AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD1981 |
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# A Double-Blind, Placebo-Controlled, Randomised, Parallel Group Phase IIa Study to Evaluate the Histological Changes, Cellularity, Clinical Efficacy and Safety of AZD1981 in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

**Study dates:** First patient enrolled: 17 November 2008
Last patient last visit: 10 June 2009

**Phase of development:** Therapeutic exploratory (IIa)

**International Co-ordinating Investigator:**

**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)

A total of 8 centres in 3 countries (Germany, Netherlands and the United Kingdom) participated in this study.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | **Primary** | |
| To evaluate the effects of 4 weeks treatment with AZD1981 on histology (lung tissue biopsy) and cellularity (bronchoalveolar lavage [BAL]), and 3 weeks treatment with AZD1981 on cellularity (induced sputum) in patients with moderate to severe COPD | Aggregate pathology score: subscore 1 (histological grade), subscore 2 (immuno-histochemistry grade), subscore 3 (leucocyte counts), subscore 4 (proliferation/apoptosis counts).<br>Cell counts of BAL fluid and induced sputum (as % for eosinophils, neutrophils, macrophages, lymphocytes and epithelial cells counts, and as $10^6$/g for total cells count) | Efficacy |
| **Secondary** | **Secondary** | |
| To evaluate the efficacy of AZD1981 compared with placebo on COPD symptoms and functional endpoints in patients with moderate to severe COPD | Forced Expiratory Volume in 1 second<br>Clinical COPD Questionnaire (CCQ)<br>SGRQ-C total score and symptom, activity and impact domains<br>FVC, SVC, IC, $FEF_{25-75\%}$<br>Variables collected in, or derived from diary cards (COPD symptoms, morning peak expiratory flow [mPEF] and evening PEF [ePEF], use of reliever medication) | Efficacy |
| To evaluate safety and tolerability of AZD1981 in patients with moderate to severe COPD | Adverse event (AE) (nature, incidence and severity)<br>Electrocardiogram (ECG)<br>Clinical chemistry, haematology and urinalysis<br>Pulse and blood pressure | Safety |
| To describe plasma exposure of AZD1981 in patients with moderate to severe COPD | AZD1981 plasma concentration | Pharmaco-kinetic |

## Study design

This was a double-blind, placebo-controlled, randomised, parallel-group multi-centre study assessing histological and cellularity changes, clinical efficacy and safety of AZD1981 after a 4-week treatment period in 51 adults (AZD1981 or placebo) with moderate to severe COPD.

Eligible patients were enrolled to a 3-week run-in period. After the run-in period, patients who fulfilled the randomisation criteria were randomised (1:1) to receive a 4-week treatment with either AZD1981 (1000 mg, orally twice daily) or placebo for AZD1981 (orally twice daily).

Lung tissue biopsies and BAL fluid were collected one week before randomisation and at Week 4 (Visits 1b and 6, respectively), and induced sputum was collected at randomisation and Week 3 (Visits 2 and 5, respectively).

### Target patient population and sample size

Provision of informed consent prior to any study-specific procedure.

Men or women ≥40 years of age. Women had to be either permanently surgically sterilised or post-menopausal, i.e., amenorrhoeic for 12 months and follicle-stimulating hormone (FSH) within the post-menopausal range as defined by the central laboratory. Clinical diagnosis of COPD, with symptoms for more than 1 year before Visit 1a. BMI between 18 and 35 $kg/m^2$ and a minimum weight of 50 kg.

Current or ex-smokers with a smoking history of at least 10 pack years (1 pack year=20 cigarettes smoked per day for 1 year). Forced expiratory volume in 1 second ($FEV_1$) 40-80% of the predicted normal (PN) value post-bronchodilator. FEV1/forced vital capacity (FVC) post-bronchodilator <70%. Use of β2-agonist and/or anticholinergics as reliever medication within one year of Visit 0.

It was planned to randomise approximately 40 patients in this study. However in order to account for drop-outs an amendment to the clinical study protocol allowed for additional patients to be recruited. The total number of randomised patient was 52.

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

| Investigational product | Dosage form, strength, dosing schedule, and route of administration | Manufacturer | Batch number |
|---|---|---|---|
| AZD1981 | Four 250 mg AZD1981 tablets, orally, twice daily in the morning and in the evening, i.e., the total daily dose was 2000 mg | AstraZeneca | Germany and United Kingdom: DKB 421<br>The Netherlands: DKB 417 |
| Placebo for AZD1981 | Four placebo tablets, orally, twice daily in the morning and in the evening | AstraZeneca | Germany, The Netherlands and United Kingdom: DKB 418 |

### Duration of treatment

The treatment period was 4 weeks.

### Statistical methods

The primary endpoints for evaluation of effect were: the change in histology and cellularity from baseline (last measurement during run-in, Visit 1b for lung tissue biopsy and BAL, and Visit 2 for induced sputum) to treatment (last measurement during treatment, Visit 6 for lung tissue biopsy and BAL, and Visit 5 for induced sputum).

The primary endpoint – the aggregated pathology score – was analysed using analysis of covariance (ANCOVA) with the effects treatment and country, and also baseline as a covariate (effects considered as fixed). The analysis was repeated for log-transformed data which meant a multiplicative model was used. An estimate of the treatment difference (AZD1981 minus placebo) based on the respective model, a corresponding 95% confidence interval (CI) and a p-value for comparison of the 2 groups were calculated.

For the secondary efficacy endpoints, for the lung function variables, the percent change from baseline to the last individual value was calculated and was analysed using ANCOVA with the effects treatment and country, and also baseline as covariate (effects considered as fixed).

Evaluation of AEs was based on the body system and preferred term. The frequency and incidences of adverse events were tabulated. In these tables, patients with multiple records of the same adverse event (preferred term) were counted only once for each level of summarization, using the worst severity and the strongest relationship to trial medication, respectively.

For clinical chemistry, haematology, coagulation, and urinalysis parameters, descriptive statistics by visit including (absolute) changes from baseline were presented. Frequency tables were produced for urinalysis. The number and percentage of patients with values below, within and above the corresponding normal range were tabulated by visit combined with shifts from baseline to subsequent (change from within at baseline to below/above at subsequent visits).

For pharmacokinetic analysis, plasma concentrations were shown graphically as g-mean value curves and individual curves in separate graphs.

**Patient population**

A total of 84 patients were enrolled at 8 centres in 3 countries. Of these, 52 were randomised to treatment at Visit 2. Overall, 98.1% of the randomised patients completed the study. There was only one patient who discontinued the study prematurely after randomisation.

All efficacy analyses were performed on the full-analysis set (FAS), which comprised of 51 patients: 25 in the AZD1981 group, and 26 in the placebo group. The main safety set was identical to FAS.

Of the 51 patients of the FAS, 38 (74.5%) were male and 13 (25.5%) were female, all White, between 41 and 80 years of age (mean age was 61.0 years). Median time since diagnosis of COPD was 4.1 years (overall range: 0 to 25.3) and median time since first COPD symptoms was 7.6 years (overall range: 1.7 to 25.3). The mean number of pack years of smoking was 45.9. The most common concomitant diagnosis at screening was hypertension. There were slight differences between the groups in some demographic and baseline characteristics, however the treatment groups were considered to be comparable.

**Summary of efficacy results**

No evidence of effect of 4 weeks of treatment with AZD1981 was observed on any of the biopsy histology assessments. Estimated mean difference in aggregate pathology score was 0.96 (95%CI 0.90, 1.03), p=0.2726 (ANCOVA log-transformed score). No evidence of effect was demonstrated for lung function measurements, Clinical COPD Questionnaire, St. George's Respiratory Questionnaire, diary-derived parameters, BAL cellularity assessments or most of the cellularity assessments in induced sputum. However, a statistically significant decrease of eosinophils (%) in sputum was observed in the AZD1981 group, compared to placebo group (p=0.0420; estimates AZD1981 minus placebo: -1.33 [95%CI: -2.61, -0.05]).

**Summary of pharmacokinetic results**

Plasma concentrations of AZD1981 showed that the treated COPD patients were exposed to drug.

**Summary of safety results**

The number of patients who experienced any AE under treatment was 17 (68.0%) in the AZD1981 group and 14 (53.8%) in the placebo group. The most frequently reported AEs were nasopharyngitis (overall 5 [9.8%] patients) and headache (4 [7.8%] patients). No clear between-group differences could be observed, because there were only a small number of patients experiencing AEs at a preferred term level. A causally related AE (as judged by the investigator) was experienced by 1 patient in the AZD1981 group (liver function test abnormal), and by 4 patients in the placebo group with 5 events (headache [2 patients], oral candidiasis, dizziness, and rash). The majority of AEs were of mild or moderate intensity; one patient (AZD1981 group) reported an AE of severe intensity: oxygen saturation decreased. One patient (AZD1981 group) experienced an SAE of hypoxia after bronchoscopy requiring hospitalisation, which was mild in intensity and unrelated to the study drug but related to the study procedure. No discontinuations due to AEs occurred during the treatment period. No deaths were reported during the study.

No marked changes in haematology, clinical chemistry and urinalysis parameters were seen. There were no clinically relevant differences between the treatment groups in safety laboratory variables, ECG, vital signs or physical examination.