AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D5892C00014
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A multi-centre, randomised, double-blind, cross-over design study to evaluate efficacy on exercise tolerance of budesonide/formoterol (Symbicort®Turbuhaler®) 320/9 µg one inhalation twice daily compared with placebo and formoterol (Oxis®) Turbuhaler 9 µg one inhalation twice daily in patients with severe chronic obstructive pulmonary disease (COPD).

Study dates:	First patient enrolled: 26 July 2007 Last patient completed: 13 August 2008
Phase of development:	Therapeutic use (IV)

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

Study centre(s)

The study was conducted at 12 centres in Germany and 1 centre in Switzerland. The first patient entered the study on 26 July 2007 and the last patient finished the study on 13 August 2008.

Publications

None as of the completion date of this report.

Objectives

The primary objective of this study was to compare the efficacy on exercise tolerance of Symbicort Turbuhaler 320/9 µg twice daily compared to placebo and Oxis Turbuhaler 9 µg twice daily in patients with severe chronic obstructive pulmonary disease (COPD) by evaluation of the exercise endurance time (EET) measured at 75% of peak work capacity (W_{max}) with cycle ergometry 1 hour post-dose at Visits 5, 7 and 9 (end of each treatment period) as the primary outcome variable.

The secondary objective of the study was to evaluate safety by assessing the nature and incidence of adverse events (AEs).

Study design

The overall study design was a randomised, double blind, active and placebo controlled, cross-over design study to assess the efficacy of Symbicort compared with placebo and Oxis on exercise endurance in patients with severe COPD. EET was measured at the end of each treatment period by a bicycle ergometry test and recordings of St. George´s Respiratory Questionnaire for COPD patients (SGRQ-C), spirometry, body plethysmography and dyspnea score (Borg CR10 scale) were performed. The patients maintained an electronic diary (eDiary) together with an electronic peak expiratory flow (ePEF) log throughout the study, to record morning peak expiratory flow (PEF), COPD symptoms, intake of investigational product and use of reliever medication.

Target subject population and sample size

Patients were outpatients, men or women, ≥40 years of age, with a clinical diagnosis of COPD with symptoms for at least 2 years, and a history of at least one COPD exacerbation requiring a course of oral steroids within 1-12 months prior to study start. The patients were current or previous smokers with a smoking history of ≥10 pack years, had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1)≤50% of predicted normal (P.N.), a pre-bronchodilator FEV_1/vital capacity (VC)<70% as well as a functional residual capacity (FRC)≥120% of P.N. Patients did also have a need for regular use of a short-acting inhaled bronchodilator (β_2-agonists or anticholinergics) as reliever medication. The patients were not allowed to use systemic corticosteroids (CS) within 4 weeks and/or inhaled corticosteroids (ICS) within 2 weeks prior to Visit 2 and during run-in. Patients with a history of asthma or seasonal allergic rhinitis before 40 years of age were excluded from the study.

With a significance level of 5%, a residual standard deviation of 60 seconds and using a pair wise comparison with a t-test, a true difference of 30 seconds was to be detected with 90% power if the sample size in total was 86 patients. Adding 15% to adjust for withdrawals would require 100 patients.

Investigational products: dosage, mode of administration and batch numbers

Symbicort Turbuhaler, inhalation powder, budesonide 320 µg/dose and formoterol fumaratedihydrate 9 µg/dose, 1 inhalation twice daily. Formulation number: 1916-01, Batch number: H 1916-010101

Oxis Turbuhaler, inhalation powder, formoterol fumaratedihydrate 9 µg/dose, 1 inhalation twice daily. Formulation number: 1919-01, Batch number: H 1919-010102

Placebo Symbicort Turbuhaler, inhalation powder, 1 inhalation twice daily. Formulation number: 1866-01, Batch number: H 1866-01-02-01 and H 1866-01-02-02

Placebo Oxis Turbuhaler, inhalation powder, formoterol 4.5 µg/dose, 1 inhalation twice daily. Formulation number: 1927-01, Batch number: H 1927-01-01-02 and H 1927-01-01-03

Duration of treatment

Eligible patients were enrolled to a one-week run-in period during which Atrovent® (ipratropium bromide 40 µg/dose) was used as maintenance medication. After the run-in period, patients who fulfilled the randomisation criteria entered the three one-week treatment periods with one-week wash-out periods between the treatment periods. Ipratropium bromide was used as maintenance medication during the wash-out periods. During the whole study period patients received Bricanyl Turbuhaler (terbutaline sulphate, 0.5 mg/dose) as reliever medication. Following the treatment periods the patients returned to their ordinary used COPD therapy, as judged by the investigator.

Criteria for evaluation - efficacy (main variables)

Primary variable

- EET measured at 75% of W_{max} with bicycle ergometry test at 1 hour after study drug intake

Secondary variables

- EET measured at 75% of W_{max} with cycle ergometry test at 6 hours after study drug intake
- Dyspnea (Borg CR10) score during the bicycle ergometry tests
- Inspiratory capacity (IC) during the bicycle ergometry tests
- Pre-dose spirometry measurements (FEV_1, forced vital capacity [FVC], VC)
- Body plethysmography (VC, IC, FRC, residual volume [RV], total lung capacity [TLC] and specific airway resistance [sRaw])

- SGRQ-C (total score including symptom, activity and impact scores)
- Change from run-in average to treatment in variables recorded in, or derived from, the eDiary

Criteria for evaluation - safety (main variables)

- AEs (nature and incidence)

Statistical methods

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant. The EET was analysed in an analysis of variance (ANOVA) model with patient, period and treatment as fixed factors. Treatment differences were estimated from the model and 95% confidence limits were calculated. For post-dose body plethysmography parameters a multiplicative ANOVA with patient, period and treatment as fixed factors was used. Pre-dose spirometry measurements were analysed in a similar way as the body plethysmography parameters, but with the values from Visits 4, 6 and 8 as covariates (log-transformed). SGRQ-C at the end of each treatment period as well as the variables recorded in the eDiary were analysed in a model similar to the one used for the primary variable, but with the corresponding run-in/washout period mean for eDiary variables as a covariate. AEs were analysed at AstraZeneca Research and Development (R&D) in Lund, by means of descriptive statistics and qualitative analysis.

Subject population

A total of 137 patients were enrolled at 13 centres in 2 countries; 12 centres in Germany and 1 in Switzerland. Of the enrolled patients, 111 were randomised and allocated to a treatment sequence. Twenty patients discontinued the study and thus 91 patients completed the study. The analysis for the primary efficacy variable was based on 96 patients and the safety analysis was based on 111 patients.

Of the 111 patients allocated to treatment, 84 (75.7%) were males and 27 (24.3%) were females. Their average age was 63.7 years (range: 42-83 years). All patients were recorded as White. Their mean FEV_1 was 1.1 L (38% of P.N., range 19-59 L) and mean W_{max} was 63 Watts (W). Totally, including data from combination products, 43 (39%) patients were on ICS. The study population was representative for the target population and in accordance with approved prescribing information. The study included enough patients to fulfil the aim in the power calculation.

Summary of efficacy results

For the primary variable, EET at 75% of W_{max} measured with bicycle ergometry performed 1 hour after the morning dose at the clinic after 1 week of maintenance treatment, Symbicort was shown to be superior to both placebo and Oxis with prolongations of 1 minute and 45 seconds ($p=0.0015$) and 1 minute and 9 seconds ($p<0.0001$). The mean EET during the placebo period was 6 minutes and 53 seconds. Also for EET measured 6 hours post-dose Symbicort was superior to both placebo and Oxis. The respective differences were estimated

to 62 seconds (p=0.0025) and 42 seconds (p=0.039). For most secondary variables Symbicort was shown to be superior to placebo. In addition, Symbicort was shown to decrease the sleep score variable compared to Oxis.

Summary of safety results

AEs were more commonly reported during the placebo period than during the Symbicort and Oxis periods. The system organ class (SOC) most commonly affected by AEs was respiratory, thoracic and mediastinal disorders and the most commonly reported preferred term was COPD. Two AEs, both reported during the placebo period, were judged by the investigator to be causally related to the investigational product. There were 4 serious adverse events (SAEs) reported during the treatment periods. All but one of the SAEs were due to COPD and no SAE was considered by the investigator to be causally related to the investigational product. Discontinuation of investigational product due to an AE (DAE) was reported by 17 patients, and was relatively even distributed among the treatment periods. There were no AEs with fatal outcome in the study and no other significant AEs (OAEs) were identified.