AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D5892C00016
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A double-blind, randomised, cross-over, multi-centre study, to evaluate onset of effect in the morning in patients with severe Chronic Obstructive Pulmonary Disease (COPD) treated with budesonide/formoterol (Symbicort®Turbuhaler®) 320/9 µg, compared with salmeterol/fluticasone (Seretide™ Diskus™) 50/500 µg, both given as one inhalation twice daily for one week each.

Study dates: First patient enrolled: 25 September 2007
Last patient completed: 6 August 2008

Phase of development: Therapeutic use (IV)

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

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Study centres

The study was conducted at 66 centres in 9 countries; Argentina, Australia, Belgium, Brazil, Denmark, Germany, India, the Philippines and the United Kingdom (UK). The first patient entered the study on 25 September 2007 and the last patient finished the study on 6 August 2008.

Publications

None as of the completion date for this report.

Objectives

The primary objective of this study was to evaluate early morning efficacy of Symbicort® Turbuhaler® 320/9 µg one inhalation twice daily compared to Seretide™ Diskus™[1] 50/500 µg one inhalation twice daily in patients with severe Chronic Obstructive Pulmonary Disease (COPD) over one week treatment.

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 double-blind, randomised, double-dummy, 2-period, cross-over, multi-centre study to compare the efficacy and safety of Symbicort Turbuhaler and Seretide Diskus in patients with severe COPD over 1-week treatment periods. Between clinic visits, Peak Expiratory Flow (PEF), Forced Expiratory Volume in 1 second (FEV_1), use of reliever medication, as well as Clinical COPD Questionnaire (CCQ) and morning activities and symptoms questionnaires - Global Chest Symptoms Questionnaire (GCSQ) for symptoms and Capacity of Daily Living during the Morning (CDLM) - for basic morning activities were recorded by the patients in an electronic diary (eDiary)[2]. At clinic visits, pre-dose and post-dose lung function was measured by spirometry. In addition, Patient Reported Outcomes (PRO) were recorded at clinic visits by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C).

Target subject population and sample size

The patients were outpatients, men or women, ≥40 years of age, with a clinical diagnosis of COPD, symptoms for more than 2 years, and a COPD exacerbation during the last year. The patients were current or previous smokers with a smoking history of ≥10 pack years, had an

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[1] Seretide™ Diskus™: Trademark owned by Glaxo Smith Kline.

[2] The terms eDiary PEF and eDiary FEV_1 are used to denote PEF and FEV_1 measurements made by the patients at home using an electronic handheld peak flow meter (PiKo), and then transferred to the eDiary either electronically or manually.

$FEV_1 \leq 50\%$ of predicted normal (P.N.) and a ratio between FEV_1 and vital capacity (VC) <70% (both pre-bronchodilator). The patients should have a previous use of a short-acting inhaled bronchodilator (β_2-agonist or anticholinergics) as reliever medication. Patients with a history of allergic rhinitis (before 40 years of age) and/or asthma were excluded from the study.

The sample size calculation indicated that 380 patients were required and adjusting for a 10% withdrawal rate during the first part of the study meant that 420 patients in total were to be randomised.

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

Symbicort Turbuhaler, inhalation powder, budesonide/formoterol fumarate dihydrate, 320/9 µg/dose, 1 inhalation twice daily. Formulation number: H 1916-01-01, Batch number: 01, 03

Seretide Diskus, inhalation powder, salmeterol xinafoate/fluticasone propionate 50/500 µg/dose, 1 inhalation twice daily. Formulation number: H 1979-01-01, Batch number: 01, 02, 03

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

Placebo Seretide Diskus, inhalation powder, 1 inhalation twice daily. Formulation number: H 1972-01-01, Batch number: 01

Duration of treatment

The patients were enrolled to an approximately 1 week run-in period, during which the patients' ordinary COPD treatment was withdrawn, except for inhaled steroids, if any. If patients were on treatment with an inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combination product, it had to be stopped and the corresponding ICS monoproduct was prescribed, keeping the same dosing regimen. Patients who fulfilled the randomisation criteria entered the two 1-week treatment periods. The treatment periods were separated by a washout period of approximately 2 weeks, during which the patients used their prescribed inhaled steroids, if any, in the same way as during the run-in period. Bricanyl Turbuhaler (terbutaline sulphate) 0.5 mg was used as reliever medication throughout the study.

Criteria for evaluation - efficacy (main variables)

Primary variable

The primary efficacy variable was the change in the average of eDiary PEF measured 5 minutes after morning dose from the run-in/washout period to the subsequent 1-week treatment period.

Secondary variables

Secondary efficacy variables were eDiary PEF measured before, and 15 minutes after morning dose and before evening dose, eDiary FEV_1 (measured before, and at 5 and 15 minutes after morning dose and before evening dose), and use of reliever medication, recorded in the eDiary. At clinic visits at the start of each treatment period, pre-dose and post-dose lung function was measured by spirometry. Between visits, PRO were recorded in the eDiary by; CCQ and morning activities and symptoms questionnaires and SGRQ-C at clinic visits.

Criteria for evaluation - safety (main variables)

The nature and incidence of AEs.

Statistical methods

The primary variable, the change in average values of eDiary PEF, from the last 7 days of the run-in period and washout period respectively, to the average of eDiary PEF measured 5 minutes after dose in the subsequent treatment period was analysed by analysis of variance (ANOVA) using a model with patient, treatment, period and treatment order as factors and the corresponding pre-treatment average as a covariate. The other variables recorded in the eDiary (eDiary PEF, eDiary FEV_1, use of reliever medication, morning activities and symptoms questionnaires and CCQ) were analysed in a similar way as for the primary variable. Onset of action (ie, the mean changes from pre-dose to 5 and 15 minutes post-dose in eDiary PEF and eDiary FEV_1) was analysed using a multivariate ANOVA. AEs were analysed by means of descriptive statistics and qualitative analysis.

Subject population

A total of 706 patients were enrolled at 66 centres in 9 countries; Argentina, Australia, Belgium, Brazil, Denmark, Germany, India, the Philippines and the UK. Of the enrolled patients, 442 were randomised and allocated to a treatment sequence. Thirty-seven patients discontinued the study and thus 405 patients completed the study. The analysis of the primary efficacy variable was based on 357 patients. Even though there were 6% fewer patients than expected in the analysis of the primary variable, this was well compensated by a 17% lower standard deviation than expected. The safety analysis sets consisted of 420 patients for Symbicort and 429 patients for Seretide.

Of the 442 patients allocated to treatment, 316 (71.5%) were males and 126 (28.5%) were females. Their average age was 63.1 years (range: 40-86). All but 108 were White. Median time since diagnosis (of disease under study [DUS]) was 6 years (range: 0-52). Their mean FEV_1 was 0.99 L (range 0.38-1.97 L, 36% of P.N.) and mean VC was 2.36 L (range 0.81-6.58 L), 359 (81%) patients were on ICS, with an average daily dose of 640.3 μg (range: 160-1600). The most common dose was 400 μg, which was prescribed for 65 (18%) patients. The study population was representative of the target population and in accordance with approved prescribing information.

Summary of efficacy results

For the primary variable, the change in average morning eDiary PEF measured at home 5 minutes after dose from run-in/washout to the subsequent 1-week treatment, the difference between Symbicort and Seretide was 1.0 L/min (95% confidence interval, -2.7 to 4.7 L/min, p=0.603). Symbicort had a greater improvement on eDiary FEV_1 measured at home 15 minutes after the morning dose compared to Seretide over the treatment period. Symbicort had faster onset of action as measured by eDiary PEF and eDiary FEV_1 5 and 15 minutes after morning dose at home, and by FEV_1 and Forced Vital Capacity (FVC) 5 minutes after first dose at the clinic. In addition, Symbicort had a greater improvement in performance of basic morning activities compared to Seretide.

Summary of safety results

The frequency of patients reporting AEs was similar in the Symbicort and Seretide treatment 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. There were 5 serious adverse events (SAEs) reported in randomised patients during the study. The most commonly reported SAE was related to COPD. 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 27 patients after first intake of investigational product. The incidences of DAEs were similar in the 2 treatment periods, with COPD as the most commonly reported DAE. No deaths occurred among the randomised patients and no other significant AEs (OAEs) were identified. In conclusion, no safety concerns were identified during the study and the treatments were considered to be safe and well tolerated.