were reported most commonly in the respiratory, thoracic and mediastinal disorders system order class (SOC; AZD1236 17%, placebo 13%) and the infections and infestations SOC (AZD1236 9%, placebo 15%). Musculoskeletal and connective tissue disorders were reported in the AZD1236 group (4 patients [11%]) but not the placebo group. These events were back pain, bone pain, muscle spasms and musculoskeletal chest pain; none was considered by the investigator to be causally related to AZD1236.

Of the most frequently reported AEs, COPD was reported with a similar incidence in both treatment groups, headache was reported for more patients in the AZD1236 group and viral infection was reported for more patients in the placebo group.

Table S5 Most frequently reported adverse events (reported by >2% of patients in total) by preferred term

Preferred term	Number (%) of patients		
	AZD1236	Placebo	All
	n=35	n=39	n=74
Chronic obstructive pulmonary disease	3 (9%)	4 (10%)	**7 (9%)**
Headache	4 (11%)	1 (3%)	**5 (7%)**
Viral infection	1 (3%)	3 (8%)	**4 (5%)**
Pyrexia	2 (6%)	0	**2 (3%)**
Nasopharyngitis	0	2 (5%)	**2 (3%)**
Blood creatine phosphokinase increased	2 (6%)	0	**2 (3%)**
Dyspnoea	1 (3%)	1 (3%)	**2 (3%)**
Rash	2 (6%)	0	**2 (3%)**

There was only 1 severe AE; this was pharyngeal cancer reported as an SAE in the AZD1236 group. This was the only SAE reported and it was not considered to be related to treatment.

Five patients discontinued the study due to AEs. Patient E1002005/3, who received AZD1236, was discontinued due to COPD exacerbation and elevation of international normalised ratio value. Patient E2001007/61, in the AZD1236 group, primarily discontinued due to a rash but also had exacerbation of COPD and microhematuria which contributed to discontinuation from the study. After discontinuation from the study, patient E2001007/61 experienced events that could be consistent with a drug induced interstitial nephritis which comprised acute renal failure, rash, fever and blood eosinophilia. These events were classified as suspected, unexpected, serious adverse reactions (SUSARs). Patient E3001002/11, in the AZD1236 group, was discontinued due to blood creatine phosphokinase increased. Patient E1002014/9, who received placebo, was discontinued due to COPD exacerbation. Patient E3004005/17, in the placebo group, was discontinued due to thyroid stimulating hormone decreased and depression.

There were no statistically significant differences between the 2 treatment groups in change from baseline in laboratory variable values, vital signs or electrocardiogram (ECG) data.

Date of the report

19 August 2009