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**Clinical Study Report**

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|---|---|
| Drug Substance | SYMBICORT® pMDI |
| Study Code | D5896C00025 |
| Edition Number | Final version |
| Date | 30 April 2008 |

# A Two-Week, Randomized, Double-Blind Study Assessing the Onset of Effect Questionnaire (OEQ) Administered Pre-dose Versus Post-dose in Adult Subjects (≥18 Years of Age) with Mild to Moderate Asthma, Receiving SYMBICORT® pMDI 80/4.5 µg x 2 Actuations Twice Daily or Budesonide HFA pMDI 80 µg x 2 Actuations Twice Daily

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|---|---|
| **Study dates:** | First subject randomized: 05 April 2007<br>Last subject completed: 06 October 2007 |
| **Phase of development:** | Phase IIIb |
| **International Co-ordinating Investigator:** | Not applicable |
| **Sponsor's Responsible Medical Officer:** | |

This study was performed in compliance with Good Clinical Practice.

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| Drug Product | SYMBICORT® pMDI | **SYNOPSIS** | |
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# A Two-Week, Randomized, Double-Blind Study Assessing the Onset of Effect Questionnaire (OEQ) Administered Pre-dose Versus Post-dose in Adult Subjects (≥18 Years of Age) with Mild to Moderate Asthma, Receiving SYMBICORT® pMDI 80/4.5 µg x 2 Actuations Twice Daily or Budesonide HFA pMDI 80 µg x 2 Actuations Twice Daily

**Study center(s)**

The study was conducted in 40 sites in the United States. A total of 134 subjects were randomized.

**Publications**

Not applicable.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First subject randomized** | 05 April 2007 | Therapeutic confirmatory (IIIb) |
| **Last subject completed** | 06 October 2007 | |

**Objectives**

The primary objective of this study was to determine whether subjects responded similarly to the Onset of Effect Questionnaire (OEQ) Items 2 and 5 when administered post-dose versus pre-dose; and if responses differed in relation to the time of dosing, whether that difference favored the bronchodilator treatment group (SYMBICORT pMDI) over the non-bronchodilator treatment group (budesonide HFA pMDI).
The secondary objectives of the study included:

- To determine if there was an association between the immediate physiological response to medication and the responses to the OEQ Items 2 and 5.
- To determine what the subjects mean when they say they feel their asthma maintenance medication working right away.
- To determine the value to subjects of feeling an asthma maintenance medication beginning to work right away.

- To assess the correlation between the subject's responses to pre-dose and post-dose OEQ.

- To assess the correlation between subject's responses pre-dose versus post-dose to the OEQ with lung function and with diary variables including asthma symptom scores, nighttime awakenings due to asthma, rescue medication use, and morning (AM) and evening (PM) peak expiratory flow (PEF).

**Study design**

This was a 2-week, randomized, double-blind, parallel-group, multi-center Phase IIIb study comparing the responses to the OEQ administered pre-dose versus post-dose in adults (≥18 years of age) receiving treatment with SYMBICORT pressurized metered-dose inhaler (pMDI) 80/4.5 μg x 2 actuations twice daily (BID) or budesonide hydrofluoroalkane (HFA) pMDI 80 μg x 2 actuations BID.

**Target subject population and sample size**

The target population included male and female subjects with a documented clinical diagnosis of asthma for at least 6 months prior to Visit 2 who were at least 18 years of age, and whose pre-bronchodilator forced expiratory volume in one second ($FEV_1$) measured ≥6 hours after the last dose of short-acting $\beta_2$-agonist (SABA) and at least 48 hours after long-acting $\beta_2$-agonist (LABA) of 60% to 90% of predicted normal.
In addition, subjects were to demonstrate reversibility of $FEV_1$ of at least 12% and ≥0.20 L. Qualification for randomization was based on lung function on day of randomization and asthma symptom scores during the placebo run-in period.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

Run-in treatment: Placebo pMDI x 2 actuations BID.
Investigational product: SYMBICORT pMDI 80/4.5 μg x 2 actuations BID.
Comparator: Budesonide HFA pMDI 80 μg x 2 actuations BID.
Rescue therapy (for oral inhalation): Albuterol pMDI (90 μg per actuation) 2 actuations taken as needed (PRN), as rescue medication for relief of bronchospasm.

**Duration of treatment**

During the 2-week (±1 week) single-blind run-in period, all enrolled subjects received placebo pMDI administered x 2 actuations BID, as well as albuterol pMDI (90μg/actuation x 2 actuations PRN) for use as rescue medication. Qualifying subjects were then randomized to 1 of 2 treatment arms utilizing an Interactive Voice Response System (IVRS) and entered a 2-week treatment period. At the conclusion of randomized treatment (Visit 6) or at discontinuation, subjects were placed on appropriate asthma therapy.

**Criteria for evaluation (main variables)**

**Outcome variables**

- Primary outcome variable: Diary assessment

- OEQ Items 2 and 5 administered pre-dose and post-dose

- Secondary outcome variables: Diary assessment
  - OEQ Items 1, 3, and 4
  - Daily asthma symptom scores (daytime [AM] and nighttime [PM])
  - Nighttime awakenings due to asthma
  - Rescue medication use

- Efficacy: Lung function
  - AM and PM PEF
  - Pre-dose $FEV_1$
  - Post-dose $FEV_1$

- Additional Patient Reported Outcomes (PROs)
  - Reason for perception checklist
  - Subject Opinion Survey

**Safety**

Adverse events (AEs), serious adverse events (SAEs), discontinuation of study treatment due to adverse events (DAEs), vital signs, and physical examination.

**Statistical methods**

The primary variables were the pre-dose and post-dose responses to Items 2 and 5 of the OEQ. The primary objective of the study was to determine whether subjects responded similarly pre-dose and post-dose to the OEQ Items 2 and 5, and if responses differed, whether the difference favored the bronchodilator treatment group over the non-bronchodilator treatment group.

For this analysis, the difference between the pre-dose and post-dose scores was calculated for each subject using a paired t-test. A point estimate and 95% confidence interval (CI) on the difference was provided. To investigate the period effect, a sensitivity analysis was also performed, which included period in the model. If assumptions required for the application of the parametric test were strongly violated then a nonparametric counterpart was used, such as the Wilcoxon signed-rank test.

Secondary objectives included assessing the correlation between the pre-dose and post-dose scores for OEQ Items 2 and 5 and the correlation between the subjects' responses to the pre-dose and post-dose OEQ responses and other variables including $FEV_1$, asthma symptom scores, nighttime awakenings due to asthma, rescue medication use, and AM and PM PEF. For these analyses, data from the two treatment groups were combined

since interest was in the correlation between variables overall. Both the Pearson and Spearman correlation coefficients were calculated. Statistical significance was assessed using the appropriate t-statistic.

**Subject population**

The study population is a representative sample of subjects requiring inhaled corticosteroids (ICS) with mild to moderate asthma, as defined by ICS use at study entry. Overall, the screen failure rate was 61.9%. Approximately 9% of subjects screened received run-in medication but were not randomized. Demographic and baseline characteristics were generally well-balanced between the treatment groups (see Table S1). There was a greater proportion of female than male subjects (62.7% and 37.3%, respectively) and most subjects (84.3%) were white. Approximately 15% of subjects in the safety analysis set were excluded from the per-protocol (PP) analysis set.

**Table S1 Subject population and disposition**

| | Treatment group[a] | | |
|---|---|---|---|
| | **SYM 80/4.5 BID (N=67)** | **BUD 80 BID (N=67)** | **Total (N=134)** |
| **Demographics** | | | |
| Sex (n and % of subjects) | | | |
| Male | 27 (40.3) | 23 (34.3) | 50 (37.3) |
| Female | 40 (59.7) | 44 (65.7) | 84 (62.7) |
| Age (years) | | | |
| Mean (SD) | 43.4 (16.16) | 42 (15.2) | 42.7 (15.64) |
| Range | 18 – 79 | 18 – 72 | 18 – 79 |
| Race (n and % of subjects) | | | |
| White | 61 (91.0) | 52 (77.6) | 113 (84.3) |
| Black/African American | 4 (6.0) | 11 (16.4) | 15 (11.2) |
| Asian | 1 (1.5) | 0 | 1 (0.7) |
| Native Hawaiian/Other Pacific Islander | 0 | 1 (1.5) | 1 (0.7) |
| Other | 1 (1.5) | 3 (4.5) | 4 (3.0) |
| **Key baseline characteristics** | | | |
| $FEV_1$ (L) before bronchodilator, mean (SD) | 2.44 (0.77) | 2.43 (0.62) | 2.43 (0.70) |
| $FEV_1$ (L) after bronchodilator, mean (SD) | 2.90 (0.93) | 2.91 (0.79) | 2.91 (0.86) |
| $FEV_1$% predicted before bronchodilator, mean (SD) | 73.23 (9.31) | 74.08 (9.93) | 73.66 (9.60) |
| $FEV_1$% predicted after bronchodilator, mean (SD) | 86.95 (11.04) | 88.58 (12.11) | 87.76 (11.57) |
| Percent reversibility in $FEV_1$, mean (SD) | 19.03 (8.93) | 20.10 (11.30) | 19.57 (10.16) |
| **Subject populations** | | | |
| Randomized subjects | 67 | 67 | 134 |
| Safety analysis set | 67 (100.0) | 67 (100.0) | 134 (100.0) |
| Efficacy analysis set | 66 (98.5) | 67 (100.0) | 133 (99.3) |
| PP analysis set | 55 (82.1) | 59 (88.1) | 114 (85.1) |

[a] SYM 80/4.5 BID: SYMBICORT pMDI 80/4.5 µg x 2 BID; BUD 80 BID: Budesonide HFA pMDI 80 µg x 2 BID.

$FEV_1$: forced expiratory volume in one second; PP: per-protocol; SD: standard deviation.

Data derived from Tables 11.1.2.1, 11.1.4.1, 11.1.5.2, and 11.1.5.3, Section 11.1.

## Outcome results

- Overall, there was a high correlation between pre-dose and post-dose responses for the OEQ Items 2 (“During the past week, you could feel your medication begin to work right away”) (Spearman correlation coefficient of 0.784) and for OEQ Item 5 (“During the past week, you were satisfied with

how quickly you felt your medication begin to work") (Spearman correlation coefficient of 0.833).

- Results of the analysis of variables associated with the primary objective showed that the difference between the pre-dose and post-dose responses for OEQ Item 2 was not statistically significant when analyzed as mean score (p=0.056) or after the responses had been dichotomized (p=0.057). The difference between the pre-dose and post-dose responses for OEQ Item 5 was not statistically significant when analyzed as mean score (p=0.574) or after the responses had been dichotomized (p=0.180). There was an agreement between the pre-dose and post-dose responses in approximately 90.0% of the subjects for the OEQ Item 2 and 93.0% for the OEQ Item 5.

- No statistically significant differences were observed between the pre-dose and post-dose results of the secondary variables OEQ Items 1, 3, or 4 on the original 5-point Likert scale (p=0.123, p=0.737, and p=0.109, respectively) or the dichotomized scale (p=0.727, p=1.000, and p=1.000, respectively).

- Subjects in the SYMBICORT pMDI treatment group showed substantially more mean improvement in AM and PM PEF from baseline to the average over the randomized treatment period than the budesonide HFA pMDI treatment group. Numerical differences in AM and PM asthma symptoms scores and AM rescue medication use favored the SYMBICORT pMDI group over the budesonide HFA pMDI treatment group.

- Relative to pre-dose at baseline, improvements of ≥12% and ≥0.20 L in $FEV_1$ were observed 15, 30, and 60 minutes post-dose at Visit 4/5 in the SYMBICORT pMDI treatment group indicating reversible airway obstruction, with the most improvement occurring within 15 minutes of study medication administration.

- Efficacy and diary parameters were collected for the purpose of investigating their potential correlation with the OEQ. Pre-dose and post-dose responses for OEQ Items 2 and 5 were not well correlated with changes from baseline (Visit 3) in typical measures of efficacy collected prior to dosing (pre-dose $FEV_1$ and diary variables).

- High percentages of subjects who achieved a 12% improvement in $FEV_1$ agreed with OEQ Item 2 (76.8%) and OEQ Item 5 (85.7%).

- Subjects who completed the Reasons for Perception Checklist reported that feeling their medication working right away was most often associated with the ability to breathe easier or deeper.

- Responses to the Subject Opinion Survey showed that 80.4% of all subjects in the efficacy analysis set agreed that when they take an asthma

maintenance medication, they want to be able to feel it work right away. For those subjects who responded that they want an asthma maintenance medication that they can feel work right away, 97.2% answered that it would reassure them that the medication was working, 79.5% answered that it would remind them to take their medication, 95.3% answered that it would let them know they took their medication properly, 90.7% answered that it would give them confidence that their asthma was under control, and 96.3% would feel more secure about managing their asthma. The response rates were similar between the SYMBICORT pMDI and budesonide HFA pMDI treatment groups.

**Safety results**

The mean duration of exposure and mean study medication compliance was comparable for both treatment groups.

For non-randomized subjects, one SAE (pneumonia) was reported during screening in a subject who did not receive run-in treatment. The event was moderate in intensity and led to discontinuation. Three other non-randomized subjects had events that led to discontinuation during run-in. The events were mild (asthma and chest discomfort) or moderate (asthma) in intensity.

During the randomized treatment period, the percentage of subjects with at least 1 AE was lower in the SYMBICORT pMDI treatment group than in the budesonide HFA pMDI treatment group (See Table S2).

There were no deaths, SAEs, DAEs, or OAEs during the randomized treatment period.

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**Table S2** **Number (%) of subjects who had an adverse event in any category during the randomized treatment period (safety analysis set)**

| Category of adverse event | Treatment group[a] | | |
|---|---|---|---|
| | SYM 80/4.5 BID (N=67) | BUD 80 BID (N=67) | Total (n=134) |
| | Number (%) of subjects who had an AE in each category[b] | | |
| Any adverse events | 11 (16.4) | 18 (26.9) | 29 (21.6) |
| Serious adverse events | 0 | 0 | 0 |
| Adverse events leading to discontinuation | 0 | 0 | 0 |
| Drug-related adverse events | 1 (1.5) | 1 (1.5) | 2 (1.5) |
| Other significant adverse events | 0 | 0 | 0 |
| | Total number of adverse events | | |
| Any adverse events | 18 | 36 | 54 |
| Drug-related adverse events | 1 | 2 | 3 |

[a] SYM 80/4.5 BID: SYMBICORT pMDI 80/4.5 µg x 2 BID; BUD 80 BID: Budesonide HFA pMDI 80 µg x 2 BID.

[b] Subjects with multiple events in the same category are counted only once in that category.

Data derived from Table 11.3.2.1.5, Section 11.3.

The most commonly reported AEs were headache, nasopharyngitis, pharyngolaryngeal pain, chest pain, dysmenorrhea, and dyspepsia (see Table S3). No clinically significant treatment group differences or changes in individual subjects from baseline to end-of-treatment for vital signs or physical findings were identified in this study.

**Table S3** **Adverse events reported by at least 2% of subjects in any treatment group during the randomized treatment (safety analysis set)**

| Preferred term[b] | Treatment group[a], n (%) of subjects | | |
|---|---|---|---|
| | SYM 80/4.5 BID (N=67) | BUD 80 BID (N=67) | Total (N=134) |
| **Number of subjects with any AE** | **11 (16.4)** | **18 (26.9)** | **29 (21.6)** |
| Headache | 4 (6.0) | 6 (9.0) | 10 (7.5) |
| Nasopharyngitis | 2 (3.0) | 1 (1.5) | 3 (2.2) |
| Pharyngolaryngeal pain | 1 (1.5) | 2 (3.0) | 3 (2.2) |
| Chest pain | 0 | 2 (3.0) | 2 (1.5) |
| Dysmenorrhea | 0 | 2 (3.0) | 2 (1.5) |
| Dyspepsia | 0 | 2 (3.0) | 2 (1.5) |

[a] SYM 80/4.5 BID: SYMBICORT pMDI 80/4.5 µg x 2 BID; BUD 80 BID: Budesonide HFA pMDI 80 µg x 2 BID.
[b] Based on MedDRA Version 10.1; sorted by decreasing order of frequency.
Data derived from Table 11.3.2.4.3, Section 11.3.

## Date of the report

30 April 2008