AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	Budesonide/ Formoterol
Study Code	D5890L00014
Edition Number	1
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STYLE - A Comparison of Symbicort SMART (Symbicort Turbuhaler 160/4,5 mcg, 1 inhalation b.i.d. plus as needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults – a 26-week, open-labelled, parallel-group, multicentre study

Study dates:	First subject enrolled: 21-07-2005 Last subject enrolled: 20-06-2006
Phase of development:	IIIb
International Co-ordinating Investigator:	Not Applicable
Sponsor's Responsible Medical Officer:	Tomas LG Andersson

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

International co-ordinating investigator

Not Applicable.

Study centre(s)

This study was conducted in Chile (2 centres), Croatia (5 centres), Czech Republic (11 centres), Greece (10 centres), Iceland (2 centres), Latvia (6 centres), Lithuania (5 centres), Portugal (9 centres), Slovakia (15 centres), Slovenia (10 centres).

Publications

None at the time of writing this report.

Study dates		Phase of development
First subject enrolled	21-07-2005	Therapeutic confirmatory (IIIb)
Last subject completed	22-12-2006	

Objectives

Primary Objective

The primary objective was to compare the efficacy of Symbicort SMART with treatment according to conventional best practice in adolescent and adult patients with persistent asthma.

The primary outcome variable is: time to first severe asthma exacerbation.

Secondary Objectives

secondary objective is to collect safety data for treatment in the two treatment groups in adolescent and adult patients with persistent asthma

Study design

This was a 26-week, randomised, open-label, parallel group study. Patients were randomised to one of the following two treatment groups in a balanced (1:1) way:

- Symbicort 160/4.5µg, 1 inhalation b.i.d. + as needed (in response to symptoms).

- Conventional best practice, active stepwise individualized treatment according to asthma treatment guidelines.

Table S1 Study Flow Chart

	Symbicort Turbuhaler 160/4.5 µg b.i.d. + as needed			
	Conventional best practice, active stepwise treatment according to asthma treatment guidelines			
	↑	↑	↑	↑
Week	0	4	13	26
Visit	1	2	3	4

Target healthy volunteer population and sample size

Adolescent (in some countries) and adult patients with persistent asthma.

Under the assumption that, at the end of the study, 11% of the patients have experienced a severe asthma exacerbation in one treatment group and 6% 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 80% probability, given that the study includes approximately 500 patients per group. A Cox proportional hazards analysis will have almost identical power as the log-rank test (since asymptotically these tests are the same).

The formula for the calculation can e.g. be found in "Freedman, L.S. (1982). Tables of the number of patients required in clinical trials using the logrank test. Statistics in Medicine, 1:121-129". The numbers 11% and 6% are estimates based on previous Symbicort SMART studies.

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

Symbicort Turbuhaler 160/4.5µg/inhalation, 1 inhalation b.i.d. + as needed (in response to symptoms). Batch numbers according to medication bought in each country.

vs

Conventional best practice, active stepwise individualized treatment according to asthma treatment guidelines. Batch numbers according to medication bought in each country.

Duration of treatment

Twenty-six weeks

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Efficacy, Health Economic's and Quality of Life

- Primary variable: Time to first severe asthma exacerbation.

- Secondary variables: Number of severe asthma exacerbations, Mean use of as-needed medication, Prescribed asthma medication during the treatment period.

- Patient Reported Outcomes: Asthma Control Questionnaire (ACQ) (ACQ assessments were performed in the countries where linguistically valid translations are available – Croatia, Portugal, Chile and Greece).The change between randomization and the average value of Visits 2-4 was assessed.

- Health Economics Variables: Asthma related health care resource utilisation (including study drug), Sick leave (subject or other person).

Criteria for evaluation - safety (main variables)

- AEs

- SAEs

- Discontinuations due to AEs

Statistical methods

All efficacy analyses were based on the full analysis set, as defined in ICH E9 guidelines.

The time to first severe asthma exacerbation were described using Kaplan-Meier curves. The treatment groups were compared using a Cox proportional hazards model with treatment as factor.

The mean number of severe asthma exacerbations per patient were compared between the treatment groups using a Poisson regression model with treatment as factors and the time in study as an offset variable.

The change in ACQ from the randomisation visit to the average value of Visits 2-4 was compared between treatments using an analysis of variance model with treatment as factor and the value at Visit 1 as a covariate.

The use of as-needed medication was extensively described. The mean number of as-needed inhalations per day was calculated for each patient and this was compared between treatments using ANOVA model with treatment as factor.

Prescribed asthma medication was extensively described. For the conventional best practice treatment group the prescribed asthma medication, excluding exacerbation treatment, was described. Special attention was given to the use of inhaled steroids, which was compared to the dose of inhaled steroids in the Symbicort SMART group. Asthma medication prescribed for treating severe asthma exacerbations was described for both treatment groups.

Asthma related health care resource utilisation and sick leave were compared between treatment groups by means of descriptive statistics.

Safety data was analysed by means of descriptive statistics.

Subject population

Table S2 Subject population and disposition

		SMART		CBP		Total	
Population							
N randomised (N planned)		506	(500)	502	(500)	1008	(1000)
Demographic characteristics							
Sex (n and % of subjects)	Male	174	(35.0)	183	(36.7)	357	(35.9)
	Female	323	(65.0)	315	(63.3)	638	(64.1)
Age (years)	Mean (SD)	44.1	(15.7)	45.2	(16.2)	44.7	(15.9)
	Range	12 to 82		13 to 84		12 to 84	
Race (n and % of subjects)	Caucasian	466	(93.8)	464	(93.2)	930	(93.5)
	Black	1	(0.2)	4	(0.8)	5	(0.5)
	Oriental	0	(0.0)	0	(0.0)	0	(0.0)
	Other	30	(6.0)	30	(6.0)	60	(6.0)
Baseline characteristics							
Body Mass Index (BMI)	Mean (SD)	27.2	(5.3)	26.8	(4.9)	27.0	(5.1)
	Range	15.8 to 55.7		16.3 to 50.0		15.8 to 55.7	
IGCS dose/day before randomisation (µg)	Mean (SD)	497.3	(253.5)	514.4	(232.0)	505.7	(243.2)
	Range	80.0 to 2000.0		80.0 to 1500.0		80.0 to 2000.0	
Median time since diagnosis (yrs)	Median	10.2		9.2		9.7	
	Range	0.7 to 62.7		0.3 to 70.9		0.3 to 70.9	
Smoking Status (n and % of subjects)	Non-Smoker	381	(76.7)	378	(75.9)	759	(76.3)
	Ex-Smoker	90	(18.1)	96	(19.3)	186	(18.7)
	Occasional Smoker	18	(3.6)	11	(2.2)	29	(2.9)
	Habitual Smoker	8	(1.6)	13	(2.6)	21	(2.1)
No of pack years	Mean (SD)	6.2	(8.2)	5.9	(3.5)	6.0	(6.2)
	Range[a]	1.0 to 80.0		1.0 to 30.0		1.0 to 80.0	
FEV1 (L) pre-bronchodilator	Mean (SD)	2.714	(0.995)	2.684	(0.914)	2.699	(0.955)
	Range	0.730 to 6.580		0.540 to 5.860		0.540 to 6.580	
FEV1 (L) post-bronchodilator	Mean (SD)	2.934	(0.996)	2.892	(0.941)	2.913	(0.968)

		SMART		CBP		Total	
	Range	0.860 to 6.850		0.940 to 6.130		0.860 to 6.850	
FEV1 % of predicted normal	Mean (SD)	87.045	(19.731)	86.928	(19.059)	86.986	(19.388)
	Range	25.382 to 145.959		23.815 to 145.181		23.815 to 145.959	
Mean (SD) daytime asthma symptom score		1.791	(1.173)	1.832	(1.221)	1.812	(1.196)
Disposition							
N (%) of subjects who	Completed	470	(92.9)	467	(93.0)	937	(93.0)
	discontinued	36	(7.1)	35	(7.0)	71	(7.0)
N analysed for safety[b]		493		493		986	
Full analysis set population[c]		497		498		995	

[a] 5 patients had smoking habits with no pack years > 10. They were classified as protocol deviations and later withdrawn

[b] included all patients who took al least 1 dose of study treatment and for whom at least 1 data point was collected after randomisation

[c] included all randomized patients regardless of whether they took study medication or not and for whom data has been recorded in the CRF

ITT=Intention to treat; N=Number; PP=Per-protocol

Summary of efficacy results

The primary outcome variable was: time to first severe asthma exacerbation. According to appropriate statistical methodology, statistically significant differences were not shown between treatments (p=0.107). However, it could be noted a tendency to a delay in first severe asthma exacerbation in SMART patients in comparison to patients in CBP treatment group. Hazard ratio was 0.728 and the 95% CI was [0.495 ; 1.071].

Secondary efficacy endpoints were: number of severe asthma exacerbations, change in ACQ score from randomisation to visit 4, use of as-needed medication per day during treatment period, prescribed asthma medication during the treatment period, use of inhaled steroids, asthma medication prescribed for treating severe asthma exacerbations and asthma related health care resource utilization and sick leave. No statistically differences between treatments were shown in all secondary efficacy endpoints with the exception of mean daily dose of inhaled steroids between treatments. The principal conclusions were:

- Total number of events was 63 in SMART and 77 in CBP; estimated mean number of severe asthma exacerbations per patient by year was 0.26 in SMART and 0.32 in CBP;
- Mean change in overall ACQ from baseline to the average value of visits 2-4 was
- 0.71 in SMART and -0.60 in CBP;

- otal per day of as-needed inhalations in the previous 14 days of each visit averaged 0.95 in SMART and 1.08 in CBP. Ranges were 0 to 7.36 in SMART and 0 to 8.96 in CBP;
- The percentage of as-needed free days averaged 59.0% in SMART and 59.4% in CBP.
- The most frequent prescribed asthma medication group in the CBP arm was inhaled short-acting Beta-2 agonists (R03AC), 93.8% of the patients;
- The mean daily dose of inhaled steroids between treatments was statistically different; 471.9 µg (737.4 µg BDP equivalent) in SMART arm and 515.5 µg (852.0 µg BDP equivalent) in CBP arm;
- None of the subjects had intensive care hospitalization during the study;
- 0.6% subjects in SMART arm and 1.3% in CBP arm had at least one general care hospitalization during the study;
- 1.7% subjects in each treatment arm had at least one emergency room visit during the study;
- 8.1% subjects in SMART arm and 10.9% in CBP had at least one visit to specialists during the study;
- 5.7% subjects in SMART arm and 6.2% in CBP had at least one visit to family practitioners during the study;
- 0.8% subjects in SMART arm and 1.7% in CBP had at least one other health care visit during the study;
- 0.2% subjects in each treatment arm had at least one physician home visit during the study;
- 1 subject (0.2%) in CBP arm had at least one other health care home visit during the study;
- 10.3% subjects in SMART arm and 13.9% in CBP have been unable to perform usual daily activities due to his/her asthma at least once during the study;
- 1.3% caregivers in SMART arm and 1.9% in CBP have been unable to perform usual daily activities due to subject's asthma at least once during the study.

Summary of pharmacokinetic results

Not Applicable

Summary of pharmacodynamic results

Not Applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not Applicable

Summary of pharmacogenetic results

Not Applicable

Summary of safety results

This study aimed also to collect safety data for treatment in the two treatment groups in adolescent and adult patients with persistent asthma.

The adverse events incidence was almost identical between treatment groups: 25.4% patients in SMART group and 27.4% patients in CBP group. Only one fatal serious adverse event was registered, on CBP group. 16 (1.6%) patients had at least one non-fatal serious adverse event (6 in SMART and 10 in CBP) and one adverse event leading to study discontinuation was registered for 9 patients (0.9%) in total (6 subjects in SMART and 3 in CBP group).

The majority of the adverse events (387 - 90.6%) were rated as unlikely related to study drug as judged by the investigator (183 in SMART group and 204 in CBP group). Of the total 40 AEs that might have been caused (reasonable possibility) by the investigational product, 18 (45.0%) were mild (13 in SMART and 5 in CBP), 19 (47.5%) were moderate (12 in SMART and 7 in CBP) and 3 (7.5%) were severe (1 in SMART and 2 in CBP).

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	**N (%) of subjects who had an adverse event in each category[a]**					
	SMART (n=493)		**CBP (n=493)**		**Total (n=986)**	
Any adverse events	**125**	**(25.4)**	**135**	**(27.4)**	**260**	**(26.4)**
Serious adverse events	**6**	**(1.2)**	**11**	**(2.2)**	**17**	**(1.7)**
Serious adverse events leading to death	0	(0.0)	1	(0.2)	1	(0.1)
Serious adverse events not leading to death	6	(1.2)	10	(2.0)	16	(1.6)
Discontinuations of study treatment due to adverse events	6	(1.2)	3	(0.6)	9	(0.9)
	Total number of adverse events					
Adverse events	209		218		427	
Serious adverse events	7		12		19	

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Table S4 Number (%) of subjects 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)	SMART (n=493)		CBP (n=493)		Total (n=986)	
Common Cold	**9**	**(1.8)**	**14**	**(2.8)**	**23**	**(2.3)**
Upper Respiratory Infection	11	(2.2)	9	(1.8)	20	(2.0)

[a] Events with a total frequency of ≥1% across all treatment groups are included in this table.

Date of the report

03 June 2008