AstraZeneca

Clinical Study Report Synopsis

Drug Substance	budesonide/formoterol
Study Code	D5897C00003
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A 6-week, phase III, double-blind, randomized, multi-centre, parallel-group study evaluating the efficacy and safety of 2 actuations Symbicort® (budesonide/formoterol) pMDI 40/2.25 µg twice daily compared with 1 inhalation Symbicort Turbuhaler® 80/4.5 µg twice daily and 1 inhalation Pulmicort® (budesonide) Turbuhaler® 100 µg twice daily in adult and adolescent asthmatics

Study dates: First patient enrolled: 14 September 2007
Last patient completed: 2 April 2008

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centres

The study was conducted in Poland (22 centres), Hungary (17 centres), Czech Republic (13 centres) and Bulgaria (11 centres).

The first patient was enrolled on 14 September 2007 and the last patient completed on 2 April 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to show that Symbicort pressurised metered dose inhaler (pMDI) 40/2.25 μg 2 actuations twice daily (bid) is more efficacious than Pulmicort Turbuhaler 100 μg 1 inhalation bid over a 6-week treatment period in adolescents and adults with asthma by evaluation of change in morning peak expiratory flow (PEF) from baseline to the treatment period as the primary outcome variable.

Furthermore, Symbicort pMDI 40/2.25 μg 2 actuations bid was also compared with Pulmicort Turbuhaler 100 μg 1 inhalation bid with regard to effect on the secondary outcome variables.

The secondary objectives of the study were:

1. to compare the efficacy of Symbicort pMDI 40/2.25 μg 2 actuations bid with that of Symbicort Turbuhaler 80/4.5 μg 1 inhalation bid over a 6-week treatment period in adolescents and adults with asthma by assessment of the same primary and secondary variables as for the primary objective

2. to investigate the safety profile of Symbicort pMDI 40/2.25 μg 2 actuations bid, Symbicort Turbuhaler 80/4.5 μg 1 inhalation bid and Pulmicort Turbuhaler 100 μg 1 inhalation bid over a 6-week treatment period in adolescents and adults with mild persistent asthma

Study design

This was a phase III, multinational, multicentre study with a randomised, double-dummy, active-controlled, parallel-group design, where the efficacy and safety of Symbicort pMDI 40/2.25 μg 2 actuations bid were compared with those of Pulmicort Turbuhaler 100 μg 1 inhalation bid and Symbicort Turbuhaler 80/4.5 μg 1 inhalation bid.

Target population and sample size

The study included patients with persistent asthma, aged ≥12 years, not adequately controlled on inhaled glucocorticosteriods (GCS) alone, and with pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥50% and ≤90% of predicted normal. Previous maintenance treatment with inhaled GCS and demonstrated symptoms during run-in were required.

A sample size of 200 patients in each group would give 90% power to detect a true difference in mean change in morning PEF of 13 L/min between Symbicort pMDI 40/2.25 µg 2 actuations bid and Pulmicort Turbuhaler 100 µg bid, assuming a standard deviation of 40 L/min. With 200 patients in each treatment group, there was a 90% probability that the 95% confidence interval for the difference between Symbicort treatments regarding change in morning PEF was contained within the equivalence limits ±15 L/min, given that the true mean difference was less than 1.5 L/min.

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

Investigational product:
Symbicort pMDI (budesonide/formoterol). 3 batches (07-011322AZ, 07-011328AZ, 07-011901AZ) were used in this study.
Dosage: 40/2.25 µg per actuations (delivered dose), 2 actuations bid by inhalation
The propellant used in Symbicort pMDI is the hydrofluoroalkane 227.

Comparators:
Pulmicort Turbuhaler (budesonide), batch 07-011167AZ was used in this study.
Dosage: 100 µg/inhalation (metered dose), 1 inhalation bid

Symbicort Turbuhaler (budesonide/formoterol), batch 07-011169AZ was used in this study.
Dosage: 80/4.5 µg per inhalation (delivered dose), 1 inhalation bid

Other medication:
Bricanyl® Turbuhaler (terbutaline sulphate) was used for reversibility test and as rescue medication. 4 batches (3520335B00, 3520335B01, 3520335B02, 3520335B03) were used in this study.
Dosage: 0.5 mg/inhalation (metered dose), 2 inhalations before reversibility measurement

Duration of treatment

The patients inhaled their regular GCS during the 2-week run-in period, and then started the 6-week treatment period.

Criteria for evaluation - efficacy (main variables)

Primary variable:

- The change in morning PEF from baseline (mean of the last 10 days of the run-in period) to the treatment period (mean of all available data during the 6-week treatment period).

Secondary variables:

- The change from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6-week treatment period) for the diary variables:

- Evening PEF
- Asthma symptom score, day, night and total
- Percentage of nights with awakening(s) due to asthma symptoms
- Use of rescue medication, day, night and total
- Percentage of symptom-free days (a night and day with no asthma symptoms and no awakenings due to asthma symptoms; main asthma symptom variable)
- Percentage of asthma control days (a night and day with no asthma symptoms, no use of rescue medication, and no awakenings due to asthma symptoms)
- Percentage of rescue free days

- The change in FEV_1 from baseline (Visit 3) to the mean of the treatment period (Visit 4 and Visit 5).

Criteria for evaluation - safety (main variables)

Cumulative incidence, severity and type of adverse events, (AEs, including changes identified by physical examination) over the 6-week treatment period.

Statistical methods

For the primary objective, p-values as well as confidence intervals for the treatment difference were obtained under an analysis of variance (ANOVA) model with treatment and country as fixed factors, and the run-in period average as a covariate. Change in average value from run-in to the treatment period for other diary variables, as well as for FEV_1 with the Visit 3 value as the covariate, was analysed in the same way as for morning PEF. Treatment differences were estimated from the model and 95% confidence limits were calculated.

The secondary efficacy objective was mainly evaluated on a descriptive level, and was addressed using confidence intervals for the difference. Therapeutic equivalence between the 2 Symbicort treatments was considered to be established if the 95% confidence level for the treatment difference in morning PEF was contained within the equivalence limits ±15 L/min. A stability analysis (per protocol), excluding patients who were randomised even though they were not eligible for randomisation, was performed as well.

All hypothesis testing was done using two-sided alternative hypotheses. P-values <0.05 were considered statistically significant.

Subject population

Table S1 Treatment group comparison of demographic and disease data

		Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
Sex	Male	101 (40%)	112 (46%)	104 (42%)	**317 (43%)**
	Female	152 (60%)	131 (54%)	142 (58%)	**425 (57%)**
Age (years)	Mean	41.2	39.3	41.4	**40.7**
	Range	12-75	12-78	12-76	**12-78**
Time since diagnosis (years)	Median	7.1	7.8	6.5	**7**
	Range	1-44	1-40	1-56	**1-56**
Inhaled GCS at entry (µg)	Mean	386.3	385.4	390.9	**387.5**
	Range	160-500	160-500	160-500	**160-500**
Use of LABA at entry	No	98 (39%)	96 (40%)	96 (39%)	**290 (39%)**
	Yes	155 (61%)	147 (60%)	150 (61%)	**452 (61%)**
FEV_1 (L)	Mean	2.267	2.360	2.295	**2.307**
	Range	0.99-4.19	1.10-4.32	0.99-4.03	**0.99-4.32**
FEV_1 (% PN)	Mean	73.0	73.9	73.4	**73.5**
	Range	50-90	50-90	50-90	**50-90**
Reversibility (%)	Mean	24.8	23.7	24.4	**24.3**
	Range	12-91	12-84	7-88	**7-91**
Morning PEF (L/min)	Mean	347.12	351.26	346.80	**348.37**
	Range	149.1-736.4	156.0-643.6	177.3-630.0	**149.1-736.4**
Evening PEF (L/min)	Mean	359.60	364.48	359.56	**361.19**
	Range	143.0-776.0	156.0-653.3	174.0-620.0	**143.0-776.0**
Total rescue use (No. of inhalations)	Mean	1.557	1.566	1.664	**1.595**
	Range	0.00-7.21	0.00-16.00	0.00-9.25	**0.00-16.00**
Symptom score (scale: 0-6)	Mean	2.174	2.181	2.167	**2.174**
	Range	0.10-4.76	0.46-4.87	0.45-5.80	**0.10-5.80**
Symptom free days (%)	Mean	6.4	5.9	7.1	**6.4**
	Range	0-80	0-60	0-60	**0-80**
Rescue free days (%)	Mean	35.0	33.7	31.8	**33.5**
	Range	0-100	0-100	0-100	**0-100**

Table S1 Treatment group comparison of demographic and disease data

		Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
Asthma control days (%)	Mean	6.1	5.7	6.8	**6.2**
	Range	0-80	0-60	0-60	**0-80**
Awakenings (%)	Mean	37.9	38.6	39.8	**38.8**
	Range	0-100	0-100	0-100	**0-100**

For categorical data, frequencies are given, for other data mean values and ranges are given.
LABA Long-acting β_2-agonist; mPEF Morning peak expiratory flow; PN Predicted normal
a No diary data were available for the treatment period for 1 patient who discontinued the study 6 days after randomisation. Thus, data from 741 patients (245 for Symbicort Turbuhaler) were included in the statistical analysis of the primary variable, morning PEF.

All patients were white. During the last 10 days of run-in, all patients had asthma symptoms, 83 (11%) patients did not use any rescue medication, and 182 (25%) patients did not experience any night-time awakenings due to asthma. On average, the patients took 97% of their maintenance medication.

Demography and baseline characteristics were representative for the population that was intended to be included in the study, and the study included a sufficient number of patients to fulfil the aim in the power calculation. The treatment groups were well balanced and comparable at baseline.

Summary of efficacy results

For the primary variable, morning PEF, Symbicort pMDI 40/2.25 µg 2 actuations bid was shown to be superior to Pulmicort Turbuhaler 100 µg 1 inhalation bid (see Table S2 and Table S3). Most secondary variables supported this superiority, ie, Symbicort pMDI increased evening PEF, reduced the total daily asthma symptoms, the night-time asthma symptoms, the awakenings due to asthma symptoms, and increased the number of rescue free days and decreased the daily use of rescue medication compared to Pulmicort Turbuhaler. No differences were detected in FEV_1, daytime symptoms, or in the composite scores symptom free days and asthma control days, which are both based on daytime symptoms.

Therapeutic equivalence between Symbicort pMDI 40/2.25 µg 2 actuations bid and Symbicort Turbuhaler 80/4.5 µg 1 inhalation bid was confirmed according to the pre-specified equivalence limits for morning PEF (see Table S2 and Table S3). The stability analysis of morning PEF, which excluded patients violating inclusion/exclusion criteria, confirmed therapeutic equivalence. Moreover, no statistically significant difference between the 2 Symbicort formulations was demonstrated for any outcome variable in the study.

Table S2 Period means and ranges morning PEF (L/min)

Treatment	n	Run-in period Mean	(Range)	Treatment period Mean	(Range)	Adjusted[a] mean change
Symbicort pMDI	253	347	(149, 736)	360	(145, 797)	12.2
Pulmicort Turbuhaler	243	351	(156, 644)	356	(147, 623)	4.15
Symbicort Turbuhaler	245	347	(177, 630)	360	(190, 672)	13.1

[a] ANOVA adjusted mean change from baseline

Table S3 Treatment comparisons for morning PEF (L/min)

Treatment	Mean difference	95% confidence interval	p-value
Symbicort pMDI vs. Pulmicort Turbuhaler	8.07	(3.26, 12.9)	0.001
Symbicort pMDI vs. Symbicort Turbuhaler	-0.921	(-5.73, 3.88)	0.707
Symbicort Turbuhaler vs. Pulmicort Turbuhaler	8.99	(4.14, 13.8)	<0.001

Summary of safety results

No deaths occurred in the study and overall, the incidence of AEs, serious adverse events and AEs that led to discontinuation of investigational product was low (Table S4). There were no clinically relevant differences in the pattern of reported AEs between Symbicort pMDI 40/2.25 µg 2 actuations bid, Symbicort Turbuhaler 80/4.5 µg 1 inhalation bid and Pulmicort Turbuhaler 100 µg 1 inhalation bid (Table S5). Overall, the treatments were well tolerated and no safety concerns were identified.

Table S4 Number (%) of patients who had an adverse event in any category

Number (%) of patients who had an adverse event in each category[a]	Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
Any adverse events	38 (15%)	31 (13%)	30 (12%)	**99 (13%)**
Serious adverse events (SAEs)				
SAEs leading to death	0	0	0	**0**
SAEs other than death	0	1 (<0.5%)	1 (<0.5%)	**2 (<0.5%)**
DAEs[b]	3 (1%)	4 (2%)	2 (1%)	**9 (1%)**
Other significant adverse events	0	0	0	**0**

[a] Patients with multiple events in the same category are counted once in each category.
[b] Discontinuation of investigational product due to AEs.

Table S5 The most frequently reported adverse events by preferred term

Preferred term	Symbicort pMDI n=253	Pulmicort Turbuhaler n=243	Symbicort Turbuhaler n=246	All n=742
bronchitis	6 (2%)	4 (2%)	5 (2%)	**15 (2%)**
pharyngitis	6 (2%)	3 (1%)	5 (2%)	**14 (2%)**
nasopharyngitis	4 (2%)	2 (1%)	6 (2%)	**12 (2%)**
viral infection	5 (2%)	3 (1%)	1 (<0.5%)	**9 (1%)**
asthma	0	4 (2%)	2 (1%)	**6 (1%)**
viral upper respiratory tract infection	2 (1%)	1 (<0.5%)	2 (1%)	**5 (1%)**

Number (%) of patients that reported AEs, sorted by decreasing order of frequency as summarised over all treatment groups. Adverse events occurring in at least 1% of the patients are included.