AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00020
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A 12-Week, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Multinational, Phase IIb Study to Evaluate the Efficacy and Safety of 60 mg AZD9668 Administered Orally Twice Daily to Subjects with Chronic Obstructive Pulmonary Disease (COPD) on Treatment with Budesonide/Formoterol

Study dates: First patient enrolled: 24 November 2009
Last patient last visit: 18 August 2010

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)

A total of 79 centres from 6 countries participated in the study: Bulgaria (18 centres), Czech Republic (8 centres), Hungary (13 centres), Poland (18 centres), Romania (6 centres) and Slovakia (16 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives	Outcome variables	Type
Primary To evaluate the efficacy of AZD9668 compared with placebo in symptomatic COPD patients by assessing effect on lung function and symptoms of COPD.	**Primary** Pre-bronchodilator FEV_1 measured at clinic visits **Secondary (aligned to the primary objective)** Lung function: FEV_1 at clinic visits (post-bronchodilator); pre- and post-bronchodilator FVC, FEV_6, $FEF_{25\%-75\%}$ and IC at clinic visits; PEF and FEV_1 measured at home by the patient Signs and symptoms: EXACT; BCSS; sputum colour assessed using Bronkotest© 5-point colour scale; use of reliever medication Exercise capacity: ISWT (including Borg); ESWT (including Borg) Health-Related Quality of Life: SGRQ-C Exacerbations: Exacerbations (including antibiotic use and/or systemic steroid use [oral or parenteral] and/or emergency room treatment and/or hospitalisation)	Efficacy
Secondary To evaluate safety and tolerability of AZD9668 in COPD patients.	Treatment-emergent adverse events, haematology, clinical chemistry, urinalysis, vital signs, 12-lead electrocardiogram and physical examination.	Safety
Exploratory To investigate the effect of AZD9668 on urinary biomarkers. This will not form part of the CSR and may be reported separately.	Urine biomarkers, including, but not limited to desmosine (creatinine normalised).	Pharmacodynamic

BCSS: Breathlessness, cough and sputum scale; COPD: Chronic obstructive pulmonary disease; CSR: Clinical study report; ESWT: Endurance shuttle walk test; EXACT: Exacerbations of chronic pulmonary disease tool; $FEF_{25\%-75\%}$: Forced expiratory flow between 25% to 75% of vital capacity; FEV_1: Forced expiratory volume in 1 second; FEV_6: Forced expiratory volume in 6 seconds; FVC: Forced vital capacity; IC: Inspiratory capacity; ISWT: Incremental shuttle walk test; PEF: Peak expiratory flow; SGRQ-C: St George's respiratory questionnaire for chronic obstructive pulmonary disease.
Note: There was another exploratory objective for this study (pharmacogenetic analysis of blood), which is not reported in the main study report.

Study design

This was a Phase IIb, 12-week, randomised, double-blind, placebo-controlled, parallel group, multinational study to evaluate efficacy and safety of AZD9668 administered orally to patients with chronic obstructive pulmonary disease (COPD) on treatment with budesonide/formoterol.

Target patient population and sample size

The patient population included males or females aged from 40 to 80 years (inclusive) who had a clinical diagnosis of COPD with symptoms for at least 1 year prior to Visit 1b, and with at least 1 COPD exacerbation during the year prior to randomisation. The patients must have been current or previous smokers with a smoking history of ≥10 pack years; have a forced expiratory volume in 1 second (FEV_1) ≥30% and <80% of predicted normal value and a FEV_1/forced vital capacity (FVC) <70% (both post-bronchodilator) at Visit 1b; and have a total COPD symptom score ≥2 per day for at least 7 days of the last 14 days before Visit 2 (by totalling breathing, cough and sputum scores from the breathlessness, cough and sputum scale [BCSS] diary card). Patients were also to have received inhaled glucocorticosteroids (ICS) as monotherapy or in combination with any long-acting bronchodilator in the last 3 months and should have completed morning recordings of daily FEV_1 data at least 10 days of the last 14 days of the run-in period.

In this study it was planned to include approximately 600 randomised patients to participate in 2 cohorts (300 patients per cohort). Patients were randomised to receive either AZD9668 or placebo. The sample size was considered sufficient to detect clinically relevant effects on clinic FEV_1; assuming a standard deviation of 250 mL, it was considered possible to demonstrate an effect at the 5% significance level, power 80% with a 1-sided test if the true difference was 50 mL. The target effect size of 50 mL on clinic FEV_1 was selected to see an effect size similar to that obtained with inhaled steroids in COPD.

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

Table S2 Details of investigational product and other study drug

Investigational product or other treatment	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number
AZD9668	Coated tablet, 30 mg[b], 2 tablets to be taken orally twice daily (4 tablets/day)	AstraZeneca	09-005028AZ
AZD9668 placebo	Coated tablet, placebo, 2 tablets to be taken orally twice daily (4 tablets/day)	AstraZeneca	09-005456AZ
Symbicort® Turbuhaler®	Inhaler, budesonide 320 µg and formoterol fumarate 9 µg per dose, administered twice daily	AstraZeneca	Not applicable[c]
Ventolin® metered dose inhaler[a]	Inhaler, salbutamol sulphate 200 µg per dose, administered as needed	GlaxoSmithKline	Not applicable[c]

[a] If preferred, the patient was permitted to use their existing reliever medication (short-acting β2-agonist [SABA] or short-acting muscarinic agonist [SAMA] or SABA/SAMA combinations).
[b] The 30 mg tablet corresponds to 39.5 mg of AZD9668 tosylate.
[c] Batch numbers were not required for the reliever and maintenance medication.

Duration of treatment

Patients were given 2 tablets twice daily for 12 weeks of the study drug (AZD9668 or placebo), with doses approximately 12 hours apart. AstraZeneca provided budesonide/formoterol maintenance therapy (to be taken twice daily) and salbutamol reliever medication (to be taken as needed) throughout the run-in and treatment periods of the study. If preferred, patients could use their existing reliever medication (short-acting β2-agonists [SABA], short-acting muscarinic antagonists [SAMA] or SAMA/SABA combinations) instead but the same reliever medication was to be used throughout the study. Before being randomised at Visit 2, all patients were stabilised on budesonide/formoterol maintenance therapy during a run-in period of either 3 weeks (for patients already on budesonide/formoterol maintenance therapy at study entry) or 4 weeks (for patients on ICS as monotherapy or in combination with any long-acting bronchodilator at study entry).

Statistical methods

The primary endpoint was the end of treatment pre-bronchodilator FEV_1 as measured at clinic visits. As the study was exploratory in nature, a 2-sided p-value of <0.1 was considered significant. However, in the summaries and analysis, 2-sided 95% confidence intervals (CIs) were produced to show the precision of the data.

The primary analysis of data obtained at the clinic (FEV_1, FVC, forced expiratory volume in 6 seconds [FEV_6], forced expiratory flow between 25% to 75% of vital capacity [$FEF_{25\%-75\%}$], inspiratory capacity [IC]), sputum colour, incremental shuttle walk test [ISWT], endurance shuttle walk test [ESWT] and St George's respiratory questionnaire for chronic obstructive pulmonary disease [SGRQ-C]) compared end-value of treatment (ie, Visit 6 or the last value recorded for each patient) between groups in an analysis of covariance (ANCOVA), with the

baseline value (Visit 2) as covariate and country and treatment as fixed factors. Data were summarised by visit.

For diary variables (daily peak expiratory flow [PEF] and FEV_1, exacerbations of chronic pulmonary disease tool [EXACT], BCSS, reliever medication usage and symptom free days), a similar ANCOVA analysis was performed as for the clinic data, with baseline defined as the average of the last 10 days before randomisation, and the end-value of treatment as the average of the last available 6 weeks. Data were also summarised by 4-weekly periods.

For on-treatment event-based exacerbations, the data were analysed using the time to first exacerbation using a Cox-proportional hazards model and Kaplan-Meier plot.

Adverse events (AEs) and safety endpoints were summarised descriptively. Informal treatment comparisons were made on safety data as an indicator of events that could require further investigation rather than as a rule regarding statistical significance.

Patient population

The first patient was enrolled on 24 November 2009 and the last patient was randomised on 30 March 2010. In total, 615 patients were randomised into the study at 79 centres across 6 countries.

All 615 randomised patients received at least 1 dose of investigational product (AZD9668 60 mg or placebo) and were included in the safety analysis set; all patients received the study treatment to which they had been randomised. One patient in the placebo group (E2507008) and 1 patient in the AZD9668 60 mg group (E2612006) did not have post-dose efficacy data and were excluded from the efficacy analysis set; these exclusions did not change the overall conclusions. In total, 42 of the 615 patients (6.8%) discontinued from the study (18 patients in the placebo group versus 24 patients in the AZD9668 60 mg group); AEs were the most common reason for study discontinuation (6 patients in the placebo group versus 9 patients in the AZD9668 60 mg group). The numbers of randomised and discontinued patients were balanced between the 2 treatment groups and over 90% of randomised patients completed the study (284 patients [94%] in the placebo group versus 289 patients [92%] in the AZD9668 60 mg group).

Overall, 53 patients (9%) had at least 1 important protocol deviation (25 patients in the placebo group versus 28 patients in the AZD9668 60 mg group). Non-compliance with walking test assessments was the most commonly reported important protocol deviation (10 patients in each treatment group); however, this deviation was balanced between the 2 treatment groups and is therefore unlikely to impact the efficacy analysis.

The demographic and baseline characteristics were representative of the target population and the 2 treatment groups were generally comparable and well balanced. Medical and surgical histories, and physical examination findings were as expected for a COPD patient population. The patients dosed were suitable for the study.

Summary of efficacy results

Primary efficacy variable: pre-bronchodilator FEV_1

AZD9668 did not demonstrate a beneficial effect on end of treatment FEV_1. Although the mean end of treatment FEV_1 was numerically higher for the AZD9668 60 mg group (AZD9668 60 mg: 1.48 L, placebo: 1.42 L), the magnitude of this difference was similar to that seen at baseline (AZD9668 60 mg: 1.49 L, placebo: 1.44 L) (Table S3). The estimate of the difference between the 2 treatment groups was 0.01 L (95% CI: -0.03, 0.05; p=0.533). FEV_1 was also unchanged at Weeks 1 to 8 in both treatment groups and appeared consistent over the 12-week treatment period in both treatment groups.

Table S3 Summary of statistical analysis of pre-bronchodilator FEV_1 (L) at the end of treatment (Efficacy analysis set)

				Analysis of Covariance			
		Baseline[a]	End of treatment[a]	End of treatment[a]	Difference between AZD9668 and placebo		
Treatment group	N	Mean (SD)	Mean (SD)	LSmean (SEM)	Estimate (SEM)	(95% CI)	p-value
Placebo	301	1.44 (0.519)	1.42 (0.527)	1.43 (0.015)	0.01 (0.020)	(-0.03, 0.05)	0.533
AZD9668 60 mg bid	309	1.49 (0.539)	1.48 (0.539)	1.45 (0.015)			

[a] Baseline = Visit 2 pre-dose absolute value; End of treatment = last value recorded for each patient.
bid: Bis in die (twice daily); CI: Confidence interval; FEV_1: Forced expiratory volume in 1 second; LSmean: Least squares mean; SD: Standard deviation; SEM: Standard error of the mean.

Secondary efficacy variables (aligned to primary objective)

The data from all of the secondary efficacy variables were consistent with the primary analysis.

Lung function

The secondary efficacy variables of post-bronchodilator FEV_1, pre- and post-bronchodilator FVC, FEV_6, $FEF_{25\%-75\%}$ and IC at clinic visits supported the conclusion drawn from the analysis of the primary variable. There was no evidence of a beneficial effect on any of the pre- or post-bronchodilator lung function variables during 12 weeks of treatment with AZD9668 60 mg twice daily compared with placebo.

Consistent with the clinic spirometry, FEV_1 and PEF measured at home by the patient showed AZD9668 60 mg to have a negligible treatment effect compared with placebo. There was no evidence that AZD9668 improved lung function variables measured daily at home.

Signs and symptoms

The effect of AZD9668 60 mg on signs and symptoms of COPD was examined using EXACT, BCSS, sputum colour and reliever medication usage (including symptom-free and reliever-free days).

There was no evidence of a beneficial effect on the secondary signs and symptoms of COPD variables during 12 weeks of treatment with AZD9668 60 mg twice daily compared with placebo.

Exercise capacity

Any improvement in exercise capacity (endurance time) by the end of treatment was examined using the ISWT and ESWT. The exertional dyspnoea measure was defined as the difference in Borg score at the last common assessment time for a patient.

There was no evidence of a beneficial effect on the ISWT or ESWT during 12 weeks of treatment with AZD9668 60 mg twice daily compared with placebo.

Health-related quality of life

Health-related quality of life (QoL) was examined using the SGRQ-C. Slight decreases in SGRQ-C over the course of the study in overall score and the 3 subdomain scores were observed for both treatment groups; however the difference between the 2 treatment groups was not statistically significant. A change of 4 units in the SGRQ-C overall score represents a clinically meaningful difference. There was a clinically meaningful improvement in SGRQ-C scores at the end of treatment for 48% of patients overall (48% in the placebo group and 47% in the AZD9668 60 mg group). There was no evidence AZD9668 improved the health-related QoL as assessed by SGRQ-C scores.

Exacerbations

The percentage of patients with on-treatment exacerbations was low and consistent between the 2 treatment groups (10% patients in the placebo group versus 7% of patients in the AZD9668 60 mg group). This was as expected given the length of the study and the study population. The profile of exacerbation subtypes (ie, those requiring antibiotics, oral glucocorticosteroids, hospitalisation, or an emergency room visit) and the time to first exacerbation were also consistent between the 2 treatment groups. There was no evidence of a beneficial effect on the time to first exacerbation or the event rate during 12 weeks of treatment with AZD9668 60 mg twice daily compared with placebo.

Summary of pharmacodynamic results

The samples collected for measurement of urine biomarkers had not been analysed at the time of writing; these data may be reported separately.

Summary of safety results

The mean exposure to investigational product was similar between the 2 treatment groups (82.3 days for placebo versus 81.5 days for AZD9668 60 mg) and consistent with the intended length of the treatment period. Overall, the majority of patients had an exposure to investigational product of >80 days (94% patients in the placebo group versus 92% patients in the AZD9668 group). During the run-in and treatment periods the mean exposure to budesonide/formoterol was similar between the 2 treatment groups (run-in period: 25.5 days for the placebo group versus 25.9 days for the AZD9668 60 mg group; treatment period: 82.4 days for the placebo group versus 81.6 days for the AZD9668 60 mg group). The patients showed adequate compliance to the maintenance medication.

Overall, the number of patients reporting treatment-emergent AEs was low and consistent between the 2 treatment groups (21% of patients in the placebo group versus 17% of patients in the AZD9668 60 mg group). In total, 170 AEs were reported: 83 AEs in the placebo group and 87 AEs in the AZD9668 60 mg group. In general, the AE profile was consistent with the population under study and balanced between the 2 treatment groups. The most commonly reported AE was headache: 7 patients in each treatment group. Treatment-related AEs were reported for 6 patients (2%) in the placebo group and 11 patients (4%) in the AZD9668 60 mg group; the most commonly reported treatment-related AEs were headache (3 patients in the AZD9668 60 mg group) and abdominal pain upper (2 patients in the placebo group). The majority of the AEs reported were of mild (10% of patients overall) or moderate (8% of patients overall) severity. Very few severe AEs were reported (3 patients [1%] in each treatment group). The proportion of patients with mild, moderate and severe AEs was consistent between the 2 treatment groups. For the most commonly reported AE of headache, the events were reported as mild in severity for all but 3 patients in the AZD9668 60 mg group, who reported moderate headache.

There were no deaths during the treatment period or up to 30 days after last dose of study medication. The incidence of serious adverse events and AEs leading to discontinuation of investigational product was low (3% of patients overall in both cases) and balanced between the 2 treatment groups. There were no other significant AEs reported during the study. None of these AEs raised any safety concerns.

There were a few isolated cases of elevated hepatic biochemistry measurements during the treatment period but overall the number of patients with hepatic biochemistry above 1.5 x the upper limit of normal (ULN) was small. A higher proportion of patients in the AZD9668 60 mg group had raised transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) above the AstraZeneca ULN (between 1 x ULN and 3 x ULN) compared with the placebo group. Raised ALT above the AstraZeneca ULN occurred in 54 patients (18%) in the placebo group and 83 patients (27%) in the AZD9668 60 mg group. Raised AST above the AstraZeneca ULN occurred in 49 patients (16%) in the placebo group and 74 patients (24%) in the AZD9668 60 mg group. Two patients in the AZD9668 60 mg group and 1 patient in the placebo group had raised ALT or AST to ≥3 x ULN (in the placebo group Patient E2701025 had raised ALT to ≥3 x ULN and raised AST to ≥3 x ULN; in the AZD9668 group Patient E2503007 had raised ALT to ≥3 x ULN and Patient E2616016 had

raised AST to ≥3 x ULN). The increases in ALT or AST were not generally associated with increases in bilirubin; there were no cases of Hy's law during the treatment period. There were no incidences of total bilirubin increasing above 2 x ULN during the treatment period in the AZD9668 60 mg group. A relationship between elevated transaminase levels and AZD9668 treatment cannot be excluded.

There were no other clinically relevant changes in laboratory parameters (haematology, clinical chemistry or urinalysis) and there were no clinically relevant findings in electrocardiograms or vital signs during the study.