AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort® Turbohaler®
ACTIVE INGREDIENT: Budesonide/Formoterol

Study No: D5890L00011
A comparison of Symbicort® Single inhaler Therapy (Symbicort® Turbuhaler® 160/4.5 µg, 1 inhalation b.i.d. plus as-needed) and conventional best practice for the treatment of persistent asthma in adults - a 26-week, randomised, open-label, parallel-group, multicentre study

Developmental Phase: IV
Study Completion Date: 23 May 2006
Date of Report: 19 May 2009

OBJECTIVES:

The primary objective was to compare the efficacy of Symbicort Single inhaler Therapy with treatment according to conventional best practice in adult subjects with persistent asthma.

A secondary objective was to collect safety data for treatment with Symbicort Single inhaler Therapy in adult subjects with persistent asthma.

METHODS:

Study design

Randomised, open-label, parallel group, and multicentre study.

Target subject population and sample size

Adult subjects with persistent asthma.

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

Investigational product: Inhalation powder containing budesonide 160 µg/inhalation and formoterol fumarate dihydrate 4.5 µg/inhalation. At least 2 inhalations daily plus as-needed inhalations leading to anticipated 120 inhalations over the 26 weeks subjective treatment period.
Batch No.: GE 1004 (expiry date: 31 May 2007).
Comparator: The comparator was to be based on the local asthma treatment guidelines. Due to labelling restrictions it was not possible to use the whole range of available products, therefore a selection of medication was to be provided which reflected the principles of the guideline treatment. The choice of medication within this group and the dosage was to be at the discretion of the Investigator and had to be within the approved label. As the included patient population had to be moderate/severe, it was mandatory to include inhaled glucocorticosteroids as part of the therapy as an anti-inflammatory baseline treatment.
The comparator medication provided for this trial had to be selected from:

- Budesonide Turbuhaler 200 µg
- Fluticasone Discus 250 µg
- Formoterol Turbuhaler 4.5 µg
- Terbutalin Turbuhaler 0.5 mg
- Salbutamol pMDI 100 µg
- Salmeterol Discus 50 µg
- Budesonide/Formoterol Turbuhaler 160/4.5 µg
- Fluticasone/Salmeterol Discus 250/50 µg
- Fluticasone/Salmeterol Discus 500/50 µg
- Theophylline 200 mg
- Theophylline 300 mg
- Singulair 10 mg

Identity, batch numbers and expiry dates of comparator medication used is provided in Appendix 12.1 (Study information).

Duration of treatment

26 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Time to first severe asthma exacerbation
- Secondary variables:
  - Number of severe asthma exacerbations
  - Mean use of as-needed medication
  - Change in FEV_1 from the end of run-in to the end of the study period
  - Prescribed asthma medication during the treatment period

Patient-reported outcomes (PROs)

- Asthma Control Questionnaire (ACQ)
- Patient's satisfaction with the treatment question

Health care resource use

- Health care contacts
- Asthma medication
- Time lost from paid and unpaid work

Safety

- SAEs
- Discontinuations due to AEs
- AEs

Statistical methods

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

Time to first severe asthma exacerbation was to be compared between treatments using a Cox proportional hazards model with treatment as a factor. The mean number of severe asthma exacerbations per patient had to be compared between treatments using a Poisson regression model. The overall asthma control questionnaire (ACQ) score and use of as-needed medication were to be analysed by separate analysis of variance models. The use of prescribed asthma medications, patient's satisfaction with the treatment and health care resource use were to be summarised for each treatment and presented descriptively. The parameters of pulmonary function and safety data were to be analysed by means of descriptive statistics.

Subject population

Table S1 provides an overview of subject population and disposition.

Table S1 Subject population and disposition

		Symbicort		Best practice		Total	
Population							
N randomised (N planned)		741	(765)	736	(765)	1477	(1530)
N analysed		736		724		1460	
Demographic characteristics							
Sex (N (%) of subjects)	Male	304	(41.3%)	299	(41.3%)	603	(41.3%)
	Female	432	(58.7%)	425	(58.7%)	857	(58.7%)
Age (years)	Mean (SD)	46.4	(14.2)	45.5	(14.1)	46.0	(14.2)
	Range	18 to 81		18 to 80		18 to 81	
Race (N (%) of subjects)	Caucasian	729	(99.0%)	721	(99.6%)	1450	(99.3%)
	Black	0	(0.0%)	1	(0.1%)	1	(0.1%)
	Oriental	7	(1.0%)	2	(0.3%)	9	(0.6%)
	Other	0	(0.0%)	0	(0.0%)	0	(0.0%)
Baseline characteristics							
FEV_1 (l)	Mean (SD)	2.837	(0.930)	2.864	(0.919)	2.851	(0.924)
FVC (l)	Mean (SD)	3.620	(1.102)	3.672	(1.092)	3.646	(1.097)
PEF (l/min)	Mean (SD)	406.36	(137.07)	404.76	(136.21)	405.57	(136.60)
Overall ACQ score	Mean (SD)	1.24	(0.97)	1.33	(1.03)	1.28	(1.00)
Disposition							
N (%) of subjects who	Completed	693	(94.2%)	670	(92.5%)	1363	(93.4%)
	discontinued	43	(5.8%)	54	(7.5%)	97	(6.6%)
N analysed for safety[a]		736		724		1460	
N analysed for efficacy (FAS)		736		724		1460	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing

FAS=Full analysis set; N=Number

The number of female subjects was higher than the number of male subjects in both treatment groups. Almost all subjects were of Caucasian race. About two-thirds of the subjects were non-smokers. Another 25% of the subjects were classified as ex-smokers. There were no relevant differences in demographic and baseline characteristics, nicotine abuse and disease data between the treatment groups.
According to the modified scheme described in GINA guidelines, about 60% of the subjects in both treatment groups suffered from asthma of low severity. The rate of subjects with intermediate and high severity asthma was about 30% and 10%, respectively.

RESULTS:

Efficacy results

Table S2 provides an overview of efficacy, subject reported outcome and health economic results.

Table S2 Efficacy, subject reported outcome and health economic results

		Treatment group		Difference between groups
		Symbicort (n=736)	Best practice (n=724)	p value
Time to first severe asthma exacerbation (days)	Mean (SE)	175.91 (1.15)	178.03 (1.48)	0.4837 [1)]
Number of severe asthma exacerbations				
in total	No. (%) of subjects	67 (9.1%)	72 (9.9%)	
	No. of events	86	84	
	Total no. of days	474	566	
with oral GCS*	No. (%) of subjects	31 (4.2%)	39 (5.4%)	
	No. of events	36	45	
	Total no. of days	405	516	
with hospitalisation	No. (%) of subjects	2 (0.3%)	2 (0.3%)	
	No. of events	2	2	
	Total no. of days	36	19	
with emergency room treatment	No. (%) of subjects	54 (7.3%)	55 (7.6%)	
	No. of events	70	63	
	Total no. of days	70	63	
Mean number of severe asthma exacerbations per subject per year	Estimate	0.24	0.24	0.972 [2)]
Mean use of as-needed medication				
Mean no. of inhalations per day	No. (%) of subjects	733 (99.6%)	722 (99.7%)	
	Mean	0.9	0.9	
	Median	0.3	0.3	
	Range	0 to 9	0 to 9	
Maximum no. of inhalations in one day	Mean	2.1	2.3	
	Median	1.7	2.0	
	Range	0 to 11	0 to 13	
Subjects with >8 as-needed inhalations at least on one day	No. (%) of subjects	14 (1.9%)	25 (3.5%)	
% of days with >8 as-needed inhalations (subjects with >8 as-needed inhalations)	Mean	11.0	14.6	
	Median	7.3	4.7	
	Range	1 to 47	2 to 51	
% of days with no as-needed inhalations (all subjects)	Mean	57.5	60.1	
	Median	68.4	71.4	
	Range	0 to 100	0 to 100	
Number of inhalations per day	Adjusted mean change (baseline - treatment period) [3)]	0.12	0.19	0.1037 [4)]
% of days with no as-needed inhalations (all subjects)		-8.86	-11.56	0.0419 [4)]
Pulmonary function test	Mean (SD) change			
FEV_1 before inhalation (l)	Adjusted mean change (baseline - treatment period) [3)]	-0.036	-0.018	0.27 [4)]
FEV_1 after inhalation (l)	Last visit - baseline	-0.012 (0.403)	-0.010 (0.384)	0.8418 [4)]
Reversibility of FEV_1 (%)	LOCF - baseline	-1.116 (11.776)	-0.204 (14.812)	0.0958 [4)]
FVC before inhalation (l)	LOCF - baseline	0.016 (0.440)	0.006 (0.458)	0.8169 [4)]

continued

		Treatment group		Difference between groups
		Symbicort (n=736)	**Best practice (n=724)**	**p value**
PEF before inhalation (l/min)	Last visit - baseline	8.356 (73.734)	6.755 (81.895)	0.5696 [4)]
PEF after inhalation (l/min)	Last visit - baseline	-1.392 (69.966)	2.068 (73.086)	0.4448 [4)]
Reversibility of PEF (%)	Last visit - baseline	-3.299 (19.746)	-1.440 (23.082)	0.1042 [4)]
Asthma medication during the treatment period	No. (%) of subjects			
Inhaled combination of long-acting β_2-agonists and GCS	before randomisation	584 (79.3%)	552 (76.2%)	
	after randomisation	736 (100.0%)	614 (84.8%)	
Inhaled short-acting β_2-agonists	before randomisation	636 (86.4%)	599 (82.7%)	
	after randomisation	19 (2.6%)	614 (84.8%)	
Inhaled GCS	before randomisation	159 (21.6%)	184 (25.4%)	
	after randomisation	5 (0.7%)	105 (14.5%)	
Xanthines	before randomisation	79 (10.7%)	97 (13.4%)	
	after randomisation	13 (1.8%)	90 (12.4%)	
Inhaled long-acting β_2-agonists	before randomisation	83 (11.3%)	89 (12.3%)	
	after randomisation	3 (0.4%)	54 (7.5%)	
Adrenergics and other drugs for obstructive airway disease	before randomisation	56 (7.6%)	64 (8.8%)	
	after randomisation	1 (0.1%)	12 (1.7%)	
Leukotriene receptor antagonists	before randomisation	46 (6.3%)	47 (6.5%)	
	after randomisation	7 (1.0%)	58 (8.0%)	
Antiallergic agents excluding corticosteroids	before randomisation	16 (2.2%)	19 (2.6%)	
	after randomisation	0 (0.0%)	0 (0.0%)	
Anticholinergics	before randomisation	10 (1.4%)	11 (1.5%)	
	after randomisation	2 (0.3%)	4 (0.6%)	
Allergen extracts	before randomisation	11 (1.5%)	8 (1.1%)	
	after randomisation	11 (1.5%)	8 (1.1%)	
Systemic glucocorticoids	before randomisation	4 (0.5%)	7 (1.0%)	
	after randomisation	34 (4.6%)	43 (5.9%)	
Use of inhaled steroids (µg BDP equivalent/day)	Mean (SD)	541.32 (200.30)	714.41 (425.19)	< 0.0001 [5)]
Treatment during severe asthma exacerbations				
Total systemic GCS	No. (%) of subjects	32 (4.35%)	44 (6.08%)	
	Total no. of days	797	766	
Prednisolone	No. (%) of subjects	20 (2.72%)	24 (3.31%)	
	Total no. of days	220	242	
Prednisone	No. (%) of subjects	12 (1.63%)	21 (2.90%)	
	Total no. of days	152	207	
Subject reported outcome				
Asthma control questionnaire				
Overall ACQ score	Adjusted mean change (baseline - treatment period) [3)]	0.205	0.222	0.62 [4)]

continued

		Treatment group		Difference between groups
		Symbicort (n=736)	Best practice (n=724)	p value
Health economic results				
Asthma related events/assessments during the treatment period				
Hospitalisation, intensive care	No. (%) of subjects	1 (0.1%)	1 (0.1%)	
Hospitalisation, general care	No. (%) of subjects	3 (0.4%)	1 (0.1%)	
Emergency room visit	No. (%) of subjects	5 (0.7%)	6 (0.8%)	
Visit to specialist	No. (%) of subjects	64 (8.7%)	47 (6.5%)	
Visit to a family practitioner	No. (%) of subjects	35 (4.8%)	45 (6.2%)	
Other health care visit	No. (%) of subjects	5 (0.7%)	4 (0.6%)	
Home visit, physician	No. (%) of subjects	2 (0.3%)	1 (0.1%)	
Home visit, other health care	No. (%) of subjects	1 (0.1%)	1 (0.1%)	
Spirometry	No. (%) of subjects	41 (5.6%)	39 (5.4%)	
Plain chest X-ray	No. (%) of subjects	11 (1.5%)	17 (2.3%)	
Change in employment status during the treatment period	No. (%) of subjects	8 (1.1%)	10 (1.4%)	
Inability to perform usual daily activities due to asthma during the treatment period				
Subjects	No. (%) of subjects	57 (7.7%)	60 (8.3%)	
Care givers	No. (%) of care givers	3 (0.4%)	7 (1.0%)	

* including one patient with i.v. GCS
[1)] Cox proportional hazards model with treatment as factor.
[2)] Poisson regression model with treatment as factor and total time in study as an offset variable.
[3)] Adjusted mean change calculated for each treatment group using an ANOVA with treatment as factor and baseline as covariate.
[4)] ANOVA with treatment as factor and baseline as covariate.
[5)] ANOVA with treatment as factor.

There was no difference in time to first severe asthma exacerbation between treatment groups.
There was no relevant difference in the number of severe asthma exacerbations and the number of subjects with severe asthma exacerbations in total, with oral application of GCS, with hospitalisation and with emergency room treatment between treatment groups. The total number of days with severe asthma exacerbations and the total number of days with severe asthma exacerbations with oral application of GCS appeared to be higher in the best practice than in the Symbicort group. The total number of days with severe asthma exacerbations with hospitalisation appeared to be higher in the Symbicort group, but the difference was caused by a single patient (E0081008) who was hospitalised 34 days.
There was no relevant difference in the mean and maximum number of as-needed inhalations per day, in the number of subjects with as-needed inhalations during the treatment period and in the percentage of days with no as-needed inhalations during the treatment period between treatment groups. The numbers of subjects with more than 8 as-needed inhalations at least on one day during the treatment period was higher in the best practice than in the Symbicort group. however, there was no difference in the percentage of days with more than 8 as-needed inhalations between subjects concerned in both

treatment groups. From baseline to the treatment period the mean number of inhalations per day decreased and the mean percentage of days with no as-needed inhalations increased in both treatment groups. The increase in the mean percentage of days with no as-needed inhalations was more pronounced in the best practice than in the Symbicort group, but no difference in the decrease of the mean number of inhalation per day between treatment groups was observed.
The parameters of pulmonary function did not show a relevant change from baseline to LOCF or from baseline to the last visit in both treatment groups.
The following changes in asthma medication were observed from prior to randomisation to the treatment period: Symbicort is an inhaled combination of a long-acting β_2-agonist and a GCS. Thus, the rate of subjects taking medication of this category increased to 100% in the Symbicort group, but also in the best practice group an increase in the rate of patients taking medication of this category could be observed. Most subjects in the Symbicort group discontinued inhaled short-acting β_2-agonists, whereas most subjects in the best practice group continued or even started the use of this medication. Most subjects in the Symbicort group discontinued inhaled GCS and inhaled long-acting β_2-agonists, whereas in the best practice group the number of subjects continuing and discontinuing these medications was about balanced. Most subjects in the Symbicort group discontinued xanthines and leukotriene receptor antagonists while in the best practice group around 19% of patients received these medications in addition to a combination of inhaled GCS and inhaled long-acting β_2-agonists.
Despite access to Symbicort as a reliever therapy the use of inhaled corticosteroid was lower in the Symbicort group than in the best practice group.
From baseline to the treatment period the mean overall ACQ score slightly decreased in both treatment groups. There was no difference in the decrease of the mean overall ACQ score between treatment groups.
There were no major differences between treatments on Health Economic outcomes. The treatments differed by no more than 2.2 % in the incidence of any outcome. This difference was in favour of best practice for visits to a specialist. Visits to a family practitioner by contrast showed a 1.4% difference in favour of Symbicort. No difference in subjects with asthma related events/assessments between treatment groups was observed. There was no difference in the number of subjects indicating a change in employment status between treatment groups during the treatment period. There was no difference in the number of subjects indicating inability to perform usual daily activities due to asthma for themselves and for their care givers during the treatment period.

Safety results

AEs that started after inclusion in the study but before first intake of study medication on the day of Visit 2 (pre-treatment AEs) and AEs that started after first intake of study medication on the day of Visit 2 or during the treatment period (treatment emergent AEs) were evaluated separately. Table S3, Table S4 and Table S5 show the number (%) of subjects with treatment emergent AEs by categories, by investigator assessments and by preferred term (only events occurring in more than 20 subjects), respectively. In addition, the total number of treatment emergent AEs by categories is displayed in Table S3.
In the Synopsis only treatment emergent AEs are mentioned.

Table S3 Number (%) of subjects who had at least 1 treatment emergent AE in any category, and total numbers of treatment emergent AEs

Category of AE	N (%) of subjects who had a treatment emergent AE in each category*			
	Symbicort (n=736)		Best practice (n=724)	
Any AEs	263	(35.7%)	249	(34.4%)
Serious adverse events	26	(3.5%)	10	(1.4%)
Serious adverse events leading to death	0	(0.0%)	0	(0.0%)
Serious adverse events not leading to death	26	(3.5%)	10	(1.4%)
Discontinuations of study treatment due to AEs	13	(1.8%)	5	(0.7%)
Other significant adverse events	0	0	0	0
	Total number of adverse events			
Adverse events	529		455	
Serious adverse events	31		11	
Other significant adverse events	0		0	

* 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.

The number of subjects with treatment emergent SAEs and the total number of treatment emergent SAEs was low. The incidence of SAEs was however nominally higher in the Symbicort group compared to the best practice group. Physicians recorded all of these SAEs as unrelated to treatment. There was no obvious clustering of any specific event while a number related to diverse surgical interventions. Similarly discontinuations were infrequent but nominally higher in the Symbicort group compared to best practice. There was no clustering around a specific reason for discontinuation with the exception of reports of a few patients with symptoms consistent with oral candidiasis. There were no alternative therapies allowed in the Symbicort treatment group while change was encouraged in the best practice group. This difference in available treatment options may have had some impact on the apparent imbalance in discontinuations of study treatment in favour of the best practice group. The trial also differed from the usual blinded comparisons in that only one group experienced withdrawal of their usual medication. This factor is also likely to influence AE reporting but the impact of treatment withdrawal cannot be evaluated in this setting.

No subject died after Visit 2.

Table S4 Number (%) of subjects who had a treatment emergent AE according to investigator assessments

		Symbicort (n=736) n (%)	Best practice (n=724) N (%)
Seriousness	Non-serious	250 (34.0%)	246 (34.0%)
	Serious	26 (3.5%)	10 (1.4%)
Action taken to the investigational product	None	249 (33.8%)	238 (32.9%)
	Dose of investigational product changed	1 (0.1%)	7 (1.0%)
	Investigational product temporarily stopped	4 (0.5%)	3 (0.4%)
	Investigational product permanently stopped	13 (1.8%)	5 (0.7%)
AE caused subject to discontinue the study	No	253 (34.4%)	243 (33.6%)
	Yes	13 (1.8%)	7 (1.0%)
Maximum intensity	Mild	183 (24.9%)	175 (24.2%)
	Moderate	115 (15.6%)	97 (13.4%)
	Severe	29 (3.9%)	14 (1.9%)
Causality	No	246 (33.4%)	241 (33.3%)
	Yes	25 (3.4%)	13 (1.8%)
Outcome	AE no longer present	237 (32.2%)	202 (27.9%)
	AE still present	57 (7.7%)	80 (11.0%)

The vast majority of subjects experienced treatment emergent AEs considered as non-serious, mild or moderate of intensity, not causally related to the study treatment and no longer present at the last visit. In the vast majority of subjects the study was not discontinued and no action to the investigational product was taken due to treatment emergent AEs.

There was no difference in the number of subjects with treatment emergent AEs. The total number of treatment emergent AEs was also similar between groups being equivalent to an average of approximately 0.72 AEs per patient in the Symbicort group and 0.63 AEs per patient in the best practice group.

Table S5 Number (%) of subjects with the most commonly reported treatment emergent AEs, sorted by decreasing order of frequency as summarised over all treatment groups (only preferred terms occurring in at least 20 subjects)

Preferred term	Symbicort (n=736) n (%)	Best practice (n=724) n (%)
Nasopharyngitis	47 (6.4%)	50 (6.9%)
Upper respiratory tract infection	31 (4.2%)	31 (4.3%)
Bronchitis	17 (2.3%)	30 (4.1%)
Sinusitis	15 (2.0%)	13 (1.8%)
Cough	9 (1.2%)	18 (2.5%)
Respiratory tract infection	9 (1.2%)	16 (2.2%)

Based on preferred terms, most subjects with a treatment emergent AE experienced naso-pharyngitis. Only few subjects experienced AEs of other preferred terms. The number of subjects experiencing bronchitis, cough and respiratory tract infection appeared to be slightly higher in the best practice than in the Symbicort group. Differences between treatments were minor and the overall incidence of any specific AE was low. As with SAEs the findings might have been influenced by the withdrawal of study medication in one group only although the impact of this factor cannot be evaluated in this setting due to the design of this trial.