Drug Product	Symbicort® Turbuhaler®	**SYNOPSIS**	
Drug Substance	Budesonide/formoterol		
Edition Number	1.0		
Study Code	SD-039-0734		
Date	17 May 2005		

Efficacy of Symbicort® Turbuhaler® 160/4.5 µg as needed versus Oxis® 4.5 µg as needed and Bricanyl® 0.4 mg as needed in adults and adolescents with asthma receiving Symbicort® Turbuhaler® 160/4.5 µg twice daily as maintenance treatment. A 12-month, randomised, double-blind, parallel-group, active-controlled, phase IIIB, multi-centre study.

Study centres

A total of 289 centres from 20 countries participated in this study. The countries were as follows: Belgium (21 centres), Bulgaria (11 centres), China (6 centres), Czech Republic (34 centres), Germany (26 centres), Greece (9 centres), Hungary (20 centres), Indonesia (6 centres), Italy (6 centres), Malaysia (3 centres), the Netherlands (30 centres), Norway (17 centres), the Philippines (11 centres), Poland (18 centres), Romania (12 centres), Russia (11 centres), Slovakia (12 centres), South Africa (30 centres), South Korea (4 centres), and Vietnam (2 centres).

Publications

None at the time of writing this report.

Study dates

First patient enrolled: 10 April 2003

Last patient completed: 21 December 2004

Phase of Development

Therapeutic confirmatory (III)

Objectives

The primary objective was to compare the efficacy of Symbicort® Turbuhaler® 160/4.5 µg /inhalation as needed with that of Oxis® Turbuhaler 4.5 µg/inhalation as needed in asthmatic patients using Symbicort Turbuhaler maintenance therapy by evaluating the time to first severe asthma exacerbation.

Secondary objectives of the study were

- to compare the efficacy of Symbicort Turbuhaler 160/4.5 µg/inhalation as needed with that of Bricanyl® Turbuhaler 0.4 mg/inhalation as needed in asthmatic patients using Symbicort Turbuhaler maintenance therapy by evaluating time to first severe asthma exacerbation and

- to investigate safety by assessing the nature, incidence, and severity of adverse events (AEs) within the treatment groups.

Study design

This was a 12-month double-blind, randomised, active-controlled, parallel-group, multi-national study in patients with moderate to severe asthma using inhaled glucocorticosteroids (GCS).

Target patient population and sample size

Adults and adolescents with moderate to severe asthma and with documented symptoms despite use of inhaled GCSs.

Under the assumption that 25% of the patients have experienced a severe asthma exacerbation in one treatment group and 19% of the patients have experienced a severe

asthma exacerbation in the other group, a log-rank test (with a two-sided alternative hypothesis and a significance level of 5%) can detect this difference with 90% probability, given that the study includes 1000 patients per group.

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

During run-in all patients received Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg /inhalation, one inhalation twice daily as maintenance treatment and Bricanyl (terbutaline) Turbuhaler 0.5 mg/inhalation to relieve asthma symptoms.

During the treatment period all patients received Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg/inhalation, one inhalation twice daily as maintenance treatment. In addition, patients were randomised to one of the following as-needed medications: Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg/inhalation, formoterol Turbuhaler 4.5 µg /inhalation (referred to as Oxis), or terbutaline Turbuhaler 0.4 mg /inhalation (referred to as Bricanyl).

Each batch used in the study can be identified by either of 2 numbers, one issued during production and one (presented in brackets) issued at AstraZeneca R&D Charnwood.

Batch numbers for Symbicort Turbuhaler used as maintenance were DL 302 (P6663) and EB 373 (P6649). Batch numbers for Symbicort Turbuhaler used as needed were DK 29 (P6664) and EB 31 (P6650).

Batch numbers for Oxis Turbuhaler used as needed were DL 15 (P6667), DL 16 (P6673), DM 17 (P6674), EB 18 (P6652), EB 19 (P6757), and EB 20 (P6758).

Batch numbers for Bricanyl Turbuhaler used as needed during the treatment period were DL 36 (P6666), DL 37 (P6671), DL 38 (P6672 and P6756), EB 41 (P6651), EB 42 (P6752), EB 43 (P6754), and EB 44 (P6755). Batch numbers for Bricanyl Turbuhaler used as needed during the run-in period were DL 1199 (P6665) and EA 1201 (P6713).

The treatment arm with Symbicort both as maintenance and as-needed treatment will be referred to as Symbicort SIT (Symbicort Single Inhaler Therapy), the treatment arm with Symbicort as maintenance plus Oxis as-needed treatment will be referred to as Symbicort + Oxis as needed (a.n.), and the treatment arm with Symbicort as maintenance plus Bricanyl as-needed treatment will be referred to as Symbicort + Bricanyl as needed (a.n.).

Duration of treatment

Two-week run-in period and 12-month treatment period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- The primary efficacy outcome variable was time to first severe asthma exacerbation, defined as the occurrence of at least one of the following:
  - hospitalisation/emergency room treatment due to asthma
  - oral glucocorticosteroid treatment due to asthma for at least 3 days, as judged by the investigator.
- The secondary efficacy outcome variables were:
  - number of severe asthma exacerbations
  - forced expiratory volume in one second (FEV_1)
  - forced vital capacity (FVC)
  - peak expiratory flow (PEF) - morning and evening
  - asthma symptom score - day, night and total
  - inhalations of as-needed medication - day, night and total
  - nights with awakenings due to asthma symptoms
  - symptom-free days
  - as-needed-free days
  - asthma-control days
  - time to first mild asthma exacerbation
  - number of mild asthma exacerbation days
  - patient-reported outcomes (PROs):
    - Asthma Control Questionnaire (ACQ) score
  - health economics:
    - healthcare resource utilization
    - sick-leave

Safety

- The safety variables were nature, incidence and severity of adverse events.

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 log-rank test. In addition, treatment differences were described using a Cox Proportional Hazards model. The mean number of severe asthma exacerbations per patient was compared between treatments using Poisson regression. For diary variables the mean change was compared between treatments using analysis of variance. Change in spirometry variables and ACQ score was compared between treatments using analysis of variance. Time to first mild asthma exacerbation was analysed in the same way as time to first severe asthma exacerbation.

The safety variables were analysed by means of descriptive statistics and qualitative analysis.

Patient population

Table S1 Treatment group comparison of demographic and disease data[a]

Variable		Symbicort SIT	Symbicort + Oxis a.n.	Symbicort + Bricanyl a.n.	All
n, randomised		1113	1140	1141	**3394**
Sex	Male	437 (39%)	458 (40%)	450 (39%)	**1345 (40%)**
	Female	676 (61%)	682 (60%)	691 (61%)	**2049 (60%)**
Age (yrs)	Mean	41.6	42.4	42.6	**42.2**
	Range	12-89	12-81	12-83	**12-89**
	12-17	114 (10%)	115 (10%)	125 (11%)	**354 (10%)**
	18-64	913 (82%)	934 (82%)	906 (79%)	**2753 (81%)**
	65-	86 (8%)	91 (8%)	110 (10%)	**287 (8%)**
Race	Caucasian	880 (79%)	907 (80%)	902 (79%)	**2689 (79%)**
	Black	5 (<0.5%)	0	7 (1%)	**12 (<0.5%)**
	Oriental	212 (19%)	217 (19%)	216 (19%)	**645 (19%)**
	Other	16 (1%)	16 (1%)	16 (1%)	**48 (1%)**
BMI (kg/m^2)	Mean	25.7	25.8	25.5	**25.7**
	Range	13-49	13-48	14-49	**13-49**
Time since diagnosis (yrs)	Median	9	10	10	**9**
	Range	0-64	1-77	1-69	**0-77**

(Continued)

Table S1 Treatment group comparison of demographic and disease data[a]

Variable		Symbicort SIT	Symbicort + Oxis a.n.	Symbicort + Bricanyl a.n.	All
Smoking status	Never	873 (78%)	872 (76%)	883 (77%)	**2628 (77%)**
	Previous	170 (15%)	196 (17%)	181 (16%)	**547 (16%)**
	Occasional	25 (2%)	21 (2%)	39 (3%)	**85 (3%)**
	Habitual	45 (4%)	51 (4%)	38 (3%)	**134 (4%)**
Pack-years	Median	5	5	5	**5**
	Range	0-19	0-10	0-10	**0-19**
Inhaled GCS at entry	n	1112	1140	1140	**3392**
dose (µg)	Mean	757.1	757.5	751.4	**755.3**
	Range	160-1600	320-1600	250-1600	**160-1600**
FEV_1 (L)	Mean	2.21	2.20	2.16	**2.19**
	Range	0.61-4.68	0.74-4.58	0.68-4.58	**0.61-4.68**
FEV_1 (% PN)	Mean	72	72	72	**72**
	Range	30-110	38-115	39-100	**30-115**
Reversibility (%)	Mean	24.0	23.7	23.5	**23.7**
	Range	6-132	0-96	11-90	**0-132**
FVC (L)	Mean	3.00	3.02	2.98	**3.00**
	Range	1.08-6.78	0.96-6.64	0.96-7.08	**0.96-7.08**
As-needed use (total), inh/day	Mean	1.83	1.90	1.91	**1.88**
	Range	0.00-8.90	0.00-9.14	0.30-9.73	**0.00-9.73**
As-needed use (for symptoms), inh/day	Mean	1.70	1.73	1.80	**1.74**
	Range	0.00-8.90	0.00-8.55	0.00-9.73	**0.00-9.73**
Symptom score (total)	Mean	1.71	1.70	1.74	**1.72**
	Range	0.00-5.71	0.00-6.00	0.00-6.00	**0.00-6.00**
Symptom-free days (%)	Mean	12.2	11.4	11.6	**11.7**
	Range	0-100	0-100	0-100	**0-100**
As-needed-free days (%)	Mean	14.5	13.1	13.6	**13.7**
	Range	0-100	0-100	0-70	**0-100**
Asthma-control days (%)	Mean	9.2	8.3	8.3	**8.6**
	Range	0-90	0-80	0-50	**0-90**

(Continued)

Table S1 Treatment group comparison of demographic and disease data[a]

Variable		Symbicort SIT	Symbicort + Oxis a.n.	Symbicort + Bricanyl a.n.	All
Awakenings (%)	Mean	31.1	28.0	30.3	**29.8**
	Range	0-100	0-100	0-100	**0-100**

a For categorical data, frequencies are given, for other data mean values and ranges are given

The treatment groups were generally well balanced in demographic and baseline characteristics.

Efficacy and pharmacokinetic results

Symbicort SIT statistically significantly prolonged the time to first severe exacerbation (the primary outcome variable) compared to both Symbicort + Oxis as needed (hazard ratio 0.73, p=0.0038) and Symbicort + Bricanyl as needed (hazard ratio 0.55, p<0.001). In other words, the instantaneous risk of having a severe asthma exacerbation for patients treated with Symbicort SIT was reduced by 27% versus Symbicort + Oxis as needed and by 45% versus Symbicort + Bricanyl as needed. Fewer patient experienced exacerbations in the Symbicort SIT group (13%) than in the Symbicort + Oxis as needed group (17%) and Symbicort + Bricanyl as needed group (22%). In addition, there were statistically significantly fewer severe exacerbations per patient-year in the Symbicort SIT group (0.19) versus the Symbicort + Oxis as needed group (0.29) and the Symbicort + Bricanyl as needed group (0.37) (p<0.001 for both comparisons). The use of oral steroids was lower in the Symbicort SIT group (1204 days) compared to Symbicort + Oxis as needed (2063 days) and Symbicort + Bricanyl as needed (2755 days). Symbicort SIT also statistically significantly prolonged time to first hospitalisation/emergency room (ER) treatment compared with Symbicort + Bricanyl as needed and reduced the total number of hospitalisations/ER treatments compared with both comparators.

Symbicort + Oxis as needed compared to Symbicort + Bricanyl as needed statistically significantly prolonged the time to first exacerbation (hazard ratio 0.76, p=0.004) and reduced the number of exacerbations per patient-year (0.29 vs. 0.37; p=0.0012).

Results from the secondary variables supported those of the primary variable. Symbicort SIT was superior to both comparators with statistically significant decreases in as-needed use; increases in as-needed-free days; increases in morning and evening PEF, FEV_1, and FVC; decreases in asthma symptoms; fewer mild exacerbation days; and improvements in ACQ score. Symbicort SIT statistically significantly prolonged the time to first mild exacerbation

compared to Symbicort + Bricanyl as needed. For symptom-free days and for asthma-control days, there was no clear difference between the 3 treatments.

The gains in asthma control seen with Symbicort SIT were achieved with a mean daily Symbicort dose of 483/13.6 µg. The average daily as-needed use and the frequency of high as-needed use were lower for Symbicort SIT compared with both comparators.

Table S2 Statistical analysis of severe asthma exacerbations.

Variable	Analysis	Treatment	Ratio or Rate	95% Conf.Int.	P-value
-Time to first	Log-rank test	SSIT vs. S+Oxis a.n.			0.0048
		SSIT vs. S+Bricanyl a.n.			<0.001
		S+Oxis a.n. vs. S+Bricanyl a.n.			0.0051
	Cox PH model	SSIT vs. S+Oxis a.n.	0.73	(0.59, 0.90)	0.0038
		SSIT vs. S+Bricanyl a.n.	0.55	(0.45, 0.68)	<0.001
		S+Oxis a.n. vs. S+Bricanyl a.n.	0.76	(0.63, 0.92)	0.004
-Events /Patient-year	Poisson regression	SSIT	0.19	(0.17, 0.22)	
		S+Oxis a.n.	0.29	(0.25, 0.32)	
		S+Bricanyl a.n.	0.37	(0.33, 0.41)	
		SSIT vs. S+Oxis a.n.	0.67	(0.56, 0.80)	<0.001
		SSIT vs. S+Bricanyl a.n.	0.52	(0.44, 0.62)	<0.001
		S+Oxis a.n. vs. S+Bricanyl a.n.	0.78	(0.67, 0.91)	0.0012

Safety results

The mean exposure time and the overall pattern of patients reporting AEs for each category was similar between the treatment groups. On a preferred term level, nasopharyngitis, upper respiratory tract infection and pharyngitis were the most frequently reported AEs, as summarised over all treatment groups. The AEs were mostly mild to moderate in intensity. The incidence of AEs due to oral fungal infections was overall low, despite instructions to the patients not to rinse the mouth after inhaling study drug. Four deaths were reported in the study, one in the Symbicort SIT group and Symbicort + Oxis as needed group respectively, and two in the Symbicort + Bricanyl as needed group. None of the deaths were considered by the investigator to be causally related to investigational product. In total, 251 non-fatal serious adverse events (SAEs) were reported, 97 in the Symbicort SIT group, 71 in the

Symbicort + Oxis as needed group and 83 in the Symbicort + Bricanyl as needed group. The most frequently reported non-fatal SAE by preferred term was asthma, and the number of patients reporting was slightly lower in the Symbicort SIT group than in the comparator groups. Four non-fatal SAEs were considered by the investigator to be causally related to investigational product, none of the SAEs were reported by patients in the Symbicort SIT group. The number of discontinuations due to adverse events (DAEs) was low overall. The most frequently reported DAE was asthma, as summarised over all treatments, but only reported for one patient in the Symbicort SIT group. No other significant adverse events (OAEs) were identified in the study.

Table S3 Summary of adverse events (AEs)

	Symbicort SIT n=1107	**Symbicort + Oxis a.n. n=1137**	**Symbicort + Bricanyl a.n. n=1138**	**All n=3382**
No. of deaths	1	1	2	**4**
No. of SAEs other than death[a]	97	71	83	**251**
No. (%) of patients with SAE	70 (6%)	55 (5%)	65 (6%)	**190 (6%)**
Max no. of SAEs/patient	5	3	3	**5**
No. of other significant AEs	0	0	0	**0**
No. (%) of patients with DAE	12 (1%)	22 (2%)	19 (2%)	**53 (2%)**
No. of AEs[a]	1204	1135	1176	**3515**
- Mild	760	712	705	**2177**
- Moderate	369	339	399	**1107**
- Severe	75	84	72	**231**
No. (%) of patients with AE	556 (50%)	551 (48%)	573 (50%)	**1680 (50%)**
Max no. of AEs/patient	11	25	13	**25**

a Events are counted by preferred term; for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

Table S4 **Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)**

Adverse event (preferred term)	Symbicort SIT n= 1107	Symbicort + Oxis a.n. n= 1137	Symbicort + Bricanyl a.n. n= 1138	All n= 3382
nasopharyngitis	112 (10%)	105 (9%)	119 (10%)	**336 (10%)**
upper respiratory tract infection	58 (5%)	74 (7%)	79 (7%)	**211 (6%)**
pharyngitis	64 (6%)	39 (3%)	49 (4%)	**152 (4%)**
influenza	49 (4%)	45 (4%)	40 (4%)	**134 (4%)**

a Events with a total frequency of ≥4% across all treatment groups are included in this table.