AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D5890L00022
Edition Number	1
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A Pan-European, open label, randomised study comparing the efficacy and cost-effectiveness of Symbicort® Maintenance And Reliever Therapy (Symbicort® SMART®) using a maintenance dose of Symbicort® 160/4.5µg of 1 or 2 inhalations twice daily in the treatment of persistent asthma. EUROSMART

Study dates:	First subject enrolled: 26 March 2007 Last subject completed: 01 December 2008
Phase of development:	Therapeutic use (IV)

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

Study centres

A total of 9695 subjects were enrolled at 929 centres in 14 countries: Belgium, Finland, France, Germany, Greece, Iceland, Ireland, Italy, The Netherlands, Norway, Russian federation, Spain, UK and Sweden. Of these, 8424 were randomised (at 895 centres) and allocated to treatment at Visit 2. The first subject was enrolled on 26 March 2007 and the last subject finished the study on 01 December 2008.

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of this study was to compare the efficacy of Symbicort® Maintenance And Reliever Therapy (Symbicort® SMART®) administered over 6 months at two different maintenance doses in adult asthmatic subjects on IGCS with an indication for long-acting β2 agonist:

- 1 inhalation of Symbicort 160µg/4.5µg bid
- 2 inhalations of Symbicort 160µg/4.5µg bid

The efficacy of Symbicort SMART treatment using the two different maintenance doses was compared for the total group and within two strata defined on the basis of the dose of IGCS taken at inclusion: Low/Medium dose (≤ 1000µg beclomethasone, ≤ 800µg budesonide (metered dose), ≤ 500µg fluticasone, ≤ 800µg mometasone, ≤ 500µg beclomethasone ultrafine particles, or ≤ 320µg ciclesonide) and High dose (> 1000µg beclomethasone, > 800µg budesonide (metered dose), > 500µg fluticasone, > 800µg mometasone, > 500µg beclomethasone ultrafine particles or > 320µg ciclesonide).

Secondary objectives

The secondary objectives were:

- To compare the cost-effectiveness of Symbicort SMART at two different maintenance doses.
- To assess the safety of Symbicort SMART at two different maintenance doses.

Third objective

The third objective of the study was to investigate whether or not subject characteristics at study entry (e.g. IGCS dose, lung function, nocturnal awakenings) may predict which subjects will benefit most from a higher maintenance dose.

Study design

This was a 6-month, randomised, open label, parallel-group, active controlled, multinational study, in subjects with moderate to severe persistent asthma who were symptomatic despite daily use of IGCS with or without LABA. The primary outcome variable was time to first severe asthma exacerbation.

Target healthy volunteer population and sample size

Enrolled outpatients of either sex, ≥ 18 years old, were required to have at least a 6-month documented history of asthma according to the American Thoracic Society definition (ATS,1987) and should have been on unchanged maintenance therapy with IGCS for at least 1 month with a constant daily dose of at least 500µg beclomethasone, or 400µg of budesonide (metered dose), or 200µg fluticasone, or 400µg mometasone, or 250µg beclomethasone ultrafine particles, or 320 µg ciclesonide. The IGCS therapy and dose was to be kept unchanged during the run-in period.

The subjects were eligible for randomisation into the study (visit 2) if they had asthma that was not well controlled, shown by a history of SABA use for symptom relief during the last month, and had used their Bricanyl® on at least 4 of the 7 last days of the run-in period if treated with IGCS without LABA, and on at least 2 of the 7 last days of the run-in period if treated with both IGCS and LABA. Asthma maintenance treatment had to be unchanged during the run-in period.

A sample size of 4000 subjects per group, and a significance level of 5%, provided 90% power to detect a reduction from 10% to 7.9% in the proportion of subjects experiencing a severe asthma exacerbation during the study.

It was planned that no more than 67% of the randomised subjects should be in the stratum Low/Medium dose users, and at least 33% should be in the stratum High dose users.

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

The details of the investigational products and any study treatment are given in below two tables.

Table S1 Details of investigational product

Maintenance and as needed therapy	
Trade name:	Symbicort® Turbuhaler®
Active ingredients:	budesonide/formoterol fumarate dihydrate
Excipient:	lactose monohydrate
Dosage form:	inhalation powder
No. of inhalations:	120
Strength:	budesonide 160 µg/inhalation and formoterol fumarate dihydrate 4.5 µg/inhalation
Manufacturer:	AstraZeneca Liquid Production, Sweden.

Table S2 Run-in medication

As-needed therapy	
Trade name:	Bricanyl® Turbuhaler®
Active ingredients:	Terbutaline sulphate
Excipient:	lactose monohydrate
Dosage form:	inhalation powder
No. of inhalations:	120
Strength:	0.25 mg/inhalation or 0.5 mg/inhalation *according to country*
Manufacturer:	AstraZeneca Liquid Production, Sweden.

This was an open label study and sales packs of investigational product from each participating country were to be used. There is no information accessible in the study database regarding batch numbers or expiry dates on subject level. This is due to that each marketing company purchased investigational product and run-in medication locally and labels for the countries were printed locally. E-code and allocated treatment was written on the label by the investigator. Batch numbers for investigational product and run-in medication is available at each marketing company only.

Duration of treatment

Subjects used Bricanyl® Turbuhaler ® for symptom relief during the 2-week run-in. If they met the randomisation criteria, the subjects were allocated to one of the two treatment groups by randomization within each strata in a 1:1 ratio, followed by a 26-weeks treatment period.

Criteria for evaluation - efficacy (main variables)

The primary outcome variable was time to first severe asthma exacerbation defined as deterioration in asthma leading to:

- need for oral/systemic glucocorticosteroids for at least 3 days.
- hospitalisation/emergency room visit* because of asthma requiring oral/systemic glucocorticosteroids.

*Or equivalent: subject initiated unscheduled health-care visit due to asthma.

Secondary efficacy outcome variables were:

- The total number of severe asthma exacerbations.
- Time to first and total number of severe asthma exacerbations that led to hospitalisation and/or emergency room treatment.
- Total number of days with oral/systemic glucocorticosteroids during severe asthma exacerbation .
- The change in mean daily number of inhalations of as-needed medication from 2 weeks prior to randomisation to 2 weeks prior to visits 3 and 4.
- The proportion of subjects with all 4 assessed weeks (2 weeks prior to visits 3 and 4) fulfilling the criteria for a well controlled asthma week.
- The change in overall ACQ score from visit 2 to the mean of the values at visits 3 and 4.
- The mean total daily dose of Symbicort® (both maintenance dose and as-needed use).

Cost-effectiveness was evaluated from data on subjects health care resource utilisation and reported sick-leave.

Criteria for evaluation - safety (main variables)

Safety was evaluated by assessment of the nature, incidence and severity of serious adverse events and/or discontinuations due to adverse event within the treatment groups.

Statistical methods

Time to first severe asthma exacerbation was described using Kaplan-Meier curves, and the treatment groups were compared using a Cox proportional hazards model. The total number of severe asthma exacerbations were compared between the treatments using a Poisson regression model. Time to first and total number of severe asthma exacerbation that led to hospitalisation and/or emergency room treatment were analysed using the same methods as for severe asthma exacerbations.

Change in ACQ5 overall score and change in mean daily number of inhalations of as-needed medication was analysed using an analysis of variance (ANOVA) model.

To investigate whether subject characteristics at study entry may predict which subjects would benefit most from a higher maintenance dose, different baseline factors and covariates were included in the Cox proportional hazards model for severe asthma exacerbations.

Subject population

It was planned to randomise 4000 subjects per treatment group. Out of these, at least 33% were planned to be included in the High dose strata (i.e.1326 subjects per treatment group).

Table S3 Subject disposition by strata and treatment

	SMART 1*2	SMART 2*2	Total
Number of subjects randomised			
Low/Medium dose strata	3267	3291	6558
High dose strata	936	930	1866
Total	4203	4221	8424
Number of subjects in Full Analysis Set (FAS)			
Low/Medium dose strata	3100	3143	6243
High dose strata	908	902	1810
Total	4008	4045	8053
Number (%) of subjects who discontinued during the study			
Low/Medium dose strata	236 (7.6)	270 (8.6)	506 (8.1)
High dose strata	73 (8.0)	70 (7.8)	143 (7.9)
Total	309 (7.7)	340 (8.4)	649 (8.1)
Number (%) of subjects who completed the study			
Low/Medium dose strata	2864 (92.4)	2873 (91.4)	5737 (91.9)
High dose strata	835 (92.0)	832 (92.2)	1667 (92.1)
Total	3699 (92.3)	3705 (91.6)	7404 (91.9)

Table S4 Treatment- and strata group comparison of demographic and disease data, FAS

		SMART 1*2 (N=4008)	SMART 2*2 (N=4045)	Total (N=8053)
Sex, n (% of subjects)	Male	1525 (38)	1533 (38)	3058 (38)
	Female	2483 (62)	2512 (62)	4995 (62)
Age, years	Mean	47.8	47.9	47.8
	Range	18 - 96	18 - 90	18 - 96

Table S4 Treatment- and strata group comparison of demographic and disease data, FAS

		SMART 1*2 (N=4008)	SMART 2*2 (N=4045)	Total (N=8053)
BMI, kg/m²	Mean	27.4	27.4	27.4
	Range	15 - 61	13 - 62	13 - 62
Time with asthma diagnose, years	Mean	15.7	15.3	15.5
	Range	0 - 74	0 - 76	0 - 76
Number of exacerbations past 12 months before study start	Low/Medium dose strata subjects Mean	1.37	1.31	1.34
	High dose strata subjects Mean	1.81	1.82	1.82
	Total Mean	1.47	1.42	1.45
IGCS dose at study entry, BDP equivalents (µg/day)	Low/Medium dose strata subjects Mean	715	705	-
	High dose strata subjects Mean	1391	1375	-
Number of subjects on treatment with LABA at baseline (% of subjects)	Low/Medium dose strata subjects	2361 (76.2)	2358 (75.0)	4719 (75.6)
	High dose strata subjects	747 (82.3)	760 (84.3)	1507 (83.3)
	Total	3108 (77.5)	3118 (77.1)	6226 (77.3)
Number of days per week with as-needed medication during run-in	Low/Medium dose strata subjects Mean	4.78	4.80	4.79
	High dose strata subjects Mean	5.44	5.38	5.41
	Total Mean	4.93	4.93	4.93
Number of days per week with asthma day-time symptoms during run-in	Low/Medium dose strata subjects Mean	4.23	4.27	4.25
	High dose strata subjects Mean	4.88	4.83	4.86
	Total Mean	4.38	4.39	4.39

Table S4 Treatment- and strata group comparison of demographic and disease data, FAS

		SMART 1*2 (N=4008)	SMART 2*2 (N=4045)	Total (N=8053)
Number of nights per week with night-time awakenings during run-in	Low/Medium dose strata subjects Mean	0.96	1.02	0.99
	High dose strata subjects Mean	1.56	1.61	1.58
	Total Mean	1.10	1.15	1.13
Mean Overall ACQ (ACQ5) score at study entry	Low/Medium dose strata subjects Mean	1.74	1.78	1.76
	High dose strata subjects Mean	2.19	2.16	2.17
	Total Mean	1.85	1.86	1.85
Pulmonary function test at baseline,	FEV1 (L) before	2.56 (N=3257)	2.55 (N=3265)	-
before and after bronchodilation	FEV1 (% pn)	84.85%	84.76%	-
(pn = predicted normal)	FEV1 (L) after	2.73 (N=3207)	2.72 (N=3190)	-
	FEV1 (% pn)	90.22%	90.37%	-
	PEF (L/min) before	392 (N=4054)	387 (N=4076)	-
	PEF (% pn)	85.4%	84.8%	-
	PEF (L/min) after	417 (N=4001)	411 (N=4003)	-
	PEF (% pn)	90.9%	90.1%	-
Relevant medical condition other than asthma, n (% of subjects)	Allergic Rhinitis	1784 (45)	1829 (45)	3613 (45)
	Allergic Conjunctivitis	873 (22)	888 (22)	1761 (22)
	Gastro Oesophageal Reflux	530 (13)	553 (14)	1083 (13)
	Arterial Hypertension	793 (20)	769 (19)	1562 (19)
	Ischemic Heart Disease	103 (3)	126 (3)	229 (3)

Table S4 Treatment- and strata group comparison of demographic and disease data, FAS

		SMART 1*2 (N=4008)	SMART 2*2 (N=4045)	Total (N=8053)
Smoking status, n (% of subjects)	Never	2778 (69)	2752 (68)	5530 (69)
	Previous	783 (20)	850 (21)	1633 (20)
	Occasional	167 (4)	154 (4)	321 (4)
	Habitual	277 (7)	288 (7)	565 (7)
Pack years among smokers, years	Mean	5.7	5.7	5.7
	Range	0 - 36	0 - 50	0 - 50
Employment status, n (% of subjects)	Full-time Employed	2079 (51.9)	2085 (51.6)	4164 (51.7)
	Part-time Employed	386 (9.6)	392 (9.7)	778 (9.7)
	House-person/Student	516 (12.9)	538 (13.3)	1054 (13.1)
	Retired/Long term sick-leave	746 (18.6)	751 (18.5)	1497 (18.6)
	Unemployed	281 (7.0)	278 (6.9)	559 (6.9)

The study included enough subjects to fulfil the aim of the power calculation for the primary outcome variable for the total population. Disposition, demography and baseline characteristics were in line with the population intended to be included in this study. Overall, the treatment groups were very similar at baseline.

Summary of efficacy results

- For the primary efficacy outcome variable, time to first severe asthma exacerbation, Symbicort SMART 2*2 was superior to Symbicort SMART 1*2 (HR 0.82, 95% CI 0.685 to 0.981, p=0.0300).
- Incidence of severe exacerbations was low in both treatment groups. There were 322 exacerbations (0.097 per subject) in Symbicort SMART 1*2 and 266 exacerbations (0.080 per subject) in the Symbicort SMART 2*2, corresponding to an 18% rate reduction of exacerbations in favour of Symbicort SMART 2*2 (p=0.0176).
- No difference could be shown between Symbicort SMART 2*2 and Symbicort SMART 1*2 for time to first and total number of severe asthma exacerbations that led to hospitalisation and/or emergency room treatment.

- In the low and high dose IGCS strata (cut point = 1000µg/day of BDP) the reduction of the number of exacerbations was 23% (p=0.0108) and 7% (p=0.618) for Symbicort SMART 2*2 vs. 1*2, respectively. Also time to first severe exacerbation was prolonged as shown by a 22% lower hazard rate (p=0.0247) and 8%(p=0.5957) Symbicort SMART 2*2 vs. 1*2, respectively.
- ACQ5 improved from 1.85 at baseline to 1.1-1.2 in both Symbicort SMART groups, with a statistically significant difference of 0.1 in favour of Symbicort SMART 2*2.
- The mean total daily dose of Symbicort (budesonide dose, both maintenance- and as-needed use) was lower in Symbicort SMART 1*2 (463µg) than in Symbicort SMART 2*2 (737µg). The mean daily dose of budesonide for as-needed use was 145µg for the Symbicort SMART 1*2 treatment group and 102µg for the Symbicort SMART 2*2 treatment group.
- Best baseline predictor to identify subjects with potential efficacy benefits of Symbicort SMART 2*2 usage was PEF postbronchodilation. A value of PEF < 80% pn was selected.
- Exacerbation rate was reduced by 27 % using Symbicort SMART 2*2 to subjects with PEF postbronchodilator < 80%. No statistically significant difference in exacerbations between treatments were recorded in subjects with PEF postbronchodilator ≥ 80%.

Summary of safety results

In this study, no clinically important differences between the two treatment groups were observed with regards to the overall pattern and frequency of reported SAEs (fatal and non-fatal) or DAEs. Both treatments were well tolerated.

Table S5 Number (%) of subjects who had an adverse event in any category (SAEs and DAEs), safety analysis set

Category of adverse event	SMART 1*2 (N=4189)	SMART 2*2 (N=4210)	Total (N=8405)*
Serious adverse events leading to death	2 (<0.1%)	2 (<0.1%)	4 (<0.1%)
Serious adverse events not leading to death	75 (1.8%)	86 (2.0%)	161 (1.9%)
Discontinuation of treatment due to adverse events	91 (2.2%)	119 (2.8%)	210 (2.5%)

* 6 subjects received study drug without being randomised. Hence, these 6 subjects are included in the safety analysis set and included in the 'Total' column in the table.

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.

Events are counted by preferred term, i.e. for subjects with multiple events falling under the same preferred term, only 1 frequency of the event is counted.