Drug Product: Symbicort Turbuhaler Drug Substance: Budesonide/formoterol Study Code: D5890C00003 Edition Number: 1 Date: 6 May 2010	**SYNOPSIS**	

A comparison of the inflammatory control of asthma provided by one inhalation of Symbicort® Turbuhaler® 160/4.5 µg/inhalation bid plus as-needed versus one inhalation of Symbicort® Turbuhaler® 320/9 µg/inhalation bid + one inhalation of Pulmicort® Turbuhaler® 400 µg/dose bid plus Terbutaline Turbuhaler® 0.4 mg/inhalation as-needed. A 12-month, randomised, double-blind, parallel-group, active-controlled, multinational, phase IIIB study in adult patients with asthma

Study dates

First patient enrolled 6 May 2005

Last patient completed 17 March 2007

Phase of Development
Therapeutic confirmatory (IIIB)

Objectives

The primary objective of the study was to compare the anti-inflammatory effects of Symbicort® maintenance and reliever therapy (SMART) (Symbicort Turbuhaler® 160/4.5 µg/inhalation bid plus as-needed) versus a fixed-dose treatment that includes both Symbicort Turbuhaler (320/9 µg/inhalation bid) and Pulmicort® Turbuhaler (400 µg/inhalation bid) plus terbutaline Turbuhaler (0.4 mg/inhalation) as-needed on the immunopathology and remodelling of the asthmatic lung. [1]

The secondary objective of the study was to evaluate safety by investigating the nature, incidence, severity of AEs, and changes in vital signs within the treatment groups.

Study design

This was a 12-month, double-blind, randomised, active-controlled, parallel-group, multi-national study, with a 2-week run in period, that was performed in adult patients with persistent asthma.

Target patient population and sample size

Men and women, from 18 to 65 years of age with asthma, a forced expiratory flow (FEV_1) ≥60% of predicted normal (PN) pre-bronchodilatory value, at least 12% reversibility or a mean morning PEF (mPEF) between 50% to 85% of the post-bronchodilatory value, and symptoms despite daily use of inhaled GCS.

The change in number of eosinophils per area subepithelial tissue in bronchial biopsies was the basis for the sample size calculation. The sample size calculation was based on an assumed 2.55-fold increase and standard deviation of 1.65 for log-transformed variable analysed in a multiplicative analysis of variance (ANOVA). A sample size of 50 in each group would have 80% power to detect a difference in means of 0.936, assuming that the common standard deviation was 1.65 and using a two group t-test with a 0.050 two-sided significance level. Due to the nature of the study, a high dropout rate might be expected. Therefore, it was decided to include 100 patients per group, for a total of 200 enrolled patients.

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

During run-in, patients were provided with Bricanyl (terbutaline) Turbuhaler 0.5 mg/dose to be taken as needed for the relief of symptoms (batch number 3521325).

At the end of the run-in period, patients were randomised to one of the following treatment arms:

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[1] Symbicort, Turbuhaler, and Pulmicort are trademarks of the AstraZeneca group of companies.

- Symbicort SMART: Symbicort Turbuhaler (160/4.5 µg/inhalation; batch numbers GL456 and FL353), one inhalation morning and evening as maintenance treatment, plus Symbicort Turbuhaler (160/4.5 µg/inhalation; batch numbers GL40 and GA38) as-needed.

- Fixed-dose treatment: Symbicort Turbuhaler (320/9 µg/inhalation; batch numbers GL388 and FM221) and Pulmicort Turbuhaler (400 µg/dose; batch numbers GK806 and FL788), one inhalation of each morning and evening as maintenance treatment, plus terbutaline Turbuhaler (0.4 mg/inhalation; batch numbers GL72, GD69, and FH64) as-needed.

N.B. The 160 µg budesonide dose for Symbicort Turbuhaler is the delivered dose, which corresponds to Pulmicort Turbuhaler's 200 µg metered dose. Terbutaline Turbuhaler 0.4 mg/inhalation, measured as delivered dose, corresponds to the marketed product Bricanyl Turbuhaler 0.5 mg/dose, which is measured as metered dose.

Duration of treatment

A 2-week run-in period was followed by a 52-week treatment period.

Criteria for evaluation (main variables)

Efficacy

- **Primary outcome variables:**

  - Change in number of eosinophils per area subepithelial tissue in bronchial biopsies from Visit 2 to Visit 8.

  - Change in number of eosinophils in induced sputum from Visit 1 to the mean of Visits 4 to 7, measured as percentage of number of non-squamous cells.

- **Secondary outcome variables:**

Biopsies: change from Visit 2 to Visit 8 in:

Immunopathology

  - Number of inflammatory (CD45+) cells per area subepithelial tissue

  - Number of mast cells measured as percentage of number of inflammatory cells

  - Number of activated CD4+ cells measured as percentage of number of inflammatory cells

Remodelling

- Reticular basement membrane (RBM) thickness, measured in µm

-After unblinding of study data, these additional outcome variables for the biopsy samples were performed as exploratory analyses:

- Number of CD3+ cells, measured as percentage of number of inflammatory cells
- Number of neutrophils, measured as percentage of number of inflammatory cells
- Number of CD8+ cells, measured as percentage of number of inflammatory cells

Induced sputum: change from Visit 1 to the mean of Visits 4 to 7 in:

Immunopathology

- Number of non-squamous cells per mL induced sputum
- Number of neutrophils, measured as percentage of number of non-squamous cells
- Number of lymphocytes, measured as percentage of number of non-squamous cells
- Number of monocytes/macrophages, measured as percentage of number of non-squamous cells
- Number of bronchial epithelial cells, measured as percentage of number of non-squamous cells

Mediators: Change from Visit 1 to the geometric mean of Visits 4 to 7 in:

- Amount of eosinophil cationic protein (ECP), measured as ng/ml induced sputum

Clinical outcome variables:

- Change from visit 2 to the mean of visit 4-8 in concentration of exhaled nitric oxide, measured as part per billion

Clinical outcome variables:

- Number of severe asthma exacerbations

- Time to first severe asthma exacerbation
- Change in FEV_1, as change from Visit 2 to the mean of Visits 4 to 8
- Number of as-needed inhalations

Safety

- Investigate nature, incidence and severity of adverse events (AE)s within the treatment groups.
- Vital signs

Statistical methods

All hypothesis testing was done using two-sided alternatives. P-values less than 5% were considered statistically significant. Differences between treatments were described using 95% confidence intervals.

The primary outcome variables were change in number of eosinophils per area subepithelial tissue in bronchial biopsies from randomisation (Visit 2) to last visit (Visit 8) and change in number of eosinophils in induced sputum from Visit 1 to the mean of Visits 4 to 7, measured as percentage of number of non-squamous cells. After unblinding of study data, it was decided to use the geometric mean of Visits 4 to 7 in calculations for the sputum variable. The ratios for each of the primary variables were compared between treatments using a multiplicative analysis of variance model with treatment as fixed factor and baseline (Visit 2 for biopsy and Visit 1 for sputum) as a covariate. Geometric mean treatment ratios were estimated, and 95% confidence intervals were calculated.

Secondary biopsy and sputum outcome variables, exhaled nitric oxide, and FEV_1, were analysed using similar methods as for the primary variables. Biopsy mast cells, CD4+ cells, neutrophils, CD3+ cells, and CD8+ cells were analysed as the protocol-specified percentage of number of inflammatory (ie, % of CD45+) cells, but are also presented as the number of cells per area subepithelial tissue (ie, cells per mm^2).

The number of severe asthma exacerbations per patient were compared between the treatments using a Poisson regression model with treatment as factor and the observation time as an offset variable. Time to first severe asthma exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a Cox proportional hazards model with treatment as factor.

The change in mean number of as-needed inhalations per day was calculated for each patient and compared between treatments using an analysis of variance model with treatment as factor and run-in mean as a covariate.

Safety data were analysed in terms of descriptive statistics and qualitative analysis.

Patient population

A total of 127 patients were randomised and allocated to treatment. All 127 were analysed for efficacy and safety. Of the 9 patients that discontinued from the study, 2 were discontinued due to eligibility criteria not fulfilled, 4 due to adverse event (1 in the Symbicort SMART group and 3 in the fixed-dose group), and 3 due to other reasons.

Of the 127 patients allocated to treatment, 54% were males, and 46% were females (Table S1). Their average age was 40.3 years. All but 4 were Caucasians. There were somewhat more patients who were previous smokers in the fixed dose treatment (37%) compared with the Symbicort SMART group (22%).

All patients were on inhaled GCS prior to study entry. The most common dose was 800 µg, which was prescribed for 44 (35%) of the patients. Mean dose of inhaled GCS before the study was 641 µg in the Symbicort SMART treatment and 711 µg in the fixed-dose group.

Mean FEV_1 at enrolment was 2.84 or 81% of the predicted normal value, and mean reversibility was 16.7%. Patients used 1.36 inhalations of as-needed reliever medication per day during the run-in period.

Table S1 Patient population and disposition

		Symbicort SMART	Fixed dose	All
N randomised (N planned)		64 (50)	63 (50)	**127 (100)**
Demographic characteristics				
Sex (N (%) of patients)	Male	35 (55)	34 (54)	**69 (54)**
	Female	29 (45)	29 (46)	**58 (46)**
Age (years)	Mean	39.4	41.3	**40.3**
	Range	19-63	20-65	**19-65**
Race (N (%) of patients)	Caucasian	62 (97)	61 (97)	**123 (97)**
	Black	0	2 (3)	**2 (2)**
	Asian	1 (2)	0	**1 (1)**
	Other	1 (2)	0	**1 (1)**
Smoking status	Never	50 (78)	40 (63)	**90 (71)**
	Previous	14 (22)	23 (37)	**37(29)**
Pack-years of previous smokers	Median	3	3	**3**
	Range	0-9	1-9	**0-9**
Baseline characteristics				
N using inhaled GCS at entry	N	64	63	**127**
Nominal dose (µg)	Mean	641	711	**676**
	Range	200-1600	160-1600	**160-1600**
Beclomethasone equivalent dose (µg)	Mean	926	1084	**1004**
	Range	250-2000	250-2000	**250-2000**
FEV_1 (L)	Mean	2.90	2.78	**2.84**
	Range	1.16-4.71	1.40-4.27	**1.16-4.71**
FEV_1 (%PN)	Mean	81.4	80.6	**81.0**
	Range	58-121	60-110	**58-121**
Reversibility (%)	Mean	16.4	17.0	**16.7**
	Range	-2-43	2-53	**-2-53**
As-needed use (daily)	Mean	1.48	1.24	**1.36**
	Range	0.00-6.01	0.00-7.44	**0.00-7.44**
Disposition				
N (%) of patients who	Completed	60 (94)	58 (92)	**118 (93)**
	Discontinued	4 (6)	5 (8)	**9 (7)**
N analysed for safety[a]		64	63	**127**
N analysed for efficacy[b]		64	63	**127**

a Number who took at least 1 dose of investigational product and had at least 1 data point after dosing

b Number with any efficacy data available post-randomisation regardless of whether they took investigational product or not.

Efficacy results

This study compared a mean daily budesonide/formoterol delivered dose of 483/13.6 µg via Symbicort SMART with a fixed daily budesonide/formoterol delivered dose of 1280/18 µg.

Primary outcome variables

The mean eosinophil counts in biopsies during treatment increased in the Symbicort SMART group (6.2 to 12.3 cells/mm^2), whereas it decreased in the fixed-dose treatment group (7.7 to 4.8 cells/mm^2). The treatment difference was statistically significant (P<0.001).

The mean for sputum eosinophil counts were relatively stable from baseline to treatment in the Symbicort SMART group (from 1.6% to 1.9%) but decreased in the fixed- dose treatment group (from 2.2% to 1.2%). This resulted in a statistically significant difference in favour of the fixed-dose treatment group (P= 0.0038).

In summary, both primary variables showed a statistically significant difference between the treatments in eosinophils in favour of the fixed-dose group.

Table S2 Change in eosinophils in biopsies and sputum in the individual treatment groups

Variable	Treatment	N	Baseline GMean	Baseline Range	Treatment period GMean	Treatment period Range	Adjusted ratio[a]
Eosinophils in biopsies (n/mm^2)	Symbicort SMART	56	6.2	0.1 - 278	12.3	0.1 - 241	1.89
	Fixed dose	56	7.7	0.1 - 379	4.8	0.1 - 124	0.65
Eosinophils in sputum (%)	Symbicort SMART	58	1.6	0.1 - 77.0	1.9	0.1 - 57.0	1.06
	Fixed dose	60	2.2	0.1 - 41.3	1.2	0.1 - 74.7	0.58

a Multiplicative ANOVA.

Table S3 Treatment comparison for biopsy and sputum eosinophils (Symbicort SMART/Fixed dose)

Variable	Ratio	95% CL	P-value
Eosinophils in biopsies (n/mm^2)	2.90	1.59, 5.29	<0.001
Eosinophils in sputum (%)	1.83	1.22, 2.75	0.0038

Secondary outcome variables

Descriptive statistics for individual treatment groups and statistical analysis for treatment comparisons for biopsy secondary outcome variables are presented in Table S4 and Table S5, respectively. For the inflammatory cell sub-types, results are presented as both number per area subepithelial tissue (ie, n/mm^2) and percentage of total inflammatory cells (ie, % of CD45+). The only statistically significant treatment difference was an increase in mast cells in the Symbicort SMART group as compared with the fixed-dose group. The absolute number of mast cells was stable in the Symbicort SMART group but decreased in the fixed-dose group. As a percentage of CD45+ cells, mast cells increased in the Symbicort SMART group but were stable in the fixed-dose group. Both treatments reduced reticular basement membrane thickness over 12 months, with no difference between groups.

Table S4 Descriptive statistics for data from biopsies

Variable	Treatment	Visit 2 GMean	Visit 2 Range	Visit 8 GMean	Visit 8 Range	Adjusted ratio[a]
CD45+ (n/mm^2)	Symbicort SMART	474	156- 1638	354	120 - 1113	0.74
	Fixed-dose	491	114 - 1232	318	123 - 1393	0.66
Mast cells (n/mm^2)	Symbicort SMART	87.1	6.84 - 436	90.7	11.1 - 381	1.07
	Fixed-dose	77.2	1.04 - 494	49.8	1.40 - 452	0.63
Mast cells (% of CD45+)	Symbicort SMART	20.9	1.9 - 155	28.6	2.09 - 122	1.42
	Fixed-dose	18.1	0.3 - 493	18.0	0.21 - 109	0.96
CD4+ cells (n/mm^2)	Symbicort SMART	115	12.6 - 946	138	8.8 - 1225	1.13
	Fixed-dose	144	19.4 - 2045	124	12.5 - 2109	0.92
CD4+ cells (% of CD45+)	Symbicort SMART	25.3	4.8 - 98.0	44.2	7.8 - 287	1.62
	Fixed-dose	31.6	7.76 - 221	45.8	8.4 - 247	1.56
Neutrophils (n/mm^2)	Symbicort SMART	87.3	4.0-323	96.3	17.3-437	1.12
	Fixed-dose	84.6	5.7-348	75.9	1.2-363	0.89
Neutrophils (% of CD45+)	Symbicort SMART	20.6	0.4-88.7	31.4	4.7-185	1.53
	Fixed-dose	20.3	1.3-420	27.7	0.8-187	1.36
CD3+ cells (n/mm^2)	Symbicort SMART	401	68.8-1324	403	76.4-1486	0.98
	Fixed-dose	455	88.7-1520	338	106.9-2467	0.77
CD3+ cells (% of CD45+)	Symbicort SMART	92.7	26.5-260	127	36.6-348	1.30
	Fixed-dose	104	48.4-809	128	55.0-569	1.30
CD8+ cells (n/mm^2)	Symbicort SMART	32.1	1.48-117	48.9	6.03-178	1.55
	Fixed-dose	30.9	6.87-121	43.8	8.19-226	1.39
CD8+ cells (% of CD45+)	Symbicort SMART	140	3.57-754	153	16.5-1134	1.09
	Fixed-dose	142	13.2-994	117	20.9-971	0.83
RBM thickness (µm)	Symbicort SMART	6.13	2.77-11.7	5.47	2.40-11.7	0.89
	Fixed-dose	6.15	3.27-9.63	5.90	2.70-10.0	0.96

a Multiplicative ANOVA.

Table S5 Treatment comparison for data from biopsies (Symbicort SMART/Fixed dose)

Variable	Ratio	95% CL	P-value
CD45+ (n/mm^2)	1.12	(0.90, 1.39)	0.32
Mast cells (n/mm^2)	1.69	(1.24, 2.31)	0.0012
Mast cells (% of CD45+)	1.49	(1.03, 2.14)	0.033
CD4+ cells (n/mm^2)	1.24	(0.86, 1.79)	0.26
CD4+ cells (% of CD45+)	1.04	(0.80, 1.34)	0.78
Neutrophils (n/mm^2)	1.13	(0.77,1.65)	0.52
Neutrophils (% of CD45+)	1.26	(0.89,1.79)	0.19
CD3+ (n/mm^2)	1.00	(0.84,1.19)	0.99
CD3+ (% of CD45+)	1.28	(0.99,1.64)	0.055
CD8+ (n/mm^2)	1.11	(0.86,1.44)	0.41
CD8+ (% of CD45+)	1.32	(0.96,1.81)	0.92
RBM thickness (µm)	0.93	(0.84, 1.03)	0.15

There were no statistically significant differences between the treatments in any of the secondary variables in sputum.

Clinical outcome variables

Exhaled nitric oxide decreased by 12% in both treatment groups during treatment, from 25.220 to 21.519 part per billion (ppb) in the Symbicort SMART group and from 19.509 to 17.804 ppb in the fixed-dose group. There was a slight increase in FEV_1 during the treatment period in both groups (from 2.97 to 3.02 L in the Symbicort SMART group and from 2.86 to 2.96 L in the fixed-dose group), but the difference between treatments was not statistically significant (P=0.36). The number of patients with at least 1 severe asthma exacerbation was 10 (15.6%) in the Symbicort SMART group and 12 (19.0%) in the fixed-dose group. There was not a statistically significant difference between treatments for either the number of severe exacerbations or the time to first severe exacerbation (Table S6). As-needed use decreased in both treatment groups after randomisation compared with the run-in level (Table S7) and was maintained during the treatment period, but there was not statistically significant difference between treatment groups (P=0.216).

Table S6 Statistical analysis of severe asthma exacerbations

Variable	Analysis	Comparison or treatment	Ratio or Rate	95% CI	P-value
-Time to first exacerbation	Cox PH model	Symbicort SMART vs Fixed-dose	0.806	(0.348, 1.865)	0.614
-Number of exacerbations patient-year	Poisson regression	Symbicort SMART	0.319	(0.198, 0.514)	-
		Fixed-dose	0.313	(0.192, 0.510)	-
		Symbicort SMART vs Fixed-dose	1.022	(0.516, 2.023)	0.951

Table S7 Period means and ranges for number of inhalations of as-needed medication

Treatment	N	Run-in period Mean	Run-in period Range	Treatment period Mean	Treatment period Range	Adjusted mean change[a]
Symbicort SMART	64	1.48	0.00-6.01	1.02	0.00-4.50	-0.39
Fixed-dose	63	1.24	0.00-7.44	0.74	0.00-4.22	-0.57

a Additive ANOVA.

The mean daily as-needed Symbicort use of 1.02 inhalation per day during treatment resulted in a mean daily delivered budesonide dose of 483 µg per day in the Symbicort SMART group, compared to 1280 µg per day in the fixed-dose group.

Safety results

The average exposure was 357 days in the Symbicort SMART group and 352 days in the fixed-dose group.

The number of patients with at least one AE was higher in the Symbicort SMART group (N=55) than in the fixed-dose group (N=46); however, the total number of AEs was similar in both groups (135 versus 136) (Table S8).

In total, 8 non-fatal serious adverse events (SAEs) were reported by 6 patients after intake of investigational product. One more serious adverse event (SAE) was reported post-study: an event of vocal cord thickening that was considered by the investigator to be causally related to study treatment. All SAEs except for one were serious due to the SAE criterion hospitalization.

There were no deaths or other significant AEs in the study. There were more SAEs and discontinuations due to adverse event (DAEs) in the fixed-dose group than in the Symbicort SMART group. Four patients discontinued study treatment due to AEs, (asthma in 1 patient in the Symbicort SMART group, and borrelia infection, throat irritation/malaise or back pain/cough in 3 patients in the fixed-dose group). The event of borrelia infection was serious.

Table S8 N (%) of patients who had at least 1 adverse event in any category and N of adverse events (safety analysis set)

Category of adverse event	Symbicort SMART N=64	Fixed-dose N=63	All N=127
N (%) of patients who had an adverse event in each category[a]			
Any adverse events	55 (86)	46 (73)	**101 (80)**
Serious adverse events			
Serious adverse events leading to death	0	0	**0**
Serious adverse events not leading to death	3 (5)	3 (5)[b]	**6 (5)**
Discontinuation of treatment with investigational product due to adverse event	1 (2)	3 (5)	**4 (3)**
Other significant adverse events	0	0	**0**
Total numbers of adverse events[c]			
Adverse events	135	136	**271**
Serious adverse events	3	5[b]	**7**

a Patients with multiple events in the same category are counted only once in that category.

b One more SAE was reported in the fixed-dose group post-treatment. An event of small granule like changes under vocal cord/VOCAL CORD THICKENING in patient (centre 51/patient number 140) became serious due to hospitalization. This event was also reported as an AE, small granule like changes under vocal cord and on tracheal wall/LARYNGEAL GRANULOMA (two changes coded as one event) on the day of last dose. For more details regarding this SAE see the SAE narratives in Section 11.3.4.3.

c Multiple events with the same preferred term are counted once for each patient and category.

The most commonly reported AEs were nasopharyngitis and pharyngolaryngeal pain (Table S9). These events are common in an asthma population, regardless of treatment intervention.

Table S9 N (%) of patients with AEs that were reported by preferred term in at least 5 patients

Preferred term	Symbicort SMART N=64	Fixed dose N=63	All N=127
Nasopharyngitis	20 (31%)	13 (21%)	**33 (26%)**
Pharyngolaryngeal pain	8 (13%)	3 (5%)	**11 (9%)**
Headache	5 (8%)	5 (8%)	**10 (8%)**
Viral upper respiratory tract infection	3 (5%)	7 (11%)	**10 (8%)**
Asthma	3 (5%)	4 (6%)	**7 (6%)**
Sinusitis	3 (5%)	4 (6%)	**7 (6%)**
Pyrexia	4 (6%)	3 (5%)	**7 (6%)**
Rhinitis	5 (8%)	1 (2%)	**6 (5%)**
Seasonal allergy	4 (6%)	2 (3%)	**6 (5%)**
Cough	3 (5%)	3 (5%)	**6 (5%)**
Lower respiratory tract infection bacterial	3 (5%)	3 (5%)	**6 (5%)**
Dyspnoea	4 (6%)	1 (2%)	**5 (4%)**

Pulse and blood pressure were measured at Visits 1, 2, and 8. There were no major changes in vital signs during the study, nor were there any obvious differences between treatments.