AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1236
Study Code	D4260C00007
Edition Number	1
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A double–blind, randomised, placebo-controlled, parallel-group multi-centre Phase IIa study to assess the effects on biomarkers in induced sputum, blood and urine of AZD1236 administered as oral tablet in moderate to severe COPD patients during a 6 week treatment period

Study dates: First subject enrolled: 12 September 2008
Last subject last visit: 7 May 2009

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

The study was performed at 12 centres in 4 countries: Finland, Norway, Denmark and The Netherlands.

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
Primary	
To assess the effects of AZD1236 on selected biomarkers in induced sputum, urine and blood compared with placebo in patients with moderate to severe COPD	Induced sputum biomarkers: Main variables: differential cell count (% of total cell count and absolute numbers) and TNF-α. Exploratory variables: MMP-activity, MMP-8 and –9 protein, MUC 5AC, hydroxyproline, IL-8, LTB4, multiplex (TNF-α, IL-1β, IL-6, MCP-1, RANTES). Urine biomarker (main variable): 24-hour urinary desmosine excretion. Blood biomarkers (all exploratory variables): differential cell count, Amyloid-A (SAA), Hs-CRP, multiplex COPD panel (IL-8, TNF-α, IL-6, IL-1β), desmosine.
Secondary	**Secondary**
To assess the effects of AZD1236 on lung function and symptoms scores compared with placebo in COPD patients	Spirometry (FEV_1, FVC, $FEF_{25-75\%}$, VC, IC), PEF measurements, assessment of health status using CCQ, daily diary recordings of symptoms (breathlessness, cough, chest tightness and night time awakenings) and use of rescue medication
To investigate the safety and tolerability of AZD1236 in COPD patients	Incidence and nature of adverse events, pulse, blood pressure, laboratory assessments and ECG data
To investigate the exposure of AZD1236 given as an oral tablet in COPD patients	AZD1236 concentrations in plasma at steady state

CCQ Clinical COPD questionnaire; CSP Clinical study protocol; $FEF_{25-75\%}$ The mean forced expiratory flow between 25% and 75% of the FVC; FEV_1 Forced expiratory volume in one (1) second; FVC Forced vital capacity; hs-CRP High-sensitivity C-reactive protein; IC Inspiratory capacity; 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 multicentre study assessing the effects of AZD1236 on biomarkers in induced sputum, urine and blood during a 6-week treatment period in patients with moderate to severe COPD. The effects on lung function, symptoms, safety, tolerability and exposure of AZD1236 were also assessed. All patients entered a 2-week run-in. After randomisation, patients received 75 mg AZD1236

twice daily (bid) or placebo for 6 weeks. Glucocorticosteroids (GCS), long-acting β_2-agonists and long-acting anticholinergics had to be discontinued prior to inclusion. Ipratropium bromide in a stable dose and short-acting rescue/reliever medication as required were allowed throughout 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. The COPD was defined as having post-bronchodilator forced expiratory volume in 1 second (FEV_1) between 40% to 80% of predicted normal (PN) value and a post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.

The target sample size of approximately 40 randomised patients (20 per arm) was considered a reasonable minimal size for this exploratory 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 (AZD1236 or placebo) after randomisation and who had any post randomisation data.

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 were log-transformed before analysis and results presented on the original scale after exponentiation. Safety and tolerability data were described using descriptive statistics.

Subject population

A total of 126 patients from 12 centres in 4 countries were enrolled and 55 patients were randomised to treatment. Eight patients (approximately 15%; 4 in each treatment group) discontinued from the study prematurely. All 8 patients were withdrawn because of adverse events (AEs).

Table S2 Disposition of patients

	AZD1236	Placebo	All
Enrolled patients			**126**
Not randomised			**71**
-Eligibility criteria not fulfilled			**46**
-Adverse event			**12**
-Patient not willing to continue study			**9**
-Patient lost to follow-up			**1**
-Other reasons(s)			**3**
Randomised	26	29	**55**
Discontinued	4	4	**8**
-Adverse event	4	4	**8**
Completers	22	25	**47**

AE Adverse event

The 2 treatment groups were generally well balanced in terms of demographic data and disease characteristics at baseline, although it appeared that FEV_1 was slightly lower in the AZD1236 group, and the use of rescue medication was slightly higher in the placebo group.

Table S3 Treatment group comparison of demographic and disease data at baseline

	AZD1236 n=26	Placebo n=29	All n=55
Sex			
Male	19	20	**39**
Female	7	9	**16**
Age (yrs)	62.9	65.7	**64.4**
	47-80	49-79	**47-80**
Race			
White	26	29	**55**
BMI (kg/m^2)	26.5	26.6	**26.6**
	17-38	19-34	**17-38**

Table S3 Treatment group comparison of demographic and disease data at baseline

	AZD1236 n=26	Placebo n=29	All n=55
Time since diagnosis (yrs)[a]	6	5.2	**5.5**
	1-23	1-31	**1-31**
Smoking status			
Previous	12	15	**27**
Habitual	14	14	**28**
Time since discontinuing smoking (yrs)[a]	8.2	11	**9**
	3-36	2-20	**2-36**
Pack-years[a]	37.5	43	**40**
	14-130	11-82	**11-130**
Inhaled GCS			
No	12	13	**25**
Yes	14	16	**30**
Inhaled GCS daily dose (µg)	682.9	599.3	**641.1**
	50-1000	200-1000	**50-1000**
FEV_1 (L)	1.507	1.619	**1.566**
	0.75-2.71	0.58-2.93	**0.58-2.93**
FEV_1 (% P.N.)	49.2	54.4	**52.0**
	29-74	23-75	**23-75**
Reversibility (%)	12.8	13.3	**13.1**
	-5-33	-4-68	**-5-68**
FEV_1 (% VC)	43.4	45.9	**44.8**
	26-74	25-64	**25-74**
Mean no. of rescue[b]	2.16	2.70	**2.45**
	0.0-5.2	0.0-7.9	**0.0-7.9**
Mean of breathlessness score	1.75	1.69	**1.72**
	0.3-3.1	0.8-2.7	**0.3-3.1**

[a] Median
[b] Mean number of rescue medication per 24 hours

BMI, Body Mass Index; FEV_1, Forced expiratory volume in one (1) second; GCS Glucocorticosteroid; PN, Predicted normal; VC Vital capacity.

For categorical data, frequencies are given, for other data mean values and ranges are given

Summary of pharmacodynamic results

Sputum

There did not appear to be any difference between AZD1236 and placebo in the change from baseline to the end of treatment, in any of the sputum biomarkers with the exception of lymphocytes, which decreased in the AZD1236 treatment group but increased in the placebo group.

Urine

There appeared to be a decrease in urine desmosine in the AZD1236 treatment group in comparison with the placebo group in the change from baseline to end of treatment. Decreases were observed for both the total and the free desmosine concentrations, but they were less apparent when desmosine concentrations were corrected for the concentration of creatinine in the same sample.

Blood

There did not appear to be any difference between AZD1236 and placebo in the change from baseline to the end of treatment, in any of the blood biomarkers with the exception of decrease in plasma desmosine and lymphocytes in the AZD1236 treatment group, and decrease of IL-6 and TNF-α in the placebo group.

Summary of efficacy results

Lung Function

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

Health status

Decreases (ie, improvements) from baseline to the end of the treatment period, were shown for the total and all domain scores in the placebo group, and for the symptoms and mental state domains in the AZD1236 group. The profile of change over the treatment period was different between the two groups and indicated a greater improvement in the placebo group at the end of the treatment period. The changes observed between the two groups were, however, considered to be small and not of clinical importance.

Diary Card Data

There was no indication of a clinical effect of AZD1236 in diary card data, and all mean values favoured numerically placebo instead of AZD1236.

Summary of pharmacokinetic results

The exposure, measured as area under the plasma concentration-time curve (AUC), was estimated to be 78.5 μM*h (relative standard deviation 20%) during a 12-hour interval at steady state. Assuming negligible circadian rhythm in PK, the 24-hour AUC was estimated to be 157 μM*h.

Exposure of AZD1236 in lung tissue was confirmed by the obtained sputum concentrations in the range between 44 and 250 nM after 4 to 6 weeks of treatment.

Summary of safety results

Treatment with AZD1236 75 mg twice daily over 6 weeks appeared to be well tolerated. The overall incidence of AEs was similar in the AZD1236 group (58%) and the placebo group (52%). Two patients in the AZD1236 group experienced serious adverse events; 1 was hospitalised for a COPD exacerbation and the other for dyspnoea, cardiac failure and COPD exacerbation. A total of 8 patients were withdrawn as a result of an AE, 4 in each treatment group. AEs that were considered by the investigator to be causally related to investigational product were fewer in the AZD1236 group that in the placebo group. With the exception of increased blood creatinine phosphokinase in 2 placebo patients, no individual AE was assessed as causally related to investigational product for more than 1 patient. The AE profiles were similar between the groups. Overall, the most common AEs were exacerbations of COPD, reported by 3 patients in each treatment group, and influenza and nasopharyngitis, each reported by 3 patients (10%) in placebo group and 1 patient (4%) in the AZD1236 group, see Table S4. There were no deaths during the study and no other significant AEs. There were no clinically relevant changes in mean or individual laboratory data or the vital signs data. There was no indication that any of the symptoms of musculoskeletal syndrome were increased in patients receiving AZD1236.

Table S4 **Adverse events by preferred term. Number (%) of patients with the most frequently reported AEs , sorted by decreasing order of frequency as summarized over all treatment groups**

Preferred term	AZD1236 n=26	Placebo n=29	All n=55
chronic obstructive pulmonary disease	3 (12%)	3 (10%)	**6 (11%)**
influenza	1 (4%)	3 (10%)	**4 (7%)**
nasopharyngitis	1 (4%)	3 (10%)	**4 (7%)**
oedema peripheral	2 (8%)	1 (3%)	**3 (5%)**
vomiting	2 (8%)	0	**2 (4%)**
dyspnoea	2 (8%)	0	**2 (4%)**
joint swelling	1 (4%)	1 (3%)	**2 (4%)**
blood creatine phosphokinase increased	0	2 (7%)	**2 (4%)**
paraesthesia	1 (4%)	1 (3%)	**2 (4%)**
musculoskeletal chest pain	1 (4%)	1 (3%)	**2 (4%)**

Only AEs reported by >2% of patients in total are displayed.

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Date of the report

30 September 2009