AstraZeneca

Drug Product	Symbicort Turbuhaler	**SYNOPSIS**	
Drug Substance	Budesonide/formoterol		
Edition Number	1		
Study Code	SD-039-0691		
Date	10 November 2004		

A comparison of the effectiveness of treatment with Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 µg) Single Inhaler Therapy and Seretide™ Diskus™ (salmeterol/fluticasone; 50/100, 50/250 or 50/500 µg) plus Ventoline™ (salbutamol) as needed in steroid-treated adult and adolescent asthmatic subjects. A randomised, open, parallel-group, phase IIIB, multicentre, 12-month study.

Study centres

A total of 246 centres from 16 countries participated in this study. The countries were as follows: Belgium (25), Canada (21), China (5), Denmark (24), France (38), Germany (10), Hong Kong (1), Iceland (1), Italy (20), Korea (South)(6), Norway (28), Spain (22), Sweden (19), Taiwan (4), Thailand (4) and the UK (18).

Publications

None at the time of writing this report.

Study dates

First patient enrolled: 31 October 2002

Last patient completed: 4 June 2004

Phase of Development

Therapeutic confirmatory (III)

Objectives

The primary objective of the study was to compare the effectiveness of treatment with Symbicort Turbuhaler Single Inhaler Therapy and Seretide Diskus plus Ventoline Diskus (or equivalent) as needed. The secondary objective was to study safety by evaluation of the incidence and type of adverse events (AEs).

Study design

This was a randomised, open, parallel-group, phase IIIB, multicentre, 12-month study comparing the effectiveness of treatment with Symbicort Turbuhaler (budesonide/formoterol; 160/4.5 μg) Single Inhaler Therapy (SIT) (ie, Symbicort 160/4.5 μg as maintenance plus as needed) and Seretide Diskus (salmeterol/fluticasone; 50/100, 50/250 or 50/500 μg) as maintenance plus Ventoline Diskus (salbutamol) (or equivalent) as needed in steroid-treated adult and adolescent asthmatic patients.

Target patient population and sample size

Male or female adults and adolescents with asthma, currently treated with inhaled glucocorticosteroids (GCSs), with at least one severe asthma exacerbation during the past year, and with a documented use of medication for relief of asthma symptoms.

Using a log-rank test, a sample size of 1000 patients per treatment group was required for 90% power to detect a decrease from 15% to approximately 10% between the groups in the percentage of patients with severe asthma exacerbations.

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

Budesonide/formoterol (Symbicort Turbuhaler) 160/4.5 μg.

- First 4 weeks: 2 inhalations twice daily plus more as needed
- Doses that could be prescribed during the 11-month dose adjustment period:
  2 inhalations twice daily plus more as needed or
  1 inhalation twice daily plus more as needed or
  2 inhalations once daily plus more as needed

Dose restrictions: If >12 inhalations of Symbicort (maintenance plus rescue medication) were taken during one single day, the patient was to contact the physician for reassessment.

Salmeterol/fluticasone (Seretide Diskus) 50/100, 50/250, 50/500 µg.

- First 4 weeks: 50/250 µg, 1 inhalation twice daily plus Ventoline Diskus (salbutamol) (or equivalent) as needed
- Doses that could be prescribed during the 11-month dose adjustment period:
  50/100 µg, 1 inhalation twice daily plus Ventoline Diskus or equivalent as needed
  or
  50/250 µg, 1 inhalation twice daily plus Ventoline Diskus or equivalent as needed
  or
  50/500 µg, 1 inhalation twice daily plus Ventoline Diskus or equivalent as needed

Dose restrictions: If >10 inhalations of Ventoline were taken during one single day, the patient was to contact the physician for reassessment.

In countries where Ventoline Diskus was not available as sales pack, Ventoline pMDI was used instead.

Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	**Dosage form** **Strength** **No. of doses**	**Manufacturer**
Test product		
budesonide/formoterol fumarate dihydrate Symbicort® Turbuhaler®	- powder for inhalation - 160/4.5 µg/inhalation - 120 (60) doses	AstraZeneca
Batch No.: DB176, DC203, DD219, DE225, DE236/1, DF134, DF235, DF244, DF246, DH139, DH265, DH270, DH275, DH2650, DI286, EF460, EH494		
Comparator product		
salmeterol/fluticasone Seretide™ Diskus™	- powder for inhalation - 50/100 µg/inhalation - 60 doses	GlaxoSmithKline

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Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form Strength No. of doses	Manufacturer
Batch No.: 02F12C, 2D060B711, 2E591A, 2F005B713, 2F031, 2H211B717/1, 2H211B717/2, 2N039B729, 3D280A, B064581, B073755, B074614, B075352, B075379, B075401, B075962, B076802, B079436, B079466, B083411/11, B084906, B087261, B087365, B088750, B090395, B090962, B091800, B093242, B093400, B094019, B095725, B095754, B095758, B096408, B097550, B098530, B098641, B099639, B103312, B103400, B103854, B105266, B105268, B108221, B111529, B118762, R17, R19, S-07, S-9, S11		
salmeterol/fluticasone Seretide™ Diskus™	- powder for inhalation - 50/250 µg/inhalation - 60 doses	GlaxoSmithKline
Batch No.: 034R, 044R, 064R, 376/2, 232, 241, 242, 292, 298, 363, 374, 398/1, 411, 423, 445, 470, 473, 505, 507, 522, 523, 540, 559, 569, 585, 638, 644, 662, 671, 688, 1403797, 1403798, A279, B074595, B075358, B078096, B081691, B084507, B084519, B087266, B092784, B093464, B098528, B099079, B100738, B103288, L557, L-554, L-548, 02D22B, 2F231U1, 2F232U1, 2L141, 2L142, 3C591		
salmeterol/fluticasone Seretide™ Diskus™	- powder for inhalation - 50/500 µg/inhalation - 60 doses	GlaxoSmithKline
Batch No.: 020R, 02E07A, 02E29A, 034, 034R, 038R, 040, 050/2, 052, 067R, 083, 122, 129, 154, 169, 170, 173, 195, 221, 221/1, 223, 224, 233, 262, 274, 2G110U1, 2G111U1, 2M808, 307, 334, 3C220, 3D253, B072519, B073418, B076844, B078492, B079900, B081620, B083870, B084921, B087249, B088762, B090561, B092911, B095722, B098045, B098049, B099406, B101717, B103714, B104691, B107567, B110033, B112085, B118291, L-233		
Rescue medication		
salbutamol Ventoline™ Diskus™	- powder for inhalation - 0.2 mg/inhalation - 60 doses	GlaxoSmithKline
Batch No.: A064, 2G556, 2L556, 058, 078, 084, 085, 089, 095, 096A, 101, 105, 108, 119, 128, 134A, 139, 148, 149, 152, 153, 154, 157, 010902A, 030401A		
salbutamol Ventoline™ pMDI	- aerosol for inhalation - 0.1 mg/inhalation - 200 doses	GlaxoSmithKline
Batch No.: 02F25A, 2061, 2557, D029588, D030546, D032507, D033546, D033955, D035361, D036029, S181, S329, S376, S409, T164, T-3		

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Table S1 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form Strength No. of doses	Manufacturer
Medication used at lung function measurements (FEV_1)		
terbutaline sulphate Bricanyl® Turbuhaler®	- powder for inhalation - 0.5 mg/dose - 200 doses	AstraZeneca
Batch No.: DG1196, EA1201		

FEV_1 Forced expiratory volume in 1 second

Duration of treatment

The run-in period was 2 weeks and the 12-month randomised treatment period consisted of 2 parts: first 4 weeks to gain control and thereafter 11 months of treatment with dose adjustments.

Criteria for evaluation (main variables)

Efficacy

- The primary efficacy variable was time to first severe asthma exacerbation, defined as a deterioration in asthma leading to either
  - oral GCS for at least 3 days
  - emergency room visit
  - admission to hospital
  - unscheduled visit (ie, patient initiated) leading to a change in asthma treatment, (eg, increased dose of inhaled GCS or addition of other asthma treatment)
- The secondary efficacy variables were:
  - total number of severe asthma exacerbations
  - forced expiratory volume in 1 second (FEV_1) (pre- and post-bronchodilator)

- use of study medication
- use of other regular asthma treatment
- Patient reported outcomes (in the Clinical Study Protocol named Health-related quality of life)
    - Asthma Quality of Life Questionnaire with standardised activities (AQLQ(S)) scores
    - Asthma Control Questionnaire (ACQ) score
    - Satisfaction of Asthma Treatment Questionnaire (SATQ) scores (added in local amendments for France, Sweden and the UK)
- Health economics
    - health care resource utilisation
    - sick-leave from work/school (patient or other person)
    - effectiveness (total number of severe asthma exacerbations)

The patient reported outcomes and the health economics are included in the secondary efficacy variables in the Clinical Study Report as opposed to in the Clinical Study Protocol where they were as separate variables. This is due to changes in the Clinical Study Report template.

Safety

Safety variables were incidence and type of AEs.

Statistical methods

All analyses were based on the full analysis set. The time to first severe asthma exacerbation was compared between the treatment groups using a log-rank test. Additional descriptions were made using Cox proportional hazards models. The total number of severe asthma exacerbations was analysed using Poisson regression. FEV_1, use of as needed medication, AQLQ(S), ACQ and SATQ were analysed using analysis of variance (ANOVA) models. Use of study medication and other regular asthma treatment are described.

Patient population

Table S2 Patient population and disposition

		Symbicort SIT	Seretide	All
Population				
N randomised (N planned)		1067 (1000)	1076 (1000)	2143 (2000)
Demographic characteristics				
Sex, n (% of patients)	Male	451 (42.3)	429 (39.9)	880 (41.1)
	Female	616 (57.7)	647 (60.1)	1263 (58.9)
Age, years	Mean	45.3	45.1	45.2
	Range	12 to 80	12 to 84	12 to 84
Age groups, years	12-17	37	39	76
	18-64	885	890	1775
	65-	145	147	292
Race, n	Caucasian	846	855	1701
	Black	11	4	15
	Oriental	207	217	424
	Other	3	0	3
Time since diagnosis, years	Median	13	12	13
	Range	1-75	0-74	0-75
No. of severe asthma exacerbations/12 months	Median	1	1	1
	Range	1-24	0-24	0-24
IGCS at entry, dose (μg/day)	n	1067	1072	2139
	Mean	887.5	881.0	884.2
	Range	50-2000	400-3000	50-3000
Baseline characteristics				
Smoking status (pack years)	Median	5	5	5
	Range	0-20	0-55	0-55

(Continued)

Table S2 Patient population and disposition

		Symbicort SIT	Seretide	All
No. of inhalations bronchodilator, rescue, 24 hours	Mean	1.81	1.82	1.82
	Range	0.0-9.5	0.0-9.7	0.0-9.7
No. of inhalations bronchodilator, prevention, 24 hours	Mean	0.83	0.83	0.83
	Range	0.0-6.0	0.0-24.0	0.0-24.0
No. of total inhalations bronchodilator, 24 hours	Mean	2.64	2.65	2.65
	Range	0.2-10.7	0.3-33.7	0.2-33.7
FEV_1 pre-bronchodilator, L	Mean	2.259	2.236	2.248
	Range	0.72-4.57	0.56-4.50	0.56-4.57
FEV_1 pre-bronchodilator, % PN	Mean	73.3	73.1	73.2
	Range	39-115	28-100	28-115
FEV_1 post-bronchodilator, L	Mean	2.533	2.502	2.517
	Range	0.77-5.72	0.55-5.45	0.55-5.72
FEV_1 post-bronchodilator, % PN	Mean	82.0	81.7	81.8
	Range	39-130	25-117	25-130
Disposition				
No. of patients who	completed	945	921	1866
	discontin-ued	119	150	269
	were not treated or had no data on treatment	3	5	8
Analysed for safety[a]	n	1064	1071	2135
Analysed for efficacy[a;b]	n	1064	1071	2135

a Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
b Full analysis set
N Number; PN Predicted normal

The treatment groups were generally well balanced in demographic and baseline characteristics. The most common reason for discontinuation of study treatment was 'Other reason' (ie, other than AE, lost to follow-up and eligibility criteria not fulfilled) and the number of patients was similar in both treatment groups.

Efficacy results

Symbicort SIT was more effective than Seretide plus Ventoline as measured by the primary variable. The risk reduction for the time to the first exacerbation was 25% (hazard ratio 0.75; 95% confidence interval 0.61 to 0.93, p=0.0076).

There were 255 exacerbations (0.24 per patient) in the Symbicort group and 329 (0.31 per patient) in the Seretide group, corresponding to a 22% reduction in the total number of exacerbations with Symbicort (hazard ratio 0.78; 95% confidence interval 0.66 to 0.91, p=0.0025).

Pre- and post-bronchodilator FEV_1 increased in both treatment groups and the increases were numerically greater in the Symbicort group. The mean difference between treatment groups was statistically significant for the post-bronchodilator value (0.025 L; p=0.045), but not for the pre-bronchodilator value (0.026 L; p=0.066).

The average total dose of inhaled corticosteroid was similar in both treatment groups (653 µg budesonide vs 583 µg fluticasone). At the end of the study, 68% of patients in the Symbicort group were on the budesonide maintenance dose of 640 µg daily and 31% received 320 µg daily. In the Seretide group, 58% received the fluticasone dose of 500 µg daily, 27% received 1000 µg daily, and 14% received 200 µg daily, at the end of the study. Use of as needed medication was lower in the Symbicort group (0.58 vs 0.93 inhalations/day, p<0.001).

Few patients used asthma medication other than study medication and oral steroids for exacerbations. Total use of oral steroids due to severe asthma exacerbations was lower in the Symbicort group than the Seretide group (12% vs 14% of patients; 1980 vs 2978 days total use).

Similar improvements in patient reported outcomes were seen for both treatment groups, and no differences were detected between the treatment groups.

Health care resource utilisation was generally numerically lower in the Symbicort group.

Table S3 shows the statistical analyses of severe asthma exacerbations.

Table S3 Statistical analyses of severe asthma exacerbations

Variable	Analysis	Treatment	estimate	95% conf.int.	P-value
Severe asthma exacerbations					
- Time to first	Log-rank test	Symbicort SIT vs. Seretide			0.0051
	Cox PH model	Symbicort SIT vs. Seretide	0.75	(0.61, 0.93)	0.0076
- Events/patient and year	Poisson regression	Symbicort SIT	0.24	(0.20, 0.29)	
		Seretide	0.31	(0.26, 0.36)	
		Symbicort SIT vs. Seretide	0.78	(0.66, 0.91)	0.0025
Severe asthma exacerbations, unscheduled visits not included					
- Time to first	Log-rank test	Symbicort SIT vs. Seretide			0.017
	Cox PH model	Symbicort SIT vs. Seretide	0.77	(0.61, 0.97)	0.025
- Events/patient and year	Poisson regression	Symbicort SIT	0.19	(0.16, 0.23)	
		Seretide	0.23	(0.19, 0.28)	
		Symbicort SIT vs. Seretide	0.81	(0.68, 0.97)	0.023
Emergency room visits and hospitalisations					
- Time to first	Log-rank test	Symbicort SIT vs. Seretide			0.18
	Cox PH model	Symbicort SIT vs. Seretide	0.70	(0.42, 1.17)	0.18
- Events/patient and year	Poisson regression	Symbicort SIT	0.04	(0.03, 0.06)	
		Seretide	0.05	(0.04, 0.07)	
		Symbicort SIT vs. Seretide	0.83	(0.55, 1.25)	0.38

Safety results

In this study, no clinically important differences between the two treatment groups were observed with regard to the overall pattern of reported AEs, Serious adverse events (fatal and non-fatal) or discontinuations due to AEs. Both Symbicort SIT and Seretide were well tolerated and no new or unexpected safety concerns were identified.