AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00012
Edition Number	1
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A 12-week, randomised, double-blind, placebo-controlled, parallel group, multinational, phase IIb dose range finding study to evaluate the efficacy and safety of AZD9668 administered orally at 3 dose levels to patients with Chronic Obstructive Pulmonary Disease (COPD) on treatment with tiotropium

Study dates: First patient enrolled: 13 July 2009
Last patient completed: 5 August 2010

Phase of development: Therapeutic exploratory (IIb)

Sponsor's Responsible Medical Officer:

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

One hundred and thirty-eight centres enrolled patients into the study: Australia (9), Canada (17), Germany (10), Japan (24), Korea (9), Philippines (3), Poland (11), Russia (13), Slovakia (12), Taiwan (9), Ukraine (10) and US (11).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives	Outcome variables[a]	Type
Primary To evaluate the dose response relationship and efficacy of AZD9668 at 3 dose levels compared with placebo in symptomatic COPD patients by assessing effects on lung function and symptoms of COPD.	**Primary** Pre-bronchodilator FEV_1 measured at clinic visits **Secondary efficacy variables aligned to the primary objective** Lung function Post-bronchodilator FEV_1 measured at clinic visits Pre- and post-bronchodilator FVC and IC measured at clinic visits PEF and FEV_1 measured at home by the patient (morning and evening) Signs and symptoms EXACT, BCSS, Sputum colour assessed using Bronkotest® 5-point colour scale, Use of reliever medication Exercise capacity 6MWT Health Related Quality of Life SGRQ-C, FPI-SF (exploratory) 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.	AEs Haematology, Clinical chemistry, Urinalysis Vital signs 12-lead ECG Physical examination	Safety
To confirm AZD9668 exposure in plasma.	Blood samples to measure concentration of AZD9668 in plasma were collected to confirm AZD9668 exposure in plasma.	Pharmacokinetic

a The exploratory objectives are presented in the main CSR.
COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; IC: Inspiratory capacity; PEF: Peak expiratory flow; EXACT: Exacerbations of chronic pulmonary disease tool; BCSS: Breathlessness, cough and sputum scale; 6MWT: 6 Minute Walk Test; SGRQ-C: St George's respiratory questionnaire for chronic obstructive pulmonary disease.

Study design

A 12-week, randomised, double-blind, placebo-controlled, parallel group, multinational, Phase IIb dose range finding study to evaluate the efficacy and safety of AZD9668 administered orally at 3 dose levels to patients with Chronic Obstructive Pulmonary Disease (COPD) on treatment with tiotropium.

Target patient population and sample size

The patient population were males or females aged between 40 to 80 years (inclusive) with a clinical diagnosis of COPD with symptoms for at least 1 year prior to screening, and with at least one 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 and have an FEV_1 between 40-80% (inclusive) of predicted normal value and an FEV_1/FVC <70% (both post bronchodilator) at screening; 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). At screening, all patients were to be on tiotropium alone as maintenance therapy. In addition to tiotropium maintenance therapy, patients were allowed to use the reliever medication provided during the study.

In this study it was planned to include approximately 800 randomised patients recruited from around 120 sites in 12 countries (200 patients per cohort: AZD9668 60 mg bid, 20 mg bid, 5 mg bid and placebo to match AZD9668 bid). The sample size of 200 patients per cohort was considered sufficient in order 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 62 mL.

Investigational products, comparator, reliever and maintenance treatment: dosage, mode of administration and batch numbers

Table S2 Investigational products, comparator, reliever and maintenance treatment

Investigational product	Dosage form and strength	Manufacturer	Material identity number	Batch number(s)
AZD9668	Coated tablet 30 mg	AstraZeneca	D0900131	09-001726AZ 09-004267AZ 09-005028AZ
AZD9668	Coated tablet 10 mg	AstraZeneca	D0900130	09-001725AZ 09-004265AZ 09-004916AZ
AZD9668	Coated tablet 2.5 mg	AstraZeneca	D0900129	09-001724AZ 09-004264AZ 09-004915AZ
Placebo to AZD9668	Coated tablet placebo	AstraZeneca	D0900132	09-001745AZ
Characteristics	**Salbutamol sulphate, used as reliever medication during run-in and treatment period**		**Tiotropium bromide, used for maintenance treatment during run-in and treatment period**	
Active ingredients:	Salbutamol sulphate		Tiotropium bromide	
Excipients:	Dependent on product provided		Lactose monohydrate	
Dosage form:	pMDI		Inhalation powder, hard capsules	
No. of doses:	200 actuations		30 capsules/package	
Strength:	100 µg /dose		18 µg/dose (once daily)	
Manufacturer:	Dependent on product provided		Boehringer Ingelheim	

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, Table S2), with doses approximately 12 hours apart. AstraZeneca provided the maintenance therapy and reliever medication (Table S2) 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 to be stabilised on maintenance therapy during a run-in period.

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 were produced to show the precision of the data. The primary analysis of data obtained at the clinic (FEV_1, FVC, IC, sputum colour, 6 Minute Walk Test (6MWT), SGRQ-C and FPI-SF [exploratory]) compared end-value of treatment (ie, last value recorded for each patient) between groups in an analysis of covariance (ANCOVA), with treatment and country as fixed factors and using baseline as a covariate. 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 summarised by 4-weekly periods. For 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 and safety endpoints were summarised descriptively.

Patient population

The first patient was enrolled on 13 July 2009 and the last patient completed on 5 August 2010. Eight hundred and thirty-eight were randomised and received investigational product and of these 735 patients completed the study.

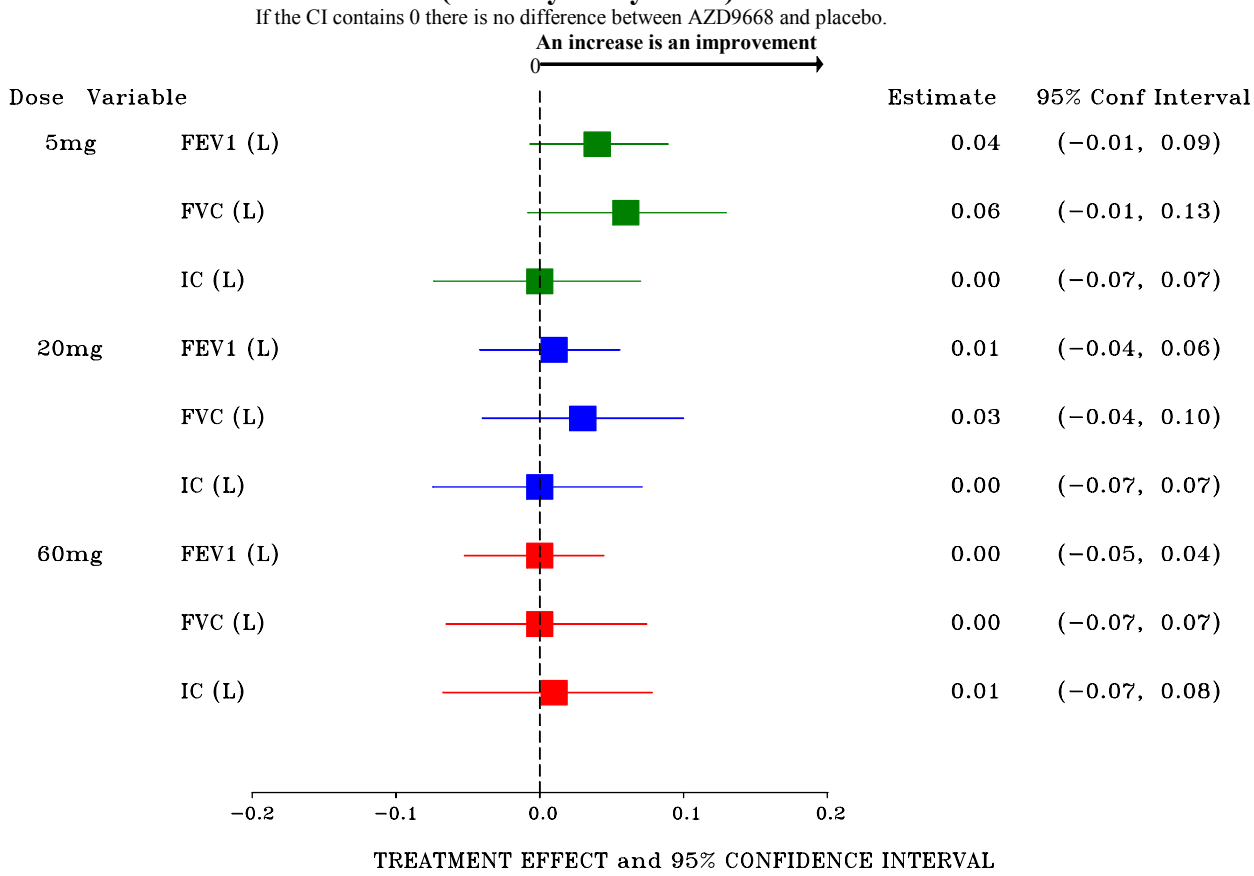
The treatment groups were well balanced for patient characteristics. Overall, the mean duration of COPD was ~9 years (9.0 to 9.8 years) with a mean smoking history of ~40 pack years; ~45% were current smokers and ~55% ex-smokers). Baseline lung functions were balanced between the treatment groups with a mean percent predicted FEV_1 ~58% and FEV_1/FVC (%) ~52%. Mean reversibility and the distribution of reversibility categories were similar across treatment groups. The mean BCSS symptom score at baseline was ~4.7, and the mean number of exacerbations experienced during the 12 months prior to screening was ~1.4. The mean period for the most recent exacerbation prior to screening was ~5.4 months.

Summary of efficacy results

Lung function

Mean pre-bronchodilator FEV_1 at baseline was balanced across the treatment groups ranging from 1.47 to 1.51 L. In the AZD9668 60 mg group at the end of treatment, the change in mean pre-bronchodilator FEV_1 compared to the placebo was 0.00 L (95% CI: -0.05, 0.04), p=0.873. A Forest plot for this end point (and for FVC and IC) is shown in Figure S1. Pre-bronchodilator FEV_1 was also unchanged at Weeks 1 to 8. The results obtained for mean pre-bronchodilator FVC and IC at the end of treatment were consistent with the primary variable (Figure S1).

Figure S1 **Plot of the difference and the 95% CI between the AZD9668 doses and placebo for pre-bronchodilator FEV_1 (L), FVC (L) and IC (L) at the end of treatment (Efficacy analysis set)**



The ANCOVA model includes country and baseline as covariates

The analysis of post-bronchodilator FEV_1, FVC (L) and IC (L) measured at clinic at the end of treatment, together with FEV_1 measured at home, were consistent with the results obtained for the primary variable. For mean PEF measured at home, in the AZD9668 60 mg group at the end of treatment, the change in mean PEF (morning and evening) compared to the placebo was -8.12 L/min (95% CI: -15.9, -0.30), p=0.042 and -7.55 L/min (95% CI: -16.0, 0.86), p=0.079, respectively suggesting a worsening of PE in the AZD9668 60 mg group compared

to placebo. The pattern in the results for the above comparison during Weeks 1-4, 5-8 and 9-12 (PEF morning and evening) was consistent with the end of treatment results.

Signs and symptoms

(i) Clinic defined exacerbation

The total number of patients with 1 or more events in each treatment group was 29 (13%), 29 (14%), 28 (14%) and 34 (17%) in the placebo, AZD9668 5, 20 and 60 mg groups, respectively, and was marginally higher in the AZD9668 60 mg group compared to the other treatment groups. Patients typically experienced a single event during the treatment period with few patients experiencing 3 or 4 events; these were confined to the AZD9668 5 and 60 mg groups. The duration of exacerbation (days) across the groups was broadly similar. An analysis of time to first clinic defined exacerbation showed no difference between placebo and the AZD9668 5 and 20 mg groups. For the comparison between placebo and the AZD9668 60 mg group, the risk of an event appears greater in the AZD9668 60 mg group HR=1.29 (95% CI: 0.78, 2.11), p=0.318.

(ii) EXACT, BCSS, sputum colour, reliever medication, exercise capacity, SGRQ-C

There was no evidence of a beneficial effect on the secondary signs and symptoms variables during 12 weeks of treatment with AZD9668 5, 20 and 60 mg compared to placebo. No dose response was observed.

Summary of pharmacokinetic results

Day 28 pre-dose trough concentrations demonstrated a 4-fold increase in plasma concentrations for AZD9668 20 vs. 5 mg and a 3-fold increase for AZD9668 60 vs. 20 mg. Plasma concentrations at the estimated C_{max} were approximately 2-3 times higher at each dose level compared to pre-dose concentrations and showed similar dose-proportionality in concentrations. At the end of treatment (Day 84) the pattern in plasma concentrations pre- and post-dose was similar to those seen at Day 28.

Summary of safety results

A high proportion of the patients in each treatment group (~88%) were exposed to >80 days treatment ie, completed randomised treatment as planned and the mean number of days on treatment was similar across the treatment groups (range 71.1 to 74.3 days).

The number of patients with AEs was similar in each treatment group with 84 (39%), 78 (37%), 66 (32%) and 67 (33%) in the placebo and AZD9668 5, 20 and 60 mg groups, respectively. One patient experienced an AE with fatal outcome during the study (placebo group: pulmonary thrombosis/embolism). The number of patients with SAEs was 8 (4%), 7 (3%), 12 (6%) and 15 (7%) in the placebo and AZD9668 5, 20 and 60 mg groups, respectively and was higher in both the AZD9668 20 and 60 mg groups vs. both the placebo and AZD9668 5 mg groups. However, there was no clear evidence of any dose dependency in the occurrence of SAEs across the AZD9668 groups. The incidence of AEs leading to discontinuation of placebo/AZD9668 was similar across the treatment groups with 10 (5%),

11 (5%), 12 (6%) and 10 (5%) patients in the placebo and AZD9668 5, 20 and 60 mg groups, respectively. No OAEs were identified in any treatment group.

Few AEs were reported at an incidence of >2% in any treatment group and most were reported at <1% (overall). The most commonly reported AE in each group was nasopharyngitis with 12 (6%), 14 (7%), 9 (4%) and 9 (4%) patients in the placebo, AZD9668 5, 20 and 60 mg groups, respectively. For the other AEs that were reported at an incidence of >2% (COPD, upper respiratory tract infection, headache, dry mouth and rash), there was no apparent evidence of any dose-dependency in tolerability. Generally, there were no important differences across the groups in the reporting of AEs by intensity.

Across the AZD9668 treatment groups, there was no evidence of any dose-dependent changes in haematology, clinical chemistry, urinalysis, vital signs, ECG and physical examination data and no apparent difference in each AZD9668 treatment group compared to placebo.

AZD9668 was generally well tolerated. A few patients developed high transaminase values during the study. Although definite evidence of dose relationship was lacking, there was a suggestion of an increased incidence of liver transaminase elevations in patients on AZD9668 for which there was no definite alternative explanation. The highest transaminase elevations occurred at the AZD9668 60 mg dose. There were no Hy's law cases.