Drug product:	N/A	**SYNOPSIS**	
Drug substance:	AZD9056		
Edition No.:	1		
Study code:	D1521C00002		
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A Randomised, Double-blind, Placebo-controlled, Parallel-group, Multicentre, Phase II Study to Assess The Efficacy of AZD9056 (single oral 400 mg dose) when Administered for 4 Weeks in Patients with Moderate to Severe COPD

Study centres

The study was performed in 28 centres (all of which enrolled patients) in 5 countries: Bulgaria, Germany, Hungary, Sweden, and UK.

Publications

None at the time of this report.

Study dates		**Phase of development**
First subject enrolled	09 January 2006	Therapeutic exploratory (II)
Last subject completed	29 September 2006	

Study design and objectives

This was a double-blind, parallel-group, randomised, multi-centre study to compare the efficacy of AZD9056 400 mg with placebo in patients with moderate to severe COPD.

The objectives of this study and their associated variables are shown in Table S1.

Table S1 Study objectives and variables

Objectives	Variables
Primary objective	**Primary variables**
To determine the efficacy of AZD9056 (single oral 400 mg dose) compared with placebo in moderate to severe COPD patients, during a 4-week treatment period.	- Lung function (specifically SVC, FEV_1, FVC, IC, and PEF). - Exercise tolerance (6 minute walk test [6MWT]). - Symptoms (as recorded on Bronkotest© diary card). - Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI). - St George's Respiratory Questionnaire (SGRQ). - Inflammatory markers in sputum in a sub-group of patients (absolute and percentage of neutrophil, macrophage, eosinophil, lymphocyte, and epithelial cells; IL-1β, IL-8, IL-18) [a]. - Inflammatory markers in blood (absolute and percentage of neutrophil, monocyte, eosinophil, and lymphocyte; IL-6, IL-8 and TNFα in plasma; serum CRP).
Secondary objective	**Secondary variables**
To determine the safety and tolerability of AZD9056 in COPD patients.	AEs, 12-lead ECG, vital signs (pulse and blood pressure), safety laboratory tests (clinical chemistry, haematology, urinalysis) and bacterial sputum culture (qualitative /quantitative, including AFB).
To determine the PK of AZD9056 in patients with moderate to severe COPD.	AZD9056 pre-dose (trough) and post-dose plasma concentrations and estimation of clearance (CL/F) and volume of distribution (Vss/F).

[a] Basophils in sputum were also specified in the protocol but these were not actually measured in the study.

There were 4 exploratory objectives (not reported in this CSR), which were as follows: to collect genetic polymorphism data to contribute to the AZD9056 pharmacogenetics database; to determine the concentration of AZD9056 in sputum (sputum inflammatory marker sub-group only); to investigate exploratory biomarkers and gene expression profiles in patients with COPD; and to investigate the PK/PD relationship of AZD9056 in patients with COPD.

Target subject population and sample size

Male and female patients aged between 40 and 80 years with a clinical diagnosis of COPD. The plan was to enrol approximately 190 patients in order to randomise 132 patients, with the intention of 120 patients completing all study procedures. Based on previous studies in COPD with other compounds, 60 patients per group was considered an adequate number for a study aiming at investigating the effect of AZD9056 on clinical outcome variables. With a 2-sided test at a 5% significance level, the study was estimated to have approximately 80% power in detecting changes in 6MWT, TDI score, PEF, and symptom scores.

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

AZD9056 administered orally as 2 x 200 mg tablets, once daily in the morning (batch number: 05-003770AZ); placebo administered orally as 2 tablets, once daily in the morning (batch number: 05-002006AZ).

Duration of treatment

Study treatment was given for 4 weeks. A follow-up visit took place 7 to 10 days after the end of study treatment.

Statistical methods

The change from baseline was compared between the 2 treatment groups for all outcome variables (exercise tolerance test [6MWT], symptoms (dyspnoea [TDI] and symptoms captured on Bronkotest© diary card), lung function (including PEF), neutrophil counts in sputum, inflammatory markers in blood/sputum, quality of life (SGRQ) using an analysis of variance model with fixed factors treatment and country, using baseline as a covariate. The neutrophil data appeared to have a log-normal distribution and were log-transformed before analysis of variance.

The full analysis set was used for all efficacy analyses. The full analysis set included all patients who took at least 1 dose of study drug and for whom at least 1 piece of evaluable data was available. Data for patients who took at least 1 dose of randomised study drug were included in the safety analyses (safety analysis set). The full analysis set was used for the primary analysis of the efficacy data. A Per-Protocol analysis was explored to check the robustness of the results for the primary objective.

Subject population

The disposition of all patients in the study, and of those in the sputum inflammatory marker sub-group, and the number of patients in each analysis set are summarised in Table S2.

Table S2 Subject disposition

Category	Placebo (n=68)	AZD9056 (n=66)	Total (n=134)
Enrolled			271
Randomised	68 (100%)	66 (100%)	134 (100%)
Prematurely Discontinued	7 (10%)	7 (11%)	14 (10%)
Completed Study	61 (90%)	59 (89%)	120 (90%)
Full Analysis Set	68 (100%)	66 (100%)	134 (100%)
Analysed for Safety	68 (100%)	66 (100%)	134 (100%)
Per Protocol Population	57 (84%)	56 (85%)	113 (84%)
Enrolled sputum inflammatory marker sub-group			113
Randomised sputum inflammatory marker sub-group	30 (100%)	30 (100%)	60 (100%)
Prematurely discontinued sub-group	2 (7%)	1 (3%)	3 (5%)
Completed study sub-group	28 (93%)	29 (97%)	57 (95%)

Table S3 summarises the key patient demographic and baseline characteristics of the Full analysis set and the inflammatory marker sub-group. Table S4 summarises respiratory function at enrolment (Full analysis set).

Table S3 Demographic characteristics

Characteristic	Statistic/category	All patients		Sputum marker sub-group	
		Placebo (n=68)	AZD9056 (n=66)	Placebo (n=30)	AZD9056 (n=30)
Sex	Male	48 (71%)	48 (73%)	20 (67%)	21 (70%)
	Female	20 (29%)	18 (27%)	10 (33%)	9 (30%)
Race	Caucasian	68 (100%)	66 (100%)	30 (100%)	30 (100%)
Age (years)	Mean (SD)	60 (8.4)	61 (7.1)	59 (7.7)	62 (7.0)
	Median	60	60	59	63
	Range	41 to 79	40 to 77	41 to 77	47 to 77
Weight (kg)	Mean (SD)	75.9 (16.19)	73.0 (13.60)	79.1 (14.68)	74.3 (14.65)
	Median	77.5	71.5	80.0	75.0
	Range	39.0 to 120.0	45.0 to 110.0	58.0 to 120.0	51.0 to 110.0
Body mass index	Mean (SD)	26.5 (4.93)	25.2 (4.25)	27.2 (4.67)	25.2 (3.80)
(kg/m^2)	Median	26.1	24.9	26.1	24.8
	Range	16.4 to 42.1	16.1 to 36.8	19.6 to 42.1	19.8 to 36.8

Table S4 Respiratory function at enrolment (Full analysis set)

Characteristic	Statistic or category	Placebo (N=68)	AZD9056 (N=66)
FEV_1 (L)	Mean (SD)	1.40 (0.384)	1.41 (0.446)
	Range	0.71 to 2.26	0.53 to 3.50
FVC (L)	Mean (SD)	2.84 (0.782)	2.91 (0.761)
	Range	1.40 to 4.87	1.28 to 5.11
% predicted FEV_1	Mean (SD)	47.1 (9.79)	46.4 (11.12)
	Range	26.3 to 65.1	24.7 to 94.1
FEV_1/FVC ratio (%)	Mean (SD)	50.1 (9.81)	48.7 (9.22)
	Range	28.9 to 67.2	28.8 to 68.5

Efficacy results

The results of the Per-Protocol analysis of the efficacy results was consistent with the results for the Full analysis set.

Lung function variables: There were no statistically or clinically significant changes in any of the variables designed to assess the effect of AZD9056 on lung function (specifically,

FEV_1, FVC, SVC, IC, and PEF) in the AZD9056-treated group compared with the placebo group.

Exercise and dyspnoea variables and SGRQ: No effect of AZD9056 was demonstrated in the 6MWT, Bronkotest© diary card symptoms, the TDI, or SGRQ, compared with placebo.

Inflammatory biomarkers sub-group: There was no effect of AZD9056 treatment on leukocyte or soluble inflammatory biomarkers measured in sputum (IL-1β, IL-8, and IL-18) and blood (IL-6, TNFα, IL-8, and CRP) compared with placebo. Although the data did not meet the numbers required to achieve statistical power for the sputum variables, there were no obvious trends for any treatment effects either across or within treatment groups.

Population PK results: a population PK model was developed for AZD9056 in patients with COPD in this Phase II study with sparse PK sampling. The results did not show that any of the patient demographic or baseline characteristics (body weight, age group, gender, renal function, or hepatic function) has a meaningful effect on AZD9056 PK in patients with COPD, to the extent that a dose adjustment for AZD9056 would be necessary in this patient population.

Safety results:

Table S5 summarises the incidence of AEs in each category, and Table S6 summarises the most commonly reported AEs by Preferred Term.

Table S5 Number (%) of patients who had an adverse event in any category during the treatment and follow-up periods- safety analysis set

Adverse event	Placebo (n=68)	AZD9056 (n=66)
Number of patients:		
SAEs	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)
Discontinued study drug due to AE	4 (6%)	5 (8%)
Other Significant AEs	0 (0%)	0 (0%)
Any AE	36 (53%)	33 (50%)
Total Number of AEs:	62	75

[a] Patients with multiple AEs in the same category are counted only once in that category. Patients with events in >1 category are counted once in each of those categories.

Table S6 Number (%) of patients with the most commonly reported AEs in the treatment and follow-up periods, sorted by decreasing order of frequency (Safety analysis set)

MedDRA Preferred Term	Placebo (n=68)	AZD9056 (n=66)	Total (n=134)
Nasopharyngitis	9 (13%)	7 (11%)	16 (12%)
Diarrhoea	3 (4%)	9 (14%)	12 (9%)

Table S6 Number (%) of patients with the most commonly reported AEs in the treatment and follow-up periods, sorted by decreasing order of frequency (Safety analysis set)

MedDRA Preferred Term	Placebo (n=68)	AZD9056 (n=66)	Total (n=134)
COPD exacerbation	4 (6%)	4 (6%)	8 (6%)
Headache	4 (6%)	3 (5%)	7 (5%)
Nausea	1 (1%)	5 (8%)	6 (4%)
Non-cardiac chest pain	3 (4%)	2 (3%)	5 (4%)
Weight decreased	4 (6%)	1 (2%)	5 (4%)
Flatulence	1 (1%)	3 (5%)	4 (3%)
Dyspnoea	0 (0%)	4 (6%)	4 (3%)
Dry mouth	1 (1%)	2 (3%)	3 (2%)
Fatigue	0 (0%)	2 (3%)	2 (1%)
Upper respiratory tract infection	0 (0%)	2 (3%)	2 (1%)

This table uses a cut-off of 3% in the AZD9056 group.

There were no deaths or SAEs in patients randomised to this study. In total, 9 (7%) patients had AEs that led to permanent discontinuation of study drug (DAEs): 4 (6%) patients in the placebo group and 5 (8%) patients in the AZD9056 group. The most frequently reported DAEs (*preferred term*) were exacerbations of '*chronic obstructive pulmonary disease*' (COPD) and '*nausea*'. Two (3%) patients in each group reported non-serious exacerbation of COPD of moderate (3) /severe (1) intensity. Of these, the investigator reported the event as causally related to study treatment for 1 patient (placebo).

One (1%) patient in the placebo group discontinued study treatment due to non-serious AEs of nausea, flatulence, and vertigo; 3 (5%) patients in the AZD9056 group discontinued study treatment due to nausea, and 1 of these patients also reported events of chest pain, abdominal distension, and dyspnoea. All of these DAEs were of moderate intensity and all were reported by the investigator as causally related to study treatment.

There were no clinically significant findings for any patients for any of the clinical laboratory parameters assessed during the study. There was no trend for an increase in any hepatobiliary biomarker over time in either treatment group.

There were no clinically significant changes from baseline in the mean or individual values of any vital signs, ECG, physical findings or other observations related to safety, and no notable differences between treatment groups.