Drug product:	Symbicort Turbohaler	**SYNOPSIS**	
Drug substance(s):	Budesonide/Formoterol		
Study code:	D5890L00009		
Date:	20 June 2008		

A comparison of Symbicort Single inhaler Therapy (Symbicort Turbohaler 160/4.5 µg, 1 inhalation b.i.d. plus as needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults - a 26-week, randomised, open-label, parallel-group, multi-centre study (SALTO)

Study centre(s)

A total of 194 centres in Belgium and Luxembourg participated in this study.

Study dates		**Phase of development**
First patient enrolled	24 December 2004	Therapeutic confirmatory (IIIb)
Last patient completed	15 June 2006	

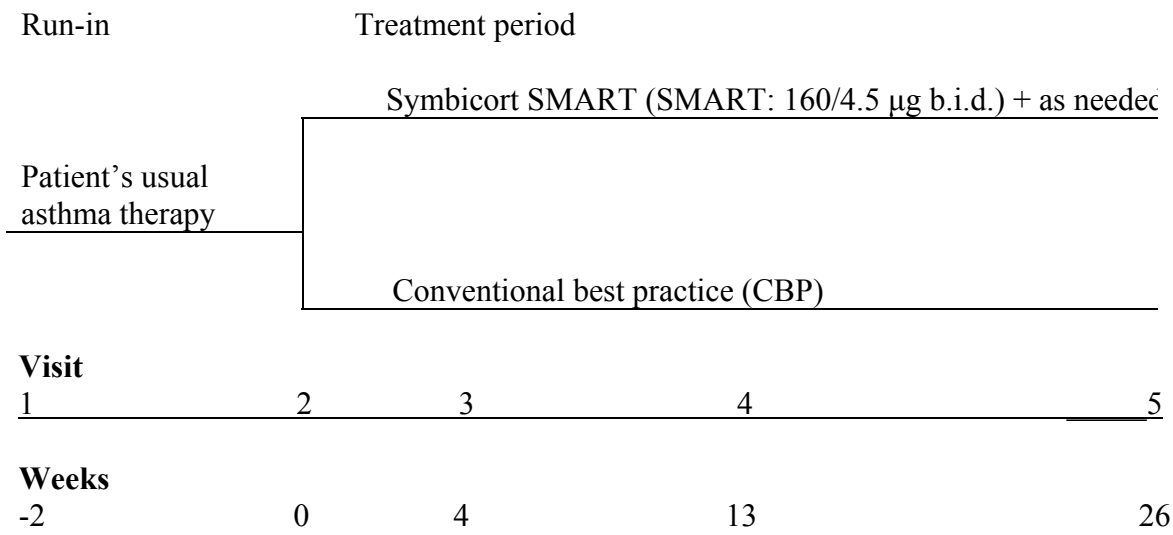
Objectives

The primary objective of the study was to compare the efficacy of Symbicort Single Inhaler Therapy (SMART *Symbicort Maintenance and Reliever Therapy)* conventional best practice in adolescent and adult patients with persistent asthma. The secondary objective was to collect safety data for treatment in the two treatment groups of adolescent and adult patients with persistent asthma by evaluating the incidence and types of serious adverse events (SAEs) and discontinuations due to adverse events (AEs).

Study design

This was a randomised, open-label, phase IIIB, multicenter study with a parallel group design. Patients were treated with either SMART i.e. Symbicort® Turbohaler® 160/4.5µg/inhalation (delivered dose), 1 inhalation b.i.d. plus as needed (in response to symptoms), or conventional best practice. The study consisted of the following periods: 2-week run-in period followed by a 26-week randomised treatment period.

Figure 1 Study flow chart



Target patient population and sample size

Male and female, adolescent (≥ 12 years of age) and adult patients with persistent asthma, currently treated with inhaled glucocorticosteroid (IGCS) or IGCS and long-acting β_2-agonist (LABA).

Using a log-rank test, a sample size of 500 patients per treatment group (a total of 1000 randomised patients) was required in order to detect a difference between the two treatment groups with 80% probability. It was under the assumption that, at the end of the study, 11% of the patients would have experienced a severe asthma exacerbation in one treatment group and 6% of the patients would have experienced a severe asthma exacerbation in the other treatment group.

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

Investigation medication was Symbicort® Turbohaler® 160/4.5µg/inhalation (delivered dose), 1 inhalation b.i.d. + as needed in response to symptoms.

Comparators were conventional best practice (CBP), active stepwise individualized treatment according to the Global Initiative for Asthma (GINA) treatment guidelines.

The following batch numbers of Symbicort Turbohaler (160/4.5µg) were used:
GL1141 exp 30/11/2007;
HA1203 exp 31/1/2008; FF695 exp 6/2006
GF1032 exp 6/2006

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

- Number of severe asthma exacerbations
- Mean use of as-needed medication
- Prescribed asthma medication
- Peak Expiratory Flow (PEF)

Patient-reported outcomes (PROs)

- Asthma Control Questionnaire (ACQ) score
- Satisfaction with Asthma Treatment Questionnaire (SATQ) score

Safety

- SAEs
- Discontinuation due to AE(s)

Health economic results

- Direct costs linked to medications

Statistical methods

All efficacy analyses were based on the full analysis set, as defined in ICH E9 guidelines.

Time to first severe asthma exacerbation was compared between treatments using a Cox proportional hazards model with treatment as a factor. The mean number of severe asthma exacerbations per patient was compared between treatments using a Poisson regression model. The overall ACQ score, overall SATQ score, use of as-needed medication, PEF and FEV_1 were all compared between treatments using separate analysis of variance models. Use of prescribed asthma medications was analysed in terms of descriptive statistics. Safety data was analysed by means of descriptive statistics.

Patient population

Table S1 Patient population and disposition

		SMART		CBP		Total	
Population							
N randomised (N planned)		450	(500)	458	(500)	908	(1000)
Demographic characteristics							
Sex (n and % of patients)	Male	198	(44.0%)	188	(41.0%)	386	(42.5%)
	Female	252	(56.0%)	270	(59.0%)	522	(57.5%)
Age (years)	Mean	43.4		42.9		43.1	
	Range	12 to 87		13 to 85		12 to 87	
Race (n and % of patients)	Caucasian	448	(99.6%)	452	(98.7%)	900	(99.1%)
	Black	2	(0.4%)	2	(0.4%)	4	(0.4%)
	Oriental	0		3	(0.7%)	3	(0.3%)
	Other	0		1	(0.2%)	1	(0.1%)
Baseline characteristics							
Mean IGCS dose (μg)/day during run-in		570		589		579	
	(range)	(100-2000)		(320-2000)		(100-2000)	
Median time since diagnosis (years)		21.0		20.2		20.4	
	(range)	(0-86)		(0-78)		(0-86)	
Mean number of as-need inhalations/day		1.09		1.02		1.06	
	(range)	(0-15)		(0-11)		(0-15)	
As-needed free days (%)		60%		61%		60%	
	(range)	(0-100%)		(0-100%)		(0-100%)	
Disposition							
N (%) of patients who	Completed	423	(94.0%)	444	(96.9%)	867	(95.5%)
	Discontinued	27	(6.0%)	14	(3.1%)	41	(4.5%)
N analysed for safety[a]		450		458		908	
N analysed for efficacy (full analysis set[b])		450		458		908	

[a] Number of patients who took at least 1 dose of the randomised investigational product and for whom data were collected after randomisation

[b] All randomised patients with data after randomisation

N=Number

At the outset, asthma severity in the largest proportion (37.2%) of subjects was classified by investigators as moderate persistent, followed by severe persistent (35.8%), with mild

persistent asthma reported in 26.8% of the population. (Information for two patients was missing).

Efficacy results

The time to first severe asthma exacerbation was not significantly different between the SMART regimen and conventional best practice, with a hazard ration of 0.979 (p=0.7517). There was also no statistically significant difference in the mean number of asthma exacerbations.

The number of severe asthma exacerbations for SMART and CBP was 4 versus 7events/year/100 patients, p=0.0909. Overall, five events required emergency room visits (four in the CBP group and one in the SMART group) and three events required hospitalisation (two in the SMART group and one in the CBP group). The total number of days of severe exacerbation was 261 days in the CBP group versus 138 days in the SMART group.

The majority of patients in both groups had at least one day during which more than one as-needed inhalation was required (58.7% in the SMART group and 63.5% in the CBP group). Three patients (0.7%) in the SMART group and nine patients (2.0%) in the CBP group had at least one day with more than 10 as-needed inhalations. Overall, daily as-needed inhalation use was comparable in the two groups.

The most commonly prescribed asthma medications in the 458 patients treated according to conventional best practice were a combination treatment of an inhaled glucocorticosteroid and long acting β_2 agonist (86%) and inhaled short acting β_2 agonists (69%). The mean daily dose of inhaled steroid use was significantly lower in the SMART group versus the CBP group (482 versus 589 μg/day, p<0.0001).

Pre- and post-bronchodilator (BD) PEF measurements were performed at Visit 2 (Baseline) and Visit 5 (final visit). For patients enrolled by a lung specialist, pre- and post-BD FEV_1 measurements were also performed at these time points. There were no statistically significant differences between the two treatment groups with respect to the change from baseline for the mean pre-BD and post-BD PEF values (p=0.5560, p=0.5970) or for the pre-BD and post-BD FEV_1 values (p=0.4790, p=0.3285).

In the SMART group, the mean ACQ overall score during the treatment period decreased by an adjusted mean change of -0.30 as compared with -0.17 in the CBP group. Treatment comparison for change in ACQ score was statistically significant (p=0.0026) indicating significantly improved asthma control in the SMART group as compared to the CBP group.

Both groups showed similar overall treatment satisfaction (improvement SATQ score) from enrolment to the end of the study.

Safety results

Both treatment regimens were considered safe and well-tolerated. No clinically important drug related safety findings were identified in this study.

Twenty patients reported a total of 20 serious adverse events during treatment (9 in the SMART group and 11 in the CBP group). Six patients discontinued treatment due to an SAE/AE [4 in the SMART group (including two patients who died : one suicide and one myocardial infarction with no relation with the treatment) and 2 in the CBP group].

Table S2 Number (%) of patients who had at least one serious adverse event and number (%) of patients with at least one AE leading to discontinuation (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	SMART (450)		CBP (458)		Total (908)	
Serious adverse events	9	(2.0%)	11	(2.4%)	20	(2.2%)
Serious adverse events leading to death	2		0		2	
Serious adverse events not leading to death	7		11		18	
Discontinuations of study treatment due to adverse events[b]	2[c]	(0.4%)	2	(0.4%)	4	(0.4%)

[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.
[b] excludes two patients in the SMART group who died
[c] one patient experienced two events

Table S3 Serious adverse events, excluding deaths, over the study period (safety analysis set)

Adverse event (preferred term)	Number (%) of patients who had an adverse event			
	SMART (n=450)		CBP (n=458)	
	n	(%)	n	(%)
Cholecystitis	0		2	(0.4%)
Salpingitis	1	(0.2%)	1	(0.2%)
Benign Prostatic Hypertrophy	0		1	(0.2%)
Breast Adenocarcinoma	0		1	(0.2%)
Cerebrovascular Accident	0		1	(0.2%)

Adverse event (preferred term)	Number (%) of patients who had an adverse event			
	SMART (n=450)		CBP (n=458)	
	n	(%)	n	(%)
Facial Palsy	1	(0.2%)	0	
Gastric Ulcer	1	(0.2%)	0	
Herniated Nucleus Pulposus	1	(0.2%)	0	
Labyrinthine Fistula	0		1	(0.2%)
Myelodysplasia	1	(0.2%)	0	
Myocardial Infarction	0		1	(0.2%)
Pneumonia	1	(0.2%)	0	
Transient Ischemic Attack	0		1	(0.2%)
Tonsillitis	1	(0.2%)	0	
Urethral Meatus Stenosis	0		1	(0.2%)
Uterine Myoma	0		1	(0.2%)
Asthma	2	(0.4%)	1	(0.2%)

Table S4 **Adverse events which led to discontinuation of treatment (safety analysis set)**

Adverse event (preferred term)	Number (%) of patients who had an adverse event			
	SMART (n=450)		CBP (n=458)	
	n	(%)	n	(%)
Cerebrovascular Accident	0	(0%)	1	(0.2%)
Dyspnoea	1	(0.2%)	0	(0%)
Myelodysplasia	1	(0.2%)	0	(0%)
Myocardial Infarction	1	(0.2%)	0	(0%)
Sore Throat	0	(0%)	1	(0.2%)
Suicide	1	(0.2%)	0	(0%)
Tingling	1	(0.2%)	0	(0%)

Health Economic results

Estimated costs for medications used for asthma during the treatment period were analysed for the two treatment groups.

The estimated cost per patient per month was higher in the CBP arm with respect to the SMART arm; on average, 66.54 € versus 51.28 €. The difference in treatment costs between groups was statistically significant ($p < 0.0001$; **Error! Reference source not found.**).