AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00014
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A 12-week, Phase-II, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multi-Centre Study to Assess the Effect of 60 mg AZD9668 Administered Orally Twice Daily on Structural Changes in the Airways by Multi-Slice Computed Tomography (MSCT) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study dates: First patient enrolled: 06 January 2010
Last patient completed: 17 November 2010

Phase of development: Therapeutic exploratory (IIb)

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

Study centre(s)

Twelve centres, across 5 countries participated in this study: Canada (2), Denmark (3), The Netherlands (2), Romania (2) and Ukraine (3).

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 structural changes effected by AZD9668 in the airways of adults with COPD by MSCT.	**Primary** AWT-Pi10 (airway wall thickness of a theoretical airway with an internal perimeter of 10 mm) **Secondary MSCT variables aligned to the primary objective** 5th generation wall area % Air Trapping Index (ATI) on expiratory scans **Exploratory MSCT variables aligned to the primary objective** Volume adjusted 15th percentile density Mean wall area % for airways of 4th to 6th generation Emphysema index (or relative area)	Efficacy
Secondary To relate structural changes in the airways to pulmonary function variables and symptoms of COPD.	**Lung function parameters** Pre-bronchodilator IC, TLC, FRC, RV and SGaw Pre-bronchodilator DL_{CO} Pre- and post-bronchodilator FEV_1, FVC and SVC PEF morning and evening (daily recordings) FEV_1 morning and evening (daily recordings) **Symptoms** Breathlessness, Cough and Sputum Scale (BCSS) EXAcerbations of Chronic Pulmonary disease Tool (EXACT) St George's Respiratory Questionnaire for COPD patients (SGRQ-C) Use of reliever medication and Exacerbations	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

a The exploratory objectives are presented in the main CSR.

Study design

A 12-week randomised, double-blind, placebo-controlled, parallel-group, multi-centre Phase IIb study to assess the effect of AZD9668 60 mg on structural changes in the airways in COPD patients.

Target patient population and sample size

The target population included COPD patients and was defined as ex-smokers for at least 12 months prior to the study with a clinical history compatible with COPD with airflow obstruction confirmed by a post-bronchodilator percent predicted FEV_1 of 40 to 70% inclusive and FEV_1/FVC of <70%. The sample size was based on similar studies in asthmatics where

anti-inflammatory treatments have shown a treatment effect in 12 weeks and has been kept low to ensure minimal radiation exposure for a feasibility study.

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

Table S2 IP, comparator, reliever and maintenance treatment

Investigational product	Dosage form and strength	Manufacturer	Material identity number	Batch number
AZD9668	Coated tablet 30 mg	AstraZeneca	D0900131	09-005028AZ
Placebo to AZD9668	Coated tablet placebo	AstraZeneca	D0900132	09-005456AZ
Characteristics	**Salbutamol sulphate: reliever medication during run-in and treatment period**		**Tiotropium bromide: 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	

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 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 airway wall thickness of a theoretical airway with an internal perimeter of 10 mm (AWT-Pi10) as measured at clinic visits. As the study was exploratory in nature, a 2-sided p-value of <0.1 was considered significant. The primary analysis of MSCT data obtained at the clinic (AWT-Pi10, 5th generation wall area %, Air Trapping Index, Volume adjusted 15th percentile density, 4th-6th Generation Wall area percentage, emphysema index) compared end of treatment value (ie, last value recorded for each patient) between groups in an analysis of covariance (ANCOVA), with treatment and scanner as fixed factors and using baseline as a covariate. The inclusion of Total Lung Volume (TLV) at baseline, Visit 6 and change from baseline as an additional covariate was explored for all MSCT variables except PD15. Data were summarised by visit. Plots of MSCT variables vs. clinic lung function and other variables of interest were produced. In addition, the correlation of MSCT results with these variables was also assessed. The analysis of all other data obtained at the clinic (clinical lung function measurements [spirometry,

plethsymography and diffusion capacity], St George's respiratory questionnaire for chronic obstructive pulmonary disease [SGRQ-C: total and components]) compared end of treatment value (ie, the last value recorded for each patient) between groups in an analysis of covariance (ANCOVA), with the baseline value as covariate and country and treatment as fixed factors. Data were summarised by visit and the principle of last value carried forward (LOCF) was used for both plots and summaries.

Following unblinding of the study and during the review of the MSCT data, it became apparent that some of the listed and summarised MSCT results included outcome measures that appeared to be inconsistent with those expected for the studied variables. Limitations in the software used for the initial analysis were discovered, which were corrected in a later release of the software. After careful investigation by the study team and in consultation with the Principal Investigator, it was agreed that these results might not be fully capable of meaningful interpretation without recourse to reanalysis of the scans (involving the use of improved analytical software). The reanalysis was also an opportunity to include data that were accidentally omitted from the original analyses. The results that follow represent the outcome of that reanalysis and are supplemented with a per protocol analysis to test the robustness of the findings from the primary analysis. It should be noted that the conclusions drawn for the primary and secondary outcome variables from the original analyses were unchanged following reanalysis. However, there was less variability in the data and greater precision therefore these results were considered more robust.

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 (except for EXACT, where 7 days was used), and the end-value of treatment as the average of the last available 6 weeks. Data were summarised by 4-weekly periods. Data on exacerbations were summarised. Adverse events and safety endpoints were summarised descriptively.

Patient population

The first patient was enrolled on 06 January 2010 and the last patient completed the study on 17 November 2010. One hundred and nine patients were enrolled and 52 were randomised and received investigational product. No patients were excluded from the ITT analysis.

The treatment groups were balanced for COPD characteristics with the exception of the most recent exacerbation prior to screening. The mean duration of COPD was ~7.7 years (mean of 8.2 and 7.1 years in the placebo and AZD9668 60 mg groups, respectively) with a mean smoking history of ~34 pack years; all were ex smokers. Baseline lung function was balanced between the treatment groups with a mean percent predicted FEV_1 ~57% and FEV_1/FVC (%) ~50%. Mean reversibility (~11% overall) and the distribution of reversibility categories were similar across treatment groups. The mean period for the most recent exacerbation prior to screening was longer in the placebo group vs. the AZD9668 60 mg group with 19.2 vs. 11.9 months, respectively; this was largely due to an outlier. However, when these data were categorised as either ≤12 or >12 months, the difference was less marked.

Summary of efficacy results

MSCT variables

The primary objective of the study was to evaluate structural changes effected by AZD9668 in the airways of adults with COPD by MSCT.

There was no difference between placebo and AZD9668 60 mg for the analysis of Airway Wall Thickness (AWT-Pi10) (mm) at the end of treatment: LS mean difference of 0.01 mm (90% CI: -0.03, 0.04) p=0.771 (Table S3).

The analysis of the 5th wall area (%) was consistent with the primary variable with no difference between placebo and AZD9668 60 mg: LS mean difference of 0.27% (90% CI: -0.25, 0.80) p=0.380. There was a small reduction in ATI in favour of the AZD9668 60 mg group with an LS mean difference of -2.57 % (90% CI: -6.48, 1.34) but the result did not reach statistical significance (p=0.269) (Table S3).

Table S3 Analysis of the MSCT variables at the end of treatment (Efficacy analysis set)

Treatment group	N	Baseline[a]	End of treatment[b]	Analysis of covariance[c]			
				End of treatment	Difference between AZD9668 and placebo		
		Mean (SD)	Mean (SD)	LS mean (SEM)	LS mean difference (SEM)[d]	90% CI	p-value
Primary variable:	**Airway Wall Thickness (AWT-Pi10) (mm)**						
Placebo bid	19	3.85 (0.171)	3.83 (0.118)	3.83 (0.017)			
AZD9668 60 mg bid	17	3.85 (0.166)	3.85 (0.172)	3.84 (0.021)	0.01 (0.022)	(-0.03, 0.04)	0.771
Secondary variables:	**5th generation wall area (%)**						
Placebo bid	19	66.59 (1.613)	66.08 (1.534)	65.94 (0.234)			
AZD9668 60 mg bid	17	66.46 (1.019)	66.60 (1.242)	66.21 (0.275)	0.27 (0.306)	(-0.25, 0.80)	0.380
	Air Trapping Index (ATI) (%)						
Placebo bid	13	57.78 (9.977)	57.17 (13.863)	57.12 (1.599)			
AZD9668 60 mg bid	15	53.86 (11.511)	51.69 (9.473)	54.56 (1.706)	-2.57 (2.248)	(-6.48, 1.34)	0.269

a Baseline = Visit 2 assessments; carried out 2-7 days prior to Visit 2.
b End of treatment = Week 12 (Day 84); carried out 0-3 days prior to Visit 6.
c Analysis of covariance includes treatment, scanner and baseline as covariates. For 5th Generation Wall Area Percentage, baseline TLV is also included as a covariate. For Air Trapping Index, the change from baseline TLV is also included as a covariate.
d LS mean difference: AZD9668 vs. placebo.
SD: standard deviation, LS: least square, SEM: standard error of mean, CI: confidence interval

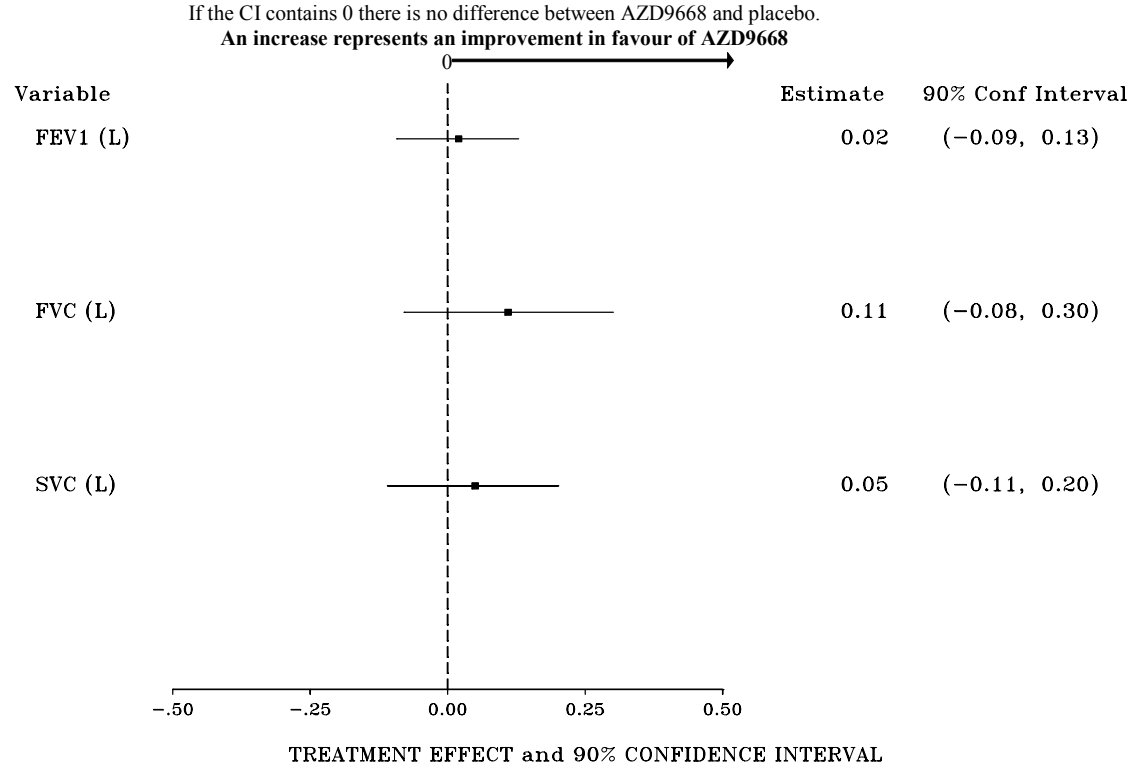
Lung function variables

(i) Clinic spirometry: pre- and post-bronchodilator FEV_1, FVC and SVC

Mean pre-bronchodilator clinic FEV_1 at baseline was lower in the placebo group vs. the AZD9668 60 mg group, 1.38 vs. 1.61 L, respectively. At Week 1, FEV_1 increased from baseline in the placebo group before decreasing at Week 4 to at or near baseline values and remained largely unchanged at Week 8; the profile of the results for the AZD9668 60 mg group decreased slightly from baseline at Week 4 but otherwise remained largely unchanged from baseline.

An analysis of mean pre-bronchodilator FEV_1 at the end of treatment showed an LS mean difference of 0.02 L (90% CI: -0.09, 0.13), p=0.784 for the comparison between placebo and AZD9668 60 mg (an increase represents an improvement in favour of AZD9668). The results from an analysis of pre-bronchodilator FVC (L) and SVC (L) were broadly consistent with FEV_1 (Figure S1). The pattern seen in the results for the post-bronchodilator clinic spirometry was similar to the pre-bronchodilator results.

Figure S1 Plot of the difference and the 90% CI between the AZD9668 60 mg and placebo for pre-bronchodilator FEV_1 (L), FVC (L) and SVC (L) at the end of treatment (Efficacy analysis set)



The ANOVA model includes country and baseline as covariates
If CI contains 0, there is no difference between AZD9668 and Placebo. An increase is an improvement

Each line represents the 90% CI around the LS mean.

(ii) Home spirometry: morning and evening FEV_1 and PEF

An analysis of mean morning FEV_1 at the end of treatment showed a statistically significant LS mean difference of 0.19 L (90% CI: 0.05, 0.34), p=0.032 for the comparison between placebo and AZD9668 60 mg (an increase represents an improvement in favour of AZD9668). The result from an analysis of mean evening FEV_1 at the end of treatment was similar: LS mean difference of 0.21 L (90% CI: 0.07, 0.35), p=0.017 for the comparison between placebo and AZD9668 60 mg. These results should be treated with caution (no adjustment was made for multiplicity. Neither result for the analysis of mean morning and evening PEF at the end of treatment for the comparison between placebo and AZD9668 60 mg was statistically significant.

(iii) Lung function diffusion capacity and body plethysmography data

The results from an analysis of mean body plethysmography data at the end of treatment showed small improvements in favour of the AZD9668 60 mg. As for DL_{CO}, the body plethysmography results did not reach statistical significance.

Signs and symptoms

(i) EXACT

An analysis of the mean EXACT total score at the end of treatment showed a statistically significant LS mean difference of -4.77 (90% CI: -9.43, -0.11), p=0.092 for the comparison between placebo and AZD9668 60 mg (a decrease represents an improvement in favour of AZD9668). A similar pattern was seen in the analysis of the sub domain scores, however, only the domain for cough and sputum was statistically significant (p=0.011). These results should be treated with caution (no adjustment was made for multiplicity).

(ii) BCSS

An analysis of the mean BCSS total score at the end of treatment showed a statistically significant LS mean difference of -1.03 (90% CI: -1.75, -0.32), p=0.020 for the comparison between placebo and AZD9668 60 mg (a decrease represents an improvement in favour of AZD9668). A similar pattern was seen in the analysis of the sub domain scores with the cough score and sputum score being statistically significant (p=0.006 and p=0.062, respectively); consistent with the results obtained for the EXACT sub domain score for cough and sputum. The breathing difficulty score did not reach statistical significance (p=0.242). These results should be treated with caution (no adjustment was made for multiplicity).

(iii) Reliever medication

An analysis of mean symptom- and reliever-free days at the end of treatment showed a statistically significant LS mean difference of 7.07 % of days (90% CI: 0.14, 14.00), p=0.094 were symptom- and reliever-free for the comparison between placebo and AZD9668 60 mg (an increase represents an improvement in favour of AZD9668); the results for the analysis of symptom free and reliever free days (the non combined data) was similar, albeit neither were

statistically significant (p=0.150 and p=0.370, respectively).

(iv) Health-related quality of life (SGRQ-C)

An analysis of the overall score for SGRQ-C questionnaire data at the end of treatment showed an improvement in QoL that approached the MCID in favour of the AZD9668 60 mg group with an LS mean difference of -3.97 (90% CI: -9.36, 1.42) but the result did not reach statistical significance (p=0.222).

(v) Exacerbation

In total, 5 patients reported an exacerbation during the study; all were from the placebo group and none required hospital treatment.

Correlation between MSCT variables and lung function and symptom variables

(i) Lung function

There was no evidence of a correlation between MSCT variables (AWT-Pi10, 5th generation wall area % and Air Trapping Index) and pre- and post-bronchodilator FEV_1, FVC, and SVC (a correlation coefficient of ≥ 0.6 or ≤ -0.6 suggests a relationship between a MSCT variable and a clinic lung function variable). There was no evidence of a correlation between MSCT variables and the other clinic lung function variables. For the per-protocol analysis there was some evidence of a correlation between MSCT variables and clinical lung functions measures and an isolated baseline correlation between Air Trapping Index and morning PEF: -0.66 (90% CI: -0.82, -0.40).

There was no evidence of a correlation between MSCT variables and the pre-bronchodilator lung function diffusion capacity and body plethysmography variables. For the per-protocol analysis there was an isolated baseline correlation between 5th generation wall area % and IC: -0.65 (90% CI: -0.81, -0.38).

(ii) Symptom variables

With the exception of AWT-Pi10 and BCSS breathing difficulty score at baseline (0.61, 90% [CI: 0.42, 0.74]), there was no evidence of a correlation between MSCT variables and the EXACT total and symptom scores, BCSS total and sub domain scores and the SGRQ-C scores.

There were no correlations between MSCT variables and the EXACT total and symptom scores, BCSS total and sub domain scores and the SGRQ-C scores for the per-protocol analysis.

Summary of safety results

A high proportion of patients in both groups completed more than 80 days of treatment with 21 (78%) patients in the placebo group vs. 21 (84%) in the AZD9668 60 mg group.

Overall, 54% of patients included in the safety population experienced at least 1 AE during the course of the study. The number of patients with AEs was identical in each treatment group with 14 (52%) vs. 14 (56%) in the placebo group vs. AZD9668 60 mg group, respectively. No patient experienced an AE with fatal outcome during the study. One SAE was reported during the study (in the placebo group); a post procedural complication (the investigator term: left pneumothorax due to bronchoscopy). Three patients (all in the placebo group) experienced an AE leading to discontinuation of study treatment. No OAEs were identified in any treatment group. Adverse events were typically reported at single incidences in both groups with few AEs reported with an incidence of ≥2 patients in any group; the most commonly reported AE was nasopharyngitis with 2 (7%) vs. 4 (16%) in the placebo group vs. AZD9668 60 mg group, respectively.

Overall, there were no clinically important abnormalities in haematology and no clinically important abnormalities in clinical chemistry that could be related to treatment with AZD9668. The results for vital signs, ECG, and physical examination and were unremarkable. AZD9668 was generally well tolerated.