AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

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

Study No: German PMS trial No. 8, NCT 00612976
SYMBIOSE - (Symbicort® in chronic obstructive pulmonary disease (COPD))

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 general practitioners 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 of a quality of life score compared to baseline, stratified by present therapy and severity of COPD;

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

Based on the current SmPC, budesonide/formoterol 320/9 µg and 160/4.5 µg could be used for treatment of COPD. General practitioners 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. Subjects were to be enrolled between February and June 2006.

However, the participating physicians had to be aware of and take into account possible risks, warnings, contraindications, etc. mentioned in the SmPC of budesonide/formoterol. It was planned to document approximately 25000 subjects in this PMS study.

METHODS:

This PMS study was a non-interventional, multi-centre, prospective observational study with approximately 5600 participating centres, i.e. general practitioners and internists, and was performed in Germany. It was planned to enrol the subjects into this PMS study between February and June 2006.
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-Feb-2006);
4. no data after Visit 1, i.e. at Visit 2;
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, 18014 subjects were documented in this PMS study by the participating investigators. In total, 1956 of 18014 subjects (10.9%) were excluded from the statistical analysis because the subjects fulfilled at least one of the criteria for non-evaluability (see above). Overall, 16058 of 18014 documented subjects (89.1%) were considered as evaluable.

The gender distribution showed a higher rate of males (9272/16058 evaluable subjects (57.7%)) than females (6682/16058 subjects (41.6%)). Average age was 60.1 ± 13.5 [62.0] years.

Assessment of smoking status revealed that the majority of subjects were smokers (5399/16058 subjects (33.6%)) or ex-smokers (5977/16058 subjects (37.2%)). Only 4481/16058 subjects (27.9%) were non-smokers. The average pack years of cigarettes amounted to 27.09 ± 15.91 [25.00] years in the 9660 subjects with a history of smoking.

Diagnosis of COPD was confirmed in 15757/16058 subjects (98.1%). No COPD was diagnosed in 154/16058 subjects (1.0%%), whereas for 147/16058 subjects (0.9%) no diagnosis was recorded. In the majority of subjects the diagnosis was already established prior to Visit 1 (11284/16058 subjects (70.3%)), whereas in 4577/16058 subjects (28.5%) COPD was diagnosed for the first time at Visit 1. The average duration of the disease amounted to 6.1 ± 6.9 [4.6] years.

11734/16058 subjects (73.07%) reported COPD medication at baseline. Most frequently this comprised ß2-agonist (7212/16058 subjects (44.91%)). Table S 1 summarises pre-trial therapy according to active pharmaceutical ingredients commonly used in the treatment of COPD and other medication. Only terms applying to at least 200 subjects were considered.

Table S 1 Pre-trial therapy (only terms applying to at least 200 subjects)

ATC level 2/ Preferred drugname	Evaluable subjects, n=16058	
	n	%
Subjects with specified long-/short-acting anticholinergic	2353	14.65
TIOTROPIUM	1912	11.91
IPRATROPIUM	435	2.71
Subjects with specified long-/short-acting ß2-agonist	6691	41.67
SALBUTAMOL	3942	24.55
FORMOTEROL	1843	11.48
FENOTEROL	760	4.73
SALMETEROL	253	1.58
Subjects with specified inhalational steroids	3691	22.99
BUDESONIDE	2899	18.05
BECLOMETASONE	470	2.93
Subjects with specified systemic steroids	1109	6.91
CORTICOSTEROIDS FOR SYSTEMIC USE	1108	6.90
PREDNISOLONE	679	4.23
PREDNISONE	204	1.27
Subjects with a fixed drug combination	2943	18.33
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	2940	18.31
DUOVENT	1835	11.43
SERETIDE MITE	686	4.27
BUDESONIDE W/FORMOTEROL FUMARATE	451	2.81
Subjects with specified theophylline	2674	16.65
THEOPHYLLINE	2657	16.55

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 14422/16058 subjects (89.81%), whereas in 866/16058 subjects (5.39%) some other dose was planned. In 770/16058 subjects (4.80%) no information regarding planned dose was recorded. At Visit 2, 13160/16058 subjects (81.95%) were prescribed budesonide/formoterol at the recommended dose of 2x1 inhalations per day, whereas the remaining subjects received some other dose (1046/16058 subjects (6.51%)) or no

remark was recorded (1852/16058 subjects (11.53%)). The average exposure to budesonide/formoterol during the study with Visit 1 as earliest possible start date was 73.0 ± 28.9 [65.0] days. The average daily dose amounted to 2.0 ± 0.4 [2.0] inhalations at Visit 1 and 2.0 ± 0.4 [2.0] inhalations at Visit 2.

Lung function

The forced expiratory volume in 1 second (FEV1) was assessed in 4302 subjects at Visit 1 and 3313 subjects at Visit 2. At Visit 1, FEV1 amounted to 1.931 ± 0.922 [1.800] l. The forced vital capacity (FVC) was assessed in 3912 subjects at Visit 1 and 3018 subjects at Visit 2. At Visit 1, FVC amounted to 2.685 ± 1.084 [2.550] l.

The average FEV1 showed a noticeable increase between Visit 1 and 2 by 0.407 ± 0.551 [0.320] l. During the same period, FVC improved by 0.394 ± 0.661 [0.300] l.

Chronic respiratory questionnaire (CRQ-SAS)

Impairment in the quality of life due to COPD was assessed using the self-administered including standardised activities chronic respiratory questionnaire" (CRQ-SAS). In the questionnaire assessment of impairment was organised into 4 domains. Table S 2 and Table S 3 summarise the assessments of CRQ-SAS at Visit 1 and change between Visit 1 and Visit 2.

Table S 2 CRQ-SAS at Visit 1 - Evaluable subjects -

	Baseline (Visit 1)			
CRQ-SAS Domain	arith. mean	SD	Median	N
Dyspnoea	3.5	1.1	3.4	15651
Fatigue	3.3	1.0	3.3	15572
Emotional function	3.5	1.1	3.4	15675
Mastery	3.4	1.1	3.3	15675

Table S 3 Change in CRQ-SAS between Visit 1 and Visit 2 - Evaluable subjects -

	Change (Visit 2 - Visit 1)			
CRQ-SAS Domain	arith. mean	SD	Median	N
Dyspnea	1.8	1.2	1.6	15444
Fatigue	1.5	1.1	1.5	15372
Emotional function	1.5	1.1	1.3	15559
Mastery	1.6	1.2	1.5	15556

Assessment of therapy

Table S 4 and Table S 5 summarise the assessment of efficacy and tolerability of pre-trial medication and study medication at Visit 1 and 2, respectively.

Table S 4 Assessment of treatment efficacy at Visit 1 and 2 - Evaluable subjects -

Efficacy	Physician		Subject		Agreements between physician's and subject's judgement		
	n	%	n	%	n	% 1)	% 2)
Visit 1 (pre-trial therapy)	16058	100.00	16058	100.00			
Very good	224	1.39	221	1.38	164	73.21	74.21
Good	1153	7.18	1159	7.22	718	62.27	61.95
Satisfactory	4268	26.58	5599	34.87	3333	78.09	59.53
Insufficient	7092	44.16	5813	36.20	5156	72.70	88.70
Not assessed	3321	20.68	3266	20.34			
Visit 2 (study medication)	16058	100.00	16058	100.00			
Very good	7059	43.96	6265	39.01	5610	79.47	89.55
Very good/good			1	0.01			
Good	7682	47.84	8053	50.15	6414	83.49	79.65
Satisfactory	1087	6.77	1474	9.18	799	73.51	54.21
Insufficient	137	0.85	200	1.25	100	72.99	50.00
Not assessed	93	0.58	65	0.40			

Percentage was calculated 1) regarding by physician's and 2) regarding by subject's judgement.

Table S 5 Assessment of treatment tolerability at Visit 1 and 2 - Evaluable subjects -

Tolerability	Physician		Subject		Agreements between physician's and subject's judgement		
	n	%	n	%	n	% 1)	% 2)
Visit 1 (pre-trial therapy)	16058	100.00	16058	100.00			
Very good	1168	7.27	1088	6.78	847	72.52	77.85
Good	5220	32.51	5240	32.63	4179	80.06	79.75
Good/insufficient			1	0.01			
Satisfactory	3812	23.74	4209	26.21	2861	75.05	67.97
Satisfactory/insufficient			1	0.01			
Insufficient	2155	13.42	1853	11.54	1545	71.69	83.38
No remark	3703	23.06	3666	22.83			
Visit 2 (study medication)	16058	100.00	16058	100.00			
Very good	8948	55.72	8271	51.51	7681	85.84	92.87
Good	6396	39.83	6869	42.78	5569	87.07	81.07
Satisfactory	353	2.20	559	3.48	276	78.19	49.37
Insufficient	30	0.19	47	0.29	25	83.33	53.19
No remark	331	2.06	312	1.94			

Percentage was calculated 1) regarding by physician's and 2) regarding by subject's judgement.

Safety results

Of the 16058 evaluable subjects, 55 subjects (0.34%) experienced at least one AE as recorded on the AE page/SAE form after the start of budesonide/formoterol therapy. In total, 24 subjects (0.15%) reported AEs that were judged by the physicians to be related to budesonide/formoterol. In 14 subjects (0.09%) AEs led to temporary or permanent treatment discontinuation. 7 subjects (0.04%) experienced serious adverse events (SAE) and one subject died. The primary system-organ class with the highest number of subjects experiencing AEs was 'infections and infestations' (20 subjects (0.12%)).

AEs observed in all subjects documented regardless of evaluability criteria affected 3 more subjects, including 3 subjects with AEs leading to temporary or permanent treatment discontinuation as well as one additional SAE.

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 was not available. This comprised 27 AEs in 23 subjects that were considered serious, including 10 deaths.