Clinical Study Report

Drug Substance	SYMBICORT® pMDI
Study Code	D5896C00023
Edition Number	Final
Date	29 April 2008

A Two-Week, Randomized, Double-Blind Study Assessing the Onset of Effect Questionnaire (OEQ) Administered Daily Versus Weekly 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 dates: First subject randomized: 20 March 2007
Last subject completed: 06 August 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 Daily Versus Weekly 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 45 centers in the United States. A total of 123 subjects were randomized.

Publications

Not applicable

Study dates		**Phase of development**
First subject randomized	20 March 2007	Therapeutic confirmatory (IIIB)
Last subject completed	06 August 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 using a 1-week recall period versus a 1-day recall period; and if responses differed by recall period, does that difference favor the bronchodilator treatment group over the non-bronchodilator treatment group.

The secondary objectives of the study included:

- To determine what the subjects mean when they say they feel their asthma maintenance medication is "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 subject's responses to weekly and/or daily OEQ with lung function and with diary variables including asthma symptom

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scores, nighttime awakenings due to asthma, rescue medication use, and morning and evening peak expiratory flow (AM and PM PEF).

- To assess the correlation between the daily and weekly responses to OEQ Items 2 and 5.

- To assess the correlation between the daily and weekly responses to OEQ and the Patient Satisfaction with Asthma Medication (PSAM) questionnaire.

Study design

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

Target subject population and sample size

The target population includes 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 1 second (FEV_1) measured ≥6 hours after the last dose of short-acting β-agonist (SABA) and at least 48 hours after long-acting $β_2$ agonist (LABA) of 60% to 90% of predicted normal. In addition, subjects had to have a demonstrated 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 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 (90 μg/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 4) 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 daily and weekly

- Secondary outcome variables: Diary assessment

    – OEQ Items 1, 3, and 4

    – Daily asthma symptom scores (daytime and nighttime)

    – Rescue medication use

    – Nighttime awakenings due to asthma

- Efficacy: Lung function

    – AM and PM PEF

    – Pre-dose FEV_1

- Additional Patient Reported Outcomes (PROs)

    – Reasons for Perception Checklist

    – Subject Opinion Survey

    – Patient Satisfaction with Asthma Medication Questionnaire (PSAM)

Safety

Adverse events (AEs), serious adverse events (SAEs), discontinuation of study treatment due to adverse events (DAEs), other significant events (OAEs), and changes in vital signs and physical examinations (PE).

Statistical methods

The primary variable was the daily and weekly responses to Items 2 and 5 of the OEQ. The primary objective was to determine whether subjects responded similarly to the OEQ Items 2 and 5 using a 1-week recall period versus a 1-day recall period and, if responses differed by recall period, did the difference favor bronchodilator treatment group (SYM 80/4.5 BID)over the non-bronchodilator treatment group (BUD 80 BID).
For these analyses, a difference between the weekly score and a mean daily score was calculated for each subject. Difference scores were calculated by subtracting weekly scores from mean daily scores. For subjects who answered the daily questions before the weekly questions, the daily score was calculated as the average of the score recorded on Treatment Days 4, 5, and 6. The difference between the weekly score recorded on Treatment Day 7 and the average of the 3 previous daily scores were computed. For subjects who answered the daily questions after the weekly questions, the daily score was calculated as the average of the score recorded on Treatment Days 8, 9, and 10. The difference between the weekly score recorded on Treatment Day 7 and the average of the

3 subsequent daily scores were computed. Although subjects also recorded a weekly score on Treatment Day 14, the score on Treatment Day 7 was the focus of this analysis to coincide with the primary time point identified in previous studies. In previous studies, questions were asked weekly but the question asked on Treatment Day 7 was primary.

The difference between daily and weekly responses was assessed 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.

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 54.6% (148 of 271 subjects screened). Approximately 7% (19 of 271 subjects) of screened subjects received run-in medication but were not randomized. Demographic and baseline characteristics were generally well balanced between the 2 treatment groups. There were a greater proportion of females than males in the randomized population (69.1% vs 30.9%, respectively) which is consistent with the disease prevalence in adults. Most randomized subjects (82.9%) were White, with Black/African American subjects comprising 8.9% of the population.

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Table S1   Subject population and disposition

	Treatment group[a]		
	SYM 80/4.5 BID (N=62)	**BUD 80 BID (N=61)**	**Total (N=123)**
Demographics			
Sex (n and % of subjects)			
Male	19 (30.6)	19 (31.1)	38 (30.9)
Female	43 (69.4)	42 (68.9)	85 (69.1)
Age (years)			
Mean (SD)	43.1 (12.31)	43.8 (13.69)	43.4 (12.96)
Min, Max	19 – 76	18 – 76	18 – 76
Race (n and % of subjects)			
White	53 (85.5)	49 (80.3)	102 (82.9)
Black/African American	3 (4.8)	8 (13.1)	11 (8.9)
Asian	2 (3.2)	2 (3.3)	4 (3.3)
Other	4 (6.5)	2 (3.3)	6 (4.9)
Key baseline characteristics			
FEV_1 (L) before bronchodilator			
Mean (SD)	2.38 (0.603)	2.39 (0.685)	2.38 (0.642)
FEV_1% predicted before bronchodilator			
Mean (SD)	73.03 (8.145)	73.62 (8.714)	73.32 (8.403)
FEV_1 (L) after bronchodilator			
Mean (SD)	2.80 (0.714)	2.86 (0.739)	2.83 (0.724)
FEV_1% predicted after bronchodilator			
Mean (SD)	85.80 (9.585)	88.59 (8.799)	87.19 (9.273)
FEV_1 Percent reversibility			
Mean (SD)	17.59 (4.808)	21.06 (11.233)	19.31 (8.755)

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Table S1   Subject population and disposition

	Treatment group[a]		
	SYM 80/4.5 BID **(N=62)**	**BUD 80 BID** **(N=61)**	**Total** **(N=123)**
Subject populations			
All randomized, n	62	61	123
Safety analysis set, n (%)	62 (100.0)	61 (100.0)	123 (100.0)
Efficacy analysis set, n (%)	60 (96.8)	60 (98.4)	120 (97.6)
Per protocol analysis set, n (%)	57 (91.9)	52 (85.2)	109 (88.6)

[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.
SD: Standard deviation; N: number; FVC: forced vital capacity.
Data derived from Tables 11.1.2.1, 11.1.4.1, 11.1.5.2, and 11.1.5.3, Section 11.1.

Outcomes results

Overall, the results of this study support the conclusion that there is no difference between daily and weekly responses to OEQ Items 2 and 5, and any small numerical differences that were observed were not driven by the presence of a bronchodilator. Responses to the daily and weekly questions were highly correlated and, in the cases where absolute agreement was not achieved on the 5-point Likert scale, the majority of assessments differed by only 1 category of response. There was no evidence that any of the observed differences favored the bronchodilator treatment group over the non-bronchodilator treatment group. Any small tendency to "agree" more with the weekly question than the daily question was not driven by the presence of a bronchodilator.
A secondary objective was to determine what subjects meant when they said they felt their asthma maintenance medication working right away. It was found that this was most often associated with the "ability to breathe easier or deeper", "lungs opening up", "chest loosening", or "chest less tight". This confirms the findings from earlier OEQ qualitative validation studies that subjects interpret "working right away" as a bronchodilator response.
Results of the Subject Opinion Survey found that subjects value an asthma maintenance medication that they feel working right away. When subjects take an asthma maintenance medication, 79.2% said they want to be able to feel it work right away (SYM 80/4.5 BID: 78.3%, 47 subjects; BUD 80 BID: 80.0%, 48 subjects). Less than 3% (2.5 %) of subjects responded that they would rather not feel their asthma medication begin to work right away.
Results for the secondary OEQ Items 1, 3, and 4 were similar to those seen for OEQ Items 2 and 5. Responses to OEQ Items 2 and 5 were reasonably well-correlated to the PSAM questionnaire. There was a poor correlation found between OEQ Items 2 and 5 and the pre-dose lung function measures (FEV_1 and PEF), and other measures of asthma control (asthma symptom scores, nighttime awakenings due to asthma, and rescue medication use).

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Safety results

Overall, the reported AEs do not suggest any new safety concerns with SYMBICORT pMDI. There were no deaths, SAEs, OAEs, or drug-related DAEs in either treatment group (SYM 80/4.5 BID or BUD 80 BID). No clinically significant treatment group differences or changes in individual subjects from baseline to end-of-treatment for vital signs or PE findings were identified in this study.

Table S2   Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

AE category	Treatment group[a] n (%)of subjects		
	SYM 80/4.5 BID (N=62)	BUD 80 BID (N=61)	Total (n=123)
Any AEs	8 (12.9)	10 (16.4)	18 (14.6)
Any drug-related AEs	1 (1.6)	3 (4.9)	4 (3.3)
SAEs	0	0	0
AEs leading to discontinuation	0	1 (1.6)	1 (0.8)
OAEs	0	0	0
	Total number of AEs		
Any AEs	11	12	23

[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.
Note: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.

Table S3   Number (%) of subjects with the most commonly reported adverse events (≥1% of subjects in either treatment group), sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)

MedDRA preferred term[b]	Treatment group[a], n (%) of subjects		
	SYM 80/4.5 BID (N=62)	BUD 80 BID (N=61)	Total (N=123)
Number of subjects with any AE	**8 (12.9)**	**10 (16.4)**	**18 (14.6)**
Pharyngolaryngeal pain	2 (3.2)	2 (3.3)	4 (3.3)
Back pain	1 (1.6)	1 (1.6)	2 (1.6)
Headache	1 (1.6)	1 (1.6)	2 (1.6)
Asthma	0	1 (1.6)	1 (0.8)
Dermatitis contact	0	1 (1.6)	1 (0.8)
Head injury	1 (1.6)	0	1 (0.8)
Influenza	1 (1.6)	0	1 (0.8)

	Treatment group[a], n (%) of subjects		
MedDRA preferred term[b]	SYM 80/4.5 BID (N=62)	BUD 80 BID (N=61)	Total (N=123)
Number of subjects with any AE	**8 (12.9)**	**10 (16.4)**	**18 (14.6)**
Insomnia	0	1 (1.6)	1 (0.8)
Joint injury	0	1 (1.6)	1 (0.8)
Loss of libido	0	1 (1.6)	1 (0.8)
Neck pain	1 (1.6)	0	1 (0.8)
Pain in extremity	0	1 (1.6)	1 (0.8)
Pharmaceutical product complaint	0	1 (1.6)	1 (0.8)
Pyrexia	1 (1.6)	0	1 (0.8)
Respiratory tract infection	1 (1.6)	0	1 (0.8)
Sinusitis	0	1 (1.6)	1 (0.8)
Skin laceration	1 (1.6)	0	1 (0.8)
Viral upper respiratory tract infection	1 (1.6)	0	1 (0.8)

[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.

There were no clinically meaningful treatment group differences for the percentage of subjects with shifts from normal to either high or low for systolic or diastolic blood pressure, or for pulse rate at any time point during run-in, randomized treatment period, or at the end of treatment.

No treatment group differences were noted for the number of subjects who had shifts from normal to abnormal, new or aggravated, for any physical examination findings.

Date of the report

29 April 2008