AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4818
Study Code	D3540C00005
Edition Number	1.0
Date	16 October 2008

A 4-week double-blind, placebo-controlled, randomised, parallel group phase IIa study to assess the tolerability/safety and efficacy of inhaled AZD4818 in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)

Study Dates	First patient enrolled: 3 January 2008 Last patient completed: 17 June 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)

11 centres in 5 countries enrolled patients into this study.

Publications

None at the time of writing this report.

Objectives

The primary objective was to investigate the tolerability and safety of inhaled AZD4818 delivered via a dry powder inhaler, Turbuhaler®, in COPD patients by assessment of;

- incidence and nature of adverse events (AE)
- Electro Cardio Graphic (ECG) parameters, vital signs, and laboratory assessments (clinical chemistry, haematology, and urinalysis parameters).

The secondary objectives of the study were to evaluate the effects of inhaled AZD4818 in COPD patients compared with placebo on:

- lung function assessed by Forced Expiratory Volume in one (1) second (FEV_1), Forced Vital Capacity (FVC), the mean Forced Expiratory Flow between 25% and 75% of the FVC ($FEF_{25-75\%}$), Vital Capacity (VC), Inspiratory Capacity (IC) and Peak Expiratory Flow (PEF)
- health status assessed by Clinical COPD Questionnaire (CCQ), and COPD Symptoms (breathlessness, cough, chest tightness and night-time awakenings) and use of rescue medication assessed by diary questions
- blood cells and soluble inflammatory markers in blood
- functional capacity by the 6-minute walk test (6MWT), including assessment of dyspnea and fatigue, using the Borg scale
- the BODE index, which is a composite variable of; body mass index (B), airway obstruction as asessed by FEV_1 (O), dyspnea as assessed by the Modified Medical Research Council dyspnea scale (D), exercise capacity as assessed by 6MWT (E).

Additional study objective was to investigate systemic exposure by assessing plasma concentration of AZD4818 after first dose, after 2 weeks, and after 4 weeks of treatment.

It was also intended that the study might be objective for a retrospective pharmacogenetic research (optional part of the study).

Study design

This was a double blind, placebo-controlled, randomised, parallel group and multi-centre study.

Target patient population and sample size

Men and women, at least 40 years of age with moderate to severe COPD, who were symptomatic.

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

AZD4818, dry powder for inhalation, 150 µg/dose, 60 doses/inhaler. Two inhalations twice daily (2x150 µg bid) via the dry powder inhaler Turbuhaler®. Batch number H 1989-01-01-01.

Placebo, dry powder for inhalation, 60 doses/inhaler. Two inhalations twice daily (2x150 µg bid). Batch number H 1866-01-03-01.

Bricanyl® Turbuhaler, Inhalation powder, 200 doses, 0.5 mg/dose, for as-needed use.

Duration of treatment

The study started with a 2-week run-in period, followed by 4 weeks of treatment with investigational product and ended with a 2-week follow-up period.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Evaluation of clinical efficacy of AZD4818 was based on a number of outcome variables: spirometric variables (IC, VC, FVC, FEV_1 and $FEF_{25-75\%}$), Clinical COPD Questionnaire, COPD Symptoms (breathlessness, cough, chest tightness and night-time awakenings), use of rescue medication, 6-minute walk test, including assessment of dyspnea and fatigue, BODE index, and blood cells and soluble inflammatory markers in blood.

Plasma concentrations of AZD4818 in samples taken 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, vital signs, ECG and various laboratory assessments.

Statistical methods

AE data were described in terms of crude frequencies. Most other data were analysed with an analysis of variance model with treatment and country as factors and baseline, when relevant,

as covariate. The outcome variable was mean of treatment period for diary card variables and mean of run-in period as baseline. For other data the last value on treatment was the outcome variable, and the last value during run-in the baseline value.

Graphically the time evolution of data was described in mean value graphs. For these the principle of last value extended was used in order to have all patient at all time points.

Subject population

Of the 66 patients randomised in the study, 65 were analysed for safety and efficacy. One randomised patient was excluded from all analyses since he was withdrawn from the study for non-treatment related reasons after the first dose of AZD4818. Of the 65 analysed patients, 47 (72%) were male and 18 (28%) were female. Patients were between 42 and 78 years old (mean 65.6 years), and all but 2 were White. All patients had a diagnosis of COPD (with a median time since diagnosis of 6 years) and 34% of patients were on inhaled corticosteroid therapy before enrolment into the study. The two treatment groups were comparable at baseline. Nearly 82% of the randomised patients completed the study. More patients (24%) discontinued in the AZD4818 than in placebo group (13%). In total, 12 of the randomised patients discontinued the study prematurely; all but one due to adverse events.

Summary of efficacy results

There was no indication that treatment with AZD4818 had any clinical benefit, as determined by assessments of lung function, functional capacity, COPD symptoms and health status. For both groups, the efficacy variables indicated a slow worsening over the 4 weeks of treatment; lung function deteriorated, walking distance decreased, while dyspnea and BODE index score increased. One test was statistically significant at 5% level (two-sided), effect on PEF evening, favouring placebo. Also other diary variables, symptom scores and use of rescue medication, were numerically in favour of placebo. For spirometric variables, 6MWT, BODE and CCQ scores, statistical analysis did not demonstrate any difference between AZD4818 and placebo.

Summary of pharmacodynamic results

The study did not detect any reduction in the number of white blood cells or levels of soluble inflammatory markers in blood after the 4 weeks of treatment with AZD4818.

Summary of pharmacokinetic results

Plasma concentrations of AZD4818, both in samples taken within 10 minutes after the first dose and those taken after 2 and 4 weeks of treatment, suggest that patients received the exposure that would be expected from the administration of 300 µg twice daily by inhalation via Turbuhaler.

Summary of safety results

The treatment with AZD4818 twice daily during 4 weeks was well tolerated. A total of 97 AEs were reported, whereof 51 in patients receiving AZD4818 and 46 in patients on placebo. Overall, the percentage of patients reporting an AE was somewhat lower in AZD4818 (67%) than placebo group (84%). However, more patients in AZD4818 group than in placebo experienced severe COPD exacerbations and also more patients on AZD4818 discontinued the treatment due to an AE. The most frequently reported AE was COPD exacerbation, reported by 9 (27%) of patients on AZD4818 and 3 (9%) on placebo, followed by cough and nasopharyngitis, which both occurred at higher rate in placebo group (22 and 25%, respectively) than AZD4818 group (9 and 3%, respectively). The 2 SAE in this study (COPD exacerbation and deep vein thrombosis) were both recorded in patients on AZD4818. There were no clinically relevant findings in vital signs, ECG or safety laboratory variables.

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