Drug product:	SYMBICORT® pMDI	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Edition No.:	Final		
Study code:	D5896C00001		
Date:	9 November 2005		

A randomized, double-blind, active-controlled, parallel-group, single-dummy, multicenter, 12 week study to assess the efficacy and safety of SYMBICORT® pMDI 160/4.5 µg x 2 actuations once-daily (qd) compared to SYMBICORT pMDI 80/4.5 µg x 2 actuations qd, SYMBICORT pMDI 80/4.5 µg x 2 actuations twice-daily (bid) and to budesonide pMDI 160 µg x 2 actuations qd in asthmatic subjects 12 years of age and older.

International co-ordinating investigator
None appointed for this study

Study centre(s)
This study was conducted in the United States (143 centers).

Publications
None as of the completion date of this report.

Study dates		**Phase of development**
First subject enrolled	20 October 2003	Therapeutic confirmatory (III)
Last subject completed	7 February 2005	

Objectives

Primary:

 To demonstrate the efficacy of SYMBICORT pMDI 160/4.5 µg x 2 actuations once-daily (qd) compared to budesonide pMDI 160 µg x 2 actuations qd, in asthmatic adults and adolescents (12 years of age and older) previously treated with SYMBICORT pMDI 80/4.5 µg x 2 actuations twice-daily (bid) by assessment of lung function, symptoms and patient/physician reported outcomes.

Secondary:

1. To demonstrate the efficacy of SYMBICORT pMDI 80/4.5 µg x 2 actuations qd compared to budesonide pMDI 160 µg x 2 actuations qd in asthmatic adults and

adolescents previously treated on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid by assessment of lung function, symptoms and patient/physician reported outcomes.

2. To demonstrate the efficacy of SYMBICORT pMDI 80/4.5 µg x 2 actuations bid compared to budesonide pMDI 160 µg x 2 actuations qd in asthmatic adults and adolescents previously treated on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid by assessment of lung function, symptoms and patient/physician reported outcomes.

3. To compare the relative efficacy of switching from SYMBICORT pMDI 80/4.5 µg x 2 actuations bid to one of the following treatments: once-daily therapy with SYMBICORT pMDI 160/4.5 µg x 2 actuations (ie step-across); qd therapy with SYMBICORT pMDI 80/4.5 µg x 2 actuations qd (ie step-down); or to the treatment group remaining on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid by assessment of lung function, symptoms and patient/physician-reported outcomes.

4. To demonstrate the health-related quality of life (HRQOL) and Patient Reported Asthma Control (ACQ) benefits of SYMBICORT pMDI 160/4.5 µg x 2 actuations qd, SYMBICORT pMDI 80/4.5 µg x 2 actuations qd and SYMBICORT pMDI 80/4.5 µg x 2 actuations bid, compared to budesonide pMDI 160 µg x 2 actuations qd in asthmatic adults and adolescents previously treated on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid.

5. To compare the relative HRQOL and Patient Reported Asthma Control (ACQ) benefits of SYMBICORT pMDI 80/4.5 µg x 2 actuations bid to once-daily therapy with SYMBICORT pMDI 160/4.5 µg x 2 actuations qd, (ie step-across) and to once-daily therapy with SYMBICORT pMDI 80/4.5 µg x 2 actuations qd, (ie, step-down) in asthmatics (12 years of age and older) previously treated with SYMBICORT pMDI 80/4.5 µg x 2 actuations bid.

6. To investigate the safety profiles of SYMBICORT pMDI 160/4.5 µg x 2 actuations qd, SYMBICORT pMDI 80/4.5 µg x 2 actuations qd, SYMBICORT pMDI 80/4.5 µg 2 actuations bid, and budesonide pMDI 160 µg x 2 actuations qd in asthmatic adults and adolescents previously treated on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid by assessment of safety parameters.

Study design

This was a 12-week, multicenter, randomized, double-blind, parallel group, active-controlled, and single-dummy Phase 3 study to investigate the efficacy, impact on health-related quality of life, and safety of SYMBICORT pMDI qd as maintenance therapy in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg x 2 actuations bid.

Target subject population and sample size

Male and female subjects who were 12 years of age and older, had a documented clinical diagnosis of asthma for at least 6 months prior to screening, and who were in stable condition were eligible for enrollment. Subjects should have received maintenance asthma treatment with inhaled corticosteroids (ICS) for at least 4 weeks prior to the screening visit. Subjects were also required to have an FEV_1, measured at least 24 hours after the last dose of long-acting β_2-agonist and 6 hours after the last dose of short-acting β_2-agonist, between 60% and 90% of predicted normal at screening.

Approximately 600 subjects were targeted for randomization to reach the goal of 532 evaluable subjects (approximately 133 in each treatment arm), to have 90% power to detect a true mean difference between groups in change from baseline in evening predose FEV_1 of 0.20 L. A standard deviation of 0.50 L was assumed, using a 2-sided group t-test with a 5% significance level, assuming that approximately 10% of randomized subjects would not be evaluable for the primary efficacy endpoint.

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

All subjects received SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid during the single-blind run-in period (batch numbers P6503, P6739, P6897). Albuterol, delivered by pMDI (Batch numbers 2000052474 and 2000056230), was used as rescue medication on an as-needed basis during both the run-in and treatment periods.
All eligible subjects were randomized to 1 of the following 4 treatment groups at Visit 2:

1. SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg per actuation, 2 actuations administered qd (hereafter referred to as SYMBICORT pMDI 320/9 qd) (Batch numbers P6675 and P6722)

2. SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered qd (hereafter referred to as SYMBICORT pMDI 160/9 qd) (Batch numbers P6503, P6739, and P6897).

3. SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered bid (hereafter referred to as SYMBICORT pMDI 160/9 bid) (Batch numbers P6503, P6739, and P6897).

4. Budesonide pMDI 160 µg per actuation, 2 actuations administered qd (hereafter referred to as budesonide 320 qd) (Batch numbers P6611 and P6716).

To maintain blinding with the twice-daily dosing regimen, all subjects randomized to receive once-daily dosing were to take the active treatment in the evening and a matched placebo device (Batch numbers P6492 and P6856) in the morning.

Duration of treatment

A 12-week randomized, double-blind treatment period preceded by a 4- to 5-week SYMBICORT pMDI single-blind run-in period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

1. Primary variable: evening predose FEV_1

2. Secondary variables:

   - Electronic diary and derived electronic diary variables (morning and evening PEF, symptom-free days, asthma-control days, rescue medication use, nighttime awakenings, and nighttime and daytime asthma symptom scores)

   - Predefined asthma events and withdrawals due to predefined asthma events[1]

   - Other evening predose spirometry variables from clinic visits (FVC, $FEF_{25-75\%}$, and PEF; to be summarized descriptively and not subject to formal analysis)

   - Global Assessments (subject global assessment and physician's global assessment)

   - Patient-Reported Outcomes (PRO) variables (standardized Asthma Quality of Life Questionnaire [AQLQ(S)], standardized Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)], and Asthma Control Questionnaire [ACQ])

Safety

Adverse events, clinical laboratory data (hematology, clinical chemistry, and urinalysis), physical examination, and vital signs were used to evaluate safety.

Statistical methods

The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double-blind treatment and for whom the primary efficacy endpoint could be calculated, was used in the primary analysis of efficacy. Sensitivity analyses were performed using the per protocol (PP) analysis set, which excluded subjects with major violations of inclusion or exclusion criteria.

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[1] Referred to as 'withdrawals due to asthma deterioration' in the clinical study protocol.

The change from baseline to the mean over the randomized, double-blind treatment period in evening predose FEV_1 – the primary efficacy endpoint – was analyzed using an analysis of covariance (ANCOVA) model with treatment and center as fixed factors and baseline evening predose FEV_1 as a covariate. The primary comparison was between SYMBICORT pMDI 320/9 qd and budesonide pMDI 320 qd, using a contrast from this ANCOVA model at the 5% significance level (2-sided). All other pairwise comparisons were also made, to support the study's secondary objectives; differences between the 2 once-daily SYMBICORT pMDI groups and between these groups and the SYMBICORT pMDI twice-daily group are presented primarily at a descriptive level, using 2-sided 95% confidence intervals. Secondary variables were analyzed, unadjusted for multiple comparisons, primarily using ANCOVA for numeric variables and chi-square tests for categorical variables.

Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models, primarily using all subjects who received at least 1 dose of double-blind treatment (safety analysis set). Additional summaries were performed using all subjects who received at least 1 dose of run-in treatment, irrespective of whether the subjects were randomized (run-in analysis set).

Subject population

A total of 2238 subjects were screened for possible study participation, 975 of whom entered the run-in period and received at least 1 dose of single-blind SYMBICORT pMDI 160/9 bid therapy. Of these, 619 subjects were subsequently randomized. Study recruitment was stopped when the target enrollment was reached. All randomized subjects except 1 received double-blind treatment and all except 13 provided at least 1 efficacy observation.

Among randomized subjects, the overall withdrawal rate was highest in the SYMBICORT pMDI 160/9 qd treatment group (17.1%); the percentages of subjects withdrawn in the other 3 treatment groups were similar and slightly lower (ranging from 11.8% to 12.4%). Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics (Table S1).

Table S1   **Demographic and key baseline characteristics (safety analysis set)**

Demographic or key baseline characteristic	Treatment group				
	SYMB 160/9 bid (N=155)	SYMB 320/9 qd (N=153)	SYMB 160/9 qd (N=157)	Budes 320 qd (N=153)	Total (N=618)
Sex (n and % of subjects)					
Male	57 (36.8)	76 (49.7)	58 (36.9)	54 (35.3)	245 (39.6)
Female	98 (63.2)	77 (50.3)	99 (63.1)	99 (64.7)	373 (60.4)
Age (yr)					
Mean (SD)	35.1 (16.22)	33.4 (15.00)	37.2 (14.86)	36.3 (15.13)	35.5 (15.34)
Median	34.0	33.0	38.0	36.0	35.0
Range	12 to 79	12 to 77	12 to 69	12 to 68	12 to 79

Table S1   **Demographic and key baseline characteristics (safety analysis set)**

Age group (yr) (n and % of subjects)					
12 to <16	23 (14.8)	24 (15.7)	16 (10.2)	18 (11.8)	81 (13.1)
16 to <65	125 (80.6)	126 (82.4)	135 (86.0)	132 (86.3)	518 (83.8)
65 to <75	6 (3.9)	2 (1.3)	6 (3.8)	3 (2.0)	17 (2.8)
≥75	1 (0.6)	1 (0.7)	0	0	2 (0.3)
Race (n and % of subjects)					
Caucasian	132 (85.2)	130 (85.0)	123 (78.3)	124 (81.0)	509 (82.4)
Black	18 (11.6)	19 (12.4)	24 (15.3)	27 (17.6)	88 (14.2)
Oriental	2 (1.3)	1 (0.7)	4 (2.5)	1 (0.7)	8 (1.3)
Other	3 (1.9)	3 (2.0)	6 (3.8)	1 (0.7)	13 (2.1)
Years since asthma diagnosis					
Mean (SD)	17.9 (14.44)	18.6 (13.04)	18.1 (14.11)	19.1 (14.73)	18.4 (14.07)
Min, Max	0.5, 63.5	1.1, 59.1	0.6, 64.4	0.6, 60.5	0.5, 64.4
ICS dose at entry (µg/day)					
N	155	153	157	152	617
Mean (SD)	360.4 (173.83)	399.0 (201.54)	389.1 (186.50)	351.0 (184.83)	375.0 (187.48)
Min, Max	80.0, 800.0	88.0, 1200.0	80.0, 1200.0	88.0, 1000.0	80.0, 1200.0
Percent reversibility in FEV_1 at screening (Visit 1)					
Mean (SD)	18.9 (8.92)	18.4 (9.22)	20.7 (9.80)	18.5 (7.62)	19.1 (8.96)
Median	15.5	15.3	17.7	16.2	16.1
Min, Max	10.5, 55.6	10.5, 71.7	10.6, 68.6	9.5, 50.4	9.5, 71.7
FEV_1 (L) at screening (Visit 1, pre-bronchodilator)					
Mean (SD)	2.5 (0.54)	2.7 (0.58)	2.5 (0.63)	2.5 (0.62)	2.6 (0.59)
Percent predicted FEV_1 at screening (Visit 1, pre-bronchodilator)					
Mean (SD)	76.1 (7.64)	76.0 (7.70)	75.1 (7.97)	76.0 (8.02)	75.8 (7.83)
Baseline FEV_1 (L) (evening predose at Visit 2)					
Mean (SD)	2.9 (0.62)	3.0 (0.59)	2.8 (0.71)	2.9 (0.72)	2.9 (0.66)
Baseline percent predicted FEV_1 (evening predose at Visit 2)					
Mean (SD)	86.5 (9.22)	85.3 (7.79)	85.6 (8.36)	85.7 (8.79)	85.8 (8.55)

Efficacy and pharmacokinetic results

Results of the primary analysis of the primary efficacy endpoint - change from baseline in evening predose FEV_1 - are summarized in Table S2 (treatment means) and Table S3 (treatment comparisons). Key findings for the primary efficacy endpoint are as follows:

- SYMBICORT pMDI 320/9 qd was shown to be superior to budesonide 320 qd (p<0.001).

- SYMBICORT pMDI 160/9 qd was shown to be superior to budesonide 320 qd (p=0.016).

- SYMBICORT pMDI 160/9 bid was shown to be superior to budesonide 320 qd (p<0.001).

- The SYMBICORT pMDI 160/9 bid treatment group maintained the mean level of pulmonary function (as assessed by evening predose FEV_1) that was established during the run-in baseline period (during which all subjects were treated with SYMBICORT pMDI 160/9 bid), without experiencing a loss of efficacy during double-blind treatment. In contrast, decreases from baseline during double-blind treatment were seen for both of the SYMBICORT pMDI once-daily treatment groups compared to the SYMBICORT pMDI 160/9 bid group (LS mean difference 0.09 L, 95% CI: 0.04 to 0.13 L for SYMBICORT pMDI 160/9 bid minus SYMBICORT pMDI 320/9 qd; LS mean difference 0.14 L, 95% CI: 0.09 to 0.19 L for SYMBICORT pMDI 160/9 bid minus SYMBICORT pMDI 160/9 qd; p<0.001 for each).

Treatment differences were seen favoring SYMBICORT pMDI 320/9 qd compared to SYMBICORT pMDI 160/9 qd (LS mean difference 0.05 L, 95% CI: 0.00 to 0.10 L; p=0.031).

Table S2   Evening predose FEV_1 (L): treatment means during the randomized treatment period (efficacy analysis set)

			Randomized treatment period[a]			
					From ANCOVA on change from baseline	
Treatment	N	Baseline value[b] Mean (SD)	Observed value Mean (SD)	Change from baseline Mean (SD)	LS mean (SEM)	95% CI
SYMB 160/9 bid	151	2.85 (0.61)	2.86 (0.62)	0.01 (0.18)	0.00 (0.02)	(-0.04, 0.04)
SYMB 320/9 qd	152	2.98 (0.59)	2.90 (0.58)	-0.08 (0.25)	-0.08 (0.02)	(-0.12, -0.05)
SYMB 160/9 qd	152	2.84 (0.71)	2.72 (0.69)	-0.12 (0.20)	-0.14 (0.02)	(-0.17, -0.10)
Budes 320 qd	151	2.89 (0.72)	2.71 (0.72)	-0.18 (0.21)	-0.20 (0.02)	(-0.23, -0.16)

[a]   Mean of all evening predose FEV_1 values obtained during the double-blind treatment period.
[b]   Baseline is defined as the evening predose FEV_1 measured on the day of randomization (Visit 2).

Table S3   Evening predose FEV_1 (L): treatment comparisons for change from baseline during the randomized treatment period (efficacy analysis set)

	ANCOVA analysis		
Comparisons	LS mean (SEM)	95% CI	p-value
SYMB 160/9 bid vs SYMB 320/9 qd	0.09 (0.02)	(0.04, 0.13)	<0.001
SYMB 160/9 bid vs SYMB 160/9 qd	0.14 (0.02)	(0.09, 0.19)	<0.001
SYMB 160/9 bid vs Budes 320 qd	0.20 (0.02)	(0.15, 0.25)	<0.001
SYMB 320/9 qd vs SYMB 160/9 qd	0.05 (0.02)	(0.00, 0.10)	0.031
SYMB 320/9 qd vs Budes 320 qd	0.11 (0.02)	(0.06, 0.16)	<0.001
SYMB 160/9 qd vs Budes 320 qd	0.06 (0.02)	(0.01, 0.11)	0.016

Note: Baseline is defined as the predose FEV_1 measured on the day of randomization (Visit 2). Double-blind treatment period refers to the mean of all predose FEV_1 values obtained during the double-blind treatment period. The bolded comparison is the prespecified primary comparison for this variable.

Results of the secondary efficacy endpoints were supportive of these primary findings. Key findings are as follows:

- For evening PEF (recorded in the daily diary), SYMBICORT pMDI 160/9 bid and SYMBICORT pMDI 320/9 qd were superior to budesonide 320 qd. However, unlike results for evening predose FEV_1, the comparison between SYMBICORT pMDI 160/9 qd and budesonide 320 qd was not statistically significant. Decreases from baseline in evening PEF were seen for both of the SYMBICORT pMDI once-daily treatment groups compared to the SYMBICORT pMDI 160/9 bid group, which maintained the level of pulmonary function that was established during the run-in period; these differences were statistically significant.

- For morning PEF, all 3 SYMBICORT pMDI treatment groups were shown to be superior to budesonide 320 qd. There were no significant differences for SYMBICORT pMDI 160/9 bid compared to the once-daily SYMBICORT pMDI groups for morning PEF (measured midway through the once-daily dosing interval), unlike results for evening PEF and evening predose FEV_1 (measured at the end of the dosing interval).

- For other secondary efficacy endpoints (symptom and rescue use measures), the SYMBICORT pMDI 320/9 qd and SYMBICORT pMDI 160/9 qd treatment groups demonstrated statistically significantly greater efficacy than budesonide 320 qd for most measures. The SYMBICORT pMDI 160/9 bid treatment group was superior to budesonide 320 qd for all symptom and rescue use measures. Across all variables, the SYMBICORT pMDI 160/9 bid treatment group maintained the level of asthma control that was established during the run-in baseline period, without experiencing a loss of efficacy during double-blind treatment. In contrast, a reduction in efficacy from baseline during double-blind treatment was seen for both of the SYMBICORT pMDI once-daily treatment groups compared to the SYMBICORT pMDI 160/9 bid group. These differences were statistically significant for several of these variables.

There were no statistically significant or clinically relevant differences between the SYMBICORT pMDI 320/9 qd and SYMBICORT pMDI 160/9 qd treatment groups for any secondary endpoint.

Statistically significant mean differences were observed that favored the SYMBICORT pMDI twice-daily group relative to budesonide for both the AQLQ(S) and the ACQ endpoints; however, the magnitude of these differences did not achieve the predetermined threshold for clinical significance. No significant differences were seen for the SYMBICORT pMDI once-daily treatment groups relative to budesonide for either endpoint. There were too few subjects aged 12 to <18 years to draw conclusions concerning the PAQLQ(S) endpoint.

Safety results

A total of 618 of the 619 randomized subjects received at least 1 dose of double-blind treatment and were included in the safety analysis set. The mean duration of run-in therapy (approximately 5 weeks) and of randomized treatment (approximately 11.5 weeks) was similar across treatment groups.

The most common AEs during the randomized treatment period for the safety analysis set are shown in Table S4. No consistent pattern with respect to budesonide or formoterol total daily dose was seen in the incidence of these events across treatment groups, except for nasopharyngitis and vomiting, each of which was slightly higher on SYMBICORT pMDI 160/9 bid compared to the other treatment groups.

Table S4   **AEs reported by at least 3% of subjects in any treatment group during the randomized treatment period (safety analysis set)**

MedDRA Preferred term	SYMB 160/9 bid (N=155)	SYMB 320/9 qd (N=153)	SYMB 160/9 qd (N=157)	Budes 320 qd (N=153)
Mean (SD) duration of exposure (days)	79.6 (18.3)	80.4 (18.0)	77.7 (19.0)	80.3 (17.1)
Number (%) of subjects with any AE	82 (52.9)	66 (43.1)	77 (49.0)	84 (54.9)
Headache	14 (9.0)	7 (4.6)	12 (7.6)	13 (8.5)
Nasopharyngitis	18 (11.6)	6 (3.9)	10 (6.4)	11 (7.2)
Pharyngolaryngeal pain	9 (5.8)	10 (6.5)	6 (3.8)	8 (5.2)
Upper respiratory tract infection	5 (3.2)	8 (5.2)	9 (5.7)	11 (7.2)
Sinusitis	4 (2.6)	6 (3.9)	11 (7.0)	11 (7.2)
Nasal congestion	4 (2.6)	8 (5.2)	5 (3.2)	2 (1.3)
Viral upper respiratory tract infection	5 (3.2)	1 (0.7)	3 (1.9)	4 (2.6)
Back pain	5 (3.2)	4 (2.6)	1 (0.6)	2 (1.3)
Vomiting	7 (4.5)	0	0	1 (0.7)
Bronchitis	0	1 (0.7)	0	5 (3.3)

Five subjects experienced serious adverse events (SAE) during the double-blind treatment period: 2 (1.3%) in SYMBICORT pMDI 160/9 bid group and 3 (1.9%) in the SYMBICORT pMDI 160 qd group. The percentage of subjects who had AEs that led to discontinuation (DAE) with onset during randomized treatment was low and similar across treatment groups (1.3% for SYMBICORT pMDI 160/9 bid, 1.3% for SYMBICORT pMDI 320/9 qd, 2.5% for SYMBICORT pMDI 160/9 qd, and 0.7% for budesonide 320 qd). One notable additional subject (SYMBICORT pMDI 160/9 bid) had a DAE 1 day following discontinuation of randomized treatment; this event (myocardial infarction) was also an SAE but was not considered related to study drug by the investigator. There were no deaths reported or OAEs identified in this study.

No clinically meaningful changes or treatment group differences were observed in clinical laboratory, vital signs (heart rate, diastolic and systolic blood pressure), or physical exam findings.

Date of the report

9 November 2005