Drug Product	Symbicort® Turbuhaler®	**SYNOPSIS**	
Drug Substance	Budesonide/formoterol		
Edition Number	1		
Study Code	SD-039-0735		
Date	27 June 2005		

Comparison of the efficacy and safety of one inhalation of Symbicort® Turbuhaler® 160/4.5 µg bid plus as-needed with two inhalations of Seretide™ Evohaler™ 25/125 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed, and one inhalation of Symbicort® Turbuhaler® 320/9 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed. A 6-month, randomised, double-blind, double-dummy, parallel-group, active-controlled, multicentre, phase IIIB study in adult and adolescent asthmatic patients.

Study centres

A total of 235 centres from 16 countries participated in this study. The countries were as follows: Argentina (15 centres), Australia (22 centres), Bulgaria (9 centres), Czech Republic (12 centres), Great Britain (25 centres), Hungary (27 centres), India (7 centres), Malaysia (4 centres), Mexico (15 centres), the Netherlands (24 centres), the Philippines (8 centres), Poland (29 centres), South Korea (7 centres), South Africa (26 centres), Thailand (4 centres), Vietnam (1 centre).

Publications

None at the time of writing this report.

Study dates

First patient enrolled: 19 December 2003

Last patient completed: 11 March 2005

Phase of Development

Therapeutic confirmatory (III)

Objectives

The **primary objective** of the study was:

- to compare the efficacy of Symbicort® Turbuhaler® 160/4.5 µg/inhalation bid plus as-needed with two inhalations of Seretide™ Evohaler™ 25/125 µg/inhalation bid plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed in asthmatic patients by evaluating the time to first severe asthma exacerbation.

The **secondary objectives** of the study were:

- to compare the efficacy of one inhalation of Symbicort Turbuhaler 320/9 µg/inhalation bid plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed with two inhalations of Seretide Evohaler 25/125 µg/inhalation bid plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed in asthmatic patients by evaluating the time to first severe asthma exacerbation.

- to compare the efficacy of one inhalation of Symbicort Turbuhaler 160/4.5 µg/inhalation bid plus as-needed with one inhalation of Symbicort® Turbuhaler® 320/9 µg/inhalation bid plus Terbutaline Turbuhaler® 0.4 mg/inhalation as-needed by evaluating the time to first severe asthma exacerbation.

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

Study design

This was a 6-month, randomised, double-blind, double-dummy, parallel-group, active-controlled, multi-national, study in patients with persistent asthma using inhaled glucocorticosteroids (GCS).

Target patient population and sample size

Adults and adolescents with persistent asthma, an FEV_1 ≥50% of predicted normal, ≥12% reversibility and with documented symptoms despite use of inhaled GCSs.

Under the assumption that 20% of the patients have experienced a severe asthma exacerbation in 1 treatment group and 14.5% 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 Comparators: dosage, mode of administration and batch numbers

Batch numbers without brackets are issued during production and batch numbers in brackets refer to batch numbers issued at AstraZeneca R&D Charnwood.

During the run-in period patients were using their regular dose and brand of inhaled steroids plus Bricanyl Turbuhaler as-needed (0.5 mg/dose). Batch numbers for Bricanyl Turbuhaler were 3521191 (P6859) and 3521232 (P6893).

Patients were randomised to one of the following treatment arms

- Symbicort Turbuhaler (budesonide/formoterol) 160/4.5 µg/inhalation, one inhalation twice daily as maintenance treatment plus Symbicort Turbuhaler 160/4.5 µg/inhalation as-needed.
- Seretide Evohaler (salmeterol/fluticasone), 25/125 µg/inhalation, two inhalations twice daily as maintenance treatment plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed.
- Symbicort Turbuhaler (budesonide/formoterol) 320/9 µg/inhalation, one inhalation twice daily as maintenance treatment plus Terbutaline Turbuhaler 0.4 mg/inhalation as-needed

Batch numbers for Symbicort Turbuhaler 160/4.5 µg/inhalation used as maintenance treatment were EI 240 (P6870), EL 252 (P6920, P6950).

Batch numbers for Symbicort Turbuhaler 160/4.5 µg/inhalation used as needed were EG 32 (P6853), EL 33 (P6919, P6949).

Batch numbers for Symbicort Turbuhaler 320/9 µg/inhalation used as maintenance were EI 90 (P6871), EL 108 (P6921, P6951).

Batch numbers for Placebo Symbicort Turbuhaler used as maintenance were EG 11(P6857).

Batch numbers for Seretide Evohaler 25/125 µg/inhalation used as maintenance were (P6901, P6923 and P6943).

Batch numbers for Placebo to match Seretide pMDI used as maintenance were (P6900 P6922 P7033)

Batch number for Terbutaline Turbuhaler used as-needed were EH 53 (P6865), EH 51 (P6866), EH 47 (P6867), EH 49 (P6889), EH 46 (P6890), EH 48 (P6891) and EH 54 (P6892).

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

Duration of treatment

A run-in period of 2 weeks and a randomised treatment period of approximately 24 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetiks

- The primary outcome variable was time to first severe asthma exacerbation, defined as deterioration in asthma leading to at least one of the following:
  - hospitalisation/emergency room treatment due to asthma
  - oral glucorticosteroid treatment due to asthma for at least 3 days, as judged by the investigator.
- The secondary outcome variables were:
  - number of severe asthma exacerbations
  - forced expiratory volume in 1 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
    - Asthma Quality of Life Questionnaire, standardised version (AQLQ(S)) overall and domain scores.
- health economics:
    - health-care resource utilization
    - sick-leave
    - Asthma Productivity Questionnaire (APQ)

Safety

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

Genetic

As an optional part of the study, a blood sample from the patient was taken for potential future research into genes which may influence therapeutic response to Symbicort Turbuhaler and/or susceptibility to, or prognosis of, asthma.

Statistical methods

All efficacy analyses were based on the full analysis set as defined in the International Conference on Harmonization (ICH) E9 guideline. Time to first severe asthma exacerbation was compared between treatments using a log-rank test. In addition, treatment differences were described using Cox Proportional Hazards models. The mean number of severe asthma exacerbations per patient was compared between treatments using Poisson regression. In addition, an extended Cox model was used to compare time to all severe asthma exacerbations. For diary variables the mean change was compared between treatments using analysis of variance. Change in spirometry variables, ACQ and AQLQ(S) 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

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

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

Variable		Symbicort SIT	Symbicort + Bricanyl a.n.	Seretide + Bricanyl a.n.	All
n, randomised		n=1107	n=1105	n=1123	n=**3335**
Sex	Male	479 (43%)	448 (41%)	484 (43%)	**1411 (42%)**
	Female	628 (57%)	657 (59%)	639 (57%)	**1924 (58%)**
Age (yrs)	Mean	37.9	37.9	38.0	**37.9**
	Range	11-79	12-83	12-83	**11-83**
	≤11	2 (<0.5%)	0	0	**2 (<0.5%)**
	12-17	197 (18%)	213 (19%)	211 (19%)	**621 (19%)**
	18-64	841 (76%)	836 (76%)	840 (75%)	**2517 (75%)**
	≥65	67 (6%)	56 (5%)	72 (6%)	**195 (6%)**
Race	Cauca-sian	768 (69%)	773 (70%)	788 (70%)	**2329 (70%)**

(Continued)

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

Variable		Symbicort SIT	Symbicort + Bricanyl a.n.	Seretide + Bricanyl a.n.	All
	Black	12 (1%)	8 (1%)	13 (1%)	**33 (1%)**
	Oriental	143 (13%)	139 (13%)	142 (13%)	**424 (13%)**
	Other	184 (17%)	185 (17%)	180 (16%)	**549 (16%)**
BMI (kg/m^2)	Mean	25.6	25.7	25.9	**25.7**
	Range	14-54	11-63	14-66	**11-66**
Time since diagnosis (yrs)	Median	9	10	10	**10**
	Range	0-70	1-69	0-66	**0-70**
Smoking status	Never	873 (79%)	865 (78%)	904 (80%)	**2642 (79%)**
	Previous	178 (16%)	169 (15%)	165 (15%)	**512 (15%)**
	Occa-sional	22 (2%)	28 (3%)	20 (2%)	**70 (2%)**
	Habitual	34 (3%)	43 (4%)	34 (3%)	**111 (3%)**
Pack-years	Median	5	5	5	**5**
	Range	0-10	0-9	0-9	**0-10**
Inhaled GCS at entry dose (µg)/day	n	1107	1105	1123	**3335**
	Mean	740.4	749.6	744.2	**744.7**
	Range	250-2000	100-3200	200-2000	**100-3200**
FEV_1 (L)	Mean	2.23	2.21	2.23	**2.22**
	Range	0.89-5.47	0.66-5.22	0.86-5.98	**0.66-5.98**
FEV_1 (% P.N.)	Mean	72	73	73	**73**
	Range	29-131	46-122	30-143	**29-143**
Reversibility (%)	Mean	23.5	24.8	23.4	**23.9**
	Range	10-106	7-150	3-92	**3-150**
FVC (L)	Mean	3.01	3.01	3.03	**3.02**
	Range	1.12-6.81	0.92-6.76	1.03-8.00	**0.92-8.00**

(Continued)

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

Variable		Symbicort SIT	Symbicort + Bricanyl a.n.	Seretide + Bricanyl a.n.	All
As-needed use (total), inh/day	Mean	2.30	2.31	2.33	**2.31**
	Range	0.00-12.60	0.22-9.53	0.00-10.75	**0.00-12.60**
As-needed use (for symptoms), inh/day	Mean	2.19	2.21	2.24	**2.21**
	Range	0.00-12.60	0.00-9.53	0.00-10.75	**0.00-12.60**
Symptom score (total)	Mean	1.92	1.93	1.93	**1.93**
	Range	0.00-5.53	0.00-5.90	0.00-6.00	**0.00-6.00**
Symptom-free days (%)	Mean	9.2	8.8	8.6	**8.9**
	Range	0-100	0-100	0-100	**0-100**
As-needed-free days (%)	Mean	8.8	9.0	8.8	**8.9**
	Range	0-100	0-90	0-100	**0-100**
Asthma-control days (%)	Mean	5.8	5.9	5.7	**5.8**
	Range	0-60	0-60	0-100	**0-100**
Awakenings (%)	Mean	33.8	32.8	31.6	**32.7**
	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.

Efficacy and pharmacokinetic results

Symbicort SIT versus Seretide plus Bricanyl as-needed

Symbicort SIT prolonged the time to first severe asthma exacerbation compared with Seretide + Bricanyl as-needed, with a hazard ratio of 0.67 (p=0.003), corresponding to a 33% reduction in instantaneous risk of having a first severe asthma exacerbation. Fewer patients experienced exacerbations in the Symbicort SIT group (9%) than in the Seretide + Bricanyl as-needed group (12%), and there were fewer severe exacerbations per patient per 6 months in the Symbicort SIT group (0.12) than the Seretide + Bricanyl group (0.19) (rate ratio 0.61; p<0.001). Symbicort SIT also statistically significantly prolonged the time to first hospitalisation/ER treatment and reduced the total number of hospitalisations/ER treatments compared with Seretide + Bricanyl as-needed. Oral steroids due to exacerbations

were used on a total of 619 days in the Symbicort SIT group and 1132 days in the Seretide + Bricanyl as-needed group.

For other secondary variables, no statistically significant difference could be detected between Symbicort SIT and Seretide + Bricanyl as-needed, with the exception of a greater reduction in as-needed-free days (difference 3.2%) in the Seretide + Bricanyl as-needed group.

Symbicort SIT versus Symbicort plus Bricanyl as-needed
Symbicort SIT prolonged the time to first severe asthma exacerbation compared with Symbicort at a higher fixed maintenance dose + Bricanyl as-needed, with a hazard ratio of 0.74 (p=0.026), corresponding to a 26% reduction in instantaneous risk of having a first severe asthma exacerbation. Fewer patients experienced exacerbations in the Symbicort SIT group (9%) than in the Symbicort + Bricanyl as-needed group (11%), and there were fewer severe exacerbations per patient per 6 months in the Symbicort SIT group (0.12) than the Symbicort + Bricanyl as-needed group (0.16) (rate ratio 0.72; p=0.0048). There was no evidence of a difference between the 2 treatment groups for hospitalisations/ER treatments. Oral steroids due to exacerbations were used on a total of 619 days in the Symbicort SIT group and 1044 days in the Symbicort + Bricanyl as-needed group.

No statistically significant differences were detected between the Symbicort SIT and Symbicort + Bricanyl as-needed groups for other secondary variables. Use of as-needed medication was similar in both groups, both regarding average daily use and frequency of high as-needed use. The mean daily dose of Symbicort in the Symbicort SIT group (including maintenance and average as-needed treatment) was 483/13.6 µg, as compared with a prescribed daily dose of 640/18 µg in the Symbicort + Bricanyl as-needed group.

Symbicort plus Bricanyl as-needed versus Seretide plus Bricanyl as-needed
No statistically significant difference was detected between Symbicort + Bricanyl as-needed and Seretide + Bricanyl as-needed regarding time to first severe asthma exacerbation, number of severe asthma exacerbations, or time to first hospitalisation/ER treatment. However, the number of hospitalisations/ER treatments per patient per 6 months was statistically significantly lower in the Symbicort + Bricanyl group (0.05 vs 0.08, rate ratio 0.68; p=0.013). Oral steroids due to exacerbations were used on a total of 1044 days in the Symbicort + Bricanyl as-needed group and 1132 days in the Seretide + Bricanyl as-needed group.

Mean total use of as-needed medication was statistically significantly lower in the Seretide + Bricanyl as-needed group than in the Symbicort + Bricanyl as-needed group (difference: 0.1 inhalations/day, attributable to day-time use), and there was an 11% lower risk of having a first mild exacerbation in the Seretide + Bricanyl as-needed group. No other differences were detected between the Symbicort + Bricanyl as-needed and Seretide + Bricanyl as-needed groups.

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	Symbicort SIT vs. Symbicort+Bricanyl a.n.			0.023
		Symbicort SIT vs. Seretide+Bricanyl a.n.			0.0034
		Symbicort+Bricanyl a.n. vs. Seretide+Bricanyl a.n.			0.52
	Cox PH model	Symbicort SIT vs. Symbicort+Bricanyl a.n.	0.74	(0.56, 0.96)	0.026
		Symbicort SIT vs. Seretide+Bricanyl a.n.	0.67	(0.52, 0.87)	0.003
		Symbicort+Bricanyl a.n. vs. Seretide+Bricanyl a.n.	0.91	(0.72, 1.16)	0.45
-Events/ Patient/6 mo	Poisson regression	Symbicort SIT	0.12[a]	(0.10, 0.14)	
		Symbicort+Bricanyl a.n.	0.16[b]	(0.14, 0.19)	
		Seretide+Bricanyl a.n.	0.19[c]	(0.16, 0.22)	
		Symbicort SIT vs. Symbicort+Bricanyl a.n.	0.72	(0.57, 0.90)	0.0048
		Symbicort SIT vs. Seretide+Bricanyl a.n.	0.61	(0.49, 0.76)	<0.001
		Symbicort+Bricanyl a.n. vs. Seretide+Bricanyl a.n.	0.85	(0.69, 1.04)	0.1

a Corresponding rate extrapolated to 1 year is: 0.23.
b Corresponding rate extrapolated to 1 year is: 0.32.
c Corresponding rate extrapolated to 1 year is: 0.38.

Safety results

The mean exposure time and the overall pattern of patients reporting AEs for each category was similar across the treatment groups. On a preferred term level, upper respiratory infection, pharyngitis, and nasopharyngitis were the most frequently reported AEs, as summarized over all treatment groups. The majority of AEs were of mild or moderate intensity. The incidence of AEs of severe intensity was overall low across all treatment groups. The incidence of AEs due to oral fungal infections was similar across treatment groups and overall low despite instructions not to rinse the mouth after as-needed medication.

Two deaths were reported in the study, 1 in the Symbicort SIT group (respiratory failure) and 1 in the Seretide + Bricanyl as-needed group (cardiac failure). One additional death was reported in the Symbicort SIT treatment group 16 weeks post study (severe acute respiratory syndrome). None of the deaths were considered by the investigator to be causally related to investigational product.

In total, 128 non-fatal SAEs were reported, 37 in the Symbicort SIT group, 49 in the Symbicort + Bricanyl as-needed group, and 42 in the Seretide + Bricanyl as-needed group. The most frequently reported non-fatal SAE by preferred term was asthma, and the number of patients reporting such AE was similar in all treatment groups. Four non-fatal SAEs were considered by the investigator to be possibly caused by the investigational product: 3 of the SAEs were reported by patients in the Symbicort SIT group (pneumonia, gastritis, asthma), and 1 in the Seretide + Bricanyl as-needed group (asthma).

The number of discontinuations of treatment with investigational treatment due to AE (DAEs) was low overall, 1% for each treatment group. The most frequently reported reason for discontinuation due to adverse event was asthma, as summarized over all treatments. No other adverse events (OAEs) were identified in the study.

Table S3 Summary of adverse events (AEs)

	Symbicort SIT	**Symbicort + Bricanyl a.n.**	**Seretide + Bricanyl a.n.**	**All**
	n=1103	**n=1099**	**n=1119**	**n=3321**
No. of deaths	1	0	1	**2**
No. of SAEs other than death[a]	37	49	42	**128**
No. (%) of patients with SAE	31 (3%)	39 (4%)	32 (3%)	**102 (3%)**
Max no. of SAEs/patient	2	3	4	**4**
No. of other significant AEs	0	0	0	**0**
No. (%) of patients with DAE	11 (1%)	13 (1%)	10 (1%)	**34 (1%)**
No. of AEs[a]	870	831	799	**2500**
- Mild	545	532	527	**1604**
- Moderate	286	250	235	**771**
- Severe	39	49	37	**125**
No. (%) of patients with AE	457 (41%)	439 (40%)	428 (38%)	**1324 (40%)**
Max no. of AEs/patient	9	10	6	**10**

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

Table S4 **Adverse events by preferred term. Number (%) of patients with the most frequently reported AEs, sorted by decreasing order of frequency as summarized over all treatment groups**

Preferred term	Symbicort SIT n= 1103	Symbicort + Bricanyl a.n. n= 1099	Seretide + Bricanyl a.n. n= 1119	All n= 3321
Upper respiratory tract infection	61 (6%)	57 (5%)	47 (4%)	**165 (5%)**
Pharyngitis	57 (5%)	44 (4%)	49 (4%)	**150 (5%)**
Nasopharyngitis	47 (4%)	46 (4%)	52 (5%)	**145 (4%)**
Rhinitis	26 (2%)	38 (3%)	33 (3%)	**97 (3%)**
Influenza	34 (3%)	31 (3%)	30 (3%)	**95 (3%)**
Sinusitis	28 (3%)	27 (2%)	27 (2%)	**82 (2%)**
Rhinitis allergic	28 (3%)	23 (2%)	29 (3%)	**80 (2%)**
Headache	29 (3%)	22 (2%)	23 (2%)	**74 (2%)**
Bronchitis	23 (2%)	20 (2%)	28 (3%)	**71 (2%)**
Bronchitis acute	26 (2%)	21 (2%)	24 (2%)	**71 (2%)**
Asthma	14 (1%)	27 (2%)	20 (2%)	**61 (2%)**

Cut-off at ≥ 2% for all treatments.