Drug product:	SYMBICORT® pMDI 160/4.5 µg	**SYNOPSIS**	
Drug substance(s):	Budesonide/Formoterol		
Document No.:			
Edition No.:			
Study code:	SD-039-0726		
Date:	13 January 2005		

A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Study of SYMBICORT® pMDI Administered Once Daily in Adults and Adolescents with Asthma.

International co-ordinating investigator

None appointed for this study

Study center(s)

This study was conducted in the United States (151 centers). A subset of 56 study centers conducted serial spirometry.

Publications

W Berger, E Bleecker, L O'Dowd, C Miller, W Mezzanotte. Efficacy of Once-daily Budesonide (BUD) and Formoterol (FM) Administered Via One Pressurized Metered-Dose Inhaler (pMDI) in Patients With Asthma. Am J Respir Crit Care Med. 2007;175:A188 (abstract).

E Bleecker, W Berger, L O'Dowd, C Miller, W Mezzanotte. Safety of Once-Daily Budesonide (BUD) and Formoterol (FM) Administered Via One Pressurized Metered-Dose Inhaler (pMDI) in Patients with Asthma. Am J Respir Crit Care Med. 2007;175:A190 (abstract).

Study dates

First subject enrolled 4 April 2003

Last subject completed 22 June 2004

Phase of development

Therapeutic confirmatory (III)

Objectives

Primary: To demonstrate the efficacy of SYMBICORT pMDI 160/4.5 µg, 2 actuations once daily (qd), compared to placebo and to budesonide pMDI 160 µg, 2 actuations qd, in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg,

2 actuations twice daily (bid), by assessment of lung function and patient- and physician-reported outcomes.

Secondary:

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

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

- To compare the relative efficacy of switching to qd therapy with SYMBICORT pMDI 160/4.5 µg, 2 actuations, or stepping down to qd therapy with SYMBICORT pMDI 80/4.5 µg, 2 actuations, to each other and to that of remaining on SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, by assessment of lung function and patient- and physician-reported outcomes.

- To demonstrate the health-related quality of life (HRQOL) benefits of SYMBICORT pMDI 160/4.5 µg, 2 actuations qd; SYMBICORT pMDI 80/4.5 µg, 2 actuations qd; and SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, compared to placebo in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, by assessment of the AQLQ(S) and ACQ.

- To investigate the safety profiles of SYMBICORT pMDI 160/4.5 µg, 2 actuations qd; SYMBICORT pMDI 80/4.5 µg, 2 actuations qd; SYMBICORT pMDI 80/4.5 µg, 2 actuations bid; budesonide pMDI 160 µg, 2 actuations qd; and placebo in asthmatic adults and adolescents previously stable on SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, by assessment of adverse events, laboratory measurements, 24-hour urinary cortisol, physical examinations, vital signs, Holter monitoring, and electrocardiograms

Study design

This was a 12-week, multicenter, randomized, double-blind, parallel group, placebo and active-controlled, Phase 3 study to investigate the efficacy, 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, 2 actuations bid.

Subjects remained on their current therapy while safety measures were captured during a ≤1-week screening period. Following the screening visit, subjects were assigned to treatment with SYMBICORT pMDI 80/4.5 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. 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) SYMBICORT pMDI 160/4.5 µg, 2 actuations qd, (2) SYMBICORT pMDI 80/4.5 µg, 2 actuations qd (3) SYMBICORT pMDI 80/4.5 µg, 2 actuations bid, (4) budesonide pMDI 160 µg, 2 actuations qd or (5) Placebo pMDI.

Target subject population and sample size

Male and female subjects, who were 16-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. Subjects should have received maintenance asthma treatment with a low to medium dose[1] 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 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.

Using a 2-group t-test with a 5% two-sided significance level, a sample size of 150 subjects per treatment arm would provide 84% power to detect a true difference in mean change in evening PEF of 12 L/min and 95% power to detect a true difference in mean change in evening PEF of 15 L/min assuming a common standard deviation of 35 L/min. It was assumed that a negligible number of randomized subjects would be unevaluable for the primary efficacy analysis; therefore approximately 150 subjects per treatment group (or approximately 750 subjects overall) were randomized to provide adequate power to achieve the objectives of this study. It was expected that approximately 1125 subjects ≥16 years of age would be sought to reach the goal of randomizing 750 subjects (150 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 5 treatment groups at Visit 2:

- SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg per actuation, 2 actuations administered qd (hereafter called the SYMBICORT 160 qd treatment group), and placebo pMDI, 2 actuations qd. Batch numbers of SYMBICORT pMDI were P6502A, P6675, and P6722.

- SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered qd (hereafter called the SYMBICORT 80 qd

[1] Consistent with the National Asthma Education and Prevention Guidelines (2002).

treatment group), and placebo pMDI, 2 actuations qd. Batch numbers of SYMBICORT pMDI were P65401A (run-in only) and P6503.

- SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg per actuation, 2 actuations administered bid (hereafter called the SYMBICORT 80 bid treatment group). Batch numbers of SYMBICORT pMDI were P65401A (run-in only) and P6503.

- Budesonide pMDI 160 µg per actuation, 2 actuations administered qd (hereafter called the budesonide 160 qd treatment group), and placebo pMDI, 2 actuations administered qd. Batch numbers of budesonide were P6495 and P6611.

- Placebo pMDI, 2 actuations administered bid (hereafter called the placebo treatment group). Batch numbers of placebo were P6491, P6547, and P6856.

In order to maintain blinding with the bid dosing regimen, all subjects randomized to receive qd dosing were to dose with the active treatment in the evening and with a matched placebo device in the morning.

SYMBICORT pMDI 80/4.5 µg per actuation, 2 actuations bid was used during the single-blind run-in period (batch numbers P6501A). 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, ACC55A, and ACF12A).

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

- Primary variable: evening PEF (from daily diary)

- Secondary variables:

  – Spirometry variables (evening pre-dose FEV_1 [the primary spirometry variable], FVC, PEF, and $FEF_{25-75\%}$; morning pre-dose FEV_1, FVC, PEF, and $FEF_{25-75\%}$; and the FEV_1 AUC $_{0-12}$ and FEV_1 at 12 hours from the 12-hour serial spirometry assessments measured after the morning dose of study medication in all subjects at selected sites at Visits 3 and 5)

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

- Predefined asthma events and withdrawals due to predefined asthma events[2]
- Global Assessments (subject global assessment and physician's global assessment)
- Patient Reported Outcomes (PRO) variables (standardized Asthma Quality of Life Questionnaire [AQLQ(S)], Asthma Control Questionnaire [ACQ])

Safety

Adverse events, clinical laboratory data, 12-lead ECGs, 24-hour Holter monitoring, 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 randomized study 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. The primary comparison consisted of a sequential testing procedure: First, SYMBICORT 160 qd was compared to placebo. If this comparison was found to be statistically significant at the 5% significance level, then SYMBICORT 160 qd was compared to budesonide 160 qd, also at the 5% significance level. Change from baseline in evening PEF was analyzed with an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center and treatment, and for the covariate of baseline evening PEF.

Secondary analyses were performed to compare SYMBICORT 80 bid to placebo and budesonide 160 qd, and to compare SYMBICORT 80 qd to placebo and budesonide 160 qd. Budesonide 160 qd, was also compared to placebo. 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. All of these secondary comparisons were performed within the context of the same ANCOVA model used for the primary analysis.

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 PROs, each SYMBICORT pMDI treatment group was compared to placebo. The continuous secondary efficacy variables and PROs were compared among treatment groups using analyses similar to those specified for the primary variable. Categorical

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

variables were analyzed with chi-square tests and also with survival analysis methodology when appropriate.

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 2711 subjects were screened for possible study participation, 1200 of whom subsequently entered the run-in period and received at least 1 dose of single-blind SYMBICORT 80 bid run-in therapy[3]. Of these, 752 subjects were subsequently randomized. Study recruitment was stopped when the target enrollment was reached. All randomized subjects, except 1 subject (E26B2004), received double-blind treatment and all but 7 subjects provided at least 1 efficacy observation.

Table S1 summarizes demographic and baseline characteristics for the safety analysis set. Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics.

Among randomized subjects, the overall withdrawal rate was highest in the placebo treatment group (41.5%) while the percentages of subjects withdrawn in the active treatment groups (3 SYMBICORT pMDI groups and the budesonide 160 qd group) were similar and notably lower (ranging from 12.4% to 19.3%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to predefined asthma events). The percentage of subjects who withdrew because of a predefined asthma event was notably lower in the SYMBICORT 80 bid (2.6%), SYMBICORT 160 qd (6.8%), and SYMBICORT 80 qd (4.6%) groups than in the placebo (35.9%) and budesonide 160 qd (12.4%) groups.

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]					
	SYMB 80 bid (N=154)	SYMB 160 qd (N=147)	SYMB 80 qd (N=152)	Budes 160 qd (N=145)	Plac bid (N=153)	Total (N=751)
Sex (n and % of subjects)						
Male	58 (37.7)	50 (34.0)	49 (32.2)	46 (31.7)	58 (37.9)	261 (34.8)
Female	96 (62.3)	97 (66.0)	103 (67.8)	99 (68.3)	95 (62.1)	490 (65.2)

[3] One additional subject (E2637018) received run-in therapy but was excluded from the run-in analysis set because (s)he was terminated from the study during the run-in period and then later failed screening at Visit 1 during rescreening (see Tables 12.2.8.7, 12.2.9.3, 12.2.10.4, 12.2.12.7, and 12.2.13.6, Appendix 12) This subject did not experience any SAEs, DAEs, or have any findings of clinical importance during the conduct of the study.

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]					
	SYMB 80 bid (N=154)	SYMB 160 qd (N=147)	SYMB 80 qd (N=152)	Budes 160 qd (N=145)	Plac bid (N=153)	Total (N=751)
Age (yr)						
Mean (SD)	38.0 (13.00)	37.0 (12.89)	39.5 (13.46)	38.6 (13.74)	36.5 (13.21)	37.9 (13.27)
Median	36.5	35.0	39.5	37.0	37.0	38.0
Range	16 to 78	17 to 79	16 to 78	16 to 75	16 to 70	16 to 79
Age groups (yr), (n and % of subjects)						
16 to <65	151 (98.1)	143 (97.3)	148 (97.4)	140 (96.6)	150 (98.0)	732 (97.5)
65 to <75	2 (1.3)	3 (2.0)	2 (1.3)	4 (2.8)	3 (2.0)	14 (1.9)
≥75	1 (0.6)	1 (0.7)	2 (1.3)	1 (0.7)	0	5 (0.7)
Race, (n and % of subjects)						
Caucasian	132 (85.7)	113 (76.9)	118 (77.6)	118 (81.4)	122 (79.7)	603 (80.3)
Black	11 (7.1)	16 (10.9)	16 (10.5)	18 (12.4)	13 (8.5)	74 (9.9)
Oriental	2 (1.3)	3 (2.0)	1 (0.7)	1 (0.7)	6 (3.9)	13 (1.7)
Other	9 (5.8)	15 (10.2)	17 (11.2)	8 (5.5)	12 (7.8)	61 (8.1)
Years since asthma diagnosis						
Mean (SD)	20.2 (13.30)	20.1 (12.70)	20.2 (13.40)	17.8 (12.62)	20.1 (14.00)	19.7 (13.22)
Min, Max	0.7, 56.0	0.8, 54.7	0.5, 53.6	0.6, 58.6	0.7, 54.3	0.5, 58.6
ICS dose at entry (µg/day)						
N	154	146	151	145	153	749
Mean (SD)	361.9 (187.47)	380.7 (175.98)	358.8 (170.21)	382.9 (198.08)	357.8 (201.96)	368.2 (186.99)
Min, Max	80.0, 1000.0	88.0, 800.0	88.0, 800.0	88.0, 1000.0	80.0, 1000.0	80.0, 1000.0
Percent reversibility in FEV_1 at screening (Visit 1)						
N	152	147	152	145	150	746
Mean (SD)	20.8 (9.24)	19.3 (9.34)	21.2 (10.47)	21.1 (9.61)	19.5 (8.75)	20.4 (9.51)
Median	17.6	15.7	17.5	18.1	16.3	16.8
Min, Max	5.4, 58.1	11.1, 73.8	11.1, 66.4	11.0, 57.1	11.3, 60.5	5.4, 73.8
FEV_1 (L) at screening (Visit 1, pre-bronchodilator)						
N	153	147	152	145	153	750
Mean (SD)	2.7 (0.68)	2.6 (0.59)	2.5 (0.61)	2.5 (0.58)	2.6 (0.54)	2.5 (0.60)
Percent predicted FEV_1 at screening (Visit 1, pre-bronchodilator)						
N	153	147	152	145	153	750
Mean (SD)	75.9 (7.77)	75.1 (7.65)	75.1 (8.33)	74.8 (8.21)	75.5 (8.33)	75.3 (8.05)
Baseline FEV_1 (L) (predose at Visit 2)						

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]					
	SYMB 80 bid (N=154)	SYMB 160 qd (N=147)	SYMB 80 qd (N=152)	Budes 160 qd (N=145)	Plac bid (N=153)	Total (N=751)
Mean (SD)	3.0 (0.76)	2.9 (0.65)	2.8 (0.66)	2.8 (0.69)	2.9 (0.64)	2.9 (0.68)
Baseline percent predicted FEV_1 (predose at Visit 2)						
Mean (SD)	86.4 (9.13)	85.2 (8.66)	85.1 (10.06)	85.7 (8.81)	85.1 (9.58)	85.5 (9.26)

[a] SYMB 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, SYMB 80 bid SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid, BUD 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac bid placebo x 2 actuations bid.

Efficacy, PRO, and pharmacokinetic results

Results of the primary analysis of the primary efficacy endpoint - change from baseline 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 160 qd was shown to be superior to both placebo and budesonide 160 qd ($p<0.001$ for each; Table S3).
- SYMBICORT 80 bid was shown to be superior to both placebo and budesonide 160 qd ($p<0.001$ for each; Table S3).
- SYMBICORT 80 qd was shown to be superior to both placebo and budesonide 160 qd ($p<0.001$ for each; Table S3).
- The SYMBICORT 80 bid treatment group maintained the mean level of pulmonary function (as assessed by evening PEF) that was established during the run-in baseline period, 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 once-daily treatment groups compared to the SYMBICORT 80 bid group (LS mean difference for SYMBICORT 80 bid minus SYMBICORT 160 qd equals 16.43 L/min, 95% CI: 8.81 to 24.05 L/min; LS mean difference for SYMBICORT 80 bid minus SYMBICORT 80 qd equals 17.94 L/min, 95% CI: 10.32 to 25.55 L/min; $p<0.001$ for each).
- There was no clinically relevant difference between the mean response seen in the SYMBICORT 160 qd group and in the SYMBICORT 80 qd group (LS mean difference 1.51 L/min, 95% CI: -6.14 to 9.15 L/min, $p=0.699$).

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	N	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SEM)	95% CI
SYMB 80 bid	152	442.00 (106.154)	443.14 (105.662)	1.14 (28.049)	1.58 (3.005)	(-4.32, 7.48)
SYMB 160 qd	147	421.91 (103.987)	407.63 (103.535)	-14.28 (35.381)	-14.85 (3.035)	(-20.81, -8.89)
SYMB 80 qd	152	412.58 (99.065)	398.60 (98.576)	-13.98 (28.880)	-16.36 (2.945)	(-22.14, -10.58)
Budes 160 qd	144	415.23 (99.523)	383.35 (95.072)	-31.88 (34.583)	-33.58 (3.035)	(-39.54, -27.62)
Plac	150	414.27 (105.431)	375.33 (96.863)	-38.95 (40.703)	-41.46 (2.995)	(-47.34, -35.58)

[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 80 bid SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; SYMB 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd; Budes 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac placebo x 2 actuations bid.

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

Comparison	ANCOVA analysis		
	LS mean (SEM)	95% CI	p-value
SYMB 80 bid vs SYMB 160 qd	16.43 (3.880)	(8.81, 24.05)	<0.001
SYMB 80 bid vs SYMB 80 qd	17.94 (3.879)	(10.32, 25.55)	<0.001
SYMB 80 bid vs Budes 160 qd	35.16 (3.892)	(27.51, 42.80)	<0.001
SYMB 80 bid vs placebo	43.04 (3.898)	(35.39, 50.70)	<0.001
SYMB 160 qd vs SYMB 80 qd	1.51 (3.892)	(-6.14, 9.15)	0.699
SYMB 160 qd vs Budes 160 qd	**18.72 (3.924)**	**(11.02, 26.43)**	**<0.001**
SYMB 160 qd vs placebo	**26.61 (3.904)**	**(18.94, 34.28)**	**<0.001**
SYMB 80 qd vs Budes 160 qd	17.22 (3.902)	(9.56, 24.88)	<0.001
SYMB 80 qd vs placebo	25.10 (3.918)	(17.41, 32.80)	<0.001
Budes 160 qd vs placebo	7.88 (3.929)	(0.17, 15.60)	0.045

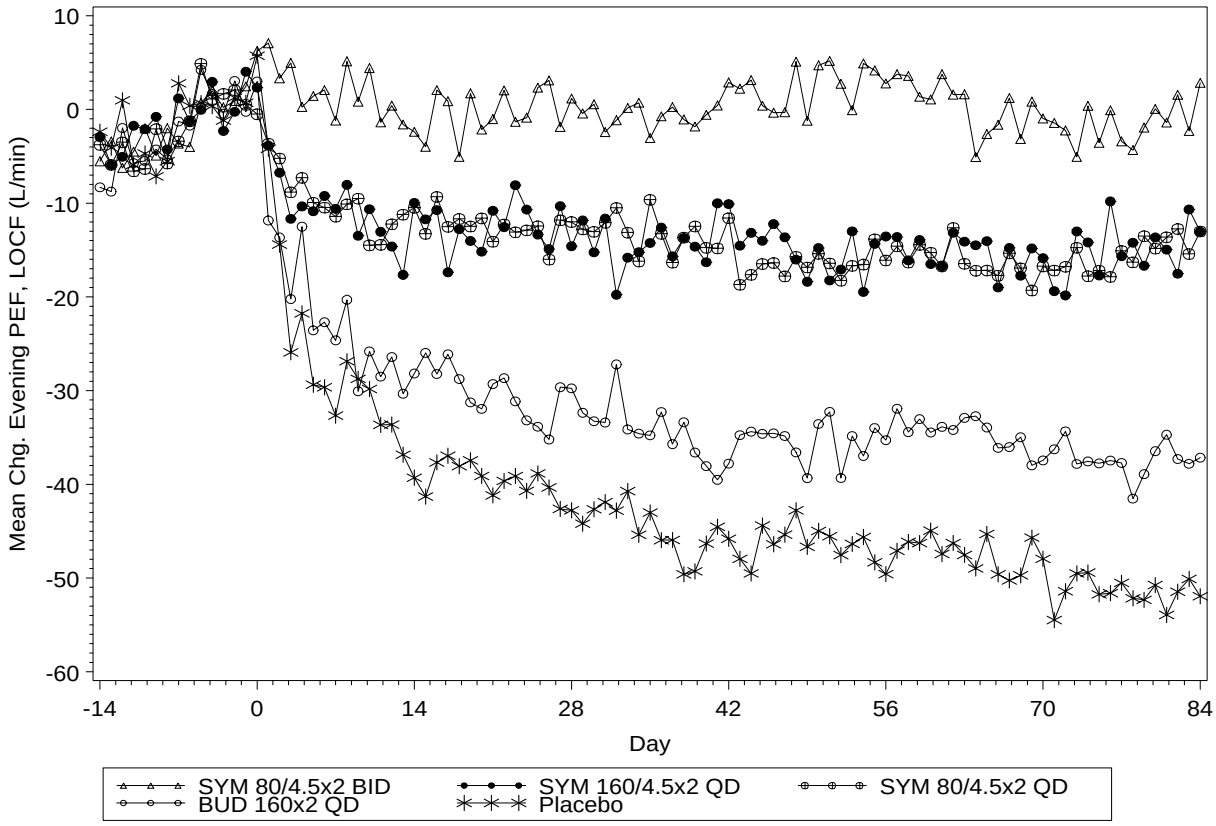
[a] SYMB 80 bid SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; SYMB 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI

80/4.5 µg per actuation x 2 actuations qd; Budes 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac placebo x 2 actuations bid.

Note: Bolded rows indicate the comparisons related to the primary objective.

Figure S1presents 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 80 bid SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; SYMB 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd; Budes 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac placebo x 2 actuations bid.

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.

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

- Evening predose FEV_1 was measured in the clinic at the end of the once-daily dosing interval and prospectively designated as the primary spirometry endpoint. The once-daily SYMBICORT pMDI groups demonstrated statistically significantly greater efficacy than placebo. However, unlike the evening PEF results, the comparisons between SYMBICORT 160 qd and

budesonide 160 qd and between SYMBICORT 80 qd and budesonide 160 qd were not statistically significant during double-blind treatment (p=0.158 and p=0.250, respectively).

- For the other secondary efficacy endpoints, the SYMBICORT 160 qd and SYMBICORT 80 qd treatment groups demonstrated consistent efficacy versus placebo; these comparisons were statistically significant for nearly all variables. The once-daily SYMBICORT pMDI groups also demonstrated statistically significantly greater efficacy than budesonide 160 qd for most variables, with the SYMBICORT 160 qd group achieving significance more consistently than the SYMBICORT 80 qd group. For endpoints reflective of efficacy at the end of the once-daily dosing interval, the magnitude of the difference between the once-daily SYMBICORT groups and the budesonide and placebo groups was notably smaller than that seen earlier during the same dosing interval. Overall, SYMBICORT 160 qd showed slightly greater efficacy than SYMBICORT 80 qd; however, between-group treatment differences were not statistically significant for most variables.

- The SYMBICORT 80 bid treatment group demonstrated efficacy versus placebo and budesonide 160 qd; these comparisons were statistically significant for all measures. Across all variables, the SYMBICORT 80 bid treatment group maintained the level of pulmonary function and asthma control that was established during the run-in baseline period, without experiencing a loss of efficacy during double-blind treatment. In contrast, reductions in efficacy from baseline during double-blind treatment were seen for both of the SYMBICORT once-daily treatment groups compared to the SYMBICORT 80 bid group. These differences were statistically significant for several lung function and symptom-related endpoints.

Statistically significant and clinically relevant treatment differences favoring the 3 SYMBICORT pMDI groups compared to placebo were observed for the PRO endpoints (AQLQ[S] and ACQ)

Safety results

A total of 751 of 752 subjects who were randomized into the study received at least 1 dose of study drug and were included in the safety analysis set. Subject E26B2004, a 56-year-old male Caucasian who was randomized to receive SYMBICORT 80 qd, was excluded from the safety analysis because he did not take study medication. The mean duration of run-in therapy was approximately 5 weeks. The majority of the subjects in each treatment group received double-blind treatment for at least 10 weeks. The mean overall exposure, in terms of days of double-blind treatment, was similar among the active treatment groups, with a lower exposure for the placebo group relative to the active treatments. These results are consistent with overall discontinuation rates, which were lower for the SYMBICORT 80 bid (14.3%), SYMBICORT 160 qd (17.0%), SYMBICORT 80 qd (12.4%), and the budesonide 160 qd treatment groups (19.3%) relative to the placebo group (45.1%). 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 overall percentage of subjects with at least 1 adverse event was similar among treatment groups during the double-blind treatment period. There were no deaths or OAEs at any time during the study. Sixteen subjects were identified as having an SAE at any time during the study. Of these, 5 subjects experienced a SAE during the double-blind treatment period: 3 subjects in SYMBICORT 80 bid group (breast cancer in situ, road traffic accident, musculoskeletal chest pain), 1 subject in the SYMBICORT 160 qd group (prostate cancer), and 1 subject in the budesonide 160 qd group (tension headache). Three of the SAEs (breast cancer in situ, prostate cancer, and tension headache) led to discontinuation from trial treatment. None of the SAEs were determined to be study drug-related by the investigators. Overall, a total of 44 subjects experienced a DAE at any time during the study; of these, a total of 19 subjects in the safety analysis set (6 subjects in SYMBICORT 80 bid group, 5 subjects in the SYMBICORT 160 qd group, 2 subjects in the SYMBICORT 80 qd group, 3 subjects in the budesonide 160 qd group, and 3 subjects in the placebo group) had at least 1 AE with onset during double-blind treatment leading to discontinuation during the double-blind treatment period. The overall percentage of subjects with drug-related AEs was low for all treatment groups.

Table S4 Overview of AEs during the double-blind treatment period (safety analysis set)

Category	Number (%) of subjects with an adverse event[a]				
	SYMB 80 bid (N=154)	**SYMB 160 qd (N=147)**	**SYMB 80 qd (N=152)**	**Budes 160 qd (N=145)**	**Plac bid (N=153)**
Mean (SD) duration of exposure (days)	77.2 (20.24)	77.3 (18.83)	79.4 (183.3)	76.0 (22.80)	61.7 (29.86)
Any adverse events (AEs)	90 (58.4)	75 (51.0)	84 (55.3)	76 (52.4)	75 (49.0)
Any drug-related Aes	12 (7.8)	9 (6.1)	10 (6.6)	10 (6.9)	13 (8.5)
Serious adverse events (SAEs)	3 (1.9)	1 (0.7)	0	1 (0.7)	0
SAEs leading to death	0	0	0	0	0
SAEs not leading to death	3 (1.9)	1 (0.7)	0	1 (0.7)	0
SAEs leading to discontinuation	1 (0.6)	1 (0.7)	0	1 (0.7)	0
DAEs	6 (3.9)	5 (3.4)	2 (1.3)	3 (2.1)	3 (2.0)
OAEs	0	0	0	0	0
	Total number of adverse events				
Any Aes	190	168	226	174	178
SAEs	3	1	0	1	0
OAEs	0	0	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 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd, SYMB 80 bid SYMBICORT

pMDI 80/4.5 µg per actuation x 2 actuations bid, Budes 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac bid placebo x 2 actuations bid.

DAE Adverse event leading to discontinuation of a subject from study; OAE Other significant adverse event.

As shown in Table S5, the most frequently occurring AEs by MedDRA preferred term were nasopharyngitis, upper respiratory tract infection, headache, pharyngolaryngeal pain, sinusitis, viral upper respiratory tract infection, influenza, nasal congestion, and back pain. The incidence of these events was generally similar across the treatment groups. An exception was the incidence of upper respiratory tract infection, which was lower for the SYMBICORT 160 qd group (4.1%) relative to the other treatment groups (6.2% to 9.2%). The incidence of frequently occurring AEs by MedDRA preferred term was generally similar for the SYMBICORT groups relative to the placebo group. Note that the comparison of SYMBICORT bid versus SYMBICORT qd tested the effect of reducing by half the daily dose of formoterol (SYMBICORT 160 qd) or the effect of reducing by half the daily dose of formoterol and budesonide (SYMBICORT 80 qd) by administering SYMBICORT once daily. There was no clear evidence of a dose response for adverse events when the SYMBICORT bid and qd treatment groups were compared.

Eleven subjects had oral candidiasis or oropharyngeal candidiasis reported as an AE during the treatment period: 4 in the SYMBICORT 80 bid group, 3 in the SYMBICORT 160 qd group, 1 in the budesonide 160 qd group, and 3 in the placebo group. In addition, 1 subject in the SYMBICORT 80 bid group and 1 subject in the SYMBICORT 80 qd group experienced hoarseness during double-blind treatment.

The occurrence of potential asthma-related AEs that might suggest asthma was rare among the treatment groups. Other AEs that might also suggest asthma were also rare.

Tremor and palpitations (ie, AEs generally associated with β_2-agonists effects) were rare. The number of cardiac and cardiac-related AEs was low, occurring in 17 subjects: 5 in the SYMBICORT 80 bid group, 6 in the SYMBICORT 160 qd group, 3 in the SYMBICORT 80 qd group, 1 in the budesonide 160 qd group, and 2 in the placebo group. The most common cardiac and cardiac-related adverse events were ventricular extrasystoles, AV block second degree, and ventricular tachycardia. All cardiac and cardiac-related AEs occurred in the 16 to <65-year age group, with most occurring during the first 6 weeks of double-blind treatment. There were no cardiac or cardiac-related SAEs.

Table S5 **Adverse events 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 80 bid (N=154)	SYMB 160 qd (N=147)	SYMB 80 qd (N=152)	Budes 160 qd (N=145)	Plac bid (N=153)
Mean duration of exposure, days (SD)	77.2 (20.24)	77.3 (18.83)	79.4 (183.3)	76.0 (22.80)	61.7 (29.86)
Number of subjects with any adverse event	90 (58.4)	75 (51.0)	84 (55.3)	76 (52.4)	75 (49.0)
Nasopharyngitis	11 (7.1)	12 (8.2)	13 (8.6)	12 (8.3)	14 (9.2)
Upper respiratory tract infection	14 (9.1)	6 (4.1)	12 (7.9)	9 (6.2)	14 (9.2)
Headache	8 (5.2)	8 (5.4)	7 (4.6)	11 (7.6)	4 (2.6)
Pharyngolaryngeal pain	6 (3.9)	7 (4.8)	7 (4.6)	6 (4.1)	8 (5.2)
Sinusitis	8 (5.2)	4 (2.7)	6 (3.9)	8 (5.5)	7 (4.6)
Viral upper respiratory tract infection	2 (1.3)	1 (0.7)	4 (2.6)	8 (5.5)	5 (3.3)
Influenza	4 (2.6)	5 (3.4)	5 (3.3)	2 (1.4)	3 (2.0)
Nasal congestion	5 (3.2)	3 (2.0)	3 (2.0)	4 (2.8)	3 (2.0)
Back pain	5 (3.2)	2 (1.4)	3 (2.0)	5 (3.4)	2 (1.3)

[a] SYMB 80 bid SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; SYMB 160 qd SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations qd; SYMB 80 qd SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations qd; Budes 160 qd Budesonide pMDI 160 µg per actuation x 2 actuations qd; Plac placebo x 2 actuations bid.

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

The SYMBICORT groups did not demonstrate any clinically significant changes in laboratory values compared with the placebo or budesonide 160 qd groups. For all hematology and clinical chemistry parameters, including serum glucose and potassium, there were no clinically meaningful changes from baseline or differences across treatment groups at any visit. There were no meaningful treatment group differences in shifts in individual subject data (using standard and extended reference ranges) at any visit. There was no evidence of an increased incidence of hyperglycemia or hypokalemia in any of the SYMBICORT groups relative to the budesonide or placebo groups. Three subjects had diabetes mellitus or elevated blood glucose as an AE.

Overall, the effect of SYMBICORT on HPA-axis function was similar to placebo. There was a slight mean decrease in 24-hour urinary cortisol and cortisol/creatinine ratio for both SYMBICORT 160 qd and budesonide 160 qd compared to the other groups. However, these small differences between treatment groups in mean values did not appear to be reflected in differences for shift or outlier data. For 24-hour urinary cortisol and cortisol/creatinine ratio, the percentage of subjects with shifts from normal to high or normal to low at all timepoints was low and generally similar across treatment groups.

Overall, there was no clear pattern across treatment groups with respect to outliers or shifts. Throughout the study, there were only 2 subjects (1 SYMBICORT 80 bid and 1 SYMBICORT 160 qd) who experienced an AE that was related to abnormal urine cortisol, and there were no SAEs or DAEs related to cortisol findings.

With respect to objective measures of cardiac safety, for heart rate, QRS, and PR intervals there were no clinically relevant treatment group differences in change from baseline or shifts to abnormal at any analyzable timepoint. Results from an ANCOVA comparing mean changes from baseline across treatment groups for QT uncorrected, QTc (Baz), and QTc (Frid) intervals revealed no clinically relevant differences between treatment groups at any analyzed timepoint when considering all subjects in the safety analysis set (in either the predose or postdose subgroups). For these parameters, there were no important differences among the treatment groups in the percentage of subjects with shifts from baselines at any specific timepoint. Inspection of QT and QTc data revealed the number of subjects with clinically important QT or QTc findings was low and similar across treatment groups. Overall, the number of subjects manifesting shifts in overall ECG evaluation was low with very few findings considered clinically important. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters.

Overall, no clinically meaningful differences were seen in the percentages of subjects shifting from normal to abnormal for key Holter assessments. The number of subjects with potentially clinically important Holter findings identified on treatment was generally low. During the conduct of the study, there were no SAEs associated with ECG or Holter findings and no DAEs related to ECG findings. There were 7 DAEs (2 SYMBICORT 80 bid, 3 SYMBICORT 160 qd, 1 SYMBICORT 80 qd, and 1 placebo) associated with Holter findings; 5 of these subjects met Holter withdrawal criteria. Overall, the minimal differences between treatment groups and the overall similarity of ECG and Holter findings across groups suggest no increased risk of atrial or ventricular dysrhythmia or the presence of significant cardiac issues related to SYMBICORT. No clinically meaningful changes or treatment group differences were observed in vital signs (pulse, diastolic and systolic blood pressure) and physical exam findings.

Date of the report

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