AstraZeneca

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|---|---|---|---|
| Drug Product | Symbicort | **Synopsis** | (For national authority use only) |
| Drug substance(s) | Budesonide/formoterol | | |
| Document No. | SD-039-CR-0667 | Referring to part of the dossier | |
| Edition No. | 1 | | |
| Study Code | SD-039-0667 | | |
| Date | 22 November, 2002 | | |

# Efficacy and Safety of Symbicort® Turbuhaler® as Single Therapy in Patients with Mild to Moderate Asthma - STEAM

## Study centre(s)

This was a multicentre study with 77 centres participating from the following countries: Argentina (5 centres), Brazil (7 centres), China (4 centres), Denmark (15 centres), Indonesia (6 centres), Norway (10 centres), The Philippines (10 centres), Spain (9 centres), and Sweden (11 centres).

## Publications

None at the time of finalising this report.

## Study dates

**Study Dates**

First subject entered: 16 January, 2001
Last subject completed: 18 April, 2002

## Objectives

The **primary objective** of this study was to compare the clinical efficacy of Symbicort® 2x80/4.5 µg OD plus Symbicort 80/4.5 µg as-needed with that of Pulmicort® 2x160 µg OD plus Bricanyl Turbuhaler® 0.4 mg as-needed.

The **secondary objective** of the study was safety, i.e. to investigate the safety of Symbicort Turbuhaler 80/4.5 µg/inhalation, 2 inhalations once daily plus Symbicort Turbuhaler 80/4.5 µg/inhalation as-needed, compared with Pulmicort Turbuhaler 160 µg/inhalation, 2 inhalations once daily plus Bricanyl Turbuhaler 0.4 mg/dose as-needed. The safety evaluation took into account several safety variables with no particular variable chosen as the main one.

## Study design

The study was double-blind, randomized, active-controlled, multi-centre and multi-national with a parallel group design comparing the efficacy and safety of Symbicort 80/4.5 µg/inhalation, 2 inhalations once daily plus Symbicort 80/4.5 µg/inhalation as-needed (Symbicort single-inhaler therapy, SiT) with that of Pulmicort 160 µg/inhalation, 2 inhalations once daily plus Bricanyl 0.4 mg/dose as-needed when given to adults and adolescents (12-80 years) for a period of 6 months in the treatment of asthma.

## Target subject population and sample size

Male and female subjects, 12 to 80 years with asthma, previously treated with 200-500 µg per day of inhaled glucocorticosteroids (IGCS). They had to have a forced expiratory volume in one second ($FEV_1$) of 60-100% of predicted normal at Visit 1 and a reversibility in $FEV_1$ from baseline of at least 12% at Visit 1 or 2, or a peak expiratory flow (PEF) variability of at least 12% on at least 3 out of the last 10 days of the run-in. During the last 10 days of the run-in period the subjects also had to have used at least 7 inhalations of the as-needed medication.

A total of 250 evaluable subjects with asthma derived from an estimated 300 recruited subjects were required per treatment group to detect a true difference in means of morning peak expiratory flow (mPEF) of 13 L/min with 90% power assuming that the common standard deviation was 45 L/min. This assumed a significance level of 5% and a two-sided alternative hypothesis.

## Investigational products: dosage, mode of administration and batch numbers

Symbicort 80/4.5 µg/dose, 2 inhalations once daily + Symbicort 80/4.5 µg/dose as-needed or Pulmicort 160 µg/dose, 2 inhalation once daily + Bricanyl Turbuhaler® 0.4 mg/dose as-needed. Doses were given in two inhalers identical between treatments, i.e. inhalers for maintenance (Symbicort or Pulmicort) were identical and inhalers for as-needed use (Symbicort or Bricanyl) were identical. Batch numbers were: Symbicort BF14, BF15, BH17, CC18; Pulmicort BH12; Bricanyl BL26, BG21-24, CC27.

The treatment arm with Symbicort, both as maintenance and as-needed, will be referred to as Symbicort SiT and the treatment arm with Pulmicort as maintenance and Bricanyl as-needed will be referred to as Pulmicort.

**Duration of treatment**

The study included a 2-week run-in period followed by a 6-month treatment period.

**Criteria for evaluation (main variables)**

**Efficacy**

The primary efficacy variable was mPEF.

Secondary efficacy variables were $FEV_1$, evening PEF (ePEF), inhalations of as-needed medication, nights with awakening(s) due to asthma symptoms, asthma symptom scores, asthma-control days, mild asthma exacerbation days and severe asthma exacerbations. To increase the understanding of the different treatments, as-needed-free days and symptom-free days were added as variables to the statistical analyses. This was done before unblinding of study data.

**Safety**

The following safety variables were to be assessed in all subjects: physical examination, pulse, blood pressure and adverse events (AEs).

In a planned subgroup of 200 subjects (100 from each treatment group), the following additional safety variables were to be analysed: clinical chemistry, S-potassium, haematology, U-albumin, U-glucose, morning P-cortisol and ECG.

**Statistical methods**

The full analysis set, as defined in ICH guideline E9, was used in all efficacy and safety analyses.

The change in average mPEF from the run-in to the treatment period was analysed using an analysis of variance model with treatment and country as fixed factors and the run-in period average as a covariate. The treatment difference was estimated from the model and 95% confidence limits were calculated.

Change in average value from the run-in to the treatment period for ePEF, inhalations of as-needed medication, nights with awakening(s) due to asthma symptoms, asthma symptom scores, asthma-control days, symptom-free days and as-needed-free days were analysed in the same way as for mPEF.

Time to both first severe and first mild asthma exacerbation was described using Kaplan-Meier plots and the treatment groups were compared using a log-rank test. Additional descriptions were made using a Cox proportional hazards model with treatment as factor.

The safety variables were analysed by means of descriptive statistics and qualitative analysis.

## Subject population

**Table S1. Treatment group comparison of demographic and disease data. For categorical data, frequencies are given, for other data mean values and ranges.**

| | | Symbicort SiT | Pulmicort | ALL |
|---|---|---|---|---|
| **Population** | | | | |
| N randomized | | 355 | 342 | 697 |
| **Demographic characteristics** | | | | |
| Sex (N) | Male | 147 | 123 | 270 |
| | Female | 208 | 219 | 427 |
| Age (yrs) | Mean | 38 | 38 | 38 |
| | Range | (12-79) | (11-78) | (11-79) |
| Race | Caucasian | 188 | 173 | 361 |
| | Black | 1 | 2 | 3 |
| | Oriental | 165 | 167 | 332 |
| | Other | 1 | 0 | 1 |
| Time since diagnosis (yrs) | Median | 10 | 10 | 10 |
| | Range | (1-70) | (1-61) | (1-70) |
| IGCS at entry (µg/day) | Mean | 353 | 343 | 348 |
| | Range | (200-500) | (200-500) | (200-500) |
| **Baseline characteristics** | | | | |
| $FEV_1$ (L) | Mean | 2.30 | 2.25 | 2.28 |
| | Range | (1.00-4.25) | (1.09-4.68) | (1.00-4.68) |
| $FEV_1$ (% P.N.) | Mean | 75 | 75 | 75 |
| | Range | (51-123) | (52-109) | (51-123) |
| Mean total symptom score (0-6) | Mean | 1.2 | 1.3 | 1.3 |
| | Range | (0.0-4.1) | (0.0-4.7) | (0.0-4.7) |
| Symptom-free days (%) | Mean | 30 | 26 | 28 |
| | Range | (0-100) | (0-100) | (0-100) |
| Asthma-control days (%) | Mean | 18 | 17 | 18 |
| | Range | (0-100) | (0-90) | (0-100) |

**(Continued)**

Table S1. Treatment group comparison of demographic and disease data. For categorical data, frequencies are given, for other data mean values and ranges.

| | | Symbicort SiT | Pulmicort | ALL |
|---|---|---|---|---|
| **Disposition** | | | | |
| N of subjects who | Completed | 327 | 311 | 638 |
| | Ciscontinued | 27 | 31 | 58 |
| N analyzed for safety | | 354 | 342 | 696 |
| N analyzed for efficacy (ITT) | | 354 | 342 | 696 |

• $FEV_1$ forced expiratory volume in one second; IGCS inhaled glucocorticosteroids; ITT intention to treat, i.e. full analysis set; N number; P.N. predicted normal; SiT single-inhaler therapy

The subjects recruited in the study were patients with mild to moderate asthma, i.e. the population intended according to the study protocol. The treatment groups were generally well balanced in demographic and baseline characteristics. Discontinuations of study treatment were relatively rare in all treatment groups.

## Efficacy results

Symbicort SiT (Symbicort 80/4.5 µg, 2 inhalations once daily plus as-needed) was shown to be more efficacious than conventional treatment with Pulmicort 160 µg, 2 inhalations once daily plus Bricanyl as-needed, as demonstrated by an effect on the primary variable, mPEF, and all secondary variables, with the exception of nights with awakenings due to asthma symptoms (not statistically significant, but numerical difference in favour of Symbicort SiT).

Asthma control was improved with Symbicort SiT, as shown by reduction in severe and mild exacerbations and improvements in all symptom-related variables. During a severe exacerbation both asthma symptoms and use of as-needed medication were reduced in the Symbicort SiT group compared to Pulmicort.

Overall steroid load was reduced with Symbicort SiT, as shown by a reduction in both inhaled and oral GCS use. A summary of the results are shown in table S2.

## Table S2. Summary of result for efficacy variables

| Variable | | Treatment comparison | Mean difference | 95% Conf.Limits | P-value |
|---|---|---|---|---|---|
| Primary | | | | | |
| | **mPEF (L/min)** | Symbicort SiT vs. Pulmicort | 25.0 | (19.4, 30.6) | <0.001 |
| Secondary | | | | | |
| | **ePEF (L/min)** | Symbicort SiT vs. Pulmicort | 18.8 | (13.3, 24.3) | <0.001 |
| | **Asthma symptoms** | | | | |
| | -total score (0-6) | Symbicort SiT vs. Pulmicort | -0.17 | (-0.26, -0.07) | <0.001 |
| | -awakenings (%) | Symbicort SiT vs. Pulmicort | -2.2 | (-4.5, 0.1) | 0.065 |
| | -symptom-free days (%) | Symbicort SiT vs. Pulmicort | 6.5 | (2.0, 11.0) | 0.0043 |
| | **Use of as-needed medication** | | | | |
| | -total daily no. of inhalations | Symbicort SiT vs. Pulmicort | -0.34 | (-0.51, -0.17) | <0.001 |
| | -as-needed free days (%) | Symbicort SiT vs. Pulmicort | 8.1 | (3.5, 12.7) | <0.001 |
| | **Asthma-control days** | | | | |
| | -% of days | Symbicort SiT vs. Pulmicort | 7.6 | (3.0, 12.3) | 0.0012 |
| | **$FEV_1$ (L)** | Symbicort SiT vs. Pulmicort | 0.148 | (0.103, 0.193) | <0.001 |
| | **Severe asthma exacerbation** | | | | |
| | -time to first[1] | Symbicort SiT vs. Pulmicort | NA | NA | <0.001 |
| | -time to first[2] | Symbicort SiT vs. Pulmicort | 0.46[4] | (0.29, 0.73) | 0.0011 |
| | -events/subject[3] | Symbicort SiT vs. Pulmicort | 0.44[4] | (0.31,0.62) | <0.001 |
| | **Mild asthma exacerbation** | | | | |
| | -time to first[1] | Symbicort SiT vs. Pulmicort | NA | NA | <0.001 |
| | -time to first[2] | Symbicort SiT vs. Pulmicort | 0.64[4] | (0.52, 0.77) | <0.001 |
| | -mild exacerbation days (%) | Symbicort SiT vs. Pulmicort | -5.98 | (-9.25, -2.72) | <0.001 |
| | -mild exacerbation days (days/subject)[3] | Symbicort SiT vs Pulmicort | 0.64[4] | (0.53, 0.78) | <0.001 |

1. Log-rank test
2. Cox PH model
3. Poisson regression
4. Ratio

ePEF evening peak expiratory flow; $FEV_1$ forced expiratory volume in one second; mPEF morning peak expiratory flow; NA not applicable; SiT single-inhaler therapy.

## Safety results

### Table S3. Number (%) of subjects who had an adverse event in any category (safety population)

| Category of adverse event | N (%) of subjects who had an adverse event in each category [a] | |
|---|---|---|
| | Symbicort SiT<br>n = 354 | Pulmicort<br>n = 342 |
| Any Adverse Event | 135 (38%) | 139 (41%) |
| Serious Adverse Events | 6 (2%) | 6 (2%) |
| - Serious Adverse Events leading to death | 0 | 0 |
| - Serious Adverse Events not leading to death | 6 (2%) | 6 (2%) |
| Other significant Adverse Event | 0 | 0 |
| Discontinuations from treatment with investigational product due to Adverse Events | 3 (1%) | 8 (2%) |
| | Total number of adverse events | |
| Any Adverse Events[b] | 213 | 254 |
| Number of Adverse Events per 1000 treatment days[b] | 3.5 | 4.3 |
| Serious Adverse Events | 6 | 8 |
| Other significant Adverse Events | 0 | 0 |

a. Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
b. Events are counted by preferred term, i.e., for subjects with multiple events falling under the same preferred term, only one occurrence of the event is counted.

N number; SiT single-inhaler therapy

**Table S4. Adverse events by preferred term: Number (%) of subjects with the most commonly reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety population)**

| Preferred term | Symbicort SiT n = 354 | Pulmicort n = 342 | All n = 696 |
|---|---|---|---|
| Respiratory infection | 53 (15%) | 54 (16%) | 107 (15%) |
| Pharyngitis | 15 (4%) | 21 (6%) | 36 (5%) |
| Rhinitis | 14 (4%) | 13 (4%) | 27 (4%) |

• SiT single-inhaler therapy

Overall, the reported AEs, including serious adverse events and discontinuations from treatment with investigational product due to AEs do not give rise to any new safety concerns. No clinically important differences were identified in this study between treatment groups or in individual subjects from baseline to end-of-treatment in clinical laboratory variables, ECG or vital signs.