Drug product:	160/4,5 µg/dose budesonide/formoterol fumarate dihydrate	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Budesonide/formoterol fumarate dehydrate		
Edition No.:	1		
Document No.	Not applicable		
Study code:	D5890L00008		
Date:	27 February 2008		

A comparison of the efficacy of Symbicort® SMART[a] (Symbicort Turbuhaler® 160/4.5 µg 1 inhalation bi.d. plus as-needed) and conventional best standard treatment for the treatment of persistent asthma in adolescents and adults. A randomized, open, parallel-group, multicentre, 26 weeks study.

[a] Symbicort® SMART was referred to as Symbicort® Single inhaler Therapy (Symbicort® SIT) in the clinical study protocol

National co-ordinating investigators

None appointed for this study.

Study centre(s)

This study was conducted in Denmark (123 centres), Finland (69 centres) and Norway (83 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	13 September 2004 (Denmark)	Therapeutic confirmatory (IIIb)
Last patient completed	18 October 2006 (Norway)	

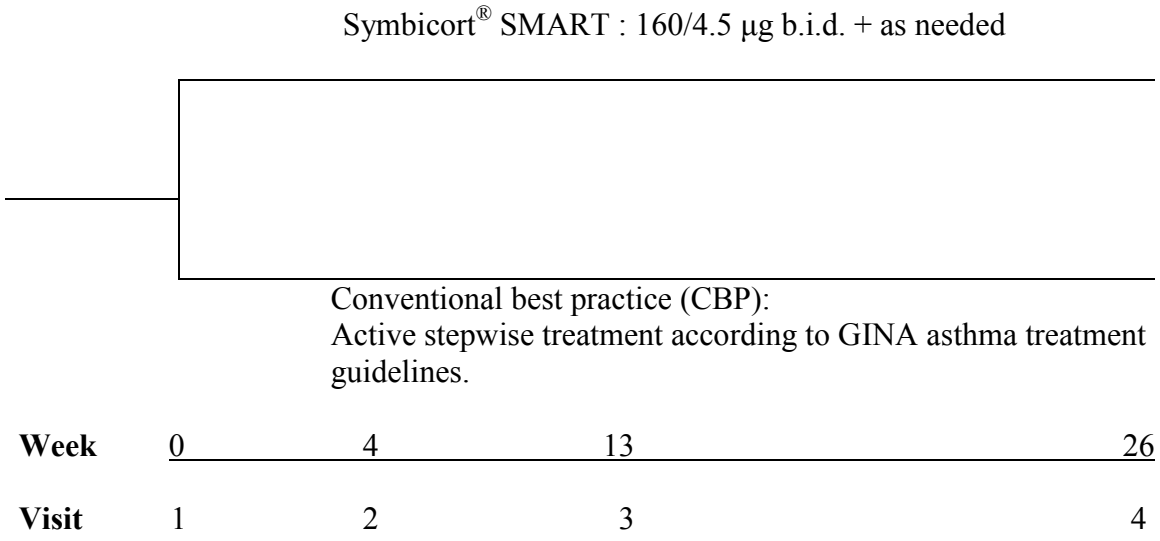
Objectives

The primary objective of the study was to compare the efficacy of treatment with Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART) with treatment according to conventional best practice (CBP) in patients with persistent asthma. The secondary objective was to collect and evaluate safety data for the two different treatment groups.

Study design

This was a randomized, open-label, parallel-group, multicentre study in 1900 patients (planned number) with persistent asthma. Patients were treated with either Symbicort® SMART (i.e. Symbicort® Turbuhaler® (budesonide/formoterol) 160/4.5 µg (delivered dose), 1 inhalation b.i.d. plus as needed), or conventional best practice according to the investigator's judgement, following GINA guidelines (Ref: Global Initiative for Asthma 2002). The treatment period lasted for 26 weeks.

Figure S1 Study flow chart



Target patient population and sample size

Male and female patients, ≥ 12 years of age, with persistent asthma who were currently treated with inhaled glucocorticosteroids (IGCSs) and long-acting β_2-agonist (LABA).

It was under the assumption that, at the end of the study, 12% of the patients would have experienced a severe asthma exacerbation in one treatment group and 8% of the patients would have experienced a severe asthma exacerbation in the other group. Using a log-rank test, a sample size of 880 patients per treatment group was required in order to detect this difference with 80% probability. In order to compensate for an estimated 7% dropout rate during the study, a total of 1900 patients were to be randomized in this study.

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

Investigational product was Symbicort® Turbuhaler®, 160/4.5 µg/dose budesonide/formoterol (delivered dose), 1 inhalation b.i.d. as maintenance treatment plus as needed, in response to symptoms.

Comparator products were any conventional best practice treatments, except Symbicort® SMART and/or maintenance with oral glucocorticosteroids prescribed at the discrection of the investigator according to GINA treatment guidelines Ref: Global Initiative for Asthma 2002).

This was an open label study and the investigator prescribed the investigational product(s). AstraZeneca did not supply the investigational product(s) to the participating sites. Instead, the patients picked up the medication at a local pharmacy, hence the batch number(s) for investigational product and comparators are not available in the study database.

Duration of treatment

The treatment period lasted for 26 weeks.

Criteria for evaluation (main variables)

Efficacy

Primary variable

- Time to first severe asthma exacerbation

Secondary variables

- Total number of severe asthma exacerbations
- Mean use of as needed medication
- Prescribed asthma medications

Patient reported outcomes (PRO)

- Change in Asthma Control Questionnaire (ACQ) score

Safety

Only information regarding SAEs and discontinuations due to AE (DAEs) were collected in this study.

Statistical methods

All analyses were based on the full analysis set, as defined in the ICH E9 guidelines. In the full analysis set, all randomized patients who have efficacy data post randomization were included.

All hypothesis testing used two-sided alternative hypotheses and p-values less than 5% were considered statistically significant. Time to first severe asthma exacerbation was compared between treatment groups using Cox proportional hazards model stratified by country and

with treatment as a factor. The mean number of severe asthma exacerbations per patient was compared between the groups using a Poisson regression model.

Safety data was analysed by means of descriptive statistics.

No interim analyses were performed during the study.

Patient population

Patient flow, demographic characteristics and analysis sets are shown in Table S1, Table S2, Table S3 below.

Table S1 Patient flow

		SMART	CBP	Total
Enrolled				1865
	Not Randomized			11a
	- Eligibility Criteria not Fulfilled			11
Randomized		931	923	1854
	Discontinued	113	74	187
	- Eligibility Criteria not Fulfilled	36	35	71
	- Adverse Event	21	9	30
	- Patient not Willing to Continue Study	25	10	35
	- Patient Lost to Follow-up	12	13	25
	- Other	19	7	26
Completed		818	849	1667

[a] Data on patient enrolled but not randomized were collected for Finland and Denmark only.

Table S2 Demographic characteristics

		SMART (n=921)	CBP (n=914)	Total (n=1835)[b]
Sex (n and % of patient)	Male	362 (39.3)	378 (41.4)	740 (40.3)
	Female	559 (60.7)	536 (58.6)	1095 (59.7)
Age	Mean (SD)	43.0 (15.9)	42.0 (15.9)	42.5 (15.9)
	Range	12-86	12-87	12-87
Race (n and % of patient)	Caucasian	911 (98.9)	901 (98.6)	1812 (98.7)
	Black	-	1 (0.1)	1 (0.1)
	Oriental	5 (0.5)	8 (0.9)	13 (0.7)
	Other	5 (0.5)	4 (0.4)	9 (0.5)
Body Mass Index (BMI)	Mean (SD)	26.86 (5.42)	26.63 (5.50)	26.74 (5.46)

		SMART (n=921)	CBP (n=914)	Total (n=1835)[b]
	Range	14.65-62.56	13.84-58.43	13.84-62.56
LABA use (n and % of patient)		685 (74.4)	691 (75.6)	1376 (75)
IGCS dose/day (µg) before randomization (expressed as BDP equivalent)[a]	Mean (SD)	1018 (549)	1051 (650)	1035 (602)
	Range	133-4000	44-6000	44-6000
Median time since diagnosis (yrs)	Median	12.8	12	12
	Range	0.1-70	0.1-72	0.1-72
No of as needed inhalations/day	Mean (SD)	1.1 (1.4)	1.1 (1.5)	1.1 (1.5)
	Range	0.0-8.6	0.0-18.0	0.0-18.0
As needed free days (%)	Mean (SD)	50.8 (40.5)	52.3 (40.6)	51.6 (40.5)
	Range	0.0-100.0	0.0-100.0	0.0-100.0
Smoking Status (n and % of patient)				
	Non Smoker	579 (62.9)	558 (61.1)	1137 (62)
	Ex-Smoker	211 (22.9)	204 (22.3)	415 (22.6)
	Occasional Smoker	41 (4.5)	55 (6)	96 (5.2)
	Habitual Smoker	90 (9.8)	97 (10.6)	187 (10.2)
No of pack years	Mean (SD)	5.4 (3.9)	4.9 (3.1)	5.1 (3.5)
	Range	0-40	0-23	0-40
PEF(L/min) pre BD	Mean (SD)	475.1 (125.3)	477.4 (129.1)	476.2 (127.2)
	Range	90-995	149-920	90-995
PEF(L/min) post BD	Mean (SD)	500.5 (129.1)	500.0 (132.0)	500.3 (130.5)
	Range	105-998	147-920	105-998

[a] IGCS dose is converted to BDP (beclomethasone dipropionate equivalent).
[b] The data represents patients included in the Full Analysis Set. This equals the patients included in the Safety Analysis Set.

Table S3 Analysis sets

Analysis sets	SMART	CBP
Patients randomized	931	923
Patients included in the Safety Analysis Set[a]	921	914

Analysis sets	SMART		CBP	
Patients excluded from Safety Analysis Set[b]	10	No SMART medication taken	9	No CBP medication taken
Patients included in the Full Analysis Set[c]	921		914	
Patients excluded from the Full Analysis Set	10	No SMART medication taken	9	No CBP medication taken

[a] Data for patients who took at least one dose of the randomized investigational product and for whom data have been collected after randomization.
[b] Patients who were enrolled in the study, but who never took the randomized investigational product.
[c] All randomized patients who have efficacy data post randomization.

A total of 1835 patients were included in the full analysis set (n=921 for Symbicort® SMART and n=914 for CBP). The baseline data were comparable between treatments.

A higher number of discontinuation was reported with Symbicort® SMART compared to CBP (113 vs. 74). In total, 30 patients discontinued treatment due to adverse events (21 vs. 9 for Symbicort® SMART and CBP, respectively).

Efficacy results

Tables and figures are presented in Sections 7.2 and 7.3.

Primary efficacy variable

- The primary variable, time to first exacerbation was not found to be significantly different between the Symbicort® SMART arm and CBP arm, with Cox hazard ratio = 0.79 [95% CI: 0.56, 1.12], p= 0.189.

Secondary efficacy variables

- There were fewer severe exacerbations with Symbicort® SMART (16 versus 22 events/100 patients/yr; 26% reduction), however the difference was not statistically significant (p=0.058).

  No differences were observed in time to first ER/hospitalization (p=0.396) and mean number of severe exacerbation leading to ER/hospitalization (p=0.340).

- No differences between Symbicort® SMART and CBP were seen in the mean as-needed use (p=0.98).

- A total of 81% of the patients in the CBP arm were prescribed a combination treatment of an inhaled glucocorticosteroid (IGCS) and long acting β_2 agonist (LABA).

The mean total IGCS dose (delivered dose) was significantly lower in the Symbicort® SMART arm versus the CBP (482 versus 670 µg/day for Symbicort® SMART and CBP, respectively; p< 0.0001). This represented a 28% reduction in the mean total steroid dose. The mean daily dose IGCS use expressed as BDP (beclomethasone) equivalent was also significantly lower in the Symbicort® SMART versus the CBP arm (753 versus 1092 ug/day; p< 0.0001). This represented a 31% reduction in the mean total steroid dose.
The total number of days with use of oral corticosteroids during severe asthma exacerbations was fewer for Symbicort® SMART compared to CBP (721 versus 941, respectively).

- ACQ was statistically improved more in Symbicort® SMART versus CBP (p=0.003).
- Other variables: The PEF pre-BD and the PEF % of predicted normal (%) values were significantly improved in the Symbicort® SMART arm versus the CBP arm (p=0.006 and p=0.002).

Safety results

Table S4 Number (%) of patients who had a serious adverse event or event leading to study discontinuation (safety analysis set)

	N (%) of patients who had an adverse event in each category[a]			
	SMART (n=921)		CBP (n=914)	
Category of adverse event	n	(%)	n	(%)
Serious adverse events	25	(2.7%)	25	(2.7%)
Serious adverse events leading to death	1	(0.1%)	0	(0.0%)
Serious adverse events not leading to death	24	(2.6%)	25	(2.7%)
AEs leading to discontinuation of study	21	(2.3%)	9	(1.0%)
	Total number of adverse events			
Serious adverse events	30		33	
Serious adverse events leading to death	1		0	
Serious adverse events not leading to death	29		33	
AEs leading to discontinuation of the study	22		10	

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

Table S5 Number (%) of patients who had at least 1 serious adverse event in any system organ class, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)[a]

	SMART (n=921)		CBP (n=914)	
System organ class	**n**	**(%)**	**n**	**(%)**
Respiratory, thoracic and mediastinal disorders	7	(0.8%)	6	(0.7%)
Infections and infestations	6	(0.7%)	6	(0.7%)
Nervous system disorders	2	(0.2%)	3	(0.3%)
Gastrointestinal disorders	3	(0.3%)	1	(0.1%)
General disorders and administration site conditions	1	(0.1%)	3	(0.3%)
Reproductive system and breast disorders	2	(0.2%)	1	(0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0%)	3	(0.3%)
Psychiatric disorders	1	(0.1%)	1	(0.1%)
Injury, poisoning and procedural complications	0	(0.0%)	2	(0.2%)
Social circumstances	0	(0.0%)	1	(0.1%)
Renal and urinary disorders	1	(0.1%)	0	(0.0%)
Ear and labyrinth disorders	0	(0.0%)	1	(0.1%)
Endocrine disorders	1	(0.1%)	0	(0.0%)
Hepatobiliary disorders	1	(0.1%)	0	(0.0%)
Pregnancy, puerperium and perinatal conditions	1	(0.1%)	0	(0.0%)

[a] The table does not count multiple events in the same SOC for the same patient. It counts the number of unique combinations of SOC and patient.

Table S6 Number (%) of patients who had at least 1 event leading to study discontinuation in any system organ class, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)

	SMART (n=921)		CBP (n=914)	
System organ class	**n**	**(%)**	**n**	**(%)**
Respiratory, thoracic and mediastinal disorders	15	(1.6%)	5	(0.5%)
Nervous system disorders	2	(0.2%)	1	(0.1%)
Cardiac disorders	2	(0.2%)	0	(0.0%)
General disorders and administration site conditions	1	(0.1%)	1	(0.1%)
Infections and infestations	1	(0.1%)	0	(0.0%)

	SMART (n=921)		CBP (n=914)	
System organ class	**n**	**(%)**	**n**	**(%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0%)	1	(0.1%)
Injury, poisoning and procedural complications	0	(0.0%)	1	(0.1%)
Skin and subcutaneous tissue disorders	1	(0.1%)	0	(0.0%)

As seen from Table S4, there were a total of 30 serious adverse events (including deaths) in the Symbicort® SMART arm versus 33 serious adverse events (no deaths) in the CBP arm (for randomized patients only). In terms of the number of AEs that led to discontinuation of the study, the number was 22 versus 10 for Symbicort® SMART and CBP arm, respectively.

There were 25 randomized patients in each treatment group who experienced a serious adverse event. A total of 30 patients discontinued the study due to an AE (21 versus 9 for Symbicort® SMART and CBP, respectively). A total of 1835 randomized patients were included in the safety analysis dataset.

One (1) death was reported in the study in the Symbicort® SMART group in Denmark. The patient contacted the investigator 16 August due to asthma deterioration. The patient discontinued the study and study medication on 9 September 2005 due to "Subject not willing to continue study" and experienced asthma exacerbation on 30 September 2005. The event was considered serious due to hospitalization, and the patient died the same day. The events pneumonia and incompensatio cordis lead to death and not the event of asthma exacerbation. The investigator considered the event to be unrelated to the study therapy. See Section 11.3.3.3 for a full narrative on the death.

In this study, no clinically important differences between the two treatment groups were observed with regard to the overall pattern of reported SAEs (fatal and non-fatal) or DAEs. Both Symbicort® SMART and CBP were well tolerated and no new or unexpected safety concerns were identified.