Drug product:	SYMBICORT® pMDI 160/4.5 µg	**SYNOPSIS**	
Drug substance(s):	Budesonide/Formoterol		
Study code:	SD-039-0728		
Edition No.:			
Date:	29 March 2006		

A 52-week, randomized, double-blind, single-dummy, parallel-group, multicenter Phase III study comparing the long-term safety of SYMBICORT® pMDI 160/4.5 µg x 4 actuations twice daily to SYMBICORT® pMDI 160/4.5 µg x 2 actuations twice daily and budesonide HFA pMDI 160 µg x 4 actuations twice daily in adult and adolescent subjects with asthma

International co-ordinating Investigator

None appointed for this study

Study center(s)

This study was conducted in the United States (77 centers).

Publications

SP Peters, BM Prenner, P Martin, C O'Brien. Long-Term Effects on Lung Function of Budesonide (BUD) and Formoterol (FM) in One Pressurized Metered-Dose Inhaler (BUD/FM pMDI) and BUD pMDI in Patients With Asthma. Am J Respir Crit Care Med. 2007;175:A192 (abstract).

C O'Brien, SP Peters, BM Prenner, P Martin . Long-Term Safety of Budesonide/Formoterol Pressurized Metered-Dose Inhaler (BUD/FM pMDI) in Asthma Patients: Adverse Events and Asthma Exacerbations. Am J Respir Crit Care Med. 2007;175:A188 (abstract).

Study dates		**Phase of development**
First subject enrolled	15 August 2003	Therapeutic confirmatory (III)
Last subject completed	03 February 2005	

Objectives

Primary:

To assess the long-term safety profile of SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily (bid) as compared to that of SYMBICORT pMDI 160/4.5 µg x 2 actuations

bid and budesonide HFA pMDI 160 µg x 4 actuations bid, over a 52-week treatment period as measured by asthma exacerbations, electrocardiograms (ECGs) and Holter monitors, forced expiratory volume in the 1st second (FEV_1), morning peak expiratory flow (AM PEF[1]), adverse events, laboratory parameters including 24-hour urinary cortisol, use of adjunctive asthma therapy due to worsening of asthma, and physical examinations. No single variable was considered to be primary.

Secondary:

- To assess the maximal FEV_1 following albuterol administration in subjects receiving SYMBICORT pMDI 160/4.5 µg x 4 actuations bid as compared to SYMBICORT pMDI 160/4.5 µg x 2 actuations bid and budesonide HFA pMDI 160 µg x 4 actuations bid, over a 52-week treatment period as measured by changes from baseline in maximal FEV_1 from Maximal Achievable Response Testing (MART) conducted at a subset of sites.

- To collect patient reported outcomes and resource utilization data for subjects treated with SYMBICORT pMDI 160/4.5 µg x 2 actuations bid, SYMBICORT pMDI 160/4.5 µg x 4 actuations bid, and budesonide HFA pMDI 160 µg x 4 actuations bid, over a 52-week treatment period as measured by symptom-free days, asthma-control days, asthma-related hospitalizations, emergency room/urgent care center visits, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications, use of rescue medication, days missed from work/school due to asthma, and days of interrupted activities due to asthma to be used in analyses of cost effectiveness.

- To measure the systemic availability of budesonide and formoterol from SYMBICORT pMDI 160/4.5 µg x 4 actuations bid, SYMBICORT pMDI 160/4.5 µg x 2 actuations bid, and budesonide HFA pMDI 160 µg x 4 actuations bid, by assessment of $AUC_{(0\text{-}t)}$ and C_{max} from 12-hour serial blood draws conducted at a subset of sites.

Study design:

This was a 52-week, randomized, double-blind, single-dummy, parallel-group, multicenter Phase III study to compare the long-term safety of SYMBICORT pMDI (pressurized metered dose inhaler) 160/4.5 µg x 4 actuations bid, SYMBICORT pMDI 160/4.5 µg x 2 actuations bid, and budesonide hydrofluoroalkane-227 (HFA) pMDI 160 µg x 4 actuations bid, in adult and adolescent subjects with moderate-to-severe asthma[2]. Randomization followed a 2-week run-in period during which all subjects

[1] Hereafter referred to as morning PEF.

[2] Hereafter, the following conventions will be observed:
SYMBICORT pMDI 160/4.5 µg x 4 actuations bid will be referred to as SYMBICORT pMDI 640/18 bid.

received budesonide pMDI 160 µg x 2 actuations bid. Eligible subjects were assigned to 1 of 4 possible design strata, based on whether the subjects were to participate in (1) pharmacokinetics (PK) testing, (2) MART testing, (3) both PK and MART testing, or (4) neither PK testing nor MART testing; randomization was stratified by these strata.

Target subject population and sample size:

The target population included male and female subjects ≥12 years of age who had a documented clinical diagnosis of moderate-to-severe asthma for at least 6 months prior to screening and who were in stable condition. Subjects should have received maintenance asthma treatment with a stable dose of 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 6 hours after the last dose of short-acting β_2-agonist and at least 24 hours after the last dose of long-acting β_2-agonist (LABA), of ≥45% of predicted normal. Approximately 570 subjects were targeted for randomization in an overall ratio of approximately 350:110:110 (SYMBICORT pMDI 160/4.5 µg x 4 actuations bid: SYMBICORT pMDI 160/4.5 µg x 2 actuations bid: budesonide 160 µg x 4 actuations bid, respectively).

Investigational product and comparator(s):

All eligible subjects were randomized to 1 of the following 3 treatment groups:

- SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg x 4 actuations bid; batches P6502A, P6675, P6722, and P6721A.
- SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg x 2 actuations bid; batches P6502A, P6675, P6722, and P6721A.
- Budesonide HFA pMDI 160 µg x 4 actuations bid; batches P6495, P6611, and P6716.

Budesonide HFA pMDI 160 µg x 2 actuations bid was used during the single-blind run-in period (batch numbers P6495 and P6611). Albuterol, delivered by pMDI (90 µg per inhalation), was used as rescue medication on an as-needed basis during both the run-in and treatment periods (batch numbers ABZ93A and ACA59A).

Duration of treatment:

The randomized, double-blind treatment period was 52 weeks long and was preceded by a 2-week budesonide HFA pMDI single-blind run-in period.

SYMBICORT pMDI 160/4.5 µg x 2 actuations bid will be referred to as SYMBICORT pMDI 320/9 bid.
budesonide pMDI 160 µg x 4 actuations bid will be referred to as budesonide 640 bid.

Criteria for evaluation (main variables): No single variable was considered primary.

Efficacy, patient-reported outcomes, health economic outcomes, and pharmacokinetics

There was no efficacy objective in this safety study. However, spirometry (predose and 2-hour postdose FEV_1) was conducted at each study visit to detect any untoward decreases in lung function over the 52-week period. In addition, diary-based measures of asthma control (morning PEF, symptom-free days, rescue medication-free days, asthma-control days, daily rescue medication use), asthma exacerbations (hospitalizations, emergency room/urgent care visits, oral and systemic corticosteroid use), and results of Maximal Achievable Response Testing (MART; postalbuterol maximal FEV_1 achieved during 52 weeks of randomized treatment, compared with results achieved prior to initiation of randomized treatment) were analyzed and are presented as efficacy variables. Health economic outcomes were assessed through measures of direct medical and indirect resource utilization. Direct medical resource utilization measures included unscheduled specialist visits, primary healthcare physician visits, number of unscheduled phone calls to physicians, hospitalizations and emergency room/urgent care center visits due to asthma exacerbation, use of adjunctive asthma medications due to worsening of asthma, use of rescue medication. Indirect resource utilization measures included days missed from work/school due to asthma and days of interrupted activities due to asthma. Pharmacokinetic parameters (area under the curve from time 0 to 12 hours [AUC_{0-12}], maximum plasma concentration [C_{max}], and time to C_{max} [T_{max}]) for plasma budesonide and plasma formoterol were calculated for subjects who consented to provide blood samples for this purpose. Blood samples were collected from subjects predose and at 9 timepoints over 12 hours postdose 2 weeks after start of randomized treatment.

Safety:

Adverse events, 12-lead ECGs, 24-hour Holter monitoring, clinical laboratory data including 24-hour urinary cortisol, physical examination, and vital signs were used to evaluate safety

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Statistical methods:

No single variable was considered the primary variable. In addition to the safety analysis set, consisting of all randomized subjects who received at least 1 dose of randomized study drug, the postdose analysis set, consisting of all subjects who had clinic visit safety assessments measured 1-2 hours after randomized treatment at all visits, was also used in the analysis of some safety data.

Continuous variables were analyzed with linear models. Event data, such as asthma exacerbations and direct and indirect resource utilization variables, were presented as follows: (1) the number and percent of subjects, analyzed using a chi-square test, and (2) event data, expressed in days per subject-treatment year and, when applicable, analyzed using Poisson regression. For asthma exacerbations, time to 1st event was additionally analyzed using survival techniques. P-values and 95% confidence intervals using 2-sided

alternatives, unadjusted for multiplicity, are presented for all pairwise comparisons; however, these were considered descriptive in nature to aid in data interpretation, and this output from statistical analyses was not associated with a decision rule.

Subject population:

A total of 1147 subjects were screened for possible study participation, 805 of whom subsequently entered the run-in period and received at least 1 dose of single-blind budesonide pMDI 160 µg x 2 actuations bid. Of these, 708 subjects were subsequently randomized (443 in the SYMBICORT pMDI 640/18 bid group, 132 in the SYMBICORT pMDI 320/9 bid group, and 133 in the budesonide 640 bid group). Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics. Table S1 summarizes demographic and key baseline characteristics for the safety analysis set. The overall discontinuation rate was highest in the budesonide 640 bid group (19.5%), compared with 18.5% in the SYMBICORT pMDI 640/18 bid group and 15.9% in the SYMBICORT pMDI 320/9 bid group. The most common reason for discontinuation among randomized subjects was adverse events (50 subjects, 7.1%).

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

	Treatment group[a]			
	SYMB 640/18 bid (N=443)	**SYMB 320/9 bid (N=132)**	**Budes 640 bid (N=133)**	**Total (N=708)**
Sex (n and % of subjects)				
Male	164 (37.0)	54 (40.9)	42 (31.6)	260 (36.7)
Female	279 (63.0)	78 (59.1)	91 (68.4)	448 (63.3)
Age (yr)				
Mean (SD)	41 (16.61)	38.6 (16.15)	39.8 (15.61)	40.3 (16.35)
Median	42	39	40	41
Min/Max	12/81	12/75	12/76	12/81
Age groups (yr) (n and % of subjects)				
12 to <16	40 (9.0)	17 (12.9)	9 (6.8)	66 (9.3)
16 to <65	364 (82.2)	109 (82.6)	115 (86.5)	588 (83.1)
≥65	39 (8.8)	6 (4.5)	9 (6.8)	54 (7.6)
Race (n and % of subjects)				
Caucasian	383 (86.5)	117 (88.6)	116 (87.2)	616 (87.0)
Black	36 (8.1)	10 (7.6)	14 (10.5)	60 (8.5)
Oriental	7 (1.6)	2 (1.5)	0	9 (1.3)
Other	17 (3.8)	3 (2.3)	3 (2.3)	23 (3.2)
Years since asthma diagnosis				
Mean (SD)	22.3 (15.34)	22.6 (15.19)	24.4 (15.48)	22.7 (15.34)
Min, Max	0.5, 69.8	0.5, 65.3	0.8, 71.8	0.5, 71.8
Total daily ICS dose at study entry (µg)				
Mean (SD)	513.9 (238.82)	471.5 (231.74)	508.7 (272.9)	505 (244.49)
Min, Max	88, 1200	100, 1000	80, 1600	80, 1600
FEV_1 (L) at screening (Visit 1, prebronchodilator)				

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

	Treatment group[a]			
	SYMB 640/18 bid (N=443)	SYMB 320/9 bid (N=132)	Budes 640 bid (N=133)	Total (N=708)
N	441	132	133	706
Mean (SD)	2.4 (0.71)	2.4 (0.69)	2.3 (0.66)	2.4 (0.7)
Percent predicted FEV_1 at screening (Visit 1, pre-bronchodilator)				
N	441	132	133	706
Mean (SD)	72.6 (14.07)	71.2 (12.93)	72.2 (13.12)	72.3 (13.68)
Baseline FEV_1 (L) (predose at Visit 2)				
Mean (SD)	2.4 (0.74)	2.4 (0.74)	2.4 (0.65)	2.4 (0.72)
Baseline percent predicted FEV_1 (L) (predose at Visit 2)				
Mean (SD)	74.8 (14.46)	72.1 (13.59)	72.7 (13.59)	73.9 (14.17)

[a] SYMB 640/18 bid SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily; SYMB 320/9 bid SYMBICORT pMDI 160/4.5 µg x 2 actuations twice daily; Budes 640 bid budesonide HFA pMDI 160 µg x 4 actuations twice daily.

Efficacy, health economics, and pharmacokinetic results:

Improvements in mean predose FEV_1 and mean 2-hour postdose FEV_1 relative to baseline were seen with all 3 treatments at all timepoints. Compared with budesonide 640 bid, SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid resulted in significantly greater improvement in both of these spirometry endpoints. For diary-based measures of asthma control, including morning PEF, symptom-free days, rescue medication-free days, asthma-control days, and daily use of rescue medication, SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid also resulted in significantly greater improvement over budesonide 640 bid. Improvements in spirometry measures and diary-based measures of asthma control were seen as early as the 1st assessment after initiation of randomized treatment, with no diminution of SYMBICORT pMDI effect relative to budesonide during the randomized treatment period. Improvements in mean predose FEV_1, mean 2-hour postdose FEV_1, mean morning PEF, and measures for mean rescue medication use (ie, rescue medication-free days and total daily rescue use) for SYMBICORT pMDI 640/18 bid were numerically, but not statistically significantly larger than improvements in the SYMBICORT pMDI 320/9 bid group.

Tables S2 and S3 show that a significantly lower percentage of subjects in the SYMBICORT pMDI 640/18 bid group experienced an asthma exacerbation compared with subjects in the budesonide 640 bid group. Time to 1st asthma exacerbation in the SYMBICORT pMDI 640/18 bid group was also significantly longer compared with the budesonide group, based on results from survival analysis. In addition, subjects in each SYMBICORT pMDI group had a significantly lower total number of asthma exacerbations per subject-treatment year compared with the budesonide group. There were no statistically significant differences between the SYMBICORT pMDI groups for these variables. Analysis of patterns of deterioration and recovery associated with asthma exacerbations, as measured by mean morning PEF, mean number of puffs/day of

rescue medication use, and mean percentage of subjects with symptom-free days during the period extending from 30 days before to 30 days after asthma exacerbation indicated no deleterious impact of formoterol on the course of an exacerbation. The number of hospitalizations and emergency/urgent care visits due to asthma were numerically, but not statistically significantly, higher in the SYMBICORT pMDI groups compared with the budesonide group; these findings for SYMBICORT pMDI were not dose-ordered.

Table S2 Summary of asthma exacerbations during the randomized treatment period (safety analysis set)

	Treatment group[a]		
Criteria	**SYMB 640/18 bid (N=443)**	**SYMB 320/9 bid (N=132)**	**Budes 640 bid (N=133)**
Asthma exacerbations (all categories)			
Subjects with at least 1 asthma exacerbation, n (%)	54 (12.2)	19 (14.4)	29 (21.8)
Total number of asthma exacerbations	68	22	37
Total number of asthma exacerbations per subject-treatment year	0.174	0.185	0.315

[a] SYMB 640/18 bid SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily; SYMB 320/9 bid SYMBICORT pMDI 160/4.5 µg x 2 actuations twice daily; Budes 640 bid budesonide HFA pMDI 160 µg x 4 actuations twice daily.

Note: Randomized treatment period is defined as the day of the 1st dose of randomized medication until the day after the last dose of randomized treatment. Subjects who had asthma exacerbations later than 1 day after the last dose of study drug were not included in the analyses.

Table S3 Asthma exacerbations: treatment comparisons for the number and percentage of subjects with at least 1 asthma exacerbation and of exacerbations per subject-treatment year during the randomized treatment period (safety analysis set)

Comparison[a]	**Estimate**	**95% CI**	**p-value**
Number (%) of subjects with at least 1 asthma exacerbation[b]			
SYMB 640/18 bid vs. SYMB 320/9 bid	0.826	(0.470, 1.450)	0.504
SYMB 640/18 bid vs. Budes 640 bid	0.498	(0.302, 0.821)	0.006
SYMB 320/9 bid vs. Budes 640 bid	0.603	(0.319, 1.140)	0.117
Number of asthma exacerbations per subject-treatment year[c]			
SYMB 640/18 bid vs. SYMB 320/9 bid	0.940	(0.581, 1.520)	0.800
SYMB 640/18 bid vs. Budes 640 bid	0.552	(0.370, 0.825)	0.004
SYMB 320/9 bid vs. Budes 640 bid	0.588	(0.347, 0.997)	0.049

[a] SYMB 640/18 bid SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily; SYMB 320/9 bid SYMBICORT pMDI 160/4.5 µg x 2 actuations twice daily; Budes 640 bid budesonide HFA pMDI 160 µg x 4 actuations twice daily.

[b] Estimate is an odds ratio. P-value is from chi-square test.

[c] Estimate is a rate ratio. P-value is derived from a Poisson regression adjusted for differential treatment exposure by using person years as an offset variable.

Note: Randomized treatment period is defined as the day of the 1st dose of double-blind medication until the day after the last dose of randomized treatment. Subjects who had asthma exacerbations later than 1 day after the last dose of study drug were not included in the analyses.

MART testing was performed to evaluate the postalbuterol maximal FEV_1 obtained during randomized treatment compared to the baseline postalbuterol maximal FEV_1 obtained prior to initiation of randomized treatment. Subjects in the SYMBICORT pMDI groups experienced small but statistically significant decreases from baseline in postalbuterol maximum FEV_1 at Week 6, end of Month 6, and for treatment average, compared with subjects in the budesonide group, although the mean maximum FEV_1 values achieved were generally higher for each SYMBICORT pMDI group than for the budesonide group. The largest difference for SYMBICORT pMDI 640/18 bid minus budesonide 640 bid occurred at end of Month 6 (LS mean difference [95% CI]=-0.12 L [-0.20, -0.04]), and the largest difference for SYMBICORT pMDI 320/9 bid minus budesonide 640 bid occurred at Week 6 (LS mean difference=-0.10 L [-0.18, -0.02]) and at end of Month 6 (LS mean difference= -0.10 L [-0.18, -0.01]). Results at Month 12 and at end of treatment were generally similar to those at earlier timepoints; however, differences between the SYMBICORT pMDI groups and the budesonide group were smaller and not statistically significant. There were no significant differences between the SYMBICORT pMDI groups at any timepoint analyzed.

For measures of direct medical and indirect resource utilization, subjects in the SYMBICORT pMDI 640/18 bid group and the SYMBICORT pMDI 320/9 bid group used significantly less rescue medication and oral steroids, and experienced significantly fewer days of interrupted activities due to asthma (8.331 and 8.339 days interrupted per subject-treatment year, respectively) than subjects in the budesonide group (17.763 days interrupted per subject-treatment year, $p<0.001$ for comparisons between each SYMBICORT pMDI group and the budesonide group). Differences between treatment groups for other measures of direct medical and indirect resource utilization were not statistically significant. There were no significant differences between the SYMBICORT pMDI groups for these variables.

Systemic exposure to budesonide was comparable for the SYMBICORT pMDI 640/18 bid and budesonide 640 bid treatment groups, as indicated by mean AUC_{0-12} and C_{max} treatment ratios (90% confidence interval) of 1.081 (0.834, 1.400) and 0.925 (0.732, 1.169), respectively. For budesonide 640 bid versus SYMBICORT pMDI 320/9 bid, mean dose-adjusted AUC_{0-12} and C_{max} treatment ratios for plasma budesonide were 0.745 (0.578, 0.962) and 0.858 (0.682, 1.081), respectively, indicating a slightly less than proportional increase in budesonide exposure in the budesonide group, compared with the SYMBICORT pMDI 320/9 bid group. For SYMBICORT pMDI 640/18 bid versus SYMBICORT pMDI 320/9 bid, mean dose-adjusted AUC_{0-12} and C_{max} treatment ratios for plasma budesonide were 0.805 (0.619, 1.048) and 0.794 (0.626, 1.007), respectively, indicating a slightly less than proportional increase in budesonide exposure in the SYMBICORT pMDI 640/18 bid group, compared with the SYMBICORT pMDI 320/9 bid group. Median T_{max} for budesonide was approximately 20 minutes in the SYMBICORT pMDI 640/18 bid and SYMBICORT pMDI 320/9 bid groups (0.358 hours

and 0.331 hours, respectively), compared with approximately 40 minutes (0.658 hours) in the budesonide group.

Mean dose-adjusted AUC_{0-12} and C_{max} treatment ratios for plasma formoterol were 1.096 (0.906, 1.325) and 1.128 (0.944, 1.346), respectively, for SYMBICORT pMDI 640/18 bid versus SYMBICORT pMDI 320/9 bid, indicating an approximately proportional increase in formoterol exposure with the doubling of formoterol dose. Median T_{max} values for formoterol were generally similar for the SYMBICORT pMDI 320/9 bid group (0.832 hours) and the SYMBICORT pMDI 640/18 bid group (0.657 hours).

Safety results:

All 708 randomized subjects received at least 1 dose of randomized study drug and were included in the safety analysis set. The mean overall exposure, in terms of days on randomized treatment, was approximately 320 days for each treatment group. For subjects in the SYMBICORT pMDI 640/18 bid group, 390 (88.0%) and 363 (81.9%) continued randomized treatment at Week 24 and Week 48, respectively.
Overall, SYMBICORT pMDI 640/18 bid, SYMBICORT pMDI 320/9 bid, and budesonide 640 bid were well tolerated in this population of subjects 12 years of age and older with moderate to severe asthma. Table S4 presents an overview of adverse events (AEs) during randomized treatment. The percentage of subjects with study drug-related AEs as judged by the investigator was higher in the SYMBICORT pMDI 640/18 bid group (28.0%) than in the budesonide 640 bid group (19.5%), while the percentage in the SYMBICORT pMDI 320/9 bid group was the lowest (15.2%). There were no deaths or "other significant adverse events" (OAEs) throughout the study period. The overall percentage of subjects with serious adverse events (SAEs) during randomized treatment was higher in the SYMBICORT pMDI 320/9 bid group (9.1%) than in the SYMBICORT pMDI 640/18 bid (4.7%) and budesonide 640 bid (3.8%) groups. There were 4 subjects with SAEs related to cholecystitis, all in the SYMBICORT pMDI 640/18 bid group; however, all were judged to be unrelated to study drug by the investigator. The overall incidence of discontinuations due to AEs (DAEs) was slightly higher in the SYMBICORT pMDI groups than in the budesonide group.

Table S4 Overview of AEs with onset during randomized treatment (safety analysis set)

Category	Number (%) of subjects who had an AE in each category[a]		
	SYMB 640/18 bid (N=443)	SYMB 320/9 bid (N=132)	Budes 640 bid (N=133)
Mean (SD) duration of exposure (days)	322.0 (104.09)	328.5 (95.79)	322.4 (103.40)
Any adverse event (AE)	394 (88.9)	111 (84.1)	118 (88.7)
Any drug-related AE	124 (28.0)	20 (15.2)	26 (19.5)
Serious adverse events (SAEs)	21 (4.7)	12 (9.1)	5 (3.8)
SAEs leading to death	0	0	0
SAEs not leading to death	21 (4.7)	12 (9.1)	5 (3.8)
SAEs leading to discontinuation	6 (1.4)	3 (2.3)	1 (0.8)
AEs leading to discontinuation (DAEs)	33 (7.4)	8 (6.1)	6 (4.5)
Other significant adverse events (OAEs)	0	0	0
	Total number of AEs		
AEs	2010	611	541
SAEs	27	15	5
DAEs	43	9	9
Other significant adverse events	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Note: SYMB 640/18 bid SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily; SYMB 320/9 bid SYMBICORT pMDI 160/4.5 µg x 2 actuations twice daily; Budes 640 bid budesonide HFA pMDI 160 µg x 4 actuations twice daily.

AE adverse event; SAE Serious adverse event.

AEs that occurred with a ≥5% incidence in any treatment group are presented in Table S5. Overall, an association between budesonide dose and AE incidence was most clearly evident for pharyngolaryngeal pain. Although the incidence of oral candidiasis was higher for SYMBICORT pMDI 640/18 bid than for 320/9 bid, the incidence for budesonide 640 bid was less than for SYMBICORT pMDI 640/18 bid; thus, the relationship to budesonide dose was not clear. A dose-ordered relationship with respect to formoterol dose was observed for several PTs typically associated with β_2-agonist effects (specifically tremor and muscle cramp). No relationship to formoterol dose was observed for the PT of asthma. Similarly, the incidence of potentially asthma-related AEs that might suggest asthma was generally similar across treatment groups. The overall incidence of AEs in the cardiac SOC and the incidence of individual cardiac-related PTs in the cardiac and investigations SOCs were slightly higher in the SYMBICORT pMDI treatment groups than in the budesonide group; the majority of individual events were related to abnormalities detected during ECG and Holter monitoring and did not result in subject discontinuation. For cardiac and cardiac-related AEs, there were no consistent differences noted between the 2 SYMBICORT pMDI groups. There were no significant patterns of AEs emerging after longer periods of treatment for any of the treatment groups.

Table S5 AEs reported by at least 5% of subjects in any treatment group during randomized treatment (safety analysis set)

Preferred term	Treatment group[a], n (%) of subjects		
	SYMB 640/18 bid (N=443)	SYMB 320/9 bid (N=132)	Budes 640 bid (N=133)
Mean (SD) duration of exposure (days)	**322.0 (104.09)**	**328.5 (95.79)**	**322.4 (103.40)**
Total number of subjects with any AE, n (%)	**394 (88.9)**	**111 (84.1)**	**118 (88.7)**
Nasopharyngitis	95 (21.4)	28 (21.2)	32 (24.1)
Upper respiratory tract infection	80 (18.1)	29 (22.0)	21 (15.8)
Sinusitis	53 (12.0)	14 (10.6)	20 (15.0)
Pharyngolaryngeal pain	57 (12.9)	11 (8.3)	17 (12.8)
Oral candidiasis	53 (12.0)	13 (9.8)	12 (9.0)
Influenza	42 (9.5)	13 (9.8)	13 (9.8)
Viral upper respiratory tract infection	33 (7.4)	9 (6.8)	14 (10.5)
Cough	34 (7.7)	7 (5.3)	9 (6.8)
Headache	28 (6.3)	11 (8.3)	10 (7.5)
Bronchitis	24 (5.4)	9 (6.8)	13 (9.8)
Sinus headache	21 (4.7)	10 (7.6)	8 (6.0)
Back pain	19 (4.3)	11 (8.3)	7 (5.3)
Myalgia	18 (4.1)	9 (6.8)	5 (3.8)
Nasal congestion	20 (4.5)	7 (5.3)	5 (3.8)
Diarrhea	14 (3.2)	8 (6.1)	9 (6.8)
Tremor	30 (6.8)	0	1 (0.8)
Nausea	22 (5.0)	7 (5.3)	1 (0.8)
Muscle cramp	23 (5.2)	3 (2.3)	1 (0.8)
Lower respiratory tract infection	15 (3.4)	3 (2.3)	8 (6.0)
Urinary tract infection	15 (3.4)	7 (5.3)	3 (2.3)
Vomiting	10 (2.3)	8 (6.1)	1 (0.8)

[a] SYMB 640/18 bid SYMBICORT pMDI 160/4.5 µg x 4 actuations twice daily; SYMB 320/9 bid SYMBICORT pMDI 160/4.5 µg x 2 actuations twice daily; Budes 640 bid budesonide HFA pMDI 160 µg x 4 actuations twice daily.

Overall, there were no clinically relevant findings in hematology or clinical chemistry assessments for the SYMBICORT pMDI 640/18 bid or SYMBICORT pMDI 320/9 bid treatment group, compared with budesonide. Small mean increases in serum glucose were observed in all 3 treatment groups, with increases greater in each SYMBICORT pMDI group than in the budesonide group. However, for the SYMBICORT pMDI groups, increases in serum glucose did not demonstrate a consistent dose-ordered relationship. For serum potassium, small mean decreases from baseline for each SYMBICORT pMDI group were more pronounced than those for budesonide, and a dose-ordered relationship was noted between the SYMBICORT pMDI doses. For all other laboratory variables, including urinalysis, there were no clinically meaningful changes from baseline or differences across treatment groups. In general, the incidence of AEs related to hematology or clinical chemistry assessments was low with no meaningful differences across treatment groups.

The effects of SYMBICORT pMDI and budesonide on hypothalamic-pituitary-adrenal (HPA)-axis function were assessed by analysis of 24-hour urinary cortisol. Treatment group comparisons showed evidence of lower mean values of 24-hour urinary cortisol for both the SYMBICORT pMDI 640/18 bid and budesonide 640 bid groups compared with the SYMBICORT pMDI 320/9 bid group, starting at 6 months following randomization and persisting thereafter.

For ECG heart rate in the postdose analysis set, small mean increases were greater in the SYMBICORT pMDI groups than in the budesonide group. The increases were dose-ordered for the 2 SYMBICORT pMDI groups; however, the differences between the groups were very small, showing little effect of doubling the dose of SYMBICORT pMDI on mean heart rate.

For both the postdose and safety analysis sets, QT, QTc (Baz), and QTc (Frid) least squares (LS) mean changes from baseline and differences between the SYMBICORT pMDI and budesonide groups were generally small across most timepoints, with the most prominent differences observed for QTc (Baz). Mean changes from baseline for QTc (Baz) were similar for the 2 SYMBICORT pMDI groups and somewhat larger in these groups compared to budesonide. For the postdose analysis set, the largest difference for QTc (Baz) for SYMBICORT pMDI 640/18 bid minus budesonide 640 bid occurred at end of Month 6: LS mean difference (95% CI)=8.0 msec (3.22, 12.81), and the largest difference for the SYMBICORT pMDI 320/9 bid minus budesonide 640 bid comparison occurred at Week 6: LS mean difference=9.2 msec (3.44, 15.05). For QTc (Frid), similar patterns were observed, though with differences of smaller magnitude. For the subjects identified with potentially significant values for QT, QTc (Baz), and QTc (Frid) (ie, crossed the high threshold [450 msec] or with changes ≥30 msec), the majority of these subjects manifested only a change ≥30 msec; for QTc (Baz) and QTc (Frid), the percentage of these subjects was highest in the SYMBICORT pMDI groups, with evidence of a formoterol dose-ordered relationship. Overall, the percentage of subjects with values crossing the 450-msec threshold was similar across treatment groups with no formoterol dose-ordered relationship noted for QTc (Baz) and QTc (Frid). Three SYMBICORT pMDI subjects had values that crossed the extremely high reference threshold of ≥500 msec for QT or for QTc (Baz) interval: 2 subjects in the SYMBICORT pMDI 640/18 bid group and 1 subject in the SYMBICORT pMDI 320/9 bid group. All 3 of these subjects also had at least 1 pre-randomization QT or QTc (Baz) interval value ≥450 msec. No subject had a QTc (Frid) ≥500 msec.

Analysis of the overall ECG evaluation (made by an independent cardiologist) indicated that the most prevalent abnormality observed across treatment groups was ST-T wave changes, which had a higher incidence in the SYMBICORT pMDI groups than in the budesonide group, but was not dose-ordered between the 2 SYMBICORT pMDI groups. For Holter assessments of average heart rate, minimum heart rate, and percent duration of tachycardia (heart rate >100 bpm), small mean increases were seen for the 2 SYMBICORT pMDI treatment groups compared to budesonide; however, these differences were not considered clinically meaningful and were not consistently

formoterol dose-ordered. Shift table analyses performed on Holter monitor data similarly revealed no consistent dose-ordered effects of formoterol or important differences in the percentages of subjects shifting from normal to abnormal for Holter assessments, including average heart rate, minimum heart rate, sinus pause, ventricular runs, total ventricular and supraventricular ectopic beats, and overall Holter interpretation. The number of subjects with potentially clinically important Holter findings identified on treatment was generally low in all treatment groups.

No clinically meaningful changes or treatment group differences were observed in vital signs (pulse rate, diastolic and systolic blood pressure) or physical exam findings during the conduct of the study.

Date of the report

29 March 2006