AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/Formoterol
Study Code	D5892C00015
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A 12-week, double-blind, randomised, parallel group, multi-centre, study to evaluate efficacy and safety of budesonide/formoterol (Symbicort® Turbuhaler®) 320/9 µg one inhalation twice daily on top of tiotropium (Spiriva®) 18 µg one inhalation once daily compared with tiotropium 18 µg one inhalation once daily, in patients with severe chronic obstructive pulmonary disease (COPD)

Study dates: First patient enrolled: 18 May 2007
Last patient completed: 16 June 2008

Phase of development: Therapeutic use (IV)

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

Study centres

This study included in total 102 centres from Australia (10 centres), Canada (16 centres), France (12 centres), Germany (12 centres), Hungary (13 centres), Poland (10 centres), Slovakia (13 centres), Spain (6 centres), and Sweden (10 centres).

Publications

None as of the completion date of this report.

Objectives

The primary objective of this study was to evaluate the efficacy on lung function of Spiriva 18 µg one inhalation once daily + Symbicort Turbuhaler 320/9 µg one inhalation twice daily compared to Spiriva 18 µg one inhalation once daily alone.

The secondary objective of the study was to evaluate safety by assessing the nature, incidence and severity of adverse events (AEs) and vital signs, within the treatment groups.

Study design

This study was a multicentre study with a randomised, double-blind, parallel group design to assess the efficacy of budesonide/formoterol as an add-on treatment to tiotropium in patients with severe chronic obstructive pulmonary disease (COPD). A total of 990 patients were enrolled in 102 centres in 9 countries. Of these patients, 660 were allocated to treatment and 659 received at least one dose of study medication.

After a 2 week run-in period, patients who fulfilled the eligibility criteria continued to the maintenance treatment with tiotropium and were allocated to add-on treatment for 12 weeks: either Symbicort 320/9 µg/dose twice daily or placebo twice daily. Bricanyl Turbuhaler 0.5 mg/dose was used as reliever medication throughout the study.

The patients maintained an electronic diary (eDiary) and an electronic peak expiratory flow meter (ePEF) throughout the study, to record data morning and evening. These data included measurements of peak expiratory flow (PEF), COPD symptoms, reliever medication, intake of study drug, morning symptoms after getting out of bed, and routine morning activities at home using a Morning Activities and Symptoms Questionnaire (MASQ). The MASQ in turn consists of the Global Chest Symptoms Questionnaire (GCSQ) and Capacity of Daily Living during the Morning (CDLM).

Patients visited the clinic after 1, 6, and 12 weeks of treatment (Visits 4, 5, and 6) for spirometry, St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), and blood sampling for evaluation of inflammatory mediators.

After completion of the treatment period, the patients returned to their ordinary COPD therapy, as judged by the Investigator.

Target patient population and sample size

The patient population was outpatients, men or women ≥40 years of age, with a clinical diagnosis of COPD, symptoms for at least 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 a forced expiratory volume in 1 second (FEV_1)≤50% of predicted normal, and a ratio between FEV_1 and vital capacity (VC)<70% (both pre bronchodilator). The patients were not allowed to use systemic glucocorticosteroids (GCSs) within 4 weeks and/or inhaled GCSs within 2 weeks prior to the start of the 2 week run-in period. Patients with a history of allergic rhinitis (before 40 years of age) and/or asthma were excluded from the study.

Based on a true difference of 6% in the primary variable (FEV_1), and a residual standard deviation of 0.21 on the logarithmic scale, 280 patients per group were required for 90% power. A significance level of 5% was used, and tests were two-sided. After an approximate adjustment for a withdrawal rate of about 10%, 620 patients needed to be randomised.

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

The investigational product was Symbicort Turbuhaler, an inhalation powder of budesonide/formoterol fumarate dihydrate. This was given as 320 µg/9 µg/dose twice daily. The batch used in this study was H 1916-01-01.

Spiriva, an inhalation powder of tiotropium bromide, given via HandiHaler was used as maintenance medication. This was given as 18 µg/dose, one inhalation every morning. The batches used in this study were H 1920-01-01-01, H 1920-01-02-01, H 1920-01-02-02, and H 1920-01-02-03.

As reliever medication and medication for reversibility testing, Bricanyl Turbuhaler was used. This is an inhalation powder of terbutaline sulphate, 0.5 mg/dose. Bricanyl was used as needed (reliever medication) or as 2 inhalations before measurement (reversibility testing). The batch used in this study was H 1639-03-02-01.

Duration of treatment

Tiotropium 18 µg once daily was given as maintenance treatment during the run-in and treatment periods, ie, a total of 14 weeks. Symbicort 320/9 µg/dose was given twice daily during the treatment period, ie, during 12 weeks.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary variable

The primary variable was pre-dose FEV_1 assessed by spirometry at clinic visits.

Secondary variables

The secondary variables were post-dose FEV_1, and pre- and post-dose forced vital capacity (FVC) and inspiratory capacity (IC), assessed by spirometry at clinic visits. In addition, symptoms and health status captured by questionnaires were evaluated; at clinic visits by SGRQ-C and in eDiary by MASQ and questions about COPD symptoms. Use of reliever medication was assessed as well as PEF, using the ePEF. Also, inflammatory mediators in blood were measured at clinic visits.

In addition to the analyses stated in the clinical study protocol, exploratory analyses were performed for FEV_1 collected in the eDiary, using the ePEF (FEV_1 piko). Also, analyses of severe exacerbations were performed.

Criteria for evaluation - safety (main variables)

Safety was assessed by AEs, vital signs, and physical examination.

Statistical methods

For lung function measured at the clinic, the change from Visit 3 to the mean of the treatment period was expressed as a ratio. Changes were then analysed using a multiplicative analysis of variance (ANOVA) with treatment and country as fixed factors and the Visit 3 value as a covariate.

For most variables measured in the eDiary (including lung function), the change from run-in to the mean of the treatment period, to the last week on treatment, and to the first week on treatment were analysed using an additive ANOVA with treatment and country as fixed factors and the run-in mean as a covariate. The time to finished morning activities was instead analysed using a multiplicative ANOVA with treatment and country as fixed factors and the run-in mean as a covariate.

For SGRQ-C, the change from visit 3 to the last visit (Visit 6) was analysed in an additive ANOVA with treatment and country as fixed factors and the Visit 3 value as a covariate.

For inflammatory biomarkers, the change from Visit 3 to Visit 6 was expressed as a ratio. Changes were analysed using a multiplicative ANOVA model with treatment and country as fixed factors and the Visit 3 value as a (log-transformed) covariate.

The number of severe COPD exacerbations and the total number of days of exacerbation were computed and tabulated. Time to first severe COPD exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a Cox proportional hazards model. The mean number of severe COPD exacerbations per patient was compared between the treatments using a Poisson regression model.

Treatment differences were estimated from the models, and 95% confidence limits were calculated.

Subject population

A total of 990 patients were enrolled at 102 centres in 9 countries. Of these, 660 were allocated to treatment at Visit 3. The first patient entered the study on 18 May 2007 and the last patient finished the study on 16 June 2008. Of the 660 patients randomised, 659 were analysed for safety and 659 were analysed for efficacy in an intention-to-treat analysis. All but 9 were included in the statistical analysis of the primary variable FEV_1.

The treatment groups were balanced in terms of demography and baseline characteristics.

Summary of efficacy results

For the primary efficacy outcome variable, pre-dose FEV_1, the geometric mean for the Symbicort + tiotropium group showed a statistically significant increase by 5% (adjusted ratio) during the treatment period, from 1.08 L (Visit 3) to 1.15 L (mean of the treatment period). For the placebo + tiotropium group, the pre-dose FEV_1 decreased with 1% over the treatment period. The average increase in FEV_1 was 6% larger in the Symbicort + tiotropium group than in the placebo + tiotropium group. The 95% confidence limits for the average increase ranged from 4% to 9%.

There were statistically significant increases for the Symbicort + tiotropium group compared with the placebo + tiotropium group for all secondary lung function variables investigated at visits to the clinic: FEV_1 5 minutes post-dose, FEV_1 60 minutes post-dose, FVC pre-dose, FVC 5 minutes post-dose, FVC 60 minutes post dose, IC pre-dose, and IC 60 minutes post-dose.

With respect to change from run-in to the full treatment period for the eDiary variables, statistically significant positive effects for the Symbicort + tiotropium group compared to the placebo + tiotropium group were found for all variables investigated: morning and evening PEF, morning and evening FEV_1 (piko), use of reliever medication, and symptom scores.

Symbicort + tiotropium statistically significantly improved morning symptoms, routine morning activities (MASQ), morning use of reliever medication, and lung function before and soon after drug administration. SGRQ-C was improved with Symbicort + tiotropium than with placebo + tiotropium.

There was a substantial reduction (62%) of severe COPD exacerbations (defined as use of systemic steroids, hospitalisation or emergency room visit due to deterioration of COPD) with Symbicort on top of tiotropium.

Summary of safety results

The study treatments were safe and well tolerated. The safety population included 329 patients in the Symbicort + tiotropium group and 330 patients in the placebo + tiotropium group. The number of patients who experienced at least one AE, and the total number of AEs, were similar in the two treatment groups (81 and 124, respectively, in the Symbicort + tiotropium group vs 82 and 113, respectively, in the placebo + tiotropium group). The most common AE

was COPD, which was reported by 13 and 20 patients in the Symbicort + tiotropium and placebo + tiotropium treatment groups, respectively. Most of the cases were of mild or moderate intensity. The frequency of pneumonia was low and not different between groups (3 cases in each group). In the Symbicort + tiotropium group there were in total 10 SAEs (including 1 SAE leading to death; Lung neoplasm) reported by 10 patients vs 16 SAEs reported by 14 patients in the placebo + tiotropium group. Nine AEs leading to discontinuation were reported for 8 patients in the Symbicort + tiotropium group vs 12 DAEs for 10 patients in the placebo + tiotropium group. No other significant AEs (OAEs) were reported in this study.