AstraZeneca

Drug product:	Symbicort pMDI	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	budesonide/formoterol		
Document No.:	SD-039-CR-0715/A	Referring to part of the dossier	
Edition No.:	1		
Study code:	SD-039-0715		
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An open, parallel-group, randomised, multi-centre phase III study to compare the long-term (52-week) safety of Symbicort® (budesonide/ formoterol) pMDI 160/4.5 μg 2 actuations b.i.d. with that of Symbicort Turbuhaler® 160/4.5 μg 2 inhalations b.i.d. in adults and adolescents with asthma - report of the first 26 weeks

Study centres

This study was conducted in Australia (14 sites), France (17 sites), the Philippines (1 site), Slovakia (18 sites), South Africa (9 sites), and Thailand (1 site).

Publications

None at the time of writing this report.

Clinical Study Report Synopsis Document No. SD-039-CR-0715/A Edition No. 1 Study code SD-039-0715	(For national authority use only)

Study dates:

First subject enrolled 18 March, 2002

Last subject completed 10 May, 2003

Phase of Development

Therapeutic confirmatory (III)

Objectives

The primary objective was to compare the long-term safety profile of Symbicort® pMDI (pressurised metered dose inhaler) 160/4.5 µg 2 actuations b.i.d. with that of Symbicort Turbuhaler® 160/4.5 µg 2 inhalations b.i.d. over a 52-week treatment period by assessment of Adverse Events (AEs), physical examination, haematology, clinical chemistry, urinalysis, U-cortisol, P-cortisol, pulse, blood pressure, and electrocardiogram (ECG). No single variable was considered as primary.

The secondary objective was to compare the efficacy of Symbicort pMDI 160/4,5 µg 2 actuations b.i.d. with that of Symbicort Turbuhaler 160/4.5 µg 2 inhalations b.i.d. by assessment of FEV_1, FVC, and time to first severe asthma exacerbation.

Study design

This was a multi-centre and multi-national study, with an open, randomised and parallel-group design, using an active control.

Target subject population and sample size

Out-patients of either sex (≥12 years), with asthma according to the American Thoracic Society (ATS) definition, diagnosed at least 6 months prior to Visit 1. The patients should have an FEV_1 value of ≥50% of predicted normal, and a reversibility of ≥12% in FEV_1 postbronchodilator at Visit 1 or as a historical value within 6 months prior to Visit 1. Daily use of inhaled glucocorticosteroids (GCS) with need for additional therapy with inhaled short-acting β_2-agonist (SABA) or long-acting β_2-agonist (LABA), including inhaled combination products containing GCS and LABA, for ≥ 3 months prior to Visit 1. During 30 days prior to Visit 1, the daily dose of inhaled GCS should have been constant and within the range of 400 - 1200 µg (any brand).

The patient should not have suffered from any respiratory infection affecting the asthma or have taken oral, rectal, nasal, or parenteral GCS within 30 days prior to Visit 1.

Investigational product and comparator: dosage, mode of administration, and batch numbers

	Investigational product	Comparator
Product	Symbicort pMDI	Symbicort Turbuhaler
Dosage	160/4.5 µg 2 actuations b.i.d.	160/4.5 µg 2 inhalations b.i.d.
Mode of administration	Inhalation	Inhalation
Batch numbers and expiry dates	P6039 - March 07, 2003 P6039B - March 07, 2003 P6040 - August 21, 2003 P6041- February 27, 2003 P6041A - February 27, 2003 P6502A - February 12, 2004	P6386 - April 30, 2003 P6499 - December 31, 2003

Duration of treatment

As a base for this report, the subjects have been treated for the first 26 weeks out of the total 52 weeks of treatment.

Criteria for evaluation (main variables)

Safety

Cumulative incidence, severity and type of AEs (including changes identified by physical examination), and changes in: haematology, clinical chemistry, urinalysis, P-cortisol, U-cortisol, pulse, blood pressure, and ECG from baseline to the end of the first 26 weeks of treatment. No single variable was considered as primary.

Efficacy

Change from Visit 1 to the average of the first 26-week treatment period (Visit 2 to Visit 4) for FEV_1, FVC, and time to first severe asthma exacerbation.

Statistical methods

No single safety variable was considered as the primary variable. With the exceptions of P-cortisol and U-cortisol, the results are described descriptively, without any formal hypothesis testing. Instead, an AstraZeneca expert has performed a qualitative analysis.

Abnormalities in laboratory variables (haematology, clinical chemistry, and urine), pulse, blood-pressure, and ECG have been identified and analysed primarily

by means of descriptive statistics. The P- and U-cortisol were analysed in a multiplicative analysis of variance (ANOVA).

The analyses of the efficacy variables are based on the full analysis set. The change from Visit 1 to the average of the treatment period (Visits 2 to 4) has been analysed in an ANOVA model with treatment and country as fixed factors, and the baseline value (Visit 1) as a covariate. For time to first severe asthma exacerbation, a logrank test was performed and further analyses were made in a Cox regression model.

The discontinuation rate has been compared between treatments using descriptive statistics.

All hypothesis testing are done using two-sided alternatives, with p-values $< 5\%$ considered statistically significant.

Subject population

The randomisation was skewed (2:1) and the aim was to have 300 evaluable subjects in the group treated with Symbicort pMDI and 150 subjects in the group treated with Symbicort Turbuhaler. To achieve this, a total of 650 patients were planned to be randomised.

Subject flow

	Symbicort pMDI	Symbicort Turbuhaler	All
Enrolled subjects			817
Not Randomised			144
- Eligibility criteria not fulfilled			117
- AE			1
- Lost to follow-up			3
- Other reason			23
Randomised	446	227	673
Discontinued	39	16	55
- Eligibility criteria not fulfilled	13	4	17
- AE	10	2	12
- Development of study-specific discontinuation criteria	3	1	4
- Lost to follow-up	2	3	5
- Other reason	11	6	17
Completed	407	211	618

Safety results

No clinically important differences between the two treatment groups were observed with regard to the nature, incidence, or severity of AEs.

The incidence of asthma aggravated was similar between the two treatment groups. The number of subjects reporting SAEs were comparable between the two treatment groups. Only 12 subjects discontinued the study due to AE.

There were no clinically important differences between the treatment groups regarding the incidence of reports of undesirable class effects either for β_2-agonists or inhaled GCSs, although reports of hoarseness and oral candidiasis were slightly more frequent in the Symbicort pMDI group compared with the Symbicort Turbuhaler group.

A statistically significant difference was seen between Symbicort pMDI and Symbicort Turbuhaler regarding P-cortisol. This difference, with the adjustment for baseline, implies higher values in the Symbicort pMDI group. Similarly, there was a statistically significant difference in P-potassium, which compared to baseline, indicated higher values in the Symbicort pMDI group .

No difference was detected for U-cortisol.

There was no statistically significant difference found between the two treatment groups regarding vital signs and ECG.

The two treatments were well tolerated and no new safety concerns were identified with the Symbicort pMDI formulation.

Efficacy results

This study could not detect any difference between Symbicort pMDI and Symbicort Turbuhaler for the efficacy parameters FEV_1, FVC, or time to first severe asthma exacerbation.