AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00010
Edition Number	1
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A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28 Day Oral Administration of AZD9668 in Patients with Bronchiectasis

Study dates: First patient enrolled: 25 September 2008
Last patient completed: 20 April 2009

Phase of development: Therapeutic exploratory (II)

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

Study centres

The study was conducted at 6 centres in Canada and 4 centres in the UK.

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	**Primary**
To investigate whether AZD9668 shows evidence of efficacy in bronchiectasis patients by investigation of:	
• Absolute and percentage neutrophil cell count in the sputum	Neutrophil counts (absolute and %) in samples of waking sputum and sputum collected during the 2-hour period following waking (the primary endpoint)
• Signs and symptoms of bronchiectasis (including effects on quality of life)	24-hour sputum weight SVC (slow vital capacity), FEV_1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and $FEF_{25-75\%}$ (forced expiratory flow between 25% and 75% of forced vital capacity) Bronkotest diary card record of signs and symptoms of bronchiectasis St George's Respiratory Questionnaire for COPD patients (SGRQ-C)
Secondary	**Secondary**
To investigate the effect of AZD9668 on neutrophil elastase (NE) activity in sputum	NE activity in samples of sputum collected on waking and during the 2-hour period following waking (the primary endpoint)
To investigate the effect of AZD9668 on other inflammatory markers in sputum	TNF-α, IL-6, IL-1β, RANTES, MCP-1, IL-8, LTB-4 in spontaneous sputum collections (waking and 2-hour)
To investigate the effect of AZD9668 on inflammatory markers in blood	Serum amyloid-A and high sensitivity CRP (hsCRP), plasma TNF-α, IL-8, IL-6 and IL-1β.
To investigate the safety and tolerability of 28 days' dosing with AZD9668 in bronchiectasis patients	Reported adverse events (AEs), haematology, clinical chemistry, urinalysis, physical examination, ECG, vital signs, bacteriology sputum culture
To confirm AZD9668 exposure in plasma and in spontaneously produced sputum	Concentration of AZD9668 in plasma Concentration of AZD9668 in sputum supernatant
To investigate the effect of AZD9668 on urine desmosine (marker of tissue degradation)	Assay of desmosine (total and free) from 24-hour urine collections at Visits 1a, 1b and 4. The endpoint was the Visit 4 sample. (Desmosine data were also normalised for creatinine)
Exploratory	
To investigate the effect of AZD9668 on other markers of tissue degradation (plasma desmosine and sputum hydroxyproline) [1]	Assay of desmosine in plasma from blood samples taken at Visits 2 and 4. Assay of hydroxyproline in spontaneous sputum collections (waking and 2-hour) at Visits 1a, 1b, 2, 3a, 3b and 4.
To investigate the effect of AZD9668 on markers of mucus hyper-secretion (MUC5AC in sputum) [1]	Assay of MUC5AC in an aliquot of sputum supernatant produced from the spontaneous sputum collection (waking and 2-hour) at Visits 1a, 1b, 2, 3a, 3b and 4.
To collect samples for possible retrospective pharmacogenetics.[2]	

1 Results for these exploratory objectives are included in the Clinical Study Report but not in the Synopsis.
2. The pharmacogenetics analysis does not form part of the CSR.

Study design

A randomised, double-blind, placebo-controlled, parallel group study.

Target subject population and sample size

It was planned to randomise 40 male, or female (of non-child bearing potential) patients, aged 18 to 80 years, with bronchiectasis diagnosed with a historical high resolution computerised tomography (HRCT) or bronchogram.

The study was exploratory and therefore the sample size was not based on obtaining power to detect specific effects. Assuming that the variability (SD=1 on logged data) would be such that a 50% decrease in neutrophil numbers in the sputum would not be missed (80% power), a sample size was 40 patients (20 per group) was chosen.

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

Patients were randomised to receive either AZD9668 tablets (2x30 mg) or placebo tablets, orally, bid (approximately 12-hourly) for 28 days (±2 days).

Batch numbers:	AZD9668 tablets:	H 2029-01-01-01, H 2029-01-01-02
	Placebo tablets:	H 2030-01-01-01, H 2030-01-01-02

Duration of treatment

28 days (±2 days).

Statistical methods

The primary outcome variables (from the Bronkotest diary card, SGRQ-C, lung function, sputum and blood collections) were compared between AZD9668 and placebo using an analysis of variance (ANOVA) model with fixed factors treatment and country and using baseline as a covariate. As the study was exploratory, a p-value of <0.1 was considered to be significant. No adjustment for multiplicity was applied.

For the neutrophil count and biomarker data the ratio of the measurement in patients on AZD9668 to those on placebo was calculated. ANOVA was used, modelling the data on a log scale and then back transforming the results to give the estimate of the ratio; the baseline values and country were covariates.

Subject population

In total, 69 patients with bronchiectasis were enrolled into the study, of whom 38 were randomised (16 patients on placebo and 22 on AZD9668), and 33 completed the study. The small numbers of patients recruited by some centres, together with randomisation in blocks of 4, is considered to have contributed to the unequal distribution of patients to the placebo and AZD9668 groups. One patient in each treatment group discontinued due to an adverse event, 1 patient in the AZD9668 group discontinued because she took a disallowed medication

(the antibiotic cefuroxime), and 2 patients in the placebo group withdrew from the study voluntarily.

The mean age of the patients in the placebo group was 63 years (range 54 years to 73 years), and in the AZD9668 group the mean age was 61 years (range 42 years to 79 years); 18 (47%) of the patients were male (the proportion of males was higher [59%] in the AZD9668 group than in the placebo group [31%]). Most of the patients were White; there was 1 Black or African American patient and one patient of Other race in the placebo group, and 3 Asians in theAZD9668 group. Mean weight and height were similar in the 2 groups, but BMI was slightly higher in the placebo group. Percent predicted FEV_1 at screening was 77.5% (range 44.9% to 125.6%) in the placebo group and 72.6% (range 31.5% to 120.4% in the AZD9668 group). Concomitant medication use differed between the 2 groups, in that fewer patients in the placebo group were taking tiotropium, inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combinations and/or azithromycin.

Summary of efficacy results

Sputum neutrophils

The ratio of the geometric mean change from baseline sputum neutrophil count between AZD9668 and placebo was similar for the waking sputum sample (ratio 1.06) and the 2-hour sputum sample (ratio 1.07), with wide 90% confidence intervals for both treatment groups. The analysis of covariance did not show a statistically significant difference between AZD9668 and placebo.

Signs and symptoms of bronchiectasis (including effects on quality of life)

24-Hour sputum weight: there was mean reduction of 5.22 g in the AZD9668 group compared with placebo, but the 90% confidence interval for the difference between the treatment groups was wide (-14.9, 4.46), and the difference was not statistically significant.

Lung function: for FEV_1, SVC, FVC and $FEF_{25-75\%}$, the mean changes from baseline in the placebo group were –0.04 L, -0.06 L, -0.01 L and 0.01 L/s, respectively, and in the AZD9668 group the changes were 0.06 L, 0.06 L, 0.05 L and 0.08 L/s, respectively. The changes from baseline in FEV_1 and SVC were statistically significantly greater for AZD9668 than placebo ($p=0.006$ and $p=0.079$, respectively). The changes in FVC and $FEF_{25-75\%}$ were also greater on AZD9668 than placebo, but the differences were not statistically significant.

Daily measurement of peak expiratory flow (PEF) (Bronkotest diary card): there were small variable changes in both treatment groups. The mean decrease in morning PEF in the placebo group was 4.98 L/min, and there was an increase of 4.06 L/min in the AZD9668 group. For evening PEF there was a mean decrease of 1.15 L/min in the placebo group and an increase of 4.56 L/min in the AZD9668 group. The differences were not statistically significant.

Daily symptom scores and use of reliever medication (Bronkotest diary card): there were no statistically significant differences between treatments and the small numerical differences favoured placebo for all variables except breathing.

SGRQ-C: the mean changes from baseline scores in the placebo group were Symptoms -1.8%, Activity 0.6%, Impact -2.3% and Overall -1.3%. In the AZD9668 group the changes were Symptoms –7.2%, Activity –3.5%, Impact –6.3% and Overall –5.6%. In the analysis of covariance the LS mean differences between AZD9668 and placebo for all 4 scores exceeded 4 units (the minimum clinically important difference). None of the differences between AZD9668 and placebo was statistically significant.

Sensitivity analysis showed no effect of concomitant medication on the efficacy results.

Summary of pharmacokinetic results

AZD9668 was measurable in plasma from all patients at 1 to 2 hours after dosing on Day 1, and both pre-dose (trough) and 1 to 2 hours after dosing on Day 28. The plasma concentrations 1 to 2 hours after dosing on Day 28 were slightly higher than on Day 1, which is consistent with the pharmacokinetic properties of AZD9668.

On Day 28 there were measurable concentrations of AZD9668 in the pre- and post-dose samples of sputum supernatant in all patients except one, in whom the post-dose concentration was <LLOQ (<2.00 nM).

Summary of pharmacodynamic results

NE activity in sputum: activity at baseline and the changes from baseline varied markedly between patients in both treatment groups. NE activity in both waking and 2-hour samples decreased from baseline in a greater proportion of individuals receiving AZD9668 than placebo. In the waking sputum samples the ratios of the NE activity at end of treatment to baseline (from the ANOVA model) showed a reduction from baseline in both the placebo and AZD9668 groups, with little difference between them. In the 2-hour samples there was a 49% reduction in NE activity in the AZD9668 group compared to the placebo group (ratio 0.51, 90% CI 0.18 to 1.49). However this comprised of a 66% increase from baseline in the placebo group and a 15 % decrease in the AZD9668 group (from the ANOVA model).

Inflammatory markers in sputum (TNF-α, IL-6, IL-1β, RANTES, MCP-1, IL 8, LTB-4): the inflammatory markers at baseline, and the changes from baseline, varied markedly between patients in both the placebo and AZD9668 groups. There were slightly greater mean reductions in sputum inflammatory markers in the AZD9668 group than the placebo group, especially in the 2-hour sputum samples. The difference between AZD9668 and placebo was statistically significant only for sputum IL-6 (ratio AZD9668:placebo 0.72, 90%CI 0.52 to 1.00, p=0.098) and RANTES (ratio AZD9668:placebo 0.63, 90%CI 0.46 to 0.86, p=0.018), in the 2-hour samples.

Inflammatory markers in blood (serum amyloid A, hs-CRP, TNF-α, IL-6, IL 1β, IL-8): the inflammatory markers at baseline, and the changes from baseline, varied between patients

in both the placebo and AZD9668 groups. There were slightly greater reductions in blood inflammatory markers (except IL-6) in the AZD9668 group than the placebo group, but the difference was statistically significant only for plasma IL-8 (ratio AZD9668:placebo 0.74, 90%CI 0.56 to 0.99, p=0.85).

Summary of safety results

There were no deaths or treatment-emergent serious adverse events. One patient in each treatment group discontinued due to an adverse event (a patient on placebo discontinued after 6 days due to low mood, lethargy, neck swelling, sleep disorder and increased appetite, and a patient on AZD9668 discontinued after 22 days on AZD9668, due to an exacerbation of bronchiectasis). The frequency of patients reporting adverse events was no higher on AZD9668 (68%) than on placebo (94%). The AE reported by the most patients was headache, which was reported by 7/22 patients (32%) on AZD9668, compared with 2/16 (13%) patients on placebo. Most of the headaches were mild, although in 2 patients on AZD9668 the headaches were moderate in intensity (both were considered to be possibly or probably related to study drug). Nasopharyngitis was reported by 4 patients on AZD9668 but none on placebo; there was no pattern in the time of onset of these AE that suggested a relationship to study drug.

One patient on AZD9668 had raised ALT and AST during study treatment, reaching a peak close to 3 x ULN for ALT on Day 22 of dosing. The ALT and AST started to decline while the patient continued treatment and returned to baseline levels after the end of the study. There were no associated symptoms and bilirubin, other liver function tests and LDH remained normal. A relationship to study drug of the raised transaminases in this patient cannot be excluded. Overall, no clinically relevant changes in clinical chemistry, haematology, urinalysis, vital signs, ECG, physical examination or sputum bacteriology were observed.