Drug product	Symbicort	**SYNOPSIS**	
Drug substance(s)	budesonide/formoterol		
Study code	D5892C00013		
Date	02-04-2008		

A 6-month phase IIIA, multi-centre, randomised, double-blind, double-dummy, parallel-group study of the efficacy and safety of budesonide/formoterol (Symbicort®) Turbuhaler® 160/4.5µg/inhalation, two inhalations twice daily plus terbutaline (Bricasol®) pMDI (0.25mg/dose) as needed compared with budesonide (Pulmicort®) Turbuhaler® (200µg/dose), two inhalations twice daily plus terbutaline (Bricasol®) pMDI (0.25mg/dose) as needed, in Chinese subjects with chronic obstructive pulmonary disease (COPD)

Study centre(s)

This was a multi-centre study in 12 centres.

Totally, 353 subjects were enrolled into this study.

Publications (not applicable)

Study dates		**Phase of development**
First subject enrolled	Sept. 22, 2006	IIIA
Last subject completed	Nov. 27, 2007	

Objectives

The primary objective of this study was to evaluate the efficacy of budesonide/formoterol (Symbicort®) Turbuhaler® 160/4.5 µg/inhalation two inhalations twice daily during 24-weeks

compared with budesonide (Pulmicort®) Turbuhaler® 200 µg/dose two inhalations twice daily in Chinese subjects with COPD. The primary efficacy variable was post-dose FEV_1, measured 1 hour after intake if study medication in the morning at the clinic.

Secondary endpoints were pre-dose, and 15 minute post-dose FEV_1, pre-dose and 1 hour post-dose FVC, health-related quality of life by using the St George's Respiratory Questionnaire (SGRQ), COPD exacerbations (defined as "The use of antibiotics and /or oral/intravenous corticosteroids and/or emergency room treatment/hospitalisation due to respiratory symptoms"), COPD symptom scores, peak expiratory flow (PEF, morning and evening), use of reliever medication and safety (AEs - nature, incidence and severity, haematology, clinical chemistry, urinalysis, ECG, vital signs and physical examination).

Study design

The study was a multi-centre, randomised, parallel-group, double blind, double-dummy study.

After a 2-week run-in period, subjects who fulfilled all inclusion criteria and not any of exclusion criteria were randomised to receive either Symbicort 160/4.5 µg/inhalation two inhalations twice daily or Pulmicort 200µg/dose two inhalations twice daily for 24 weeks. The metered dose of 200µg budesonide in Pulmicort corresponds to a delivered dose of 160µg budesonide in Symbicort.

The subjects visited the clinical at recruitment (Visit 1), at randomisation (Visit 2), and after 2, 4, 8, 12, 19, and 24 weeks of treatment (Visit 3, 4, 5, 6, 7 and 8). Terbutaline (Bricasol®) pMDI (0.25mg/dose) was used as reliever medication from Visit 1 and throughout the study. No other bronchodilators were allowed during the study period (from run-in and throughout the study). Spirometry, including FEV_1 and FVC were measured at Visit 1,2,3,5,6 and 8. The measurements were performed at approximately the same time of the day for each individual subject. The following were recorded in the diary cards: COPD symptom scores, morning and evening PEF, and reliever medication use. The use of antibiotics and/or oral/intravenous corticosteroids and /or emergency room treatment/hospitalisation due to respiratory symptoms from Visit 1 to 8 was also recorded in the diary cards and was judged by investigators as an COPD exacerbation. The SGRQ was measured at Visit 1 (training), Visit 2 (baseline), Visit 6 and Visit 8.

Adverse events were collected from Visit 2 to Visit 8.

Target subject population and sample size

The target subject population were men and women ≥40 years with a clinical diagnosis of COPD, whose baseline $FEV_1 \leq 50\%$ of predicted normal value, pre-bronchodilator and FEV_1/FVC <70% pre-bronchodilator.

According to the statistical calculation and SFDA requirement, it was designed to randomise 300 COPD subjects. Finally, 353 subjects were enrolled and 308 subjects were randomised

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

Product	Dosage and mode of administration	Batch No.
Symbicort	160/4.5µg/inhalation, 2 inhalations twice daily	HD41
Pulmicort	200µg/dose, 2 inhalations twice daily	HE1380
Placebo Pulmicort	2 inhalations twice daily	HE43
Placebo Symbicort	2 inhalations twice daily	HD22

Duration of treatment

The study included 2-week run-in period followed by a 24-week active treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Post-dose FEV_1 (1 hour after intake of study medication)
- Secondary variables:
  - Pre-dose and 15 min post-dose FEV_1
  - Pre-dose and 1 hour post-dose FVC
  - Health related quality of life (The SGRQ)
  - COPD exacerbations
  - COPD symptom scores
  - Morning and evening PEF
  - Use of reliever medication

Safety

- Adverse Events (cumulative incidence, severity, and type of adverse event)
- Changes in laboratory measurements (haematology, clinical chemistry and urinalysis)
- Changes in ECG and Vital signs
- Physical examination

Statistical methods

The change FEV_1 from Visit 2 to the average value of available data for Visits 3, 5, 6 and 8 were analyzed using a multiplicative ANOVA model with treatment and centre as fixed factors and the Visit 2 value as a covariate (logarithmic). Treatment differences were estimated from the model and 95% confidence limits were calculated. These were then exponentiated to express differences as ratios. FEV_1 measured pre-dose and 15 minutes after dose were analysed in a similar way. The change in FVC from Visit 2 to the average value of available data for Visits 3, 5, 6 and 8 were analyzed, separately for measurements pre-dose and 1 hour after intake of study medication, in the same way as FEV_1.

The changes in the SGRQ from Visit 2 to last available visit (Visit 8 or Visit 6 if Visit 8 was missing) were analysed using an analysis of variance (ANOVA) model with treatment and centre as fixed factors and the Visit 2 value as a covariate. Treatment differences were estimated from the model and 95% confidence limits were calculated.

The time to first COPD exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a log-rank test. Additional descriptions were made using a Cox proportional hazards model with treatment as factor. The total number of COPD exacerbations was compared between the treatment groups using a Poisson regression model with treatment and centre as factors and the time in study as an offset variable. The confidence limits and the p-value were adjusted for over dispersion.

For diary card variables, COPD symptom scores, morning and evening PEF, number of reliever medication use, data were reduced to a run-in mean and a treatment period mean for each subject. The run-in mean included the last 10 days, the treatment period mean included data from Visit 3, 5, 6 and 8 (24 weeks). Mean was based on all days with registered data without replacement of missing values. The change in period means were analysed in an ANOVA with factors of centre and treatment and the run-in mean as a covariate.

For COPD symptom scores the sum of scores was computed by adding the period means for the individual symptoms shortness of breath, cough, chest tightness and nighttime awakenings to a total mean score. This was analysed in the same way as the individual diary card symptom variables.

The withdrawal rates were compared between the treatments by a log rank test.

The adverse events were analysed by means of descriptive statistics and qualitative analysis.

The primary endpoint of post-dose FEV_1 (1 hour after intake of study medication) was used for the sample size estimation. In order to detect a treatment difference of 8.5% in FEV_1 at a 2-sided significance level of 5% and 90% of power, approximately 125 subjects per group were needed, assuming a standard deviation of 0.2 on the logarithmic scale (based on previous studies Calverley PM et al 2003 and Szafranski W et al 2003). Considering a 20% withdrawal rate, the total sample size was increased to 300 subjects, randomised in a ratio of 1:1 to two treatment groups, with 150 in each treatment arm.

Subject population

A total of 353 subjects from 12 centres were enrolled into this study. 308 were randomized. All subjects received study medication and were included in the safety analysis set. Full analysis set included 292 subjects. Per-Protocol analysis set included 285 subjects.

Of all the subjects randomised, 250 (81.2%) subjects completed the trial. The total discontinuation rate was 18.8%. The percentage of withdrawn subjects was higher in the Pulmicort group than in the Symbicort group (23.0% vs. 14.7%). Due to the difference of COPD incidence and smoking habit between men and women, there were few women subjects involved in this trial, i.e. 3 women in the Symbicort group and 12 women in the Pulmicort group (Table S1).

Table S1 Subject population and disposition

		Symbicort		Pulmicort		Total	
Population							
N randomised (N planned)		156	(150)	152	(150)	308	(300)
Demographic characteristics							
Sex (n and % of subjects)	Male	153	(98.1%)	140	(92.%)	293	(95.1%)
	Female	3	(1.9%)	12	(7.9%)	15	(4.8%)
Age (years)	Mean (SD)	65.70	(8.75)	64.71	(9.61)	65.21	(9.18)
	Range	40 to 81		42 to 87		40 to 87	
Race (n and % of subjects)	Caucasian	0		0		0	
	Black	0		0		0	
	Oriental	156	(100.0%)	152	(100.0%)	308	(100.0%)
	Other	0		0		0	
Baseline characteristics							
GOLD classification							
Moderate		7	4.5%	5	3.3%	12	3.9%
Severe		98	62.8%	94	61.8%	192	62.3%
Very severe		51	32.7%	53	34.9%	104	33.8%
Disposition							
N (%) of subjects who	Completed	133	(85.3%)	117	(77.0%)	250	(81.2%)
	discontinued	23	(14.7)	35	(23.0%)	58	(18.8 %)
N analysed for safety[a]		156		152		308	

Table S1 Subject population and disposition

	Symbicort	Pulmicort	Total
N analysed for efficacy (FAS)	149	143	292
N analysed for efficacy (PP)	145	140	285

[a] Number of subjects who took at least 1 dose of study treatment.
FAS=Full analysis set; N=Number; PP=Per-protocol

Efficacy results

In summary, this study showed that treatment with the combination of budesonide/formoterol (Symbicort) Turbuhaler 160/4.5µg two inhalations twice daily for 24 weeks resulted in a statistically significant and clinically relevant improvement of lung function, measured by the primary efficacy variable (1 hour post-dose FEV_1), compared with budesonide (Pulmicort) Turbuhaler 200/µg two inhalations twice daily. Symbicort was also superior to Pulmicort in several secondary variables, e.g. pre-dose FEV_1, COPD symptoms, reliever medication use and health related quality of life (the SGRQ). The mean difference in the SGRQ total score between the Symbicort and the Pulmicort was –4.5, which can be considered a clinically relevant improvement. The superiority of the Symbicort vs the Pulmicort was shown in both the FAS and PP population sets.

Safety results

In the study, the incidence of As was higher in the Pulmicort group than the Symbicort group. There was one death in the study. It occurred in the Symbicort group. The reason of death was COPD exacerbation and it was judged to be no relation to the study medication. The results of lab measurements (haematology, clinical chemistry and urinalogy), vital signs, ECG and physical examination showed no clinically important difference between the Symbicort and Pulmicort groups. Overall, the reported AEs, including SAEs and discontinuations due to AE from treatment with investigational medication do not give rise to any new safety concern (Table S2).

Table S2 Overview of adverse event (Safety Population)

	Symbicort (N=156)	Pulmicort (N=152)	Total (N=308)
Number of adverse events	58	72	130
Number of severe adverse events	9	12	21
Number of drug-related adverse events	6	7	13
Number of death	1	0	1
Number of serious adverse events other than death	13	18	31
Number of adverse events leading to discontinuation of investigational drug	5	5	10

Table S2 Overview of adverse event (Safety Population)

	Symbicort (N=156)	Pulmicort (N=152)	Total (N=308)
Number of other significant adverse events	0	0	0
Number of subjects with at least one adverse event	40 (25.6%)	49 (32.2%)	89 (28.9%)
Number subjects with at least one severe adverse event	9 (5.8%)	8 (5.3%)	17 (5.5%)
Number Subjects with at least one study medication related adverse event	4 (2.6%)	5 (3.3%)	9 (2.9%)
Death	1 (0.6%)	0	1 (0.3%)
Number of subjects with at least one serious adverse event other than death	11 (7.1%)	13 (8.6%)	24 (7.8%)
Number of subjects with at least one adverse event leading to discontinuation of investigational drug	5 (3.2%)	4 (2.6%)	9 (2.9%)
Number of subjects with at least one other significant adverse event	0	0	0

This table includes adverse events that occurred on or after the first day of randomised treatment.

Conclusions

Date of the report

02-04-2008