Drug product:	Symbiocort	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Document No.:	D5890L00001		
Edition No.:	1.0		
Study code:	D5890L00001		
Date:	8 February 2008		

Symbicort and Health Economics in a Real Life Evaluation – SHARE – A randomised, open-label, parallel-group, multicentre study to assess the asthma related health care costs, in ordinary clinical practice during 12 months

Study centre(s)

This was a multicentre study conducted in 222 primary and secondary health care centres in Sweden.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First patient enrolled	5 April 2004	Therapeutic confirmatory (IIIb)
Last patient completed	12 May 2007	

Objectives

The primary objective of this study was to assess the direct asthma related costs, in ordinary clinical practice during 12 months, for Symbicort® maintenance and reliever therapy (SMART) (i.e. Symbicort Turbuhaler® given as a low maintenance dose once or twice daily plus as needed), compared to a free combination of Pulmicort® and Oxis® plus Bricanyl® as needed, and Symbicort fixed dosing plus Bricanyl as needed, in asthmatic patients that were not adequately controlled on inhaled glucocorticosteroids (GCS) alone.

Secondary objectives of the study were:

- to compare different costs (e.g. asthma medication cost, direct non-medication costs and indirect costs) between treatment groups.
- to investigate patient reported outcomes (PROs) using EQ-5D, patient willingness to pay (WTP), Asthma Control Questionnaire (ACQ), patient rating of asthma symptoms, patient rating of asthma status and patient reported compliance.
- to investigate the efficacy by evaluation of exacerbation frequency, number of treatment failures, and sick-leave.
- to investigate safety by the evaluation of Serious Adverse Events (SAEs), and Discontinuations due to Adverse Events (DAEs).

Study design

This was a 12-month, randomised, open-label, parallel-group, multicentre study of patients with persistent asthma, that were already treated with a free combination of both inhaled GCS and long-acting β_2-agonist (LABA), or that were symptomatic despite regular use of inhaled GCS alone.

Target patient population and sample size

Out-patients of either sex aged ≥12 years with an asthma diagnosis according to the American Thoracic Society definition, regular daily inhaled GCS (of any brand) ≥400 µg during the last 30 days prior to randomisation and either daily maintenance treatment with a free combination of both inhaled GCS and LABA or daily treatment with inhaled GCS alone and sub-optimal asthma control manifested by current asthma symptoms and/or use of ≥3 inhalations/week of as needed medication (for symptom relief or prevention of symptom), as judged by the investigator.

The sample size calculation was based on the primary outcome variable: direct asthma related costs. With a two-sided test, a significance level of 5%, and a power of 80%, a sample size of 394 evaluable patients was needed in each treatment group, based on a need to find a difference of 500 SEK per patient, and an assumption that the standard deviation would be 2500 SEK. A drop out percentage of 9% was anticipated. Therefore the total number of needed randomised patients was estimated to 1732.

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

Patients were randomly assigned to 1 of the 4 following open-label treatment groups:

- Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg) or Symbicort Mite Turbuhaler (budesonide/formoterol 80/4.5 µg) 1 inhalation twice daily plus Symbicort as needed (budesonide/formoterol 160/4.5 µg or budesonide/formoterol 80/4.5 µg) (SMART 1*2)

- Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg) or Symbicort Mite Turbuhaler (budesonide/formoterol 80/4.5 µg) 2 inhalations once daily plus Symbicort as needed (budesonide/formoterol 160/4.5 µg or budesonide/formoterol 80/4.5 µg) (SMART 2*1)
- Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg) or Symbicort Mite Turbuhaler (budesonide/formoterol 80/4.5 µg) 2 inhalations twice daily plus Bricanyl as needed (terbutaline 0.25 or 0.5 mg) (Symbicort 2*2)
- Pulmicort Turbuhaler (budesonide 100, 200 or 400µg) and Oxis Turbuhaler (formoterol 4,5 or 9 µg) plus Bricanyl as needed (terbutaline 0.25 or 0.5 mg) (Pulmicort+Oxis)

Duration of treatment

A 12-month randomised treatment period.

Criteria for evaluation (main variables)

Primary variable

Health Economics

- Direct asthma related costs, i.e.sum of asthma medication and direct non-medication resource use

  Asthma medication:

  – Total amount of prescribed study medication that was actually collected from pharmacy

  – Use of other asthma medication

  Direct non-medication resource use:

  – Number of (asthma related) visits to nurse or physician

  – Number of (asthma related) telephone contacts with nurse or physician

  – Number of (asthma related) emergency room visits

  – Number of (asthma related) hospital nights

Secondary variables

Health Economics

- Direct asthma related costs
- In-direct asthma related resource use:

  – Number of days absent from work (for the patient) due to asthma

  – Number of days absent from work for assistant person due to patient's asthma (caregiver cost)

- Total costs including direct and in-direct costs

Patient Reported Outcomes

- EQ-5D
- Patient WTP
- ACQ
- Patient rating of asthma symptoms
- Patient rating of asthma status
- Patient reported compliance

Efficacy

- Number of patients with an asthma exacerbation
- Number of treatment failures
- Sick-leave

Safety

- SAE
- DAE

Statistical methods

The Group Mean Approach was used in which means were calculated as the sum of all resource use (and cost) in the group divided by the total observation time for the group (in days) and scaled to one year. Significance tests and confidence intervals were calculated using the bootstrap principle, a resampling procedure. The costs were calculated from resource usage by applying defined unit prices, which was defined prior to clean file.

The secondary health economic variables and the patient reported outcomes (EQ-5D, WTP, ACQ, patient rating of asthma symptoms, and patient rating of asthma status) were compared using an analysis of covariance with treatment and centre as factors and baseline value as covariate. The secondary efficacy variables (number of patients with an asthma exacerbation, number of treatment failures and both number of patients with sick-leave and number of days with sick-leave) were analysed using a Cochrane-Mantel-Haenzel test. The safety variables (SAE and DAE) and patient reported compliance were analysed by descriptive methods.

Patient population

Patient disposition is presented in Table S1 and baseline patient characteristics in Table S2. In total, 1776 patients from 222 centres were enrolled in the study. The randomised study population comprised 1776 patients. The first patient was enrolled on 5 April 2004 and the last patient completed the study on 12 May 2007. 456 patients were randomised to Symbicort 2*2 treatment, 438 to SMART 1*2 treatment, 449 to SMART 2*1 treatment and 433 to Pulmicort+Oxis treatment. All of the 1776 patients assigned to treatment were included in the safety analysis set.1769 patients were included in the full analysis set and 1554 patients in the PP analysis set. A total of 1565 patients completed the study: 396 on Symbicort 2*2,

390 on SMART 1*2, 391 on SMART 2*1 and 388 on Pulmicort+Oxis, respectively. The overall number of discontinuations, and the number of patients who discontinued study treatment due to AEs, were similar between the treatment groups. There were no differences between the treatment groups in the number of patients who had protocol deviations. Overall, the treatment groups were well-matched with respect to demographic and baseline characteristics, the latter indicative of a patient population with mild to moderate asthma, not adequatly controlled on ICS alone.

Table S1 Patient disposition

	Symbi-cort 2*2	SMART 1*2	SMART 2*1	Pulmicort +Oxis	Total
Number of patients enrolled					1776
Number of patients randomised	456	438	449	433	1776
Number of patients in full analysis set (FAS)	452	437	447	433	1769
Number (%) of patients who discontinued during the study	60 (13.2)	48 (11.0)	58 (12.9)	45 (10.4)	211 (11.9)
Reasons for discontinuation: n (%)					
Eligibility criteria not fulfilled	3 (0.7)	2 (0.5)	6 (1.3)	8 (1.8)	
Adverse event	25 (5.5)	12 (2.7)	23 (5.1)	11 (2.5)	
Development of study-specific discontinuation criteria	0 (0.0)	4 (0.9)	1 (0.2)	1 (0.2)	
Subject lost to follow-up	11 (2.4)	7 (1.6)	7 (1.6)	11 (2.5)	
Other	21 (4.6)	23 (5.3)	21 (4.7)	14 (3.2)	
Number (%) of patients who completed the study	396 (86.8)	390 (89.0)	391 (87.1)	388 (89.6)	1565 (88.1)

Note: Percentages calculated for each reason for discontinuation are based on the number of patients randomised.
SOURCE DOCUMENT: DISPOSITION.SAS GENERATED: 16:54:29 05JUN2007 DB version DEV: D5890L00001

Table S2 Demographic details and baseline characteristics, Full Analysis set.

	Symbicort 2*2 (N=452)	SMART 1*2 (N=437)	SMART 2*1 (N=447)	Pulmicort+ Oxis (N=433)	Total (N=1769)
Sex					
Male	200 (44)	177 (41)	173 (39)	176 (41)	726 (41)
Female	252 (56)	260 (59)	274 (61)	257 (59)	1043 (59)
Age (years)					
N	452	437	447	433	1769
Mean (SD)	44.6 (19.4)	43.8 (19.1)	42.3 (19.3)	43.0 (18.6)	43.4 (19.1)
Range	12 , 95	12 , 87	12 , 87	12 , 86	12 , 95

Table S2 Demographic details and baseline characteristics, Full Analysis set.

	Symbicort 2*2 (N=452)	SMART 1*2 (N=437)	SMART 2*1 (N=447)	Pulmicort+ Oxis (N=433)	Total (N=1769)
PEF (L/min)					
N	437	416	432	417	1702
Mean (SD)	461.2 (116.9)	461.8 (111.0)	462.1 (108.1)	464.7 (105.5)	462.4 (110.4)
Range	170 , 855	150 , 790	199 , 800	150 , 850	150 , 855
FEV_1 (L)[a]					
N	279	278	282	279	1118
Mean (SD)	3.07 (0.87)	3.04 (0.91)	3.09 (0.91)	3.16 (0.84)	3.09 (0.88)
Range	0.9 , 5.5	0.3 , 5.7	0.7 , 5.6	1.0 , 5.8	0.3 , 5.8
FEV_1 in % of predicted normal[a]					
N	279	278	282	279	1118
Mean (SD)	96.53 (15.97)	94.52 (17.87)	94.81 (18.20)	96.16 (17.24)	95.50 (17.34)
Range	43.1 , 139.2	8.5 , 141.3	29.2 , 209.8	44.8 , 141.2	8.5 , 209.8
Total daily dose inhaled steroids (µg)					
Mean (SD)	649.8 (314.8)	633.0 (283.0)	639.5 (302.4)	640.4 (285.4)	640.8 (296.7)
Total daily dose inhaled formoterol (µg)[b]					
Mean (SD)	12.3 (5.4)	12.7 (5.8)	13.4 (5.8)	13.0 (5.9)	12.8 (5.7)
Current employment status					
Full-time employed	191 (42)	185 (42)	188 (42)	182 (42)	746 (42)
Part-time employed	47 (10)	58 (13)	60 (13)	61 (14)	226 (13)
Student	87 (19)	86 (20)	95 (21)	91 (21)	359 (20)
House-person	5 (1.1)	5 (1.1)	5 (1.1)	5 (1.2)	20 (1.1)
Retired/long-term sick leave	110 (24)	93 (21)	88 (20)	80 (18)	371 (21)
Unemployed	12 (2.7)	10 (2.3)	11 (2.5)	14 (3.2)	47 (2.7)

FEV_1 Forced expiratory volume in one second
PEF Peak expiratory flow
[a] Post-bronchodilator FEV_1
[b] Information on salmeterol usage was also collected, see Table 11.1- 10.
Data derived from Table 11.1- 2 , Table 11.1- 6 and Table 11.1- 10 in Section 11.1.

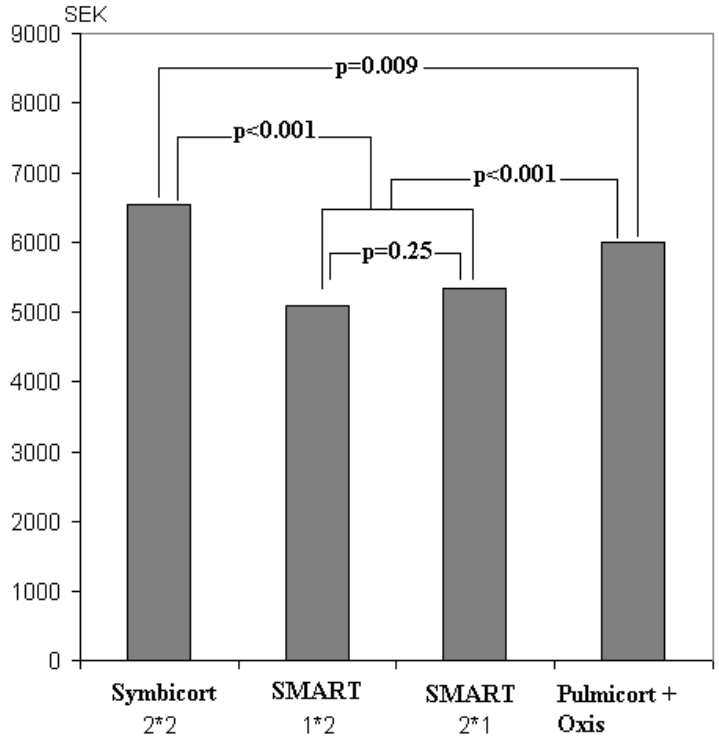
Efficacy results

Direct asthma related costs (the primary variable of the study) were significantly lower with SMART 1*2+2*1 than with Pulmicort+Oxis over 12 months of treatment in patients with asthma in ordinary clinical practice (-795 SEK, p<0.001) (see Figure S1). The secondary variables included cost comparisons between the different treatment groups and showed that the direct costs also were significantly lower with SMART 1*2+2*1 than with Symbicort 2*2 (-1335 SEK, p>0.001), and that Symbicort 2*2 costs were significantly higher than

Pulmicort+Oxis costs (540 SEK, p=0.009). Only 12.6% of the patients had in-direct asthma related costs, where SMART 1*2 and SMART 2*1 presented numerically higher costs than Pulmicort+Oxis and Symbicort 2*2. A small number of SMART 1*2 and SMART 2*1 patients were cost drivers. There were no significant differences between treatments in total costs.

The secondary variables also included PRO, where EQ-5D showed no difference between the treatments and indicated a study population valuing its health status very high all through the study. WTP demonstrated that patients were significantly more willing to pay for SMART 1*2+SMART 2*1, as well as for Symbicort 2*2, than for the Pulmicort+Oxis (both $p<0.0001$). ACQ, patient rating of asthma symptoms and asthma status presented a similar pattern with patients reporting good asthma control and mild symptoms across treatments groups. All groups improved during the study and there were no significant differences between treatments. Patient reported compliance, with regard to telephone interviews, was generally high, >90%, and similar between treatment groups. The secondary efficacy variables demonstrated that patients on SMART 1*2+2*1 had fewer exacerbations than patients on Symbicort 2*2 and Pulmicort+Oxis (7%, 9% and 10%, respectively), but the difference did not reach statistical significance. Significantly more patients on SMART 1*2+2*1, as well as on Symbicort 2*2, had treatment failures than patients on Pulmicort+Oxis (5%, 5% and 2%, respectively) and the differences reached statistical significance in favour of Pulmicort+Oxis ($p=0.004$ and $p=0.014$). It is noteworthy that some Symbicort patients changed back to Pulmicort+Oxis treatment and received Bricanyl as rescue medication. These patients were included in the analyses according to the randomisation. There was no difference in medication changes across treatments in relation to preceding exacerbations.

Figure S1 Direct asthma related costs in ordinary clinical practice during 12 months in the full analysis set



Data derived from Table 11.2.1- 2 and Table 11.2.1- 4 in Section 11.2.1.

Safety results

The number (%) of patients who had at least 1 adverse event in any category is summarised in Table S3. In general, the study treatments were well tolerated and no new or unexpected safety findings were identified in this study. SAE and DAE data were collected. The number and type of SAEs and DAEs were low and similar between the treatment groups. No clinically important differences were seen. There were four deaths in the study (2 in the SMART 2*1 group and 2 in the Pulmicort+Oxis group); none of them considered causally related to study treatment. Three of the patients died of myocardial infarction, 2 of them had a history of cardiovascular disease. One patient was found dead at home. Suggested cause of death was acute drug poisoning with sertraline in combination with alcohol. There were 2 patients with in all 4 SAEs that were attributed to drug treatment by the investigator (pneumonia/chest pain/hypertension [Symbicort 2*2] and confusional state [SMART 2*1]). Exacerbation of asthma was the most frequently reported SAE and DAE across treatments. The steroid load was lower with SMART 1*2 and SMART 2*1 than with Symbicort 2*2 and Pulmicort+Oxis, both for calculations based on returned inhalers (331 µg and 350 µg vs. 431 µg and 750 µg) and on telephone interviews (289 µg and 293 µg vs. 368 µg and 688 µg).

Table S3 Number (%) of patients who had an adverse event in any category[a] (safety analysis set)

Category of adverse event	Symbicort 2*2 (N=456)	SMART 1*2 (N=438)	SMART 2*1 (N=449)	Pulmicort +Oxis (N=433)	Total (N=1776)
Serious adverse events	15 (3.3%)	11 (2.5%)	18 (4%)	22 (5.1%)	66 (3.7%)
Serious adverse events leading to death	0 (0%)	0 (0%)	2 (0.4%)	2 (0.5%)	4 (0.2%)
Serious adverse events not leading to death	15 (3.3%)	11 (2.5%)	16 (3.6%)	20 (4.6%)	62 (3.5%)
Discontinuations of treatment due to adverse events	25 (5.5%)	12 (2.7%)	23 (5.1%)	11 (2.5%)	71 (4.0%)

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.

SOURCE DOCUMENT: T_8_3_1_AE.SAS GENERATED: 13:33:49 25SEP2007 DB version DEV: D5890L00001