AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/Formoterol
Study Code	D589BL00022
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A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) in severe chronic obstructive pulmonary disease (COPD) patients

Study dates:	First subject enrolled: 31 Aug 2011
	Last subject last visit: 07 Dec 2012
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)

Patients were enrolled at 25 study centres in the People's Republic of China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of Symbicort Turbuhaler (160/4.5µg, two inhalations twice daily) on top of ipratropium (Atrovent™, Boehringer Ingelheim, 20µg/dose, two inhalations four times daily) + theoph ylline SR (Shufumei, Guangzhou Med Xinhua, 0.1g p.o. twice daily) compared to ipratropium (2 0µg/dose, two inhalations four times daily) + theophylline SR (0. 1g p.o. twice daily).	Change in pre-dose FEV_1

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary		To assess the efficacy of Symbicort Turbuhaler (160/4.5µg, two inhalations twice daily) on top of ipratropium (Atrovent™, Boehringer Ingelheim, 20µg/dose, two inhalations four times daily) + theoph ylline SR (Shufumei, Guangzhou Med Xinhua, 0.1g p.o. twice daily) compared to ipratropium (2 0µg/dose, two inhalations four times daily) + theophylline SR (0. 1g p.o. twice daily).	Change in post-dose FEV_1 at 5 and 60 minutes Change in pre-dose FVC Change in post-dose FVC at 5 and 60 minutes Change in pre-dose IC change in post-dose IC at 60 minutes Change in morning pre-dose PEF Change in morning post-dose PEF at 5 minutes Change in inhalations of reliever medication Change in COPD symptoms Number of COPD exacerbations Time to first COPD Change in SGRO-C

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Safety	To assess the tolerability and safety of Symbicort Turbuhaler (160/4.5μg, two inhalations twice daily) on top of ipratropium (Atrovent™, Boehringer Ingelheim, 20μg/dose, two inhalations four times daily) + theoph ylline SR (Shufumei, Guangzhou Med Xinhua, 0.1g p.o. twice daily) compared to ipratropium (2 0μg/dose, two inhalations four times daily) + theophylline SR (0. 1g p.o. twice daily).	AE and SAE

Study design

This was a multicentre study with a randomised, parallel group, open-label designed to assess the efficacy and tolerability of Symbicort Turbuhaler as an add-on treatment to ipratropium + theophylline SR in patients with severe COPD. Eligible patients were enrolled to a 2-week run-in period during which their ordinary COPD treatment was replaced with ipratropium + theophylline SR. The patients were provided with a short-acting β_2-agonist, salbutamol pMDI (Ventolin, GlaxoSmithKline), for symptom relief during the study. After the run-in period, patients who fulfilled the eligibility criteria were randomised to add Symbicort Turbuhaler 160/4.5 μg/inhalation, two inhalations twice daily on top of ipratropium + theophylline or continue their run-in treatment for 12 weeks.

Target subject population and sample size

The target subject population were outpatients, men or women, ≥40 years of age, with a clinical diagnosis of COPD, symptoms for at least 2 years, and they had the COPD exacerbation during the last year. As the current or previous smokers with a smoking history of ≥10 pack years, they had an FEV_1 ≤50% of predicted normal and an FEV_1/Forced Vital Capacity (FVC) <70% (both pre-bronchodilator). The patients should not have used systemic

glucocorticosteroids (GCS) within 4 weeks and/or inhaled GCS within 2 weeks prior to Visit 2. Patients with a history of seasonal allergic rhinitis (before 40 years of age) and/or asthma were excluded from the study.

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

Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg/inhalation, two inhalations twice daily

Comparator, None.

Additional drugs,

Atrovent (ipratropium) pMDI, 20 µg/dose, 2 inhalations four times daily

Shufumei (theophylline SR), 0.1g /tablet, 1 tablet p.o. twice daily

Ventolin (salbutamol) pMDI, 0.1 mg/dose, as reliever medication

Duration of treatment

The study consisted of a 2-week run-in period and thereafter a 12-week treatment period. The study visits were enrolment visit (Visit 1), start of run-in (Visit 2), randomisation (Visit 3), and after 1, 3, 6, 9 and 12 weeks of treatment (Visit 4, 5, 6, 7 and 8).

Statistical methods

The efficacy variables were summarized and analyzed in Full Analysis Set (FAS). It included all patients for whom any efficacy data had been collected after randomization. The summaries for the safety variables were based on Safety Analysis Set (SAS). Data for patients who took at least one dose of the add-on treatment with Symbicort or Atrovent or Theophylline SR and for whom any data had been collected after randomization are included in the SAS.

The change in pre-dose FEV_1, expressed as a ratio, from visit 3 to the mean of visits 4, 6 and 8 was analyzed after log-transformation using a multiplicative analysis of covariance (ANCOVA) model with treatment and centre as fixed factors and the Visit 3 value as a (log-transformed) covariate. A treatment difference was estimated from the model and 95% confidence limits are calculated. The change in other spirometry variables were analysed in the same way. For the Patient Reported Outcomes (PRO) and diary card variables, the mean changes were compared between treatments using an additive ANOVA model.

Subject population

Patients were enrolled in 25 centres in the People's Republic of China. The first subject in was on 31 Aug 2011, the last subject completed the last visit on 07 Dec 2012 and the date of database lock was on 08 Feb 2013.

A total of 774 patients were screened (informed consent signed and CRF started) and 584 patients were randomized for this study. There were 190 screened patients who were not randomised in the study. The reasons that a patient was a screen failure were eligibility criteria not fulfilled, subject decision, subject lost to follow-up, adverse event and severe non-compliance to protocol. There were 292 randomized patients in Symbicort+ Ipratropium+ Theophylline SR group and 292 in Ipratropium+ Theophylline SR group. In Symbicort+ Ipratropium+ Theophylline SR group, 2(0.7%) patients did not receive treatment (One patient withdrawn due to AE of mouth ulcer. One patient withdrawn duo to inclusion criteria No. 6 not fulfilled.), and all patients in Ipratropium+ Theophylline SR group received treatment. For patients who completed study, there were 276 (94.5%) patients in Symbicort+ Ipratropium+ Theophylline SR group and 261 (89.4%) patients in Ipratropium+ Theophylline SR group.

Summary of efficacy results

For the primary variable, pre-dose $FEV_{1,}$ treatment with Symbicort + Ipratropium+ Theophylline SR was shown to be superior to treatment with Ipratropium+ Theophylline SR. The adjusted ratio for treatment comparison is 1.069 (95% CI[1.043, 1.096], $P < 0.0001$), corresponding to a 6.9% difference in pre-dose FEV_1 between the groups.

Symbicort added to Ipratropium+ Theophylline SR was superior compared to Ipratropium+ Theophylline SR for improvement of lung function for post-dose FEV_1 at 5 minutes and 60 minutes, pre-dose and post-dose at 5 minutes and 60 minutes for FVC, pre-dose and post-dose at 60 minutes for IC over the study period.

Symbicort added to Ipratropium+ Theophylline SR was superior in improvement of pre-dose and post-dose at 5 minutes of morning PEF compared to Ipratropium+ Theophylline SR.

Symbicort added to Ipratropium+ Theophylline SR was superior in reduction of reliever medication during the day, improvement of COPD symptoms and health related quality of life (SGRQ) compared to Ipratropium+ Theophylline SR.

Symbicort added to Ipratropium+ Theophylline SR reduced COPD exacerbations rate (defined as use of systemic steroids, hospitalisation or emergency room visit due to deterioration of COPD) compared to Ipratropium+ Theophylline SR.

Summary of pharmacokinetic results

Not Applicable

Summary of pharmacodynamic results

Not Applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not Applicable

Summary of pharmacogenetic results

Not Applicable

Summary of safety results

The treatment duration (days) for Safety population is summarized in Table 34. As the mean treatment durations were 83.3 days and 81.1 days for Symbicort+ Ipratropium+ Theophylline SR group and Ipratropium+ Theophylline SR group respectively, exposure in the two groups was comparable.

In safety population, 277 (94.5%) patients in Symbicort+ Ipratropium+ Theophylline SR group completed the study while 260 (90.0%) patients in Ipratropium+ Theophylline SR group completed the study.

Number of patients with at least one AE in treatment period is 33 (11.3%) for Symbicort+ Ipratropium+ Theophylline SR group and 31 (10.7%) for Ipratropium+ Theophylline SR group. The most common AEs are Chronic obstructive pulmonary disease, Nasopharyngitis, and Upper respiratory tract infection (>2%).

Number of patients with at least one causally related AE in treatment period is 3 (1.0%) in Symbicort+ Ipratropium+ Theophylline SR group and none in Ipratropium+ Theophylline SR group.

Two deaths were reported in this study. One is in Symbicort+ Ipratropium+ Theophylline SR group in follow up period and another is in Ipratropium+ Theophylline SR group during treatment period. Both death cases were judged by investigators not related to study treatment.

There are 9 (3.1%) and 10 (3.5%) patients with at least one SAE in treatment period for Symbicort+ Ipratropium+ Theophylline SR group and Ipratropium+ Theophylline SR groups respectively. Most SAEs are chronic obstructive pulmonary disease (1.7% and 2.4% respectively in Symbicort+ Ipratropium+ Theophylline SR group and Ipratropium+ Theophylline SR group).

For patients with at least one DAE during treatment period, the number is 3 in Symbicort+ Ipratropium+ Theophylline SR group and 6 in Ipratropium+ Theophylline SR group.