AstraZeneca

Drug product:	Symbicort® Turbuhaler®	**SYNOPSIS**	
Drug substance(s):	Budesonide/Formoterol		
Edition No.:	1		
Study code:	LD-039-0003		
Date:	20 May 2005		

An open, randomized, parallel group, multicentre, phase IIIB study to evaluate the efficacy of Symbicort® Turbuhaler® Single Inhaler Therapy (SiT) given as a low maintenance dose once or twice daily plus as needed compared to a higher maintenance dose of Symbicort Turbuhaler given twice daily plus Oxis® Turbuhaler® as needed during 24 weeks in asthmatic patients.

Study centres

This was a multicentre study conducted in 53 centres in Sweden.

Publications

An abstract entitled "Symbicort Single Inhaler Therapy compared to an optimized fixed combination treatment in patients with moderate to severe asthma" was reviewed and accepted by *Riksstämman* (Swedish Physician's Congress) 2004.

Study dates		**Phase of development**
First patient enrolled	24 February 2003	IIIB
Last patient completed	27 May 2004	

Objectives

The primary objective of this study was to evaluate the efficacy of 2 Symbicort Single inhaler Therapy (SiT) regimens, with Symbicort given as a low maintenance dose either once or twice daily plus as needed, compared to a higher maintenance dose of Symbicort plus Oxis Turbuhaler as needed.

The secondary objectives were to assess the health economics of the treatments by evaluation of health care resource utilization and sick leave from work and to assess the safety of the treatments by evaluation of non-asthma related and asthma-related Serious Adverse Events (SAEs) and Discontinuations due to Adverse Events (DAEs).

Study design

This was an open, randomized, parallel-group, multicentre phase IIIB study comparing the efficacy and safety of 3 treatments for persistent asthma.

Target patient population and sample size

The study included male and female asthma patients from the age of 6 years either not well controlled on inhaled GCS alone or well controlled on inhaled GCS plus LABA, thus making them appropriate for treatment with combination GCS/LABA products.

The sample size calculation was based on both the Asthma Control Questionnaire (ACQ) variable and the morning peak expiratory flow (mPEF) variable. The variable that determines the sample size is the ACQ. A total of 139 randomized and completed patients with asthma, derived from an estimated 155 randomized patients, were required per treatment group to detect a 0.5 unit difference between groups in change from baseline in ACQ score with a power of 80%. This assumed a 5% significance level and a 2-sided alternative hypothesis. Similarly, a total of 139 randomized and completed patients with asthma, derived from an estimated 155 randomized patients, were required per treatment group to detect a 15 L/min difference between groups in change from baseline in mPEF with a power of 80%. This also assumed a 5% significance level and a 2-sided alternative hypothesis.

Investigational product: dosage, mode of administration and batch numbers

Symbicort Turbuhaler 160/4.5 µg one inhalation twice daily plus Symbicort Turbuhaler160/4.5 µg as needed for patients 12 years or older	Batch No DL302
Symbicort Turbuhaler 80/4.5 µg one inhalation twice daily plus Symbicort Turbuhaler 80/4.5 µg as needed for patients 6 to 11 years of age	Batch No DL45
or	
Symbicort Turbuhaler 160/4.5 µg one inhalation once daily plus Symbicort Turbuhaler 160/4.5 µg as needed for patients 12 years or older	Batch No DL302
Symbicort Turbuhaler 80/4.5 µg one inhalation once daily plus Symbicort Turbuhaler 80/4.5 µg as needed for patients 6 to 11 years of age	Batch No DL45

Comparator product: dosage, mode of administration, and batch numbers

Symbicort Turbuhaler 160/4.5 µg 2 inhalations twice daily plus Oxis (formoterol) Turbuhaler 4.5 µg as needed, for patients 12 years or older	Batch No DL302 Batch No 485
Symbicort Turbuhaler 80/4.5 µg 2 inhalations twice daily plus Oxis (formoterol) Turbuhaler 4.5 µg as needed, for patients 6 to 11 years of age	Batch No DL45 Batch No 485

Symbicort SiT treatment with 1 inhalation twice daily as maintenance plus as needed will be referred to as SiT 1x2 and the Symbicort SiT treatment with 1 inhalation once daily as maintenance plus as needed will be referred to as SiT 1x1. The fixed Symbicort treatment with the 2 inhalations twice daily as maintenance plus Oxis as needed will be referred to as Symb 2x2+Oxis prn.

Duration of treatment

The run-in period was 2 weeks, and the treatment period was 24 weeks. If the patient withdrew due to worsening of asthma, there was to be a follow-up contact 12 to 16 days after withdrawal.

Criteria for evaluation

Efficacy

Primary efficacy outcome variables are:

- Change in ACQ score from baseline to Visit 4
- Change in mPEF from baseline to all treatment period data.

Secondary efficacy variables are:

- Change in overall and domain Asthma Quality of Life Questionnaire, standardized version (AQLQ(S)) or Pediatric Asthma Quality of Life Questionnaire (PAQLQ(S)) scores from baseline to Visit 4
- Change in overall and domain Satisfaction with Asthma Treatment Questionnaire (SATQ) scores from baseline to Visit 4
- Subject rating of asthma status
- Number of inhalations of maintenance medication

- Number of inhalations of as-needed medication (ie, for both symptom relief and for prevention of symptoms)
- Percent of asthma control days
- Percent of nights with awakenings due to asthma
- Time to first asthma exacerbation and number of exacerbations
- Change in mPEF from baseline to Visit 4
- Change in ACQ score from baseline to Visit 3

Health economics

The health economic variables included direct and indirect costs, defined as the quantity of each resource item consumed by the patient multiplied by their respective unit cost of each resource item.

Safety

Safety variables include number of SAEs and number of DAEs.

Statistical methods

The full analysis set was used in all efficacy analyses, defined as all randomized patients that have taken at least 1 inhalation of the study drug with at least 1 post-randomisation measurement.

Patient population

Table S1 Patient population and disposition

		2x2+Oxis	SiT 1x2	SiT 1x1	Total
N randomized (N planned)		164 (155)	165 (155)	162 (155)	491 (465)
Demographic characteristics					
Sex N (%) of patients	Male	80 (48.8)	80 (48.5)	69 (42.6)	229 (46.6)
	Female	84 (51.2)	85 (51.5)	93 (57.4)	262 (53.4)
Age (years)	Mean	40.8	38.2	39.7	39.6
	Median	42.2	39.2	43	41.9
	SD	19.9	20.6	19.6	20.1
	Range	6-82	6-79	7-78	6-82
Age interval N (%) of patients	6-11	17 (10)	23 (14)	18 (11)	58 (12)
	12-17	13 (8)	18 (11)	20 (12)	51 (10)
	18-64	106 (65)	106 (65)	104 (64)	316 (65)
	>64	27 (17)	17 (10)	20 (12)	64 (13)
Race N (%) of patients	Caucasian	161 (99)	161 (98)	159 (98)	481 (98)
	Black	2 (1.2)	0 (0)	0 (0)	2 (0.4)
	Oriental	0 (0)	3 (1.8)	1 (0.6)	4 (0.8)
	Other	0 (0)	0 (0)	2 (1.2)	2 (0.41)
Smoking N (%) of patients	Non-smoker	117 (72)	125 (76)	118 (73)	360 (74)
	Ex-smoker	32 (20)	28 (17)	34 (21)	94 (19)
	Occasional smoker	4 (2.5)	7 (4.3)	3 (1.9)	14 (2.4)
	Habitual smoker	10 (6.1)	4 (2.4)	7 (4.3)	21 (4.3)
Mean no of missed work or school days or social occasions 2 weeks prior to Visit 1	6-11 years	0.29	0.17	0	0.16
	>12 years	0.15	0.06	0.10	0.11
Baseline characteristics					
FEV_1 post-bronchodilation (L)	Mean	2.99	3.00	2.98	2.99
	SD	0.88	0.85	0.85	0.86

			2x2+Oxis	SiT 1x2	SiT 1x1	Total
FEV_1 post-bronchodilation % of predicted normal		Mean	96.5	96.2	95.7	96.1
		SD	15.2	14.7	13.7	14.5
Pre-study daily inhaled corticosteroid dose (μg)	6-11 years	Mean	435.3	434.8	419.4	430.2
		Range	400-500	400-500	250-500	250-500
		SD	49.3	48.7	71.0	56.1
	>12 years	Mean	771.2	720.9	708.3	733.8
		Range	500-1600	400-2000	100-1600	100-2000
		SD	224	208	200	212
N (%) of patients using LABA pre-study			104 (63)	119 (72)	121 (74)	344 (70)
Mean percentage of symptom-free days during run-in			69.2	77.4	75.7	74.1
Mean number of daily as-needed inhalations for symptom relief during run-in		Mean	0.6	0.4	0.4	0.5
		Range	0-8.9	0-5.4	0-5.6	0-8.9
		SD	1.25	0.8	0.92	1.01
Disposition						
N (%) completed			143 (87)	151 (92)	136 (84)	430 (88)
N (%) discontinued/no data on treatment			21 (13)	14 (8)	26 (16)	61 (12)
N analysed for safety			163	164	162	489
N analysed for efficacy			163	164	162	489

Efficacy results

There were no statistically significant differences between the 3 treatment groups in change in ACQ score from baseline to Visit 4 (Table S2). There were statistically significant differences in mean change in mPEF from baseline to the treatment period, favouring the Symb 2x2+Oxis prn group versus both the SiT 1x1 group (+12.2 L/min, $p<0.001$) and the SiT 1x2 group (+8.6 L/min, $p=0.006$).

For the majority of secondary efficacy variables, no differences between the treatment groups were shown. There was no statistically significant difference between the 3 treatment groups in the change from baseline in overall AQLQ(S), overall PAQLQ(S), SATQ overall scores, percent of nights with awakenings due to asthma, the number of and time to first severe exacerbation, or change in ACQ score from baseline to Visit 3 (12 weeks). However, there was statistically significantly greater daily use of as-needed medication for asthma symptoms, in the SiT 1x1 group compared to both the Symb 2x2+Oxis prn group (+0.28 inhalations, $p<0.001$) and the SiT 1x2 group (+0.21 inhalations, $p=0.004$). There was no statistically

significant difference in as-needed use for symptoms between the Symb 2x2+Oxis prn and the SiT 1x2 groups. Similarly, the percent of asthma control days was statistically significantly lower in the SiT 1x1 group compared to the Symb 2x2+Oxis prn group (-10.8%, p<0.001) and SiT 1x2 group (-9.6%, p=0.001), but no difference was seen between the Symb 2x2+Oxis prn and the SiT 1x2 groups.

Both Symbicort SiT groups had lower mean use of inhaled GCS and LABA compared to the Symb 2x2+Oxis prn group.

Table S2 Primary efficacy endpoints

	ACQ score			mPEF (L/min)		
	Mean difference	**P-value**	**Confidence Limits**	**Mean difference**	**P-value**	**Confidence Limits**
Symb 2x2+Oxis prn vs SiT 1x2	-0.10	0.249	(-0.26, 0.07)	8.62	0.006	(2.52, 14.72)
Symb 2x2+Oxis prn vs SiT 1x1	-0.07	0.441	(-0.24, 0.10)	12.19	<0.001	(6.11, 18.27)
SiT 1x1 vs SiT1x2	0.03	0.723	(-0.14, 0.20)	3.57	0.249	(-2.51, 9.65)

Safety results

Overall, this study did not identify any new or unexpected safety findings. Data on SAEs and DAEs were collected, and their frequencies in the 3 treatment groups were similar. The incidence of patients reporting SAEs or DAEs was low and similar in all treatment groups (Table S3).

During randomized treatment, 17 patients reported 20 SAE case reports (including 22 symptoms/diagnoses by preferred term). In total, 6 (3.7%) of the patients in the Symb 2x2+Oxis prn treatment group, 7 (4.3%) patients in the SiT 1x2 group, and 4 (2.5%) in the SiT 1x1 group had one or more SAE. One SAE was reported by the investigator as being causally related to the investigational product (diabetes mellitus in the SiT 1x2 group). In addition, 2 SAEs were reported post-study: one in the Symb 2x2+Oxis group (stillbirth), and one in the SiT 1x1 group (pneumonia in a newborn). Both events were assessed as not related to the investigational product. No patients died during in the study.

There were 14 patients reporting DAEs during randomized treatment: 3 (1.8%) in the Symb 2x2+Oxis prn treatment group, 6 (3.7%) in the SiT 1x2 group, and 5 (3.1%) in the SiT 1x1 group.

Two pregnancies were reported during the study, and both resulted in post-study SAEs.

Table S3 Number (%) of patients who had an adverse event in any category, and number of adverse events by category

Category of adverse event	2x2+Oxis (n=163)	SiT 1x2 (n=164)	SiT 1x1 (n=162)
	Number (%) of patients who had an adverse event in each category[a]		
Serious adverse events[b]	6 (3.7%)	7 (4.3%)	4 (2.5%)
- Serious adverse events leading to death	0	0	0
- Serious adverse events not leading to death	6 (3.7%)	7 (4.3%)	4 (2.5%)
Discontinuations due to adverse events	3 (1.8%)	6 (3.7%)	5 (3.1%)
	Total number of adverse events[c]		
Serious adverse events	8	8	6
Discontinuations due to adverse events	5	7	6

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

[b] In addition, 2 post-study SAEs occurred in 2 babies whose mothers had previously been included in the study; one SAE leading to death in the 2x2+Oxis group (stillbirth), and one SAE other than death in the SiT 1x1 group (pneumonia).

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

No safety or tolerability concerns were seen in this study.

Health economics results

The Symbicort SiT treatment regimen resulted in a significantly lower consumption of study medication in both SiT treatment groups, compared to the fixed treatment regimen, over 24 weeks of treatment. Asthma medication costs, direct costs, and total costs were all statistically significantly lower in both of the Symbicort SiT treatment arms than in the Symb 2x2+Oxis prn group.