AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9831C00001
Edition Number	1
Date	26 May 2009

A 4 week double-blind, placebo-controlled, randomized, parallel group phase IIa study to assess the efficacy and safety of AZD1981 in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)

Study Dates	First patient enrolled: 26 May 2008 Last patient completed: 17 December 2008
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)

22 centres in 5 European countries (Bulgaria, Denmark, Poland, Slovakia and Sweden) enrolled patients into this study.

Publications

There was none at the time of writing this report.

Objectives

The **Primary objective** was to evaluate the efficacy of AZD1981 as compared with placebo in patients with moderate to severe COPD.

The **Secondary objectives** were:

- to evaluate safety and tolerability of AZD1981 in patients with moderate to severe COPD
- to describe the plasma exposure of AZD1981 in COPD patients

The **Exploratory objectives** were:

- to collect blood samples for biomarker analysis including future analysis of biomarkers relevant to COPD and inflammation
- to collect pharmacogenetic samples for possible retrospective pooled analysis (participation was optional)

The exploratory data do not form part of the clinical study report.

Study design

This was a randomised, double blind, placebo controlled, parallel group study to assess the efficacy and safety of AZD1981 in patients with moderate to severe COPD (GOLD stages II and III).

Eligible patients were enrolled to a 2 week run-in period. After the run-in period, patients who fulfilled the randomisation criteria were randomised to receive a 4-week treatment with either AZD1981 or placebo (1:1). The patients who were on inhaled glucocorticosteroids prior to run-in were allowed to continue on their pre-study regimen throughout the study. Ipratropium/oxitropium at stable dose were also allowed, however, long-acting β_2-agonists (LABA) and long-acting anticholinergics (LAMA) had to be discontinued prior to inclusion. The patients on combination GCS/LABA products were therefore shifted to the corresponding inhaled GCS monotherapy. All patients received short-acting β_2-agonist

to be used as needed throughout the study. During the treatment period patients returned weekly for study measurements. Following the treatment period the patients returned to their ordinary COPD therapy, as judged by the investigator.

Target population and sample size

Outpatients, men and postmenopausal/surgically sterile women, at least 40 years of age with a clinical diagnosis of moderate to severe COPD, with symptoms for more than one year. The patients were eligible for enrolment provided they were current or ex-smokers, with a smoking history of ≥10 pack years, had a Body Mass Index (BMI) of 18-30 kg/m^2 and a minimum weight of 50 kg, a post-bronchodilator Forced Expiratory Volume in 1 second (FEV_1) 30-80% of the predicted normal (PN) value and a post-bronchodilator FEV_1/Forced Vital Capacity (FVC) <70%.

The sample size of 100 randomised patients, 50 in each treatment group, was considered sufficient to detect clinically relevant effects on FEV_1.

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

AZD1981 1000 mg (given as 4x250 mg) oral tablets (batch number H 2032-01-01-01), twice daily plus Bricanyl ®Turbuhaler® (0.25 mg/dose) as-needed.

Placebo for AZD1981 oral tablets (batch number H 2033-01-01-01), twice daily, plus Bricanyl®Turbuhaler® (0.25 mg/dose) as-needed.

Duration of treatment

The study included a 2-week run-in period followed by a 4-week treatment period. A follow-up visit was scheduled approximately 1 week after the end of treatment period.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary efficacy variables were pre-bronchodilator FEV_1 and Clinical COPD Questionnaire (CCQ).

Secondary efficacy variables included 4 spirometric variables (FVC, Slow Vital Capacity (SVC), Inspiratory Capacity (IC), the mean Forced Expiratory Flow between 25% and 75% of the FVC ($FEF_{25-75\%}$)), 6-minute walk test (6MWT) including Borg score, St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), diary card variables (COPD symptoms, Peak Expiratory Flow (PEF) morning and evening, use of reliever medication) and Modified Medical Research Council (MMRC) dyspnoea score.

Exploratory efficacy variable was the BODE index, which is a composite variable of body mass index (B), airway obstruction as assessed by FEV_1 (O), dyspnoea as assessed by the MMRC dyspnoea scale (D) and exercise capacity as assessed by 6MWT (E).

CRP in serum was assessed as an exploratory **pharmacodynamic** variable.

Plasma concentration of AZD1981 were determined after first dose, after 2 weeks, and after 4 weeks of treatment.

Criteria for evaluation - safety (main variables)

Nature, incidence and severity of adverse events, Electro Cardio Graphic (ECG) parameters, pulse, blood pressure and safety laboratory assessments (clinical chemistry, haematology, and urinalysis parameters)

Statistical methods

Efficacy data was analysed with an additive analysis of variance (ANOVA) model, with treatment and country as factors and baseline measurements as covariate. The outcome variable for diary card variables was the change from run-in period average to treatment period average. For other data the outcome variable was the change from last pre-dose value to last post-dose value. For analysis of serum CRP, data were logged before analysis and a multiplicative model was used. Pharmacokinetic data was analysed descriptively and AE data was summarized for each treatment and analysed as means of descriptive statistics and qualitative analysis. All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 10% were considered statistically significant on two-sided tests (ie, 5% on one-sided).

Subject population

In total, 156 patients with COPD were screened, of whom 118 met the inclusion criteria and were randomised to study treatments (61 to AZD1981 and 57 to placebo); 94% completed the study. Of the seven patients (6%) who dropped out of the study during treatment, 3 were withdrawn because of adverse events, 1 because of incorrect enrolment, 1 because of non-allowed concomitant medication, 1 met stopping criterion based on elevated liver enzymes and 1 patient withdrew consent after having received the first dose of investigational product. This patient was excluded from the analyses. Of the 117 patients analysed for efficacy and safety, 83% were male and 17% female, all White, aged 43-83 years (mean 63 years), with a mean duration of COPD of 6 years. They all were current or ex-smokers with a history of 10 pack years or more, all but one with FEV_1 between 31% and 80% of predicted normal (mean 54%) and $FEV_1/FVC \leq 70\%$. Most patients (72%) were on inhaled GCS prior to study start (50% on GCS monoproducts and 22% on GCS/LABA combinations). Baseline patient demographics, lung function and COPD medications use were generally well balanced between the groups, except that the AZD1981 group had somewhat higher

mean inhaled GSC dose at entry and slightly lower FEV_1. These slight baseline imbalances had no consequences for the study results since adjusting for covariates in statistical analysis has not changed the outcomes. Compliance to treatment was high (99.6%) and similar between the 2 treatment groups.

Summary of efficacy results

Administration of AZD1981 to a group of patients with COPD did not result in improvement of any of the assessed clinical parameters compared to placebo. Lung function, disease symptoms, functional capacity and health status of patients remained in both groups relatively unchanged over the 4 weeks of treatment. In particular, AZD1981 treatment did not affect the two primary variables, pre-brochodilator FEV_1 and CCQ scores more than placebo. Among the secondary variables, two tests were statistically significant; for PEF evening and $FEV_{25-75\%}$, indicating a decrease in lung function in AZD1981 group compared to placebo. However, most of efficacy variables did not differ between the two treatment arms.

Summary of pharmacokinetic results

Plasma concentrations of AZD1981, both in samples taken after the first dose and those taken after 4 weeks of treatment, confirmed that patients receiving active treatment were exposed to AZD1981. Plasma levels of AZD1981 observed in COPD patients were on average higher than in healthy volunteers and asthma patients given the same dose via suspension.

Summary of pharmacodynamic results

A small but statistically significant increase in serum CRP (exploratory variable) was observed in the AZD1981 treated patients

Summary of safety results

Treatment with AZD1981 1000 mg twice daily over 4 weeks was well tolerated. A total of 65 AEs were reported, whereof 38 in patients receiving AZD1981 and 27 in patients on placebo. Although there were numerically more AEs reported in the AZD1981 group, the proportion of patients experiencing AEs was similar between AZD1981 (33%) and placebo groups (32%). The AEs profiles were similar between the groups. The most common adverse event was nasopharyngitis, which was more common in AZD1981 group (10%) than in placebo (5%), and exacerbations of COPD, reported by 7% of patients in both groups. There were no SAE in patients on AZD1981 and only a few patients discontinued due to AEs (3 in AZD1981 and 1 in placebo group), mainly because of COPD worsening. There were no clinically relevant findings in vital signs, ECG or safety laboratory variables. A slight increase of liver enzymes was noticed in AZD1981 groups compared with placebo, as well as a slight decrease of hematocrit, total leucocytes in the blood and neutrophils. In addition, there was a tendency toward an increase of eosinophils. The changes were numerically small and raised no safety concerns.