AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort 320/9µg
ACTIVE INGREDIENT:

Study No: SRP-RB-COPD-2005/1
A Scientific Research Program to evaluate the effects of SYMBICORT 320/9µg® in the treatment of COPD in real life environment by General Practitioners

Developmental phase: NIS
Study Completion Date: 30 May 2007
Date of Report: 4 January 2008

OBJECTIVES:

The primary objective will be to evaluate and compare the efficacy of SYMBICORT 320/9µg® in smoking and non-smoking COPD patients in routine clinical practice using the CCQ

METHODS:

During the first visit, the patient is enrolled and baseline assessments will be recorded: age, gender, smoking habits, prior and concomitant COPD medication and the prescribed dose of SYMBICORT 320/9µg®.
During the next two visits, adverse drug reactions, concomitant COPD and the prescribed dose of SYMBICORT 320/9µg® will be recorded. During the last visit, the general practitioner will also be asked for his/her opinion on the general clinical improvement of the patient during SYMBICORT 320/9µg® treatment.
In addition, the patient will be asked to complete a 2-minute questionnaire, the COPD Control Questionnaire (CCQ) for each visit. The patient will score a number of the most important aspects of COPD, like his/her COPD symptoms, his/her general functioning and his/her mental state. The CCQ was developed by prof. dr. T. van der Molen (University of Aberdeen) and will be used to score changes in these aspects of COPD before and after drug treatment.
Except for the completion of the CCQ, no additional effort will be required from the patients.

RESULTS:

A total of 171 physicians (165 Belgian and 6 “Luxembourgeois”) enrolled 788 patients who completed the baseline visit and received at least one dose of Symbicort 320/9µg.
Patient disposition and reason for discontinuation were presented in table below.
15 patients discontinued the study before visit 2 and 20 other patients discontinued before visit 3.

Table 1 Patient disposition

Visit 1 n=788	
Visit 2 n=773	Discontinuation n=15 Death= 1 Patient decision= 7 Unspecified= 3 Work disability= 1 Lost to follow-up= 3
Visit 3 n= 753	Discontinuation n= 20 Death= 5 Patient decision= 4 Unspecified= 2 Work disability= 1 Lost to follow-up= 8

Protocol deviations and violations
Protocol deviations and violations were not recorded in this study.

STUDY POPULATIONS ANALYSED

All patients were included in the analysis set.
Study demographics
Demographic characteristics are summarized in Table 2.
The average age was 63.3 years, ranging from 19 to 95 years. Most patients (64%) were male.
Half are current smoker (53%). Average duration of smoking was 37.2 years ranging from 1 to 71 years. Mean number of cigarettes consumption was 20.2 cigarettes per day ranging from 3 to 66 cigarettes per day.

Table 2 Patient characteristics at inclusion (values are means ± SD)

	Male	Female	Total
N (%)	477 (60.5%)	310 (39.3%)	788
Age (years) Median	64.2 ±13.4 66.5	61.8 ±14.5 63.0	63.3 ±14.0 65.0
Smoker (%)	52.1	53.5	52.7
Smoking duration (years)	39.0 ±131	34.7 ±12.4	37.2 ±13.1
Number of cigarettes per day	20.9 ±9.5	20.0 ±10.2	20.2 ±9.8
Patient under treatment during last two weeks before enrolment (%)	89.7	92.6	90.9
Mean number of COPD medications used during the last two weeks before enrolment	2.1	2.1	2.1
Mean number of concomitant COPD medications prescribed at inclusion	1.3	1.2	1.3

COPD MEDICATIONS BEFORE THE INCLUSION IN THE STUDY

Table below gives number of patients using medications during the previous two weeks before inclusion. A very large number of combinations of COPD medications was used. This result can not be presented here.

Table 3 COPD medications before inclusion

	N	%
B_2short acting	455	57.7
Corticosteroids	269	34.1
CSI/ B_2LA	126	16.0
Theophylines	109	13.8
Antibiotics	96	12.2
Oral corticosteroids	73	9.3
B_2 long acting	190	24.1
Anticholergenics	291	36.9
Others	58	7.4

SYMBICORT 320/9µG DOSE DURING STUDY

Table 4 Mean number of Symbicort inhalation per day

	Visit 1	Visit 2	Visit 3
Mean number of Symbicort inhalation per day	2.1 ± 0.6	2.1 ±0.7	2.1 ± 0.7
Mean number of concomitant COPD medication	1.3 ± 1.1	1.2 ±1.1	1.1 ± 1.1

CONCOMITANT COPD MEDICATIONS DURING THE STUDY

	Visit 1		Visit 2		Visit 3	
	N	%	N	%	N	%
None	189	24.0	218	27.7	263	33.4
B_2short acting	388	49.2	358	45.4	320	40.6
Corticosteroids	18	2.3	28	3.6	25	3.2
CSI/ B_2LA	2	0.3	9	1.1	9	1.1
Theophylines	94	11.9	93	11.8	82	10.4
Antibiotics	75	9.5	31	3.9	26	3.3
Oral corticosteroids	46	5.8	39	4.9	30	3.8
B_2 long acting	32	4.1	39	4.9	31	3.9
Anticholergenics	280	35.5	274	34.8	260	33.0
Others	75	9.5	87	11.0	64	8.1

EFFICACY RESULTS

Primary outcome CCQ questionnaire

Evolution of CCQ domains and total scores during the study

Table 5 Evolution of CCQ scores during study.

Score	Visit 1	Visit 2	Visit 3
Symptom domain	3.3 ± 1.2	2.4 ± 1.1	1.9 ± 1.1
Functional domain	2.7 ± 1.3	1.9 ± 1.2	1.6 ± 1.1
Mental domain	2.1 ± 1.6	1.5 ± 1.4	1.2 ± 1.2
Total CCQ	2.8 ± 1.1	2.0 ± 1.1	1.6 ± 1.0

Total CCQ score decreased significantly over time (non parametric Friedman anova p value <0.0001), same conclusion might be drawn for each domain.

Improvement assessed by CCQ

Clinically relevant improvement (defined as an increase in CCQ score of 0.47 or more) was computed from data for each patient. Table 5 presents proportion of improved patients.

Table 6 Proportion of improved patients as assessed by CCQ questionnaire

	Proportion of improved patients (decrease of at least 0.45 in CCQ total score)		
	N	%	Exact 95% CI
Visit 2	736	62.2	[64.7-71.6]
Visit 3	708	81.2	[78.1-84.0]
Overall	747	79.9	[76.7-82.7]

Relation of CCQ scores with Clinical General Impression (CGI)

Difference between visit 3 and visit 1 CCQ scores were computed and tabulated according to CGI score.

Results of non parametric Kruskal-Wallis test showed that all CCQ scores differed significantly between patients grouped accordingly to treatment assessment using the Clinical General Impression (at the end of the study). Examining mean ranks for each of the CGI levels shows that CCQ scores were ranked adequately to CGI. Median CCQ total score decreased by ±0.40 between 'favourable' CGI levels and by ±0.65 between 'worse' CGI levels.

Table 7 Decrease in CCQ total score at visit 3 from baseline according to CGI at visit 3

	Excellent	Very good	Good	Moderate	Bad
N	84	332	232	49	6
Mean	1.78	1.36	0.96	0.49	-0.47
Std Dev	1.03	0.80	0.75	1.10	0.90
Median	1.70	1.30	0.95	0.30	-0.40
Range	-1.9;4.4	-0.1;4.0	-1.1;3.4	-1.3;3.5	-1.9;0.6
Missing	5	16	16	10	1
Mean ranks	461.8	391.2	295.8	200.9	51.9

There was a significant difference in CCQ total score depending on CGI score (Kruskal-Wallis test p-value<0.0001)

Table 8 Decrease in CCQ symptom score at visit 3 from baseline according to CGI at visit 3

	Excellent	Very good	Good	Moderate	Bad
N	86	337	236	51	6
Mean	2.01	1.57	1.13	0.50	-0.33
Std Dev	1.18	0.97	0.98	1.24	1.45
Median	2.00	1.50	1.00	0.50	0.00
Range	-0.3;5.3	-1.8;4.5	-1.8;4.5	-1.8;4.5	-3.0;1.0
Missing	3	11	12	8	1
Mean ranks	464.0	396.9	306.7	196.8	100.5

There was a significant difference in CCQ symptom score depending on CGI score (Kruskal-Wallis test p-value<0.0001)

Table 9 Decrease in CCQ functional score at visit 3 from baseline according to CGI at visit 3

	Excellent	Very good	Good	Moderate	Bad
N	85	342	243	56	7
Mean	1.71	1.29	0.90	0.55	-0.25
Std Dev	1.21	0.95	0.86	1.33	0.99
Median	1.50	1.25	0.75	0.25	0.00
Range	-0.5;5.0	-3.5;4.5	-1.8;3.3	-1.8;4.8	-1.8;1.3
Missing	4	6	5	3	0
Mean ranks	463.2	404.4	318.2	235.9	115.2

There was a significant difference in CCQ functional score depending on CGI score (Kruskal-Wallis test p-value<0.0001)

Table 10 Decrease in CCQ mental score at visit 3 from baseline according to CGI at visit 3

	Excellent	Very good	Good	Moderate	Bad
N	87	341	245	55	7
Mean	1.43	1.07	0.68	0.37	-0.86
Std Dev	1.33	1.12	1.13	1.50	1.68
Median	1.50	1.00	0.50	0.00	-1.00
Range	-1.5;5.0	-3.0;4.5	-3.0;5.0	-3.0;4.0	-3.5;1.5
Missing	2	7	3	4	0
Mean ranks	446.5	396.9	329.9	261.9	149.8

There was a significant difference in CCQ mental score depending on CGI score (Kruskal-Wallis test p-value<0.0001)

Correlation between changes from baseline in CCQ scores and CGI

Correlation between changes in CCQ scores was investigated using Spearman rank correlation coefficient. Results were significant for all CCQ scores.

Table 11 Correlation between decreases from baseline in CCQ scores and CGI

	Spearman coefficient	P-value
Total CCQ score	0.356	<0.0001
Symptom score	0.343	<0.0001
Functional score	0.306	<0.0001
Mental score	0.248	<0.0001

SMOKING HABITS EFFECT

The proportions of smoker in male and female were similar, respectively 52.1% and 53.5% (Fisher P-value= 0.715). Non smokers were significantly older than smokers. Baseline CCQ total score did not differ significantly between smokers and non-smokers.

Table 12 Baseline characteristics according to smoking habits

	Smokers	Non smokers	P-value
Males (%)	59.8	61.2	0.715
Age (mean ± SD)	60.2 ± 12.6	66.7 ± 14.7	<0.0001
Baseline CCQ total score (mean ± SD)	2.86 ± 1.11	2.76 ±1.03	0.256
Mean number of treatment during last 2 weeks	1.98	2.27	0.003
Mean number of treatment prescribed at visit 1	1.24	1.31	0.505

In order to evaluate effect of smoking habits, comparisons were done in terms of improvement and CCQ scores changes.
No significant difference was observed in improvement (assessed as at least 0.47 decrease in CCQ total score) as well at visit 2 than at visit 3 (Fisher exact Visit 2 P-value=0.670 and Visit 3 P-value= 0.937).

Table 13 Comparison of proportion of improved patients between smokers and non-smokers

	Proportion of improved patients (decrease of at least 0.47 in CCQ total score)		
	Smoker	Non smoker	P-value
Visit 2	68.0	68.5	0.937
Visit 3	80.7	81.6	0.670
Overall	79.4	80.6	0.714

Table 14 Comparisons of change in CCQ total score from baseline between smokers and non-smokers

		Mean change in scores		
		Smoker	Non smoker	P-value (Mann-Whitney test)
Visit 2	CCQ total score	0.77	0.84	0.208
	Symptom score	0.94	0.96	0.920
	Functional score	0.74	0.80	0.338
	Mental score	0.52	0.61	0.074
Visit 3	CCQ total score	1.21	1.21	0.642
	Symptom score	1.42	1.36	0.490
	Functional score	1.20	1.16	0.437
	Mental score	0.91	0.93	0.615

SAFETY RESULTS

Due to the non-interventional character of this study, no safety data collection was foreseen in the CRF.