AstraZeneca

Study Report Summary

Finished product: powder for inhalation

Active ingredient: budesonide / formoterol

Study N° D5890L00005
A comparison of Symbicort Single inhaler Therapy (Symbicort Turbuhaler 200/6 µg, 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, randomised, open, parallel group multicentre study.

Development Phase: III

First subject recruited : September 29, 2004

Last subject completed : January 14, 2006

Date of report: January 24, 2007

OBJECTIVES

Primary objective
The primary objective was to compare the efficacy of Symbicort® as maintenance and reliever therapy with treatment according to conventional best practice in adult and adolescent patients with persistent asthma.
The primary variable was the time to first severe asthma exacerbation. The secondary variables were the number of severe asthma exacerbations, the number of as-needed treatment doses during treatment period, prescribed asthma medications during treatment period, change in FEV1 pre and post-bronchodilatation between Visit 1 and Visit 4, change in PEF pre and post-bronchodilatation between Visit 1 and Visit 4, change in Asthma Control Questionnaire (ACQ 5) score between Visit 1 and the average value of Visits 2 to 4 and change in Satisfaction with Asthma Treatment Questionnaire (SATQ) overall and domain score between Visit 1 and Visit 4
Secondary objectives
The secondary objective of the study was to collect safety data for treatment with Symbicort® as maintenance and reliever therapy in adolescent and adult patients with persistent asthma.

METHODS

Design: This was a 26-week, randomised, open label study, conducted on parallel groups.
The patients were randomised in one of the following two groups in a balanced (1:1) way:
o Symbicort® 200/6 µg, 1 inhalation b.i.d. + as needed (in response to symptoms). The delivered dose for Symbicort® 200/6 µg was 160 µg of budesonide and 4.5 µg of formoterol fumarate dihydrate.
o Conventional Best Practice treatment, in the investigator's judgement, respecting the stepwise approach therapy in accordance with current international and national asthma guidelines: GINA and ANAES. Four visits were planned for the study: at inclusion and at weeks 4, 13 and 26 weeks.

Population:
Male or female patient aged 12 years or over having given his/her free and informed consent.
Patient whose diagnosis of asthma has been established for at least three months and treated by a glucocorticoid (GCS) inhaled at a dose of ≥ 400 µg/day during the 3 months preceding Visit 1.
Patient receiving a daily treatment with both inhaled GCS and a long-acting beta-agonist Or receiving daily

treatment with inhaled GCS alone and whose asthma is insufficiently controlled in the month prior to inclusion and who has used 3 inhalations or more of the treatment on request in the 7 days prior to inclusion.

RESULTS

Group A: Symbicort® as maintenance and reliever therapy
Group B: Conventional Best Practice treatment

Population:

Table 1: Disposition of patients

Treatment groups	Group A (N = 517)	Group B (N = 491)	Total (N = 1008)
Population			
Number of patients			
Included (N)			1013
Randomised (N)	517	491	1008
Completing the study (N and %)	464 (89.8%)	451 (91.9%)	915 (90.8%)
Premature discontinuation (N and %)	53 (10.3%)	40 (8.2%)	93 (9.2%)
Number of patients analysed for:			
Efficacy in ITT* (N)	515	489	1004
Safety** (N)	515	489	1004

* ITT = Number of patients randomised, having signed the informed consent form, and for whom the data have been recorded in the CRF after randomisation, apart from the end-of-study page
** Safety = Number of patients analysed for efficacy (ITT) and taking at least one dose of one of the study treatments

The main patient characteristics on inclusion are summarized in the following table.

Table 2: Patient characteristics on inclusion (ITT population)

Treatment groups	Group A (N = 515)	Group B (N = 489)	Total (N = 1004)
Demographic characteristics (ITT)			
Sex (N and %)			
Male	207 (40.2%)	204 (41.7%)	411 (40.9%)
Female	308 (59.8%)	285 (58.3%)	593 (59.1%)
Age (years)			
Number (N)	515	489	1004
Mean (SD)	44 (17)	45 (17)	45 (17)
Range (min - max)	12 - 89	12 - 87	12 - 89
Characteristics at inclusion (ITT)			
Duration of the asthmatic complaint (years)			
Number (N)	514	488	1002
Median	14.4	13.2	13.6
Range (min - max)	0.2 - 71.8	0.3 - 74.5	0.2 - 74.5
Daily dose of GCS inhaled (µg/day)			
Number (N)	515	489	1004
Mean (SD)	784 (341)	800 (380)	792 (360)
Range (min - max)	0 - 2000	0 - 3000	0 - 3000
Daily dose of inhaled corticoids in beclometasone equivalent (µg/day)			
Number (N)	515	489	1004
Mean (SD)	1220 (652)	1247 (756)	1233 (704)
Rank (min - max)	0 - 4000	0 - 6000	0 - 6000
FEV1 pre-bronchodilatation (%)			
Number (N)	511	487	998
Mean (SD)	81.96 (19.02)	80.83 (19.84)	81.41 (19.42)
Range (min - max)	17.03 - 140.43	27.62 - 134.90	17.03 - 140.43

The two treatment groups are homogenous concerning the principal characteristics at inclusion and concerning distribution in the course of the study in the ITT population.

Efficacy:

Table 3: Proportion of patients presenting at least one severe asthma exacerbation (primary variable) (ITT)

Treatment groups	Group A (N = 515)	Group B (N = 489)	Total (N = 1004)
Variables defining the occurrence of a severe asthma exacerbation (N and %)*			
Treatment by oral corticosteroid for asthma ≥ 3 days	42 (8.2%)	45 (9.2%)	87 (8.7%)
Hospitalisation due to asthma	5 (1.0%)	5 (1.0%)	10 (1.0%)
Emergency-room treatment due to asthma	15 (2.9%)	14 (2.9%)	29 (2.9%)
Severe asthma exacerbations (Total)	49 (9.5%)	46 (9.4%)	95 (9.5%)

* *A patient is liable to present more than a single variable for the same severe asthma exacerbation (treatment by oral corticosteroid ≥ 3 days and/or hospitalisation and/or emergency room treatment).*

Of the 1004 patients of the ITT population, 95 (9.5%) presented at least one severe asthma exacerbation during the study period: 49 patients (9.5%) in Group A and 46 patients (9.4%) in Group B.

Table 4: Cox proportional hazards model: comparison of the probability of occurrence of the first severe asthma exacerbation between treatment groups A and B (ITT)

Comparison#	RR*	CI 95%~	p-value
Group A versus Group B	1.037	[0.693 , 1.551]	0.860

\# *Univariate Cox proportional hazards model, including the study treatment as factor*
* *RR = Relative Risk*
~ *CI 95% = 95% Confidence Interval*

The probability of occurrence of the first severe asthma exacerbation is not significantly different between treatment groups A and B in the ITT population.

There were 62 severe asthma exacerbations in Group A and 69 in Group B, corresponding respectively to 0.25 and 0.29 exacerbations per patient year. The reduction on the total number of severe asthma exacerbations in Group A compared to Group B was not significant (RR=0.87, p=0.413).

Table 5: Comparison between treatment groups A and B of the mean daily dose of inhaled corticoids in beclometasone equivalent (µg/day) during the treatment period (ITT)

Comparison Group A versus group B	Mean difference Group A vs B#	95%CI	Value p
Mean daily dose of inhaled corticoids in BDP* equivalent (µg/day)	- 548.8	[-618.2 , -479.3]	< 0.01

* *BDP = Béclometasone*
\# *1-factor ANOVA*

The mean daily dose of inhaled corticoids in beclometasone equivalent during the treatment period is significantly lower in Group A than in Group B in the ITT population: 679.9 µg/day in the Symbicort® group versus 1228.6 µg/day in the Conventional Best Practice group ($p < 0.01$). In Group A, the patients took on average 0.73 (+1.28) supplementary inhalations of Symbicort® 200/6 µg as needed. The breakdown of as-needed intakes is similar in the 2 groups.

Table 6: Variation of the global ACQ 5 score between visit V1 and the treatment period (ITT)

Variable	Treat.	Visit V1 (Baseline) Mean	(Rank)	Treatment period (average of visits V2 to V4) Mean	(Rank)	Difference Baseline – Treatment period. N	Adjusted mean difference#

Global ACQ 5 score*	A	1.51	(0.00 - 5.20)	1.02	(0.00 - 4.60)	501	- 0.47
	B	1.50	(0.00 - 5.20)	1.12	(0.00 - 4.60)	475	- 0.38

* *The global ACQ 5 score corresponds to the average of the scores of the 5 ACQ items*

\# *Analysis of covariance ANCOVA with the study treatment as factor and the value of baseline variable as covariable*

Table 7: Comparison between treatment groups A and B of the variation of the global ACQ 5 score between visit V1 and the treatment period (ITT)

Comparison Group A versus Group B	Mean difference Group A vs B#	CI 95%	p-value
Global ACQ 5 score	- 0.090	[-0.177 , -0.003]	0.043

\# *Analysis of covariance ANCOVA with the study treatment as factor and the value of baseline variable as covariable*

Concerning all the other secondary efficacy variables (i.e. number of as-needed treatment doses, change in FEV1, PEF and Satisfaction with Asthma Treatment Questionnaire (SATQ), the comparisons between visit V1 and the treatment period (visits V2 to V4) by Symbicort® and Conventional Best Practice did not show a statistically significant difference between the 2 treatment groups in the ITT population ($p > 0.05$).

Safety:

Table 8: Number (%) of patients having at least one AE per category and total number of AEs

Treatment groups	Group A (N = 515)	Group B (N = 489)	Total (N = 1004)
Number (%&) of patients having at least 1 AE~ in each category*			
AE~	22 (4.3%)	14 (2.9%)	36 (3.6%)
SAE	13 (2.5%)	12 (2.5%)	25 (2.5%)
Death	1 (0.2%)	0 (0.0%)	1 (0.1%)
Other SAEs	12 (2.3%)	12 (2.5%)	24 (2.4%)
SAE related to the study treatment#	2 (0.4%)	0 (0.0%)	2 (0.2%)
AE leading to the definitive discontinuation of the treatment	14 (2.7%)	3 (0.6%)	17 (1.7%)
Total number of AEs~			
AE~	27	24	51
SAE	14	22	36
Death	1	0	1
Other SAEs	13	22	35
SAE related to the study treatment#	2	0	2
AE leading to the definitive discontinuation of the treatment	18	13	31

* *Patients presenting several AEs in the same category are only counted once in each category. Patients having AEs in different categories are counted once in each category .*

& *The percentage of patients is calculated in relation to the total number of patients of the treatment group under consideration (Group A: N = 515, Group B: N = 489, Total: N = 1004)*

~ *SAE or AE leading to the definitive discontinuation of the treatment*

\# *Related to the study treatment in the investigator's judgement*

The most frequent AEs are asthma (11 patients), dyspnea (2 patients), snoring (2 patients), headaches (2 patients), angioneurotic edema (2 patients) and pruritis (2 patients).

One death was declared in Group A. In the case of this SAE, the investigator judged that death was not attributable to the study treatment.