AstraZeneca

DRUG PRODUCT	Symbicort® Turbuhaler®	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Budesonide/formoterol	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-039-CR-0670		
VERSION NO.	1		
STUDY CODE	SD-039-0670		
DATE	06 September, 2002		

FINAL

A placebo-controlled 12-month efficacy study of the fixed combination budesonide/ formoterol compared to budesonide and formoterol as monotherapies in patients with Chronic Obstructive Pulmonary Disease (COPD)

STUDY CENTRE(S)

109 centres from 15 countries participated in this study: Belgium (4 centres), Brazil (8), China (5), France (11), Greece (2), Hungary (8), Malaysia (1), Norway (10) Poland (14), Portugal (3), South Africa (3), Sweden (14), Taiwan (3), Thailand (2) and UK (21).

PUBLICATION (REFERENCE)

Not applicable.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	April 3, 2000	Therapeutic use
- **DATE OF LAST PATIENT COMPLETED**	February 25, 2002	

OBJECTIVES

The primary objective was to evaluate efficacy i.e. to show that the combination of formoterol/budesonide prolongs the time to first severe COPD exacerbations and reduces the decline in lung function compared with placebo and the monoproducts. The primary efficacy variables were the time to first severe exacerbation and FEV_1. Secondary efficacy variables were number of mild exacerbations (number of days with intake of 4 or more puffs of rescue medication (Bricanyl® Turbuhaler® inhaler 0.5 mg terbutaline/dose) above baseline i.e. run-in) and the number of severe exacerbations (intake of a course of oral steroids and/or antibiotics and/or hospitalization due to respiratory symptoms), vital capacity (VC), quality of life (QoL) questionnaires and diary card data (peak expiratory flow (PEF) morning and evening, short-acting β_2-agonist use (rescue medication), use of antitussives

and other COPD medication, COPD symptom scores, night-time awakenings due to COPD symptoms, health care contacts and sick-leave related to COPD symptoms).

The secondary objective was to evaluate safety through adverse event (AE) reporting.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study with a 2-week run-in period followed by a 12-month treatment period.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria

1. Out-patients, men or women ≥ 40 years.
2. A clinical diagnosis of COPD with symptoms for more than 2 years (10).
3. A current or previous smoker with a smoking history equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for one year).
4. $FEV_1 \leq 50\%$ of predicted normal value, pre-bronchodilator.
5. $FEV_1/VC \leq 70\%$, pre-bronchodilator.
6. Documented use of a short-acting inhaled bronchodilator (β_2- agonists or anticholinergics) as rescue medication.
7. A history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 2-12 months before visit 1 (i.e. not within the 4 weeks prior to visit 1).
8. Written informed consent obtained prior to conducting any study-related procedures.

Exclusion criteria

1. A history of asthma and/or seasonal allergic rhinitis before 40 years of age.
2. Patients with significant or unstable ischaemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension as defined by the investigator, or any other relevant cardiovascular disorder as judged by the investigator.
3. Any current respiratory tract disorder other than COPD e.g. bronchiectasis, which is considered by the investigator to be clinically significant.
4. Any other significant disease or disorder (e.g. gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment, current peptic ulcer or history of steroid-induced peptic ulcer) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patients ability to participate in the study.
5. Exacerbation of COPD within 4 weeks prior to Visit 1 and/or during run-in requiring hospitalization, a course of antibiotics and/or a course or increased doses of oral and/or inhaled steroids and/or parenteral treatment and/or nebulized treatment.
6. A requirement for regular use of oxygen therapy

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide/formoterol (Symbicort® Turbuhaler®) 2 x 160/ 4.5 μg b.i.d ; batches: AF 19, AI 25, CA 27 delivered via inhalation.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide (Pulmicort® Turbuhaler) 2 x 200 μg b.i.d.; batches: AK 11, BK 12, formoterol (Oxis® Turbuhaler) 2 x 4.5 μg b.i.d.; batches: AH 18, CC 22, BA 19, BI 20 and placebo (lactose monohydrate); batches: AF 22, AI 23, BL 24, AF 16, AI 18, BL 19, CC 20, all delivered via inhalation.

N.B. The strengths of budesonide and formoterol in Symbicort Turbuhaler and Oxis Turbuhaler are expressed as delivered doses (160/4.5 μg and 4.5 μg, respectively), whereas the strength of budesonide in Pulmicort Turbuhaler is expressed as metered dose (200 μg). Thus, 160 μg delivered dose corresponds to 200 μg metered dose.

DURATION OF TREATMENT

12 months.

MAIN VARIABLE(S):

Efficacy

The primary efficacy variables included time to first severe COPD exacerbation and FEV_1. Secondary efficacy variables comprised number of mild and severe exacerbations, vital capacity (VC), quality of life (QoL) and diary card data (morning and evening peak expiratory flow (PEF), short-acting β_2-agonist use (rescue medication), use of antitussives and other COPD medication, COPD symptom scores, night-time awakenings due to COPD symptoms, health care contacts and sick-leave related to COPD symptoms)

Safety

Safety was evaluated through adverse event (AE) reporting.

STATISTICAL METHODS

An intention to treat type approach was used, where the full analysis set was used in the analysis. All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant. Both primary variables were required to give significance on the 5% level in order to claim treatment effect. The time to first exacerbation was described using a Kaplan-Meier plot and analysed using a log rank test and further described with a Cox proportional hazards model (Cox PHM). The analysis of number of severe exacerbations used a generalized linear model (GLM) with Poisson distribution (Poisson regression), and with treatment and country as factors, and time in study as offset, adjusting for overdispersion. For FEV_1 the endpoint was the average of all available measurements during the treatment period and this was analysed in a multiplicative ANOVA with treatment and country as factors and the Visit 2 value as covariate. Diary card variables were analysed in a similar but additive model.

PATIENTS

Table 1. Treatment group comparison of demographic and disease data at visit 1.

Variable	Symbicort	budesonide	formoterol	placebo	ALL
No. randomized and treated	254	257	255	256	1022
Male/Female	198/56	189/68	191/64	192/64	770/252
Mean **age (yrs)**	64	64	63	65	64
Smoking habits					
Previous smokers	171	157	163	178	669
Occasional smokers	6	9	8	8	31
Habitual smokers	77	91	84	70	322
Packyears	39	39	38	39	39
IGCS at entry (number of patients)	120	132	121	118	491
FEV_1 (L)	0.98	0.99	1.00	0.98	0.99
FEV_1 (% P.N.)	36	36	36	36	36
Reversibility (% P.N.)	6	6	6	6	6
No. analysed for severe exacerbations	254	257	255	256	1022
No. analysed for FEV_1	234	223	213	214	884
No. analysed for safety	254	257	255	256	1022
No. completed	180	155	144	150	629

SUMMARY - CONCLUSION(S)

Efficacy results

Symbicort prolonged the time to first severe exacerbation compared with placebo, budesonide and formoterol (Table 2). The median time to first severe exacerbation was prolonged by 158, 76, 100, days for Symbicort as compared to placebo, budesonide and formoterol, respectively. The risk of getting a severe exacerbation was reduced with Symbicort as compared with placebo, budesonide and formoterol (29%, 23% and 30% lower hazard rates, respectively). Symbicort also reduced the mean number of severe exacerbations as compared to placebo and formoterol by 24% and 26%, respectively. The mean number of severe exacerbations/patient/year was: 1.38 for Symbicort, 1.60 for budesonide, 1.85 for formoterol and 1.80 for placebo. The time to first oral steroid course was prolonged and the number of oral steroid courses were reduced with Symbicort as compared with all the other treatments. Symbicort reduced the mean number of oral steroid courses/per patient/year by 45%, 28% and 30%, compared to placebo, budesonide and formoterol, respectively. Further, there was a lower withdrawal rate for Symbicort than for the other three treatments.

Table 2. Statistical analysis of severe exacerbation data.

Variable	Treatment	Rate ratio[1]	95% Conf.Limits	P-value
Time to first severe exacerbation				
- log-rank test	Symbicort vs. placebo			0.017
	budesonide vs. placebo			0.796
	formoterol vs. placebo			0.490
	Symbicort vs. budesonide			0.037
	Symbicort vs. formoterol			0.002
- hazard rate	Symbicort vs. placebo	0.715	0.562 - 0.910	0.006
	budesonide vs. placebo	0.925	0.733 - 1.168	0.512
	formoterol vs. placebo	1.015	0.805 - 1.279	0.901
	Symbicort vs. budesonide	0.773	0.611 - 0.980	0.033
	Symbicort vs. formoterol	0.705	0.558 - 0.891	0.003
Number of severe exacerbations				
- rate	Symbicort vs. placebo	0.764	0.600 - 0.973	0.029
	budesonide vs. placebo	0.884	0.698 - 1.120	0.308
	formoterol vs. placebo	1.026	0.813 - 1.295	0.828
	Symbicort vs. budesonide	0.864	0.679 - 1.100	0.236
	Symbicort vs. formoterol	0.745	0.587 - 0.945	0.015

[1] Hazard rates from Cox PHM and rates from Poisson regression model.

The geometric mean FEV_1 (L) values at baseline i.e. after run-in (Visit 2) were: Symbicort 1.11, budesonide 1.13, formoterol 1.18, placebo 1.14. Symbicort gave improvements in FEV_1 compared with placebo, budesonide and formoterol by 14%, 11% and 5%, respectively (Table 3).

Table 3. Statistical analysis of FEV_1 data.

Variable	Treatment	mean ratio	95% Conf.Limits	P-value
FEV_1 (L)	Symbicort vs. placebo	114.09	110.45 - 117.84	<0.001
	budesonide vs. placebo	102.47	99.16 - 105.89	0.145
	formoterol vs. placebo	108.28	104.75 - 111.94	<0.001
	Symbicort vs. budesonide	111.34	107.82 - 114.97	<0.001
	Symbicort vs. formoterol	105.36	101.99 - 108.84	0.002

Regarding QoL, Symbicort demonstrated improvements in the total score for the SGRQ compared with placebo, budesonide and formoterol by -7.46, -4.46 and -3.33, respectively.

Advantages for Symbicort were also shown for most of the other secondary variables i.e. VC, COPD symptoms, PEF, SF-36 and rescue medication use. Moreover, Symbicort demonstrated better effects than all three treatments for morning PEF (mean differences between Symbicort and placebo, budesonide and formoterol for morning PEF were 18, 15, and 7 L/min, respectively).

Safety results

The overall incidence of Adverse Events (AEs) was comparable between the treatments and there were no apparent differences between treatments on the level of System Organ Classes (SOCs). The SOC to which most AEs were assigned was Respiratory System Disorders. The most frequently reported AEs were Chronic Obstructive Airways Disease (COAD), with the lowest incidence in the Symbicort group, and Respiratory Infection, which had a comparable incidence in all active treatment groups.

There were 29 deaths in the study, most often related to the respiratory system, with the lowest number in the Symbicort and placebo groups, followed by budesonide and formoterol.

The lowest incidence of SAEs other than death was found in the Symbicort and placebo groups. Events related to Chronic Obstructive Airways Disease were the most common SAEs, with the lowest incidence in the Symbicort and budesonide groups followed by placebo and formoterol.

The frequency of discontinuations due to AEs was lowest during Symbicort treatment, due to fewer reports of Disease Under Study (DUS) deterioration in this group.

In conclusion, Symbicort was well tolerated and showed a safety profile that compares well with that of budesonide, formoterol and placebo.