Drug product:	SYMBICORT® pMDI 160/4.5 µg	**SYNOPSIS**	
Drug substance(s):	Budesoinde/Formoterol		
Document No.:			
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A Twelve-Week, Randomized, Double-blind, Double-Dummy, Active-Controlled Study of SYMBICORT® pMDI Administered Once Daily in Children and Adolescents 6 to 15 Years of Age with Asthma

International co-ordinating investigator

None appointed for this study

Study center(s)

This study was conducted in the United States (128 centers).

Publications

None as of the completion date of this report.

Study dates		**Phase of development**
First subject enrolled	29 January 2003	Therapeutic confirmatory (III)
Last subject completed	12 August 2004	

Objectives

Primary:

To demonstrate the efficacy of SYMBICORT pMDI 80/4.5 µg, 2 actuations once daily (qd), compared to budesonide pMDI 80 µg, 2 actuations qd, in asthmatic children and adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations twice daily (bid), by assessment of lung function and patient-, caregiver-, and physician-reported outcomes.

Secondary:

- To demonstrate the efficacy of SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, compared to budesonide pMDI 80 µg, 2 actuations qd, in asthmatic children and

- adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, by assessment of lung function and patient-, caregiver-, and physician-reported outcomes.

- To compare the relative efficacy of switching to once-daily therapy with SYMBICORT pMDI 80/4.5 µg, 2 actuations to that of remaining on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, in asthmatic children and adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, by assessment of lung function and patient-, caregiver-, and physician-reported outcomes.

- To demonstrate the health-related quality of life (HRQOL) benefits of SYMBICORT pMDI 80/4.5 µg, 2 actuations qd, and SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, compared to budesonide pMDI 80 µg, 2 actuations qd, in asthmatic children and adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, by assessment of the PAQLQ(S) and PACQLQ[1].

- To investigate the safety profiles of SYMBICORT pMDI 80/4.5 µg, 2 actuations qd; SYMBICORT pMDI 40/4.5 µg, 2 actuations bid; and budesonide pMDI 80 µg, 2 actuations qd, in asthmatic children and adolescents previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, by assessment of adverse events, laboratory measurements, 24-hour urinary cortisol, physical examinations, vital signs, and electrocardiograms.

Study design

This was a 12-week, multicenter, randomized, double-blind, parallel group, active-controlled, Phase 3 study to investigate the efficacy, health-related quality of life, and safety of SYMBICORT pMDI once daily as maintenance therapy in asthmatic children and adolescents 6 to 15 years of age, inclusive, previously stable on SYMBICORT pMDI 40/4.5 µg, 2 actuations bid. The randomization was stratified based on the age of the subject at Visit 1 (6 to 11 years of age versus 12 to 15 years of age) to ensure an approximately uniform distribution of subjects across treatment groups within each of these 2 strata. The trial was intended to be recruited in such a way that no more than 20% of the randomized subjects would be in the older age stratum (ie, adolescents 12 to 15 years of age). At the screening visit, all eligible subjects were assigned to treatment with SYMBICORT pMDI 40/4.5 µg, 2 actuations bid, to be taken during a 4- to 5-week single-blind run-in period designed to stabilize the subjects' asthma symptoms. At Visit 2, subjects who demonstrated stable asthma symptoms during the run-in period and who met the other inclusion/exclusion criteria were then randomized to 12 weeks of double-blind treatment with 1 of the following treatments:

[1] PAQLQ(S) Pediatric Asthma Quality of Life Questionnaire (Standardized); PACQLQ Pediatric Asthma Caregiver Quality of Life Questionnaire.

(1) SYMBICORT pMDI 80/4.5 µg, 2 actuations qd (total daily dose: 160/9.0 µg); (2) SYMBICORT pMDI 40/4.5 µg, 2 actuations bid (total daily dose: 160/18.0 µg); or (3) budesonide pMDI 80 µg, 2 actuations qd (total daily dose: 160 µg).

Target subject population and sample size

The target subject population included male and female subjects who were 6 to 15 years of age, inclusive, at the time of screening. Subjects had a documented clinical diagnosis of asthma for at least 6 months prior to screening, and were in stable condition. 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 approximately 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 of between 60%-90% of predicted normal. Subjects with an FEV_1 between 90-95% predicted could be included if they had an FEV_1/FVC ratio measured on screening spirometry of <80%. In addition, subjects were required to demonstrate reversibility of FEV_1 of at least 12% and ≥0.20 L from baseline within 15 to 30 minutes after administration of a standard dose of fast-acting β_2-agonist, except for subjects ≤11 years of age, who were required to show reversibility of ≥12%, but not also a change of ≥0.20 L.

To detect a true difference in mean change in evening PEF of 10 L/min, assuming a common standard deviation of 30.0 L/min, a 2-group t-test with a 5% two-sided significance level and 88% power required a sample size of 180 subjects per treatment arm. It was assumed that a negligible number of randomized subjects would be unevaluable for the primary efficacy analysis. It was expected, therefore, that approximately 650 subjects would be sought for randomization in order to reach the goal of randomizing 540 evaluable subjects (approximately 180 subjects per treatment group).

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

All eligible subjects were randomized to 1 of the following 3 treatment groups at Visit 2:

- SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations qd, administered in the evening (hereafter called the SYMBICORT 80 qd treatment group) (batch number P6503).

- SYMBICORT pMDI (budesonide/formoterol) 40/4.5 µg per actuation, 2 actuations bid (hereafter called the SYMBICORT 40 bid treatment group) (batch number P6695).

- Budesonide pMDI 80 µg per actuation, 2 actuations qd, administered in the evening (hereafter called the budesonide 80 qd treatment group) (batch numbers P6494 and P6676A).

In order to maintain blinding with the twice-daily dosing regimen, all subjects randomized to receive once-daily dosing were to receive the active treatment in the evening and placebo treatment with a matched device in the morning (batch number P6492).

SYMBICORT pMDI (40/4.5 μg per actuation, 2 actuations bid) was used during the single-blind run-in period (batch numbers P6352, P6350, and P6695). Albuterol, delivered by pMDI, was used as rescue medication on an as-needed basis, during both the run-in and treatment periods (batch numbers ABP33A, ACA31A, ACA59A, and ACF09A). Batch numbers for the placebo pMDI training devices were P6351 and P6492. Batch numbers for EMLA Cream, used as needed for local anesthesia prior to phlebotomy, were 203083, 211051, 301148, and 302074.

Duration of treatment

This study consisted of 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 HRQOL

- Primary variable: evening PEF (from daily diary)

- Secondary variables:

  - Spirometry variables (evening predose FEV_1 [the primary spirometry variable], FVC, PEF, and $FEF_{25-75\%}$; morning predose FEV_1, FVC, PEF, and $FEF_{25-75\%}$); and overall FEV_1 [predose FEV_1, irrespective of whether measured in morning or evening]

  - Electronic diary variables (morning PEF, asthma symptom scores [daytime and nighttime], nighttime awakenings due to asthma, and rescue medication use)

  - Predefined asthma events[2] and withdrawals due to predefined asthma events

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

  - HRQOL (hereafter referred to as Patient-Reported Outcomes [PRO] variables): PAQLQ(S), PACQLQ

[2] In the clinical study protocol, "predefined asthma events" is referred to as "asthma deteriorations."

Safety

Adverse events (AEs), clinical laboratory data, 12-lead electrocardiograms (ECGs), 24-hour urinary cortisol, 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 who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis. Sensitivity analyses of evening PEF were performed using the per protocol (PP) analysis set.

The primary analysis for this study was the change from baseline to the mean over the double-blind treatment period in evening PEF. Change from baseline in evening PEF was analyzed with an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center, age strata, and treatment, and for the covariate of baseline evening PEF. Pairwise comparisons between treatments were made by formulating contrasts within the context of this model. The primary comparison was between SYMBICORT 80 qd and budesonide 80 qd. SYMBICORT 40 bid was compared to budesonide 80 qd to support the secondary objectives. In addition, the SYMBICORT pMDI once-daily group and the SYMBICORT pMDI twice-daily group were compared to each other using two-sided 95% confidence intervals obtained from the same ANCOVA model described above; this comparison was on a descriptive level and was not associated with a decision rule.

For all secondary variables, p-values, unadjusted for multiple comparisons, are presented for all pairwise comparisons. For the secondary efficacy variables, the primary comparisons were the same as those specified for the primary efficacy variable. For the PRO variables, each SYMBICORT pMDI treatment group was compared to budesonide. The continuous secondary efficacy variables and PROs were compared among treatment groups using analyses similar to those specified for the primary variable. Categorical variables were analyzed with the Cochran-Mantel-Haenszel test (adjusting for age strata) and also with survival analysis methodology (for predefined asthma events).

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 or not the subjects were randomized (run-in analysis set).

Subject population

A total of 1478 subjects were screened for possible study participation, 719 of whom subsequently entered the run-in period and received at least 1 dose of single-blind SYMBICORT 40 bid run-in therapy. Of these, 522 subjects were subsequently randomized. Randomization was stratified by age (6 to 11 years of age versus 12 to 15 years of age) at the time of screening, to ensure an approximately uniform distribution of subjects across treatment groups within each of these 2 strata; the primary analysis included all subjects from both strata. Study recruitment was stopped when it was estimated that the target number for randomized subjects would be reached. The safety

analysis set is comprised of all randomized subjects, except 1 subject who did not receive double-blind treatment. Consequently, this subject was not included in the safety analysis set or in the efficacy analysis set. Two of the remaining 521 randomized subjects were excluded from the efficacy analysis set (EAS) because of insufficient efficacy data.

Table S1 summarizes demographic and baseline characteristics for the safety analysis set. There were no apparent differences between treatment groups with respect to demographic and disease severity characteristics that would affect the interpretation of the results of the study.

Among randomized subjects, the overall withdrawal rate was highest in the SYMBICORT 80 qd group (22.0%), followed by the budesonide 80 qd group (19.4%) and the SYMBICORT 40 bid group (11.4%). The most common reason for withdrawal was development of study-specific discontinuation criteria (ie, withdrawals due to predefined asthma events). The percentage of subjects who withdrew because of a predefined asthma event was 16.7% in the SYMBICORT 80 qd group, 14.9% in the budesonide 80 qd group, and 7.1% in the SYMBICORT 40 bid group.

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]			
	SYMB 40 bid (N=184)	SYMB 80 qd (N=168)	Budes 80 qd (N=169)	Total (N=521)
Sex (n and % of subjects)				
Male	130 (70.7)	110 (65.5)	107 (63.3)	347 (66.6)
Female	54 (29.3)	58 (34.5)	62 (36.7)	174 (33.4)
Age (yr)				
Mean (SD)	10.5 (2.43)	10.2 (2.53)	10.1 (2.51)	10.3 (2.49)
Median	10	10	10	10
Min, Max	6 – 15	6 – 15	6 – 15	6 – 15
Age groups (yr), (n and % of subjects)				
6 – 11	120 (65.2)	117 (69.6)	114 (67.5)	351 (67.4)
12 – 15	64 (34.8)	51 (30.4)	55 (32.5)	170 (32.6)
Race, (n and % of subjects)				
Caucasian	140 (76.1)	120 (71.4)	128 (75.7)	388 (74.5)
Black	28 (15.2)	29 (17.3)	23 (13.6)	80 (15.4)
Oriental	1 (0.5)	2 (1.2)	4 (2.4)	7 (1.3)
Other	15 (8.2)	17 (10.1)	14 (8.3)	46 (8.8)
Years since asthma diagnosis				
Mean (SD)	6.8 (3.39)	6.7 (3.37)	6.8 (3.48)	6.8 (3.41)

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]			
	SYMB 40 bid (N=184)	SYMB 80 qd (N=168)	Budes 80 qd (N=169)	Total (N=521)
Min, Max	0.6 – 14.6	0.6 – 15.6	0.5 – 14.5	0.5 – 15.6
ICS dose at entry (µg/day)				
Mean (SD)	243.4 (155.08)	241.9 (153.79)	250.8 (175.21)	245.3 (161.22)
Min, Max	80 - 1160	80 - 1000	44 - 1000	44 - 1160
Percent reversibility in FEV_1 at screening (Visit 1)				
N	183	165	168	516
Mean (SD)	19.8 (8.34)	18.3 (8.02)	19.1 (7.65)	19.1 (8.03)
Median	16.8	16.0	16.6	16.4
Min, Max	10.8 - 60.8	8.8 - 60.2	10.9 - 53.2	8.8 - 60.8
FEV_1 (L) at screening (Visit 1, pre-bronchodilator)				
Mean (SD)	1.9 (0.56)	1.9 (0.64)	1.8 (0.54)	1.9 (0.58)
Percent predicted FEV_1 at screening (Visit 1, pre-bronchodilator)				
Mean (SD)	77.9 (8.21)	79.0 (8.63)	77.9 (8.86)	78.3 (8.56)
Baseline FEV_1 (L) (predose at Visit 2)				
Mean (SD)	2.2 (0.62)	2.1 (0.69)	2.0 (0.63)	2.1 (0.65)
Baseline percent predicted FEV_1 (predose at Visit 2)				
Mean (SD)	88.9 (10.40)	88.3 (9.22)	88.0 (8.72)	88.4 (9.49)

[a] SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.

Efficacy and PRO results

Results of the primary analysis of the primary efficacy endpoint - change from baseline to the mean of the double-blind treatment period in evening PEF - are summarized in Table S2 (treatment means) and Table S3 (treatment comparisons). The study subjects recorded this variable each evening in their electronic diary. Key findings for the primary efficacy endpoint are as follows:

- SYMBICORT 80 qd was shown to be superior to budesonide 80 qd (p=0.027).
- SYMBICORT 40 bid was shown to be superior to budesonide 80 qd (p<0.001).
- There was no clinically relevant difference in mean response between the SYMBICORT 40 bid group and the SYMBICORT 80 qd group (LS mean difference 4.55 L/min, 95% CI: -2.75 to 11.84 L/min, p=0.222).

There was no clear evidence of differences in treatment effects on evening PEF across age strata, the design stratification (age strata-by-treatment interaction p=0.713).

Table S2 Evening PEF (L/min): treatment means during double-blind treatment (EAS)

Evening PEF L/min		Baseline value[b]	Double-blind treatment period[a]			
			Observed value	Change from baseline	From ANCOVA on change from baseline	
Treatment[c]	N	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SEM)	95% CI
SYMB 40 bid	183	299.29 (82.809)	305.98 (85.347)	6.69 (35.524)	9.10 (3.091)	(3.02, 15.17)
SYMB 80 qd	168	294.64 (98.514)	295.09 (97.324)	0.45 (34.927)	4.55 (3.220)	(-1.78, 10.88)
Budes 80 qd	168	284.46 (81.979)	278.62 (83.239)	-5.84 (29.898)	-3.86 (3.224)	(-10.20, 2.47)

[a] Mean of all values obtained during the double-blind treatment period, beginning on the 1st day after randomization (Day 2) and ending on the last day of treatment, inclusive.
[b] Baseline is defined as the mean of all values obtained during the last 10 days of the run-in period, excluding day of randomization data.
[c] SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.
EAS Efficacy analysis set.

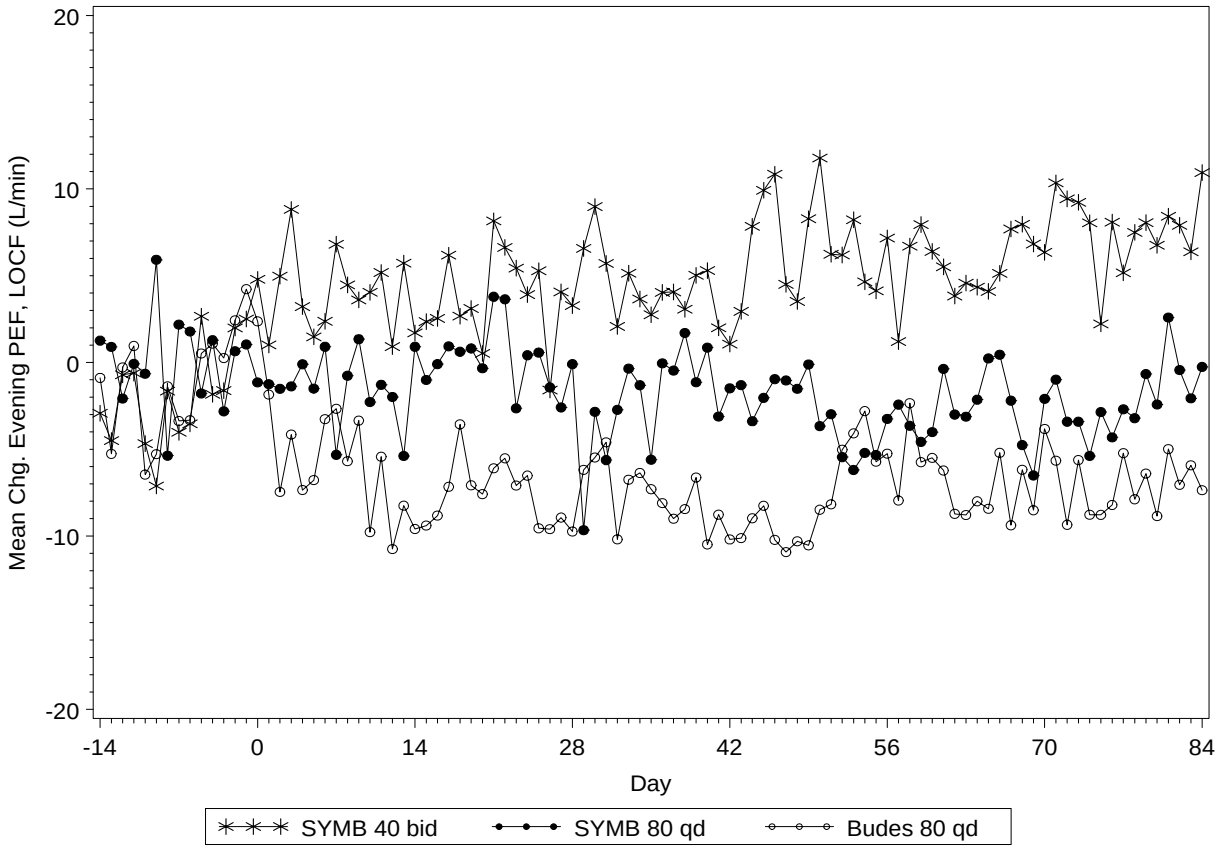
Table S3 Evening PEF (L/min): treatment comparisons for change from baseline during double-blind treatment (EAS)

Comparison[a]	ANCOVA analysis		
	LS mean (SEM)	95% CI	p-value
SYMB 40 bid minus SYMB 80 qd	4.55 (3.713)	(-2.75, 11.84)	0.222
SYMB 40 bid minus Budes 80 qd	12.96 (3.700)	(5.69, 20.23)	<0.001
SYMB 80 qd minus Budes 80 qd	**8.41 (3.801)**	**(0.94, 15.89)**	**0.027**

[a] SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.
Note: Baseline is defined as the mean of all values obtained during the last 10 days of the run-in period, excluding day of randomization data.
Note: Double-blind treatment period refers to the mean of all values obtained during the double-blind treatment period, beginning on the 1st day after randomization (Day 2) and ending on the last day of treatment, inclusive.
Note: Bolded row indicates the primary comparison.
EAS Efficacy analysis set.

Figure S1 presents plots of the mean changes from baseline over time in evening PEF.

Figure S1 **Mean change from baseline over time in evening PEF by study day, LOCF (EAS)**



Note: SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.

Note: Day 1 is the day of randomization; days before Day 1 represent the run-in period; days after Day 1 represent the double-blind treatment period.

LOCF Last observation carried forward (for missing diary data and for subjects who withdrew before Day 84);
EAS Efficacy Analysis Set; Chg Change.

Evening predose FEV_1 was measured in the clinic at the end of both the once-daily and twice-daily dosing intervals and was prospectively designated as the primary spirometry endpoint. Results for this endpoint are as follows:

- SYMBICORT 80 qd was not statistically different from budesonide 80 qd (p=0.183); this was in contrast to evening PEF results, where the results between these treatments were significantly different. SYMBICORT 40 bid was superior to budesonide 80 qd (p<0.001), similar to results for evening PEF. There was also a treatment difference favoring SYMBICORT 40 bid compared with SYMBICORT 80 qd (LS mean difference 0.06 L, 95% CI: 0.01 to 0.10 L, p=0.011).

Key findings of the other secondary efficacy and PRO endpoints are as follows:

- For the remaining pulmonary function variables, ie, morning PEF, morning predose FEV_1 and overall FEV_1, SYMBICORT 80 qd and SYMBICORT 40 bid each demonstrated statistically significantly greater efficacy than budesonide 80 qd. There were no clinically relevant differences in mean responses between the SYMBICORT 40 bid and SYMBICORT 80 qd treatment groups for these variables.

- The percentage of subjects reporting predefined asthma events (asthma deteriorations) was 19.6% for SYMBICORT 80 qd, 15.5% for budesonide 80 qd, and 8.2% for SYMBICORT 40 bid. There was no statistically significant difference between the SYMBICORT 80 qd and budesonide 80 qd treatment groups. Treatment with SYMBICORT 40 bid resulted in statistically significantly fewer subjects with a predefined asthma event compared with budesonide 80 qd. There was also a treatment difference favoring SYMBICORT 40 bid compared with SYMBICORT 80 qd (odds ratio equals 0.37, 95% CI: 0.19 to 0.71, p=0.002). The results for this variable in the 6 to 11 year-old age stratum were similar to the overall results; however, there were no substantial differences among the 3 treatment groups in the 12 to 15 year-old age stratum.

- For the other secondary efficacy endpoints relating to asthma control, there were no statistically significant differences between the SYMBICORT 80 qd and budesonide 80 qd treatment groups. SYMBICORT 40 bid showed statistically significantly greater efficacy than budesonide 80 qd for variables relating to the use of rescue medication. Differences between SYMBICORT 40 bid and SYMBICORT 80 qd for these variables also favored SYMBICORT 40 bid. For the Physician Global Assessment, SYMBICORT 40 bid was superior to budesonide 80 qd for ease of physician management of subject's asthma. There were no other significant differences among treatment groups in secondary efficacy endpoints relating to asthma control.

- There were no statistically significant or clinically meaningful differences between the 3 treatment groups for the PRO endpoints, PAQLQ(S) and PACQLQ overall scores.

Safety results

A total of 521 of 522 randomized subjects received at least 1 dose of double-blind treatment and were included in the safety analysis set. One subject was excluded from the safety analysis set because she did not take double-blind study medication. The mean duration of run-in therapy was approximately 5 weeks. In all 3 groups, most subjects received at least 10 weeks of double-blind therapy. Mean exposure, in terms of days of double-blind treatment, was similar among the 3 treatment groups, with slightly longer exposure in the SYMBICORT 40 bid group compared with the SYMBICORT 80 qd and budesonide 80 qd groups. These results are consistent with overall discontinuation rates for subjects in the safety analysis set, which were lower for the SYMBICORT 40 bid group compared with the budesonide 80 qd and SYMBICORT 80 qd groups. The size of

the study population and the duration of overall study drug exposure were adequate to draw safety conclusions.

As shown in Table S4, the percentage of subjects with at least 1 AE with onset during double-blind treatment was similar among the 3 treatment groups. The overall percentage of subjects with drug-related AEs, as assessed by the investigators, was low for all treatment groups. There were no deaths or other significant adverse events (OAEs) at any time during the study.

A total of 13 subjects were identified as having a serious adverse event (SAE) during the study. Of these, 6 subjects had an SAE with onset during the double-blind treatment period: 2 subjects in the SYMBICORT 40 bid group (abdominal pain, asthma), 3 subjects in the SYMBICORT 80 qd group (influenza, asthma [2 subjects]), and 1 subject in the budesonide 80 qd group (asthma). Five of these 6 SAEs (the influenza and all 4 SAEs of asthma) led to discontinuation from study treatment. None of the SAEs with onset during double-blind treatment was considered by the investigator to be related to study drug. Three subjects had an SAE with onset during the run-in period (convulsion, asthma, constipation); the convulsion and the asthma led to discontinuation. Two subjects had an SAE with onset prior to the run-in period (asthma, postprocedural cellulitis); the asthma led to the subject's discontinuation before any study treatment was given. Two subjects had an SAE with onset after the end of the double-blind treatment period (major depression, asthma); the asthma was reported as leading to discontinuation.

Overall, 22 subjects had at least 1 AE leading to discontinuation during the study (DAE). Of these, 8 had at least 1 AE with onset during double-blind treatment that led to discontinuation during the treatment period (3 subjects in the SYMBICORT 40 bid group, 4 subjects in the SYMBICORT 80 qd group, and 1 subject in the budesonide 80 qd group). The most common DAE with onset during double-blind treatment was asthma; this occurred in 5 subjects: 2 SYMBICORT 40 bid, 2 SYMBICORT 80 qd, and 1 budesonide 80 qd. These DAEs were not considered by the investigator to be related to study drug. Eleven subjects experienced a DAE with onset during the run-in period; the most common DAE was upper respiratory tract infection. There were 2 nonrandomized subjects who each experienced an AE prior to the run-in period that led to discontinuation from the study. One subject in the SYMBICORT 80 qd group experienced a DAE of asthma, with onset after the end of the double-blind treatment period.

Table S4 Overview of adverse events with onset during the double-blind treatment period (safety analysis set)

Category	Treatment group[a], n (%) of subjects with an adverse event[b]		
	SYMB 40 bid (N=184)	SYMB 80 qd (N=168)	Budes 80 qd (N=169)
Mean (SD) duration of exposure (days)	79.5 (16.6)	75.1 (20.5)	75.9 (20.8)
Any AEs	120 (65.2)	104 (61.9)	100 (59.2)
Any drug-related AEs	3 (1.6)	6 (3.6)	6 (3.6)
SAEs			
SAEs leading to death	0	0	0
SAEs not leading to death	2 (1.1)	3 (1.8)	1 (0.6)
SAEs leading to discontinuation	1 (0.5)	3 (1.8)	1 (0.6)
DAEs	3 (1.6)	4 (2.4)	1 (0.6)
OAEs	0	0	0
	Total number of AEs		
Any AEs	276	258	199
SAEs	2	3	1
OAEs	0	0	0

[a] Note: SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd; Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.

[b] 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.

AE Adverse event, DAE Discontinuation of study treatment due to adverse event, OAE Other significant adverse event, SAE Serious adverse event; SD Standard deviation.

Adverse events that occurred in ≥3% of the subjects in any treatment group during double-blind treatment are shown by MedDRA preferred term in Table S5. Among the most common AEs, some (eg, pharyngolaryngeal pain, viral upper respiratory tract infection) were reported more frequently for SYMBICORT pMDI than for budesonide. Overall, the relationship among treatment groups with respect to the incidence of AEs did not appear to differ across age strata. There were no notable differences between the SYMBICORT pMDI bid and qd treatment regimens with respect to the profile of commonly reported AEs.

There were 7 subjects who had oral candidiasis reported as an AE during double-blind treatment: 1 in the SYMBICORT 40 bid group, 3 in the SYMBICORT 80 qd group, and 3 in the budesonide group. There were no reported AEs of oropharyngeal candidiasis. One subject, in the SYMBICORT 80 qd group, experienced hoarseness during double-blind treatment.

No AEs of tremor or palpitations (ie, AEs generally associated with β_2-agonist effects) were observed. There were no AEs reported in the cardiac System Organ Class (SOC) or cardiac-related AEs in the investigations SOC.

Table S5 AEs reported by at least 3% of subjects in any treatment group during the double-blind treatment period (safety analysis set)

Preferred term	Treatment group[a], n (%) of subjects		
	SYMB 40 bid (N=184)	SYMB 80 qd (N=168)	Budes 80 qd (N=169)
Mean (SD) duration of exposure (days)	79.5 (16.6)	75.1 (20.5)	75.9 (20.8)
Number of subjects with any AE	120 (65.2)	104 (61.9)	100 (59.2)
Headache	21 (11.4)	13 (7.7)	17 (10.1)
Pharyngolaryngeal pain	20 (10.9)	14 (8.3)	8 (4.7)
Nasopharyngitis	15 (8.2)	15 (8.9)	10 (5.9)
Upper respiratory tract infection	11 (6.0)	13 (7.7)	16 (9.5)
Viral upper respiratory tract infection	14 (7.6)	15 (8.9)	3 (1.8)
Pyrexia	14 (7.6)	9 (5.4)	7 (4.1)
Sinusitis	4 (2.2)	10 (6.0)	10 (5.9)
Abdominal pain upper	8 (4.3)	7 (4.2)	5 (3.0)
Vomiting	5 (2.7)	4 (2.4)	6 (3.6)
Influenza	5 (2.7)	6 (3.6)	3 (1.8)
Otitis media	7 (3.8)	1 (0.6)	5 (3.0)
Pharyngitis streptococcal	4 (2.2)	3 (1.8)	6 (3.6)
Nausea	6 (3.3)	5 (3.0)	1 (0.6)
Epistaxis	2 (1.1)	3 (1.8)	6 (3.6)
Upper respiratory tract infection bacterial	2 (1.1)	5 (3.0)	1 (0.6)
Musculoskeletal chest pain	2 (1.1)	5 (3.0)	0

[a] SYMB 40 bid SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd; Budes 80 qd budesonide pMDI 80 µg per actuation x 2 actuations qd.

AE Adverse event; SD Standard deviation.

Note: This table uses a cut-off of ≥3% based on the AE incidence in any treatment group.

The SYMBICORT pMDI groups did not demonstrate any clinically significant changes in laboratory values compared with the budesonide group.

Comparison of mean 24-hour urinary cortisol and cortisol/creatinine ratio levels during double-blind treatment revealed no clinically relevant differences among treatment groups, and shift and outlier data showed similar patterns across treatments. During double-blind treatment, there were no reported AEs related to urinary cortisol findings.

The number of subjects manifesting shifts in overall ECG evaluation from normal at baseline to abnormal during double-blind treatment was low overall, with very few

findings considered clinically important. With respect to objective measures of cardiac safety, for heart rate, QRS and PR intervals, there were no clinically relevant treatment group differences in mean change from baseline or shifts to abnormal at any analyzable timepoint or across age strata.

Results from the ANCOVA analysis comparing mean changes from baseline across treatment groups for QT uncorrected, QTc (Bazett), and QTc (Fridericia) intervals revealed no clinically relevant differences between any bid or qd treatment groups. For these parameters, there were no important differences among the treatment groups in the percentage of subjects with shifts from baseline at any specific timepoint. The number of subjects with clinically important QT or QTc findings (≥450 msec or change ≥60 msec) was low and similar across treatment groups as well as across age strata.

During the conduct of the study, there were no SAEs or DAEs related to ECG findings. Overall, the minimal differences between treatment groups and overall similarity of ECG findings across groups suggest no increased risk of atrial or ventricular dysrhythmia or the presence of significant cardiac issues related to SYMBICORT pMDI.

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

Date of the report

17 February 2005