AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort®
ACTIVE INGREDIENT: budesonide/formoterol 320/9 µg

Study No: German PMS trial No. 7, NCT 00611520
SYMBOL - (Symbicort® in Chronic Obstructive Pulmonary Disease)

Developmental phase: Phase IV, German PMS trial (NIS)
Study Completion Date:
Date of Report: 18-November-2008

OBJECTIVES:

This PMS study had the objective to evaluate under ordinary outpatient medical care conditions the efficacy and tolerability of budesonide/formoterol in subjects with COPD who were treated by pneumologists and internists. In detail, this PMS study had the following objectives:

1. Efficacy:

- to gain further insight into the efficacy of budesonide/formoterol regarding the treatment of COPD under ordinary outpatient medical care conditions by estimating the change on a quality of life total score compared to baseline, stratified by present therapy, and overall;

2. Tolerability (adverse events):

- to gain further insight into the occurrence of unknown, unexpected and/or rarely occurring adverse events (AE) by estimating the incidence under ordinary outpatient medical care conditions.

In addition, this study had the objective to get further insight into the details of the use, dosage scheme and duration of treatment with budesonide/formoterol in this population.

SUBJECT SELECTION

Pneumologists and internists were asked to document relevant information for this PMS study for those subjects with COPD for whom they wanted to use budesonide/formoterol. However, the participating physicians had to be aware of and take into account possible risks, warnings, contraindications, etc. mentioned in the SPC. It was planned to document approximately 8000 subjects to be enrolled between September and October 2005 in this PMS study.

METHODS:

This PMS study was a non-interventional, multi-centre, prospective observational study with approximately 1000 centres in Germany. It was planned that each centre documented their experience with budesonide/formoterol for a maximum of 10 subjects. It was planned to document approximately 8000 subjects in this PMS study.
Due to the non-interventional character of this PMS study, only an exploratory-descriptive statistical analysis covering all parameters (qualitative, quantitative, text fields including derived and coded variables) from the CRFs has been performed.

Subjects fulfilling at least one of the criteria below:

1. missing CRF page 1;
2. date of Visit 1 is missing;
3. date of Visit 1 is before start date of the PMS study (01-Sep-2005);
4. no data after Visit 1, i.e. at Visits 2 and 3;
5. dates of consecutive visits are not in a consecutive order;
6. date of termination is before date of Visit 1;
7. no information, that the subject had been treated with budesonide/formoterol (i.e. all information on the start date and daily dose of budesonide/formoterol was missing)

were considered as non-evaluable. All other subjects were considered as evaluable for the statistical analysis.

RESULTS:

Patient population

Overall, 6473 subjects were documented in this PMS study by the participating investigators. In total, 1615 of 6473 subjects (24.9%) were excluded from the statistical analysis because the subjects fulfilled at least one of the criteria for non-evaluability. Overall, 4858 of 6473 documented subjects (75.1%) were considered as evaluable.

The gender distribution showed a considerably higher rate of males (2897/4858 evaluable subjects (59.6%)) than females (1924/4858 subjects (39.6%)). Average age was 60.2 ± 12.9 [62.0] years.

Assessment of smoking status revealed that the majority of subjects were smokers (1781/4858 subjects (36.7%)) or ex-smokers (1912/4858 subjects (39.4%)). Only 1099/4858 subjects (22.6%) were non-smokers. The average pack years of cigarettes amounted to 28.9 ± 16.2 [28.0] years in the 3246 subjects with a history of smoking.

Diagnosis of COPD was confirmed in 4535/4858 subjects (93.4%). No COPD was diagnosed in 178/4858 subjects (3.7%), whereas for 145/4858 subjects (3.0%) no diagnosis was recorded. The average duration of the disease amounted to 6.5 ± 7.0 [5.0] years.

The severity of illness was assessed at Visit 1 (from Stage I to IIa, IIb and III). Most frequently reported were Stage IIa in 1651/4858 subjects (34.0%) and Stage IIb in 1539/4858 (31.7%).

3541/4858 subjects (72.89%) received prescribed medication at Visit 1. Most frequently this comprised ß2-agonists (2222/4858 subjects (45.74%)). Table S 1 summarises pre-trial therapy according to active pharmaceutical ingredients commonly used in the treatment of COPD and other medication.

Table S 1 Pre-trial therapy (only terms applying to at least 20 subjects)

ATC level 2/ Preferred drug name	Evaluable subjects, n=4858	
	n	%
Patients with pre-trial prescribed medication	3541	72.89
Subjects with specified long-/short-acting anticholinergic	1035	21.31
TIOTROPIUM	843	17.35
IPRATROPIUM	191	3.93
Subjects with specified long-/short-acting ß2-agonist	2056	42.32
SALBUTAMOL	1148	23.63
FORMOTEROL	594	12.23
FENOTEROL	257	5.29
SALMETEROL	118	2.43
Subjects with specified inhalational steroids	1086	22.35
BUDESONIDE	812	16.71
BECLOMETASONE	177	3.64
FLUTICASONE	66	1.36
Subjects with specified fixed combination compound	1103	22.70
FENOTEROL / IPRATROPIUM	675	13.89
SEREVENT / FLUTIDE	295	6.07
BUDESONIDE W/FORMOTEROL FUMARATE	126	2.59
CROMOGLYCERAT / REPPROTEROL	41	0.84
Subjects with specified theophylline	919	18.92
THEOPHYLLINE	912	18.77
Other COPD medication	261	5.37

Multiple entries per patient possible, drug assignment was performed by ClinResearch physician

Efficacy results

Therapeutic decisions

At Visit 1, the most frequently planned dose of medical treatment with budesonide/formoterol was the recommended 2x1 inhalations per day in 4539/4858 subjects (93.43%). At Visit 2 and 3, 4186/4819 subjects (86.86%) and 3827/4492 subjects (85.20%), respectively, were prescribed budesonide/formoterol at the recommended dose of 2x1 inhalations per day. The average exposure to budesonide/formoterol was 57.3 ± 12.3 [58.0] days. The average daily dose amounted

to 2.0 ± 0.4 [2.0] inhalations at Visit 1, 2.0 ± 0.4 [2.0] inhalations at Visit 2 and 2.0 ± 0.0 [2.0] inhalations at Visit 3.

Physical performance under budesonide/formoterol therapy

The average walking distance as well as walking velocity showed a slight but continuous improvement under budesonide/formoterol therapy from Visit 1 to Visit 3. Table S 2 and Table S 3 summarise the assessments of walking distance and velocity at Visit 1, 2 and 3.

Table S 2 Walking distance under budesonide/formoterol therapy from Visit 1 to Visit 3

Evaluable subjects, n=4858	Length of defined walking distance [m]					
	arith. mean	SD	minimum	median	maximum	n
Walk test before first inhalation	162.5	154.9	1	100.0	900	4618
Walk test 20 minutes after first inhalation	164.7	158.0	1	100.0	964	4589
Walk test at Visit 2	166.9	161.1	1	100.0	930	4493
Walk test at Visit 3	169.3	163.3	1	100.0	930	4195

Only walking velocity equal to or less than 3.0 m/s was analysed.

Table S 3 Walking velocity under budesonide/formoterol therapy from Visit 1 to Visit 3

Evaluable subjects, n=4858	walking velocity [m/s]					
	arith. mean	SD	minimum	median	maximum	n
Walk test before first inhalation	0.93	0.50	0.0	0.84	3.0	4485
Walk test 20 minutes after first inhalation	1.00	0.52	0.0	0.94	3.0	4425
Walk test at Visit 2	1.07	0.53	0.0	1.00	3.0	4304
Walk test at Visit 3	1.11	0.54	0.0	1.05	3.0	4005

Quality of life and the severity of impairment in quality of life by COPD were assessed using a questionnaire at Visit 1, 2 and 3. Table S 4 summarises the changes in the ordinal scale between Visit 1 and the end of the observational period (Visit 3 (LOCF)) for each item of the questionnaire as well as for the total score (sum of all scores).

Table S 4 Change of the quality of life questionnaire between Visit 1 and Visit 3 (LOCF)

	Absolute change			
Item	arith. mean	SD	Median	N
Short of breath at rest?	-1.1	1.3	-1.0	4797
Short of breath doing physical activities?	-1.5	1.2	-1.0	4800
Concerned about getting a cold or your breathing getting worse?	-1.3	1.4	-1.0	4784
Depressed because of your breathing problems?	-1.2	1.4	-1.0	4784
Did you cough?	-1.6	1.3	-2.0	4793
Did you produce phlegm?	-1.6	1.4	-1.0	4794
Breathing problems in strenuous physical activities?	-1.5	1.3	-1.0	4791
Breathing problems in moderate physical activities?	-1.5	1.3	-1.0	4793
Breathing problems in daily activities at home?	-1.2	1.3	-1.0	4786
Breathing problems in social activities?	-1.0	1.3	-1.0	4793
Total score	-13.5	10.2	-12.0	4806

Assessment of therapy

Pre-trial medication was assessed for efficacy and tolerability at Visit 1 and trial medication at Visit 2 and 3. At Visit 1, efficacy was assessed most frequently as "satisfactory" by the subjects (2056/4858 subjects (42.3%)) as well by the investigator (1724/4858 subjects (35.5%)). In most cases assessment of efficacy improved under trial medication at Visit 2 and 3 and the assessment of efficacy by patient and physician was good or very good.

Tolerability of pre-trial therapy was assessed most frequently as "good" by the subjects (177936.6/4858 subjects (36.6%)) as well as by the investigator (1786/4858 subjects (36.8%)). The proportion of assessments with very good tolerability increased noticeably at Visit 2 and 3. At these time points, tolerability of trial medication was assessed as good or very good in most cases by the subject as well as by the physician.

Safety results

Of the 4858 evaluable subjects, 57 subjects (1.17%) experienced at least one AE as recorded on the AE page/SAE form after the start of budesonide/formoterol therapy. In total, 21 subjects (0.43%) reported AEs that were judged by the physicians to be related to budesonide/formoterol. In 18 subjects (0.37%) AEs led to temporary or permanent treatment discontinuation. No deaths occurred in the context of analysable AEs. 4 subjects (0.08%) experienced serious adverse events (SAE) as recorded on the SAE form. The primary system-organ class with the highest number of subjects experiencing AEs was 'infections and infestations' (26 subjects (0.54%)). Most frequent preferred term was bronchitis affecting 7 subjects (0.14%).
Additional AEs that were recorded in the comment fields on the EOT form and were retrospectively coded by ClinResearch physicians were not analysed because date of onset and/or stop date were not available. From these non-analysable AEs, 10 AEs were assessed as serious. This concerned 2 documented and 8 evaluable subjects. In the latter, two subjects had an SAEs with fatal outcome.