AstraZeneca

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STUDY REPORT SUMMARY

FINISHED PRODUCT: Symbicort® Turbuhaler®

ACTIVE INGREDIENT: Budesonide/formoterol

Trial title (number): Efficacy and safety of Symbicort® Turbuhaler® 160/4.5 mcg/inhalation, two inhalations twice daily plus as-needed compared with Seretide™ Diskus™ 50/500 mcg/inhalation, one inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed - a 6-month, randomised, double-blind, parallel-group, active controlled, multinational phase IIIB study in adult and adolescent patients with persistent asthma.

Developmental phase: III
First subject recruited: 02 May 2005
Last subject completed: 29 May 2006

OBJECTIVES

The primary objective of this study was to compare the efficacy of 2 inhalations of Symbicort Turbuhaler 160/4.5 mcg/inhalation twice daily plus Symbicort Turbuhaler 160/4.5 mcg/inhalation as-needed with 1 inhalation of Seretide Diskus 50/500 mcg/inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed in patients with persistent asthma by evaluation of time to first severe asthma exacerbation as the primary outcome variable.

The secondary objective of the study was to investigate safety by assessing the nature, incidence, and severity of adverse events within the treatment groups.

METHODS

Study design

This was a 6-month, randomised, double-blind, parallel-group, active-controlled, multi-national study in patients with persistent asthma.

Target subject population and sample size

Males and females, at least 12 years old, with persistent asthma, and a pre-bronchodilatory forced expiratory volume (FEV1) >50% of predicted normal value with at least 12% reversibility. Patients were to require frequent use of as-needed reliever medication (ie, 5 out of the last 7 days of run-in), despite daily use of inhaled glucocorticosteroid and should have experienced at least 1 clinically important asthma exacerbation within 1 to 12 months before enrolment in the study.

Assuming that 11% of patients would experience a severe asthma exacerbation in the Symbicort group and 16% of patients would experience a severe asthma exacerbation in the Seretide group, 985 randomised and evaluable patients per group would be required to detect this difference with 90% probability using a log-rank test with a two-sided alternative hypothesis and a significance level of 5%. In order to compensate for withdrawals, the sample size was set to 1050 patients per group. It was estimated that approximately 3000 patients would need to be enrolled to randomise 2000 to 2300 patients.

Investigational product and comparator: dosage and mode of administration

During the run-in-period, patients used their regular dose and brand of inhaled glucocorticosteroid and maintenance long-acting β2-agonist (if used before study entry). In addition, all patients used Bricanyl® (terbutaline) Turbuhaler as-needed for relief of asthma symptoms (0.5 mg/dose; batch number 3521325.

During the treatment period, patients received 1 of 2 double-blinded treatments. Maintenance medication was administered in a double-dummy fashion due to the different outward appearances of the 2 inhalers. As-needed medication was administered with identical inhalers. The treatments were as follows:

- Two inhalations of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 mcg/inhalation and one inhalation of placebo Diskus twice daily as maintenance treatment plus Symbicort Turbuhaler 160/4.5 mcg/inhalation as-needed
- Two inhalations of placebo Turbuhaler and one inhalation of Seretide (salmeterol/fluticasone) Diskus 50/500 mcg/inhalation twice daily as maintenance treatment plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed.

Duration of treatment

A run-in period of 2 weeks was followed by a treatment period of 26 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- 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 (or equivalent) treatment due to asthma
    - oral glucocorticosteroid treatment due to asthma for at least 3 days
- Secondary outcome variables included the following:
    - number of severe asthma exacerbations
    - time to first mild asthma exacerbation
    - number of mild asthma exacerbations
    - changes from Visit 2 to the mean value Visits 3 to 5 in:
        - forced expiratory volume in 1 second (FEV1)
        - Asthma Control Questionnaire overall score
    - changes in average value from the run-in to the treatment period in:
        - peak expiratory flow (PEF) - morning and evening
        - asthma symptom score - day, night, and total
        - number of as-needed inhalations - day, night, and total
        - percentage of nights with awakenings due to asthma symptoms
        - percentage of symptom-free days
        - percentage of as-needed-free days
        - percentage of asthma-control days
    - health economics:
        - health-care resource utilisation
        - sick-leave

Safety

The safety variables were nature, incidence, and severity of adverse events within the treatment groups.

Pharmacogenetics

As an optional part of the study, a blood sample was taken from consenting patients for genetic analysis to explore the relationship between polymorphisms and inter-individual differences in the response to Symbicort Turbuhaler, Seretide Diskus, and their constituent monoproducts. Genetic data are not reported in the study report.

Statistical methods

All efficacy and safety analyses were based on the Full Analysis Set as defined in the ICH E9 guidelines.

Time to first severe asthma exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a Cox proportional hazards model, stratified by country and with treatment as factor. Mean number of severe asthma exacerbations per patient was compared between the treatments using a Poisson regression model with treatment and country as factor and total time in study as an offset variable. Time to first mild asthma exacerbation was analysed in the same fashion as time to first severe asthma exacerbation. For other diary variables, spirometry, and ACQ score, the change from run-in to treatment was compared between treatment groups using analysis of variance.

Safety data was analysed in terms of descriptive statistics.

RESULTS

Patient population

Table S1 **Patient population demographics, baseline characteristics, and disposition**

Variable		Symbicort	Seretide	All
N randomised (planned)		1154 (1050)	1155 (1050)	**2309 (2100)**
Sex	Male	443 (38%)	444 (38%)	**887 (38%)**
	Female	711 (62%)	711 (62%)	**1422 (62%)**
Age (yrs)	Mean	39.6	39.2	**39.4**
	Range	12-80	12-80	**12-80**
	12-17	163 (14%)	161 (14%)	**324 (14%)**
	18-64	910 (79%)	912 (79%)	**1822 (79%)**
	>64	81 (7%)	82 (7%)	**163 (7%)**
Race	Caucasian	670 (58%)	688 (60%)	**1358 (59%)**
	Black	45 (4%)	32 (3%)	**77 (3%)**
	Oriental	267 (23%)	256 (22%)	**523 (23%)**
	Other	172 (15%)	179 (15%)	**351 (15%)**
BMI (kg/m^2)	Mean	25.9	26.0	**26.0**
	Range	13-58	14-52	**13-58**
Time since diagnosis (yrs)	Median	14	13	**13**
	Range	1-67	1-77	**1-77**
Smoking status	Never	949 (82%)	952 (82%)	**1901 (82%)**
	Previous	154 (13%)	151 (13%)	**305 (13%)**
	Occasional	24 (2%)	20 (2%)	**44 (2%)**
	Habitual	27 (2%)	32 (3%)	**59 (3%)**
Pack-years of smokers	Mean	4	4	**4**
	Range	0-20	0-36	**0-36**
Inhaled glucocorticosteroid at entry dose	N of patients	1149	1149	**2298**
	Mean dose (mcg)	704.7	719.6	**712.1**
	Dose range (mcg)	250-1600	200-2000	**200-2000**
Inhaled long-acting bronchodilator at entry	N (%) of patients	645 (56%)	622 (54%)	**1267 (55%)**
FEV_1 (L)	Mean	2.08	2.10	**2.09**
	Range	0.60-4.65	0.72-4.89	**0.60-4.89**
FEV_1 (% predicted normal)	Mean	70.2	71.0	**70.6**
	Range	45-114	45-222	**45-222**
Post-bronchodilator	Mean	2.56	2.58	**2.57**
FEV_1 (L)	Range	0.83-5.35	0.96-7.32	**0.83-7.32**
Reversibility (%)	Mean	23.9	23.9	**23.9**
	Range	7-103	7-95	**7-103**
As-needed use (daily)	Mean	2.23	2.29	**2.26**
	Range	0.00-8.26	0.10-8.00	**0.00-8.26**
Symptom score (scale: 0-6)	Mean	1.88	1.89	**1.88**
	Range	0.00-6.00	0.00-5.72	**0.00-6.00**
N (%) of patients who	Completed	1056 (92%)	1041 (90%)	**2097 (91%)**
	Discontinued	95 (8%)	112 (10%)	**207 (9%)**
N analysed for safety		1151	1153	**2304**
N analysed for efficacy		1151	1153	**2304**

The study included enough patients to fulfill the aim in the power calculation. The treatment groups were comparable at baseline. The patient population recruited is within the target population for Symbicort Turbuhaler.

Efficacy results

In this comparison of Symbicort as maintenance and reliever with Seretide administered at its highest approved dose, there were fewer severe asthma exacerbations and fewer patients that experienced severe asthma exacerbations in the Symbicort group (137 events among 108 patients) than in the Seretide group (173 events among 130 patients). There was not a statistically significant difference in the primary outcome variable, time to first severe asthma exacerbation (Symbicort versus Seretide hazard ratio 0.82; P=0.12). There was a statistically significant advantage for Symbicort in the number of severe exacerbations per patient per 6 months (Symbicort 0.12 versus Seretide 0.16; risk ratio: 0.79, P=0.039). Additional analysis performed on the individual criteria for severe exacerbations showed statistically significant differences in favour of Symbicort for the time to first asthma hospitalisation/ER treatment (Symbicort versus Seretide hazard ratio 0.64; P=0.031) and the number of asthma hospitalisations/ER treatments per patient per 6 months (Symbicort 0.05 versus Seretide 0.07; risk ratio 0.69; P=0.046). For all other secondary variables, no statistically significant differences were detected between the Symbicort and Seretide treatments.

The Symbicort group used on average 0.95 as-needed inhalations of Symbicort per day, while the Seretide group used on average 1.01 as-needed inhalations of terbutaline per day. Patients in the Symbicort group thus received a mean budesonide dose of 792 mcg, compared to the fixed 1000-mcg fluticasone dose in the Seretide group. The use of a high number of as-needed inhalations was somewhat more frequent in the Seretide group than in the Symbicort group.

Safety Results

The mean exposure time and overall pattern of patients reporting AEs was similar between treatment groups. AEs were mostly mild to moderate in intensity. The one death in the study was not considered to be causally related to the investigational product (treatment group: Symbicort; cause of death: typhoid fever). The number of patients reporting AEs and SAEs was similar in both treatment groups, with no obvious differences in the pattern of reported preferred terms. Although discontinuations due to adverse events (DAEs) were rare in both treatment groups, there were more DAEs in the Seretide group than in the Symbicort group (20 versus 11).

Table S2 **Summary of adverse events**

	Symbicort N=1151	Seretide N=1153	All N=2304
Number (%) of patients with			
Any adverse event	451 (39%)	460 (40%)	**911 (40%)**
SAEs leading to death	1 (<0.5%)	0	**1 (<0.5%)**
SAEs not leading to death	29 (3%)	31 (3%)	**60 (3%)**
DAEs	11 (1%)	20 (2%)	**31 (1%)**
Other AEs	0	0	**0**
Total number of adverse events			
AEs	730	739	**1469**
Maximum Intensity			
- Mild	471	456	**927**
- Moderate	228	250	**478**
- Severe	31	33	**64**
- Not assessed	0	0	**0**
Max no. of AEs/patient	10	6	**10**
SAES (fatal and non-fatal)	37	38	**75**
DAEs	11	24	**35**
Other AEs	0	0	**0**

Patients with multiple events in the same category are counted once in each category and multiple events in a single patient with the same preferred term are counted once for each patient and category.

REFERENCE

Bousquet J, Boulet L-P, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, and Carlsheimer Å. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Resp Med ePublication

Bousquet J, Boulet L-P, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, and Carlsheimer Å. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Article in press.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Symbicort™ (budesonide/formoterol), Healthcare Professionals should view their specific country information.