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-0629		
VERSION NO.	01		
STUDY CODE	SD-039-0629		
DATE	06 Dec, 2001		

FINAL

A placebo-controlled 12 month efficacy study of the fixed combination budesonide/ formoterol compared with budesonide and formoterol as monotherapies in patients with chronic obstructive pulmonary disease (COPD)

STUDY CENTRE(S)

Eighty-nine (89) centres from eleven countries participated in this study: Argentina (8 centres), Brazil (5), Denmark (10), Finland (5), Great Britain (14), Italy (6), Mexico (6), Poland (15), Portugal (7), South Africa (6) and Spain (7).

PUBLICATION (REFERENCE)

Not applicable.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	March 23, 1999	Therapeutic use
- **DATE OF LAST PATIENT COMPLETED**	July 16, 2001	

OBJECTIVES

The primary objective was to evaluate efficacy i.e. to show that the combination of formoterol/budesonide reduced the number of exacerbations of COPD and improved lung function. The primary efficacy variables were the number of severe exacerbations (intake of a course of oral steroids and/or antibiotics and/or hospitalization due to respiratory symptoms) and FEV_1. Secondary efficacy variables comprised 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).

The secondary objective was to evaluate safety through adverse event (AE) reporting, electrocardiography (ECG), haematology and clinical chemistry.

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 (9).
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. Total symptom score of 2 or more per day during at least 7 days of the run-in period or during at least half of the run-in period if it is longer than 14 days.
7. Documented use of a short-acting inhaled bronchodilator (β_2- agonists or anticholinergics) as rescue medication.
8. A history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 2-12 months before visit 1.
9. 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, arhythmia, cardiomyopathy, heart failure, uncontrolled hypertension as defined by the investigator, or any other relevant cardiovascular disorder as judged by the investigator.
3. Patients using beta-blocking agents.
4. Any current respiratory tract disorder other than COPD e.g. bronchiectasis, which is considered by the investigator to be clinically significant.
5. Any other significant disease or disorder (e.g. current peptic ulcer or history of steroid-induced peptic ulcer) including laboratory tests taken at Visit 1 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 patient's ability to participate in the study.
6. 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.
7. A requirement for regular use of oxygen therapy

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide/formoterol (Symbicort® Turbuhaler®); batches: AF 19, AI 25, ZG 15, ZM 16; 2 x 160/4.5 μg b.i.d., delivered via inhalation.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Budesonide (Pulmicort® Turbuhaler); batches: AA 1072, AD 1102, AI 1144, BC 1175, ZF 1014; 2 x 200 μg b.i.d., formoterol (Oxis® Turbuhaler); batches: AH 18, ZL 17; 2 x 4.5 μg b.i.d. and placebo (lactose monohydrate); batches: AD 32, AI 33, ZD 29, ZF 30, AF 22, AI 23, ZF 15, ZL 19, AF 16, AI 18, ZM 14, 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 the number of severe exacerbations of COPD (intake of a course of oral steroids and/or antibiotics and/or hospitalization due to respiratory symptoms) and FEV_1. Secondary efficacy variables comprised 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, electrocardiography (ECG), haematology and clinical chemistry.

STATISTICAL METHODS

An intention to treat type approach was used, which means that 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. Since there was two primary variables in this study the significance level was adjusted such that both primary variables should give significance on the 5% level in order to claim treatment effect. In the analysis of severe exacerbations a generalized linear model (GLM) was used with Poisson distribution, 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 analyzed in a multiplicative ANOVA with factors treatment and country and the Visit 2 value as covariate. Diary card variables were analyzed in a similar but additive model.

PATIENTS

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

		Symbicort	budesonide	formoterol	placebo	Total
No. planned		150	150	150	150	600
No. randomized and treated		208	198	201	205	812
	Males/Females	159/49	158/40	153/48	171/34	641/171
	Mean age	64	64	63	65	64
Smoking habits						
	Previous smoker	145	127	125	135	532
	Occasional smoker	6	9	11	10	36
	Habitual smoker	57	62	65	60	244
Packyears		44	44	45	45	44
FEV_1 (L)		0.96	1.01	1.00	0.98	0.99
FEV_1 (% P.N.)		36	37	36	36	36
Reversibility (% P.N.)		6	5	6	5	6
No. analysed for severe exacerbations		204	192	199	201	796
No. analysed for FEV_1		201	182	191	185	759
No. analysed for safety		208	198	201	205	812
No. completed		149	136	137	115	537

SUMMARY

- EFFICACY RESULTS

Symbicort reduced the number of severe exacerbations compared with placebo and formoterol by 24% and 23%, respectively (Table 2). The mean rates (exacerbations/patient/year) were; Symbicort 1.42, budesonide 1.59, formoterol 1.84, placebo 1.87.

Table 2. Statistical analysis of severe exacerbation data.

Variable	Treatment	Rate ratio	95% Conf.Limits	P-value
Severe exacerbations				
	Symbicort vs. placebo	0.758	0.586 - 0.981	0.035
	budesonide vs. placebo	0.852	0.659 - 1.103	0.224
	formoterol vs. placebo	0.984	0.770 - 1.257	0.895
	Symbicort vs. budesonide	0.889	0.682 - 1.159	0.385
	Symbicort vs. formoterol	0.771	0.599 - 0.992	0.043

Symbicort also showed improvement in lung function compared with placebo and budesonide by 15% and 9% increments in FEV_1, respectively (Table 3). The geometric mean FEV_1(L) values at baseline (Visit2) were; Symbicort 0.96, budesonide 0.98, formoterol 1.00, placebo 0.98.

Table 3. Statistical analysis of FEV_1 data.

Variable	Treatment	mean ratio	95% Conf.Limits	P-value
FEV_1 (L)	Symbicort vs. placebo	114.94	110.96 - 119.06	*<0.001*
	budesonide vs. placebo	105.27	101.54 - 109.14	0.005
	formoterol vs. placebo	113.52	109.54 - 117.65	*<0.001*
	Symbicort vs. budesonide	109.18	105.38 - 113.12	*<0.001*
	Symbicort vs. formoterol	101.25	97.76 - 104.86	0.487

Advantages for Symbicort versus placebo and budesonide were shown for a wide range of secondary variables i.e. VC, COPD symptoms, PEF, QoL and rescue medication use. Moreover, Symbicort demonstrated better effects than formoterol for morning and evening PEF (mean differences between Symbicort and formoterol for morning PEF and evening PEF were 11.6 and 11.3 L/min, respectively).

All active treatments demonstrated lower withdrawal rates compared with placebo.

Compared with placebo, both formoterol and budesonide improved FEV_1, VC, PEF and use of rescue medication, while formoterol also improved the COPD symptom variables.

- **SAFETY RESULTS**

The safety of Symbicort and its monocomponents has been extensively studied in asthma and in COPD patients and the present study does not raise any new safety concerns.