Drug Product	Symbicort (budesonide/formoterol) 160/4.5 µg delivered by pressurised metered dose inhaler (pMDI)	**SYNOPSIS**	
Drug Substance	Budesonide/formoterol		
Edition Number	1		
Study Code	D5899C00748		
Date	23 August 2005		

A randomised, placebo-controlled, double-blind, double-dummy, crossover study to assess the onset of action of two inhalations of Symbicort 160/4.5 µg, compared with two inhalations of Seretide 25/250 µg, two inhalations of Ventoline 100 µg, and placebo, delivered by pressurised metered dose inhalers, in patients with chronic obstructive pulmonary disease (COPD).

International Co-ordinating investigator

Study centre(s)

This was a multicentre study conducted in Sweden (10 centres) and Hungary (9 centres).

Publications

None at the time of writing this report.

Study dates

First patient enrolled: 1 March 2004

Last patient completed: 26 February 2005

Phase of Development

Therapeutic confirmatory (III)

Objectives

Primary objective

- The primary objective was to evaluate efficacy, ie to study the bronchodilating effect within the first 180 minutes after two inhalations of Symbicort 160/4.5 µg compared with two inhalations of Seretide 25/250 µg, two inhalations of Ventoline 100 µg and placebo. The primary outcome variable was forced expiratory volume in one second (FEV_1) 5 minutes after dose.

Secondary objectives

- To study efficacy of two inhalations of Symbicort 160/4.5 µg compared with two inhalations of Seretide 25/250 µg, two inhalations of Ventoline 100 µg and placebo by assessment of the Perception of Onset of Effect questionnaire (POE) and inspiratory capacity (IC).
- To study safety of two inhalations of Symbicort 160/4.5 µg compared with two inhalations of Seretide 25/250 µg, two inhalations of Ventoline 100 µg and placebo by assessing the nature, incidence and severity of adverse events (AEs).

Study design

This was a double-blind, double-dummy, placebo-controlled and crossover study, consisting of four randomised visits. Efficacy and safety of two inhalations of Symbicort 160/4.5 µg compared with two inhalations of Seretide 25/250 µg, two inhalations of Ventoline 100 µg and placebo was evaluated, in patients with chronic obstructive pulmonary disease (COPD).

Target patient population and sample size

Male and female patients aged 40 years or older with COPD; FEV_1 of 30-70% of the predicted normal value (≤85% post-bronchodilator), FEV_1/vital capacity (VC) ≤70%, reversibility of 9-25% of the predicted normal FEV_1 value, a clinical diagnosis of COPD, COPD symptoms for more than 2 years, smoking history of ≥10 pack years, no history of asthma and no symptoms of allergic rhinitis within the last 20 years.

For the measurement of FEV_1 at 5 minutes, assuming 80 patients and a residual standard deviation of 0.083 (logarithmic scale) a difference of 4.4% in FEV_1 would be detected with 90% power using a t-test.

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

Test product

Symbicort 160/4.5 µg, two inhalations given as a single dose via a pressurised metered dose inhaler (pMDI); batch numbers P6675 and P6722, or placebo inhalations to match the Symbicort treatment; batch numbers P6547 and P6856.

Comparators

Salmeterol/fluticasone (Seretide Evohaler) 25/250 µg, two inhalations given as a single dose via a pMDI; batch numbers P6910, P7029 and P7063, or placebo inhalations to match the salmeterol/fluticasone treatment; batch numbers P7033 and P6900.

Salbutamol (Ventoline Evohaler) 100 µg, two inhalations given as a single dose via a pMDI; batch numbers P6997 and P6907, or placebo inhalations to match the salbutamol treatment; batch numbers P6909 and P7077.

Duration of treatment

Including time for withdrawal of non-allowed medication, run-in and treatment periods, the study consisted of approximately 4 weeks. Investigational products were given in single doses on 4 different occasions separated by a minimum of 3 days.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- The primary outcome variable was the change in FEV_1 expressed as the ratio in percent between the FEV_1 measurement at 5 minutes after study drug administration and the baseline FEV_1 before study drug administration.

- Secondary outcome variables were:

  - FEV_1

    - The change in FEV_1 expressed as the ratio in percent between the FEV_1 measurement at 3 and 180 minutes, respectively, after study drug administration and the baseline FEV_1 before study drug administration.

    - The change in FEV_1 expressed as the ratio in percent between the maximal FEV_1 measurement after study drug administration and the baseline FEV_1 before study drug administration.

    - The average effect during the 180 minutes observation interval after dosing expressed in the same way as the other FEV_1 variables. This average effect has been calculated as the area under the curve (AUC) divided by the observation time.

  - IC

    - The change in IC expressed as the ratio in percent between the IC measurement 15 minutes after study drug administration and the baseline IC before study drug administration.

    - The change in IC expressed as the ratio in percent between the maximal IC measurement after study drug administration and the baseline IC before study drug administration.

    - The average effect during the 185 minutes observation interval after dosing expressed in the same way as the other IC variables. This average effect has been calculated as the AUC divided by the observation time.

  - POE questionnaire, measured as the first time point when the patient experienced effect of the investigational product. The POE question was answered immediately prior to the FEV_1 measurements (time-points 3, 5, 10, 20, 30, 60, 120 and 180 minutes after administration of investigational product).

Safety

Safety variables were nature, incidence and severity of AEs.

Statistical methods

The full analysis set has been used in all efficacy analyses. The primary comparison of the statistical analysis was between Symbicort and Seretide.

The mean change in FEV_1, expressed as the ratio in percent between the FEV_1 measurement at 5 minutes after study drug administration and the baseline FEV_1 before study drug administration, was compared between treatments using a multiplicative analysis of variance model (ANOVA) with patient, period and treatment as fixed factors and the baseline FEV_1 before drug intake as a covariate. Similar analyses were performed for secondary variables derived from the FEV_1 and IC measurements.

The time to first perception of onset of effect, ie a "yes" answer, was compared between treatments using Wilcoxon's signed rank test.

Patient population

Table S1 Patient population and disposition

		All
Population		
N randomised (N planned)		90 (80)
Demographic characteristics		
Sex, n (% of patients)	Male	50 (55.6%)
	Female	40 (44.4%)
Age, years	Mean	61.7
	Range	41-79
Race, n (% of patients)	Caucasian	90 (100%)
BMI, kg/m^2	Mean	26.3
	Range	18-40
Time since diagnosis, years	Median	5
	Range	0-34
Time with symptoms, years	Median	9
	Range	2-44

(Continued)

Table S1 Patient population and disposition

		All
Baseline characteristics		
Smoking status, n (% of patients)	Previous	54 (60%)
	Occasional	3 (3%)
	Habitual	33 (37%)
Pack years	Median	35
	Range	10-114
IGCS at entry, n (% of patients)		44 (49%)
Dose, µg/day	Mean	633.4
	Range	200-1600
VC, L	Mean	2.96
	Range	1.7-5.5
FEV_1, L	Mean	1.32
	Range	0.6-2.4
FEV_1, % PN	Mean	47.8
	Range	30-69
FEV_1, % VC[a]	Mean	45.5
	Range	24-68
Reversibility, % PN	Mean	12.5
	Range	9-24
Disposition		
N (%) of patients who	Completed	87 (96.7%)
	Discontinued	3 (3.3%)
N analysed for safety[b]		89
N analysed for efficacy (ITT)[c]		88

a The ratio of FEV_1 and VC expressed as %.

b Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

c Number of patients with data from more than one treatment period after randomisation.

N = Number, PN = Predicted normal, ITT = Intention to treat

The study included more than enough patients to fulfill the aim in the power calculation. Demographic and disease severity data indicate that the intended population was recruited into the study.

There were 3 discontinuations among the randomised patients, 2 due to adverse event and 1 due to other reason.

Efficacy and pharmacokinetic results

Symbicort pMDI was superior to placebo (ratio 116%, $p<0.001$) and to Seretide pMDI (ratio 105%, $p<0.001$) for FEV_1 at 5 minutes (the primary outcome variable) and also at 3 minutes after study drug administration. The onset of effect with Symbicort pMDI was similar to that for Ventoline pMDI (ratio at 5 min 99%, NS).

The FEV_1 values for all three active treatments were superior to placebo after 180 minutes, but at that time point both Symbicort pMDI and Seretide pMDI appeared to maintain the effect on FEV_1 better than Ventoline pMDI. No differences were detected between the active treatments for maximal FEV_1 or for the average FEV_1 (AUC) over 180 minutes.

For IC, a statistically significant difference versus placebo was registered at the first measurement, ie at 15 minutes after study drug administration for all active treatments, with no evidence of a difference between treatments at this time. The maximal IC was statistically significantly higher for Symbicort pMDI than Seretide pMDI (ratio 104%, $p=0.0184$). No differences could be shown between the active treatments for average IC during the 185 minutes interval after study drug administration.

The median time to first positive response to perception of onset of effect question, was 5 minutes for all active treatments and 20 minutes for placebo. No differences were seen between the active treatments but they were all superior to placebo.

Safety results

In total 24 adverse events were reported with no causality related to investigational product, as judged by the investigator. All AEs were of mild or moderate intensity. No deaths and no serious adverse events were reported. There were 2 AEs leading to discontinuation after intake of investigational product. The treatments were well tolerated.

Table S2 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

	Symbicort pMDI (n=88)	Seretide pMDI (n=88)	Ventoline pMDI (n=88)	Placebo (n=88)
Category of adverse event	**N (%) of patients who had an adverse event in each category[a]**			
Any adverse events	8 (9%)	1 (1%)	3 (3%)	7 (8%)
Serious adverse events	0	0	0	0
Serious adverse events leading to death	0	0	0	0
Serious adverse events not leading to death	0	0	0	0
Discontinuations of study treatment due to adverse events	0	0	1 (1%)	1 (1%)
Other significant adverse events	0	0	0	0
	Total numbers of adverse events			
Adverse events	10	1	5	8
Serious adverse events	0	0	0	0
Other significant adverse events	0	0	0	0

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Conclusion(s)

Date of the report

23 August 2005