Drug product	SYMBICORT® pMDI 80/4.5 µg	**SYNOPSIS**	
Drug substance(s)	Budesonide/formoterol		
Document No.			
Edition No.			
Study code	SD-039-0716		
Date	30 April 2004		

A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® pMDI (80/4.5 µg) versus its Monoproducts (budesonide and formoterol) in Children (≥6 Years of Age) and Adults with Asthma – SPRUCE 80/4.5

International Coordinating investigator

None for this study.

Study center(s)

This study was conducted in the United States (63 centers). A subset of study centers (15) enrolled pediatric subjects between the ages of 6 and 11 years, in addition to adolescent and adult subjects.

Publications

Corren J, Korenblatt PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Therapeutics 2007;29:823-843.

Study dates		**Phase of development**
First subject enrolled	31 July 2002	Phase III
Last subject completed	24 September 2003	

Objectives

Primary: To compare the safety and efficacy (including health-related quality of life [HRQOL] and patient satisfaction variables) of SYMBICORT® pMDI, a fixed-combination metered-dose inhaler product containing budesonide and formoterol (80/4.5 µg per puff[1] respectively) administered as 2 puffs twice daily, to that of budesonide (80 µg per puff) alone in a metered-dose inhaler and to that of formoterol

[1] Note that "actuation" will be used instead of "puff" in the remainder of this report.

(4.5 µg per inhalation) alone in a dry powder inhaler, both administered as 2 inhalations twice daily, in subjects ≥12 years of age with asthma.

Secondary: To compare the safety, efficacy (including HRQOL and patient satisfaction variables), and onset of effect of all 3 active products alone relative to placebo in subjects with asthma.

Study design

This was a randomized, double-blind, double-dummy, placebo-controlled trial comparing the efficacy and safety of SYMBICORT® pMDI (pressured metered-dose inhaler) with those of its monoproducts (budesonide pMDI and formoterol Turbuhaler® [TBH]) in children (6 to 11 years of age) and adolescents and adults with asthma (≥12 years of age). Randomization was stratified by age group (≥12 years and <12 years old). The study comprised a screening visit, a 14 (±7) day single-blind placebo run-in period, and a 12-week double-blind treatment period.

Target subject population and sample size

Male and female subjects with asthma who were at least 12 years of age (all centers) or, in a subset of centers, between the ages of 6 and 11 years; who were chronically treated with a low to medium dose[2] of inhaled corticosteroid (ICS); and whose forced expiratory volume in the first second (FEV_1) on ICS therapy was within the entrance range (60% to 90% of predicted normal for subjects ≥12 and ≥75% of predicted normal for subjects <12), were eligible for enrollment. In addition, subjects ≥12 years of age had to demonstrate reversibility of FEV_1 of at least 12% and ≥0.20 L from the pre-albuterol baseline value within 15 to 30 minutes after administration of a standard dose of fast-acting beta$_2$ agonist (β_2-agonist) (albuterol pMDI, 2 to 4 actuations [90 µg per actuation], with or without a spacer, or after administration of up to 2.5 mg nebulized albuterol if required). Subjects <12 years of age had to show reversibility of ≥12% only. Qualification for randomization was based on lung function and asthma symptom scores during the run-in period.

To detect a true mean difference between treatment groups of 0.25 L for the co-primary efficacy variables (baseline-adjusted average 12-hour FEV_1 and predose FEV_1) with 95% power for each variable (assuming a population standard deviation of 0.50 L, a 2-group t-test, and a 5% two-sided significance level for each test), 105 evaluable subjects ≥12 years of age per treatment group were required. Allowing for up to 5% of randomized subjects to be unevaluable for efficacy, 112 randomized subjects ≥12 years of age per treatment group (448 subjects ≥12 years of age overall) were sought to meet the primary objective. In addition, the protocol allowed for up to 92 subjects 6 to <12 years of age to be randomized, for a potential grand total of 540 subjects ages 6 years and older to be randomized.

[2] Consistent with National Asthma Education and Prevention Program Guidelines (1997).

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

Subjects were randomly assigned to 1 of the 4 following treatment groups. Treatments were given in double-dummy fashion because of the difference in devices.

- SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg (delivered dose) per actuation, 2 actuations administered twice daily (bid), and placebo TBH, 2 inhalations bid. Batch numbers of SYMBICORT pMDI were P6037, P6501A.
- Budesonide pMDI 80 µg (delivered dose) per actuation, 2 actuations administered bid, and placebo TBH, 2 inhalations administered bid. Batch numbers of budesonide pMDI were P6456.
- Formoterol TBH 4.5 µg (delivered dose) per inhalation, 2 inhalations administered bid, and placebo pMDI, 2 actuations administered bid. Batch numbers of formoterol TBH were P6474, P6508, P6624.
- Placebo pMDI, 2 actuations administered bid, and placebo TBH, 2 inhalations administered bid. Batch numbers were P6349, P6490, P6491, P6204 for placebo pMDI and P6476, P6512, P6625, P6677 for placebo TBH.

Albuterol, delivered by pMDI, was used as rescue medication on an as-needed basis, during both the run-in and treatment periods. Batch numbers for albuterol were ABL97A and ABP33A. Batch numbers for placebo pMDI used during run-in were P6349 and P6351. Batch numbers for EMLA Cream, used as needed for local anesthesia prior to phlebotomy, were 203083, 211051, 301148, and 302074.

Duration of treatment

A 12-week randomized treatment period preceded by a 2-week (± 1 week) placebo run-in period.

Criteria for evaluation

Efficacy (including HRQOL assessments; hereafter referred to as Patient Reported Outcomes [PRO])

- Co-primary variables: baseline-adjusted average 12-hour FEV_1 and predose FEV_1
- Secondary variables:

  (a) Pre-defined asthma events and withdrawals due to pre-defined asthma events

  (b) Other spirometry or spirometry-related variables (2-hour postdose FEV_1, maximum FEV_1, onset of effect [15% improvement in FEV_1], time to onset of effect, and subject perception of onset of effect [POE] collected during spirometry)

(c) Diary variables (morning and evening peak expiratory flow [PEF], nighttime and daytime asthma symptom scores, nighttime awakenings, rescue medication use, and the Onset of Effect Questionnaire [OEQ])

(d) PRO variables (standardized Asthma Quality of Life Questionnaire [AQLQ(S)], standardized Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)], Patient Satisfaction with Asthma Medication Questionnaire [PSAM], Medical Outcome Study [MOS] Sleep Scale) and Global Assessments

Safety

Adverse events, clinical laboratory data, 12-lead ECGs, 24-hour Holter monitoring (subjects ≥12 years of age only), physical examination, and vital signs were used to evaluate safety.

Statistical methods

The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed sufficient data for at least 1 co-primary endpoint. Primary efficacy analyses are based on subjects from the EAS population who were ≥12 years of age (EAS ≥12 yr). Secondary efficacy analyses were performed using the EAS (all ages) and per-protocol (PP) analysis sets.

The co-primary variables – baseline-adjusted average 12-hour FEV_1 and predose FEV_1 – were each analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center and treatment and for the covariate of baseline FEV_1. Baseline-adjusted average 12-hour FEV_1 was analyzed at Week 2, last observation carried forward (LOCF) as the primary timepoint and was used to compare SYMBICORT pMDI to budesonide. Predose FEV_1 was analyzed as a change from baseline to the average over the double-blind treatment period as the primary timepoint and was used to compare SYMBICORT pMDI to formoterol.

For all secondary variables, the primary comparison was between SYMBICORT pMDI and placebo. Because of the multitude of secondary variables, 3 were prespecified as key: percentage of subjects who experienced a pre-defined asthma event; asthma symptoms as measured by percentage of symptom-free days (a variable derived from symptom scores and nighttime awakenings); and overall score from the Asthma Quality of Life Questionnaire (AQLQ[S]). The Simes-Hommel method was applied to the results of the analysis of these key secondary variables, to control for multiplicity of testing. All other secondary variables are presented without adjustment for multiple comparisons. The continuous secondary efficacy and PRO variables were compared between treatment groups using analyses similar to those specified for the primary variables. Categorical 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 using all subjects who received at least one dose of study medication (safety analysis set).

Subject population

A total of 1092 subjects were screened, of whom 511 were subsequently randomized (480 were ≥12). Study recruitment was stopped when the target for subjects ≥12 years of age was reached. All randomized subjects received study treatment and provided at least one efficacy observation; therefore, the population of all randomized subjects, the safety analysis set, and the efficacy analysis set (EAS all ages) are the same in this study.

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

Among randomized subjects, the overall withdrawal rate was highest in the placebo group (51%), followed by the formoterol group (32%). The percentage of subjects withdrawn in the SYMBICORT pMDI and budesonide groups was similar and notably lower (15%). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to pre-defined asthma events), which occurred in a higher percentage of subjects in the placebo and formoterol groups (33.6% and 20.3%, respectively) than in the SYMBICORT pMDI and budesonide groups (7.7% and 6.3%, respectively).

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]				
	SYMB N=130	Budes N=127	Form N=123	Plac N=131	Total N=511
Sex (n and % of subjects)					
Male	50 (38.5)	50 (39.4)	46 (37.4)	55 (42.0)	201 (39.3)
Female	80 (61.5)	77 (60.6)	77 (62.6)	76 (58.0)	310 (60.7)
Age (yr)					
Mean (SD)	35.6 (16.64)	35.8 (16.67)	33.4 (16.85)	34.1 (15.66)	34.8 (16.43)
Median	36.5	38.0	32.0	34.0	35.0
Range	6 to 77	7 to 78	7 to 73	6 to 66	6 to 78
Age strata (yr), (n and % of subjects)					
6 to <12	7 (5.4)	6 (4.7)	9 (7.3)	9 (6.9)	31 (6.1)
≥12	123 (94.6)	121 (95.3)	114 (92.7)	122 (93.1)	480 (93.9)
Age group (yr), (n and % of subjects)					
6 to <12	7 (5.4)	6 (4.7)	9 (7.3)	9 (6.9)	31 (6.1)
12 to <16	12 (9.2)	14 (11.0)	15 (12.2)	11 (8.4)	52 (10.2)
16 to <65	108 (83.1)	103 (81.1)	92 (74.8)	110 (84.0)	413 (80.8)
65 to <75	2 (1.5)	3 (2.4)	7 (5.7)	1 (0.8)	13 (2.5)
≥75	1 (0.8)	1 (0.8)	0	0	2 (0.4)
Race (n and % of subjects)					
Caucasian	113 (86.9)	107 (84.3)	107 (87.0)	119 (90.8)	446 (87.3)
Black	11 (8.5)	12 (9.4)	13 (10.6)	8 (6.1)	44 (8.6)
Oriental	0	1 (0.8)	1 (0.8)	2 (1.5)	4 (0.8)
Other	6 (4.6)	7 (5.5)	2 (1.6)	2 (1.5)	17 (3.3)
ICS use at entry (µg/day)[b]					
N	130	126	123	131	510
Mean (SD)	345.4 (156.2)	352.6 (189.3)	328.7 (173.3)	339.0 (183.1)	341.5 (175.6)
Min, Max	80, 1000	88, 1200	88, 1200	80, 1000	80, 1200
FEV_1 at screening (Visit 1, pre-bronchodilator) (L)					
Mean (SD)	2.5 (0.64)	2.5 (0.61)	2.5 (0.62)	2.5 (0.67)	2.5 (0.64)
Baseline FEV_1 (L) (predose at Visit 2)					
Mean (SD)	2.4 (0.63)	2.3 (0.61)	2.4 (0.64)	2.3 (0.66)	2.3 (0.63)
Percent predicted FEV_1 at screening (Visit 1, pre bronchodilator)					
Mean (SD)	76.3 (9.48)	75.6 (7.96)	76.5 (8.22)	74.3 (8.82)	75.7 (8.67)
Baseline percent predicted FEV_1 (predose at Visit 2)					
Mean (SD)	71.6 (11.41)	70.8 (10.69)	71.5 (10.39)	71.2 (11.10)	71.3 (10.89)
Percent reversibility in FEV_1 at Visit 1					
N	130	127	122	131	510
Mean (SD)	18.2 (7.35)	19.3 (6.73)	18.8 (7.61)	19.4 (8.86)	18.9 (7.68)
Median	15.4	17.6	16.0	15.7	16.0

[a] SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

[b] Baseline ICS is defined as the last ICS dose reported prior to run-in.

Avg Average; Max Maximum; Min Minimum; Yr years.

Efficacy and PRO results

Results of the primary analysis of the co-primary efficacy endpoints — baseline-adjusted average 12-hour FEV_1 and change from baseline in predose FEV_1 — are summarized in Table S2 and Table S3, respectively. Figure S1 shows the mean percent change from baseline in FEV_1 over 12 hours at the primary timepoint (Week 2 LOCF), and Figure S2 shows the mean percent change from baseline in predose FEV_1 by study week.
Key findings for the co-primary efficacy endpoints are as follows:

- The mean baseline-adjusted average 12-hour FEV_1 was significantly greater for SYMBICORT pMDI compared to budesonide ($p<0.001$), thereby demonstrating the contribution of formoterol to the efficacy of SYMBICORT pMDI. The mean baseline-adjusted average 12-hour FEV_1 was significantly greater for formoterol compared to placebo ($p<0.001$), thereby demonstrating the effect of formoterol alone. SYMBICORT pMDI demonstrated clinically significant improvement in lung function that was maintained over 12 hours, and there was no diminution of the 12-hour bronchodilatory effect of SYMBICORT pMDI observed over time, as assessed by comparison of the 12-hour FEV_1 profiles after the first dose and after 2 weeks and 12 weeks of therapy.
- A significantly greater mean increase from baseline in predose FEV_1 was seen for SYMBICORT pMDI versus formoterol ($p=0.001$), thereby demonstrating the contribution of budesonide to the efficacy of SYMBICORT pMDI. A significantly greater mean increase from baseline in predose FEV_1 was seen for budesonide versus placebo ($p<0.001$), thereby demonstrating the effect of budesonide alone. Following the initial dose of SYMBICORT pMDI, predose FEV_1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and showed no diminution of effect at Week 12.

Table S2 **Baseline-adjusted average 12-hour FEV_1 (L): treatment comparisons at Week 2 LOCF using the WV Pre-CF imputation method (EAS ≥12 yr)**

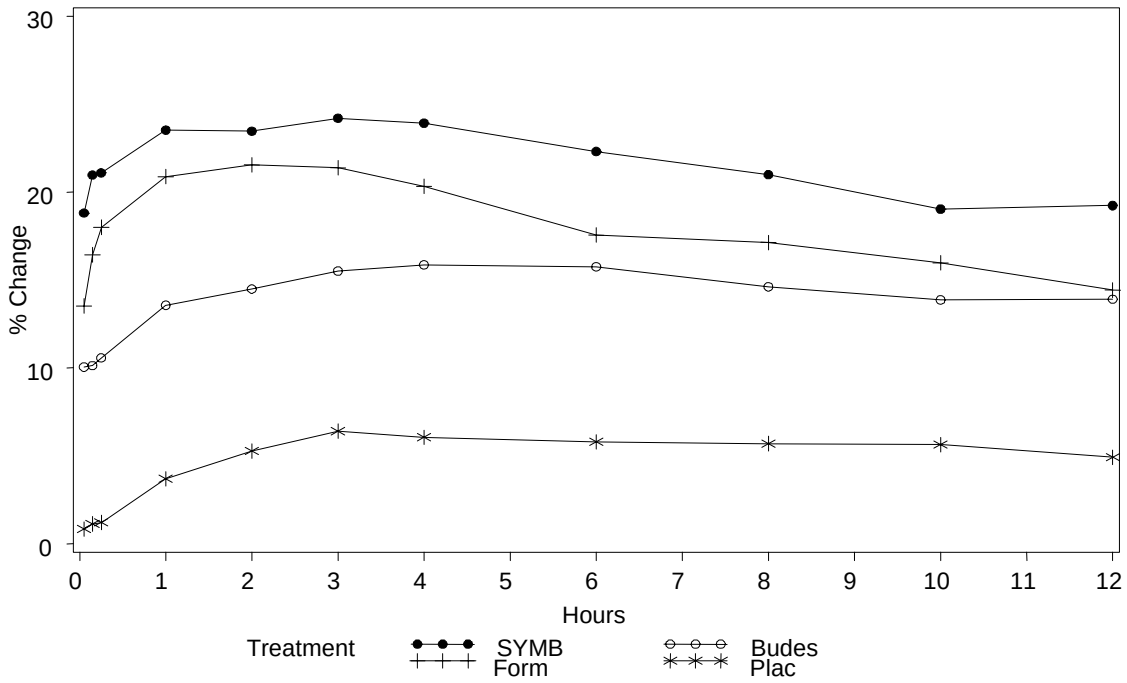
	ANCOVA analysis		
Comparison [a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB minus Plac	0.35 (0.04)	(0.26, 0.44)	<0.001
SYMB minus Budes	**0.18 (0.04)**	**(0.09, 0.27)**	**<0.001**
SYMB minus Form	0.07 (0.05)	(-0.02, 0.16)	0.148
Budes minus Plac	0.17 (0.04)	(0.08, 0.25)	<0.001
Form minus Plac	0.28 (0.05)	(0.19, 0.37)	<0.001

[a] SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

Note: The bolded comparison is the prespecified primary comparison for this variable.

EAS Efficacy Analysis Set; LOCF Last observation carried forward; WV Pre-CF Within-visit predose value carried forward.

Figure S1 **Mean percent change from baseline in FEV_1 at Week 2 LOCF, using the WV Pre-CF imputation method (EAS ≥12 yr)**



Note: The first timepoint displayed is the 3-minute postdose timepoint. Baseline is defined as the predose FEV_1 measured on the day of randomization (Visit 2).

SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac x 2 actuations bid; EAS Efficacy Analysis Set; LOCF Last observation carried forward; WV Pre-CF Within-visit predose value carried forward.

Table S3 Predose FEV_1 (L): treatment comparisons for change from baseline to the double-blind treatment period (EAS ≥12 yr)

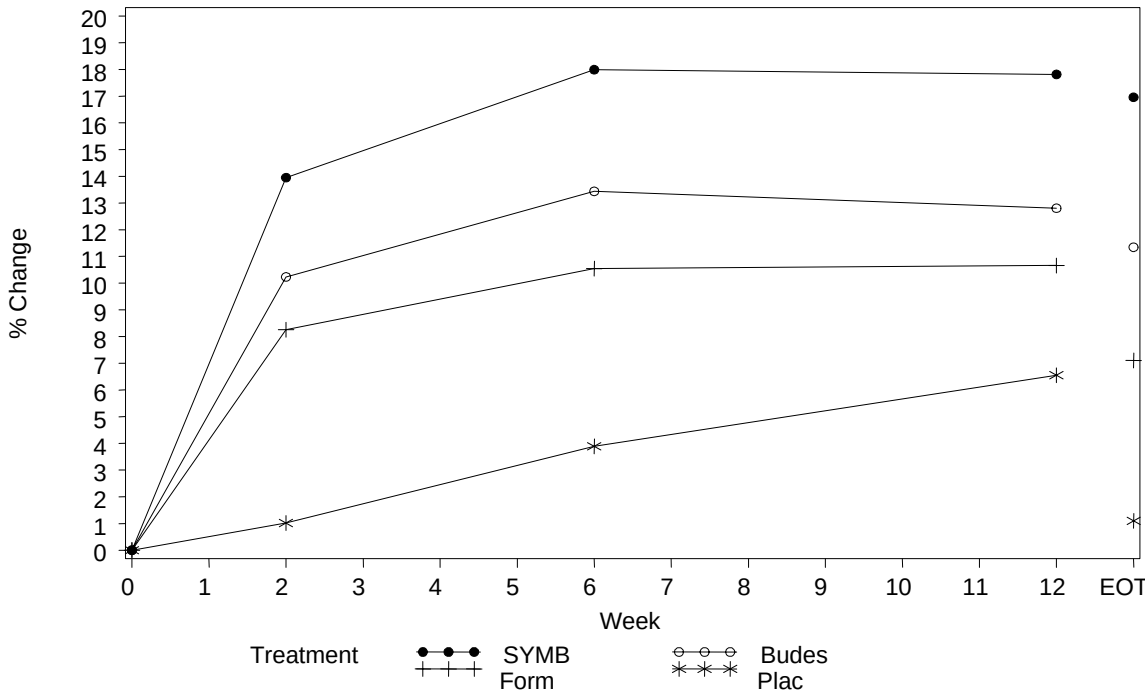
	ANCOVA analysis		
Comparison[a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB minus Plac	0.31 (0.05)	(0.21, 0.40)	<0.001
SYMB minus Budes	0.14 (0.05)	(0.04, 0.23)	0.005
SYMB minus Form	**0.16 (0.05)**	**(0.06, 0.26)**	**0.001**
Budes minus Plac	0.17 (0.05)	(0.08, 0.27)	<0.001
Form minus Plac	0.15 (0.05)	(0.05, 0.25)	0.004

[a] SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

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

EAS Efficacy Analysis Set.

Figure S2 Mean percent change from baseline in predose FEV_1 by visit (EAS ≥12 yr)



SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.
EAS Efficacy Analysis Set; EOT End of treatment.

For all 3 key secondary endpoints, SYMBICORT pMDI was statistically superior to placebo ($p<0.001$ for all endpoints). The percentage of subjects with at least 1 pre-defined asthma event was lower in the SYMBICORT pMDI (19%) and budesonide (22%) groups than in the formoterol (42%) and placebo (57%) groups. Subjects taking SYMBICORT pMDI reported a higher percentage of symptom-free days, compared with placebo. The percentage of subjects with symptom-free days was greater for SYMBICORT pMDI than for placebo on the day after randomization, and the response to SYMBICORT pMDI continued to improve during the double-blind treatment period. Based on results of the change from baseline analysis of the AQLQ(S), subjects taking SYMBICORT pMDI experienced a statistically significant as well as clinically meaningful improvement (defined as a mean difference between treatment groups of ≥0.5 points) in overall score compared to placebo.

For all secondary endpoints measured in subjects ≥12 years of age, SYMBICORT pMDI showed superiority over placebo. In addition, SYMBICORT pMDI was more efficacious than formoterol or budesonide (or both) for most of the secondary endpoints. Notably, SYMBICORT pMDI showed a statistically significantly greater mean improvement than both formoterol and budesonide alone for morning and evening PEF. In general, SYMBICORT pMDI showed greater effects on pulmonary function than did budesonide alone, while SYMBICORT pMDI showed greater improvements in symptom control than did formoterol alone. Subjects perceived the onset of effect faster following SYMBICORT pMDI than following placebo and budesonide, based on results of the

Perception of Onset of Effect Questionnaire (POE). Similar results were observed for the Onset of Effect Questionnaire (OEQ), a diary variable. Results of all patient-reported outcomes assessments and physician Global Assessments conducted at the end of treatment demonstrate statistically significant improvement for SYMBICORT pMDI relative to placebo with respect to health-related quality of life, treatment satisfaction, sleep, and global measures.

Safety results

The overall percentage of subjects with at least 1 AE during double-blind treatment was slightly lower in the formoterol and placebo groups than in the SYMBICORT pMDI and budesonide groups; this pattern is consistent with the duration of exposure across treatment groups (see Table S4). The incidence of serious adverse events (SAEs) during the double-blind treatment period was very low (2 subjects in each of the SYMBICORT pMDI [lobar pneumonia, facial bones fracture] and placebo [abdominal pain, intestinal obstruction] groups). None of the SAEs was considered study drug-related by the investigator. The percentage of subjects with adverse events leading to discontinuation (DAEs) was lower in the SYMBICORT pMDI, budesonide, and formoterol groups compared to the placebo group. Asthma was the most commonly observed DAE (8 subjects), with all occurrences in the placebo (6 [4.6%]) and budesonide (2 [1.6%]) groups. There were no deaths or other significant adverse events (OAEs) during the study period.

Table S4 Overview of adverse events during the randomized treatment period (safety analysis set)

Category	Number (%) of subjects with an adverse event[a]			
	SYMB (N=130)	Budes (N=127)	Form (N=123)	Plac (N=131)
Mean duration of exposure (days)	78.2	76.7	66.8	55.2
Any adverse events (AEs)	84 (64.6)	77 (60.6)	67 (54.5)	77 (58.8)
Serious adverse events (SAEs)	2 (1.5)	0	0	2 (1.5)
SAEs leading to death	0	0	0	0
SAEs not leading to death	2 (1.5)	0	0	2 (1.5)
SAEs leading to discontinuation	1 (0.8)	0	0	2 (1.5)
Subjects discontinued due to AEs	4 (3.1)	3 (2.4)	3 (2.4)	12 (9.2)
Other significant adverse events (OAEs)	0	0	0	0
	Total number of adverse events			
Any Aes	221	227	186	166
SAEs	2	0	0	2
OAEs	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 SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

The most common AEs (≥3% incidence in any treatment group) are shown in Table S5. The incidence of each of these events was generally similar across treatment groups, although the percentage of subjects with pharyngolaryngeal pain was slightly higher in the SYMBICORT pMDI group compared to the other treatment groups, and a higher percentage of subjects in the budesonide group had influenza reported as an AE compared to the other treatment groups. The majority of AEs were mild or moderate in intensity. Adverse events for cardiac disorders and asthma or asthma-related events were not increased for any of the active treatment groups as compared to placebo.

Table S5 Adverse events reported by at least 3% of subjects in any treatment group during the randomized treatment period (safety analysis set)

	Treatment group[a], n (%) of subjects			
Preferred term	**SYMB (N=130)**	**Budes (N=127)**	**Form (N=123)**	**Plac (N=131)**
Mean duration of exposure (days)	78.2	76.7	66.8	55.2
Number of subjects with any adverse event	**84 (64.6)**	**77 (60.6)**	**67 (54.5)**	**77 (58.8)**
Nasopharyngitis	20 (15.4)	17 (13.4)	16 (13.0)	14 (10.7)
Headache	12 (9.2)	14 (11.0)	9 (7.3)	13 (9.9)
Pharyngolaryngeal pain	12 (9.2)	6 (4.7)	4 (3.3)	9 (6.9)
Sinusitis	9 (6.9)	7 (5.5)	6 (4.9)	7 (5.3)
Upper respiratory tract infection	7 (5.4)	10 (7.9)	8 (6.5)	3 (2.3)
Cough	7 (5.4)	3 (2.4)	5 (4.1)	5 (3.8)
Influenza	5 (3.8)	9 (7.1)	3 (2.4)	2 (1.5)
Dyspepsia	5 (3.8)	5 (3.9)	3 (2.4)	3 (2.3)
Asthma	0	2 (1.6)	4 (3.3)	7 (5.3)
Diarrhea	1 (0.8)	6 (4.7)	1 (0.8)	4 (3.1)
Back pain	4 (3.1)	3 (2.4)	3 (2.4)	1 (0.8)
Nausea	1 (0.8)	6 (4.7)	2 (1.6)	2 (1.5)
Viral upper respiratory tract infection	4 (3.1)	4 (3.1)	0	2 (1.5)
Gastroenteritis viral	3 (2.3)	1 (0.8)	4 (3.3)	1 (0.8)
Myalgia	5 (3.8)	1 (0.8)	0	3 (2.3)
Nasal congestion	2 (1.5)	4 (3.1)	2 (1.6)	1 (0.8)
Arthralgia	4 (3.1)	2 (1.6)	0	2 (1.5)

[a] SYMB SYMBICORT pMDI 80/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 80 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

Note: This table uses a cut-off of ≥3% based on the AE incidence in any treatment group. Events are sorted by decreasing order of frequency across all treatment groups.

Twelve-lead ECG and chemistry (glucose and potassium) assessments timed to coincide with peak sustained pharmacodynamic activity generally did not reveal meaningful differences in mean changes from baseline between treatment groups. Small mean increases in QTc (Bazett's correction) that were not clinically significant were noted in

SYMBICORT pMDI and formoterol groups. Individual clinically important findings were infrequent with no meaningful differences between treatment groups. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters. Twenty-four hour Holter monitoring (performed on subjects ≥12 years of age only) did not reveal significant differences in findings between treatment groups. Other than a higher incidence of abnormal lung exams in formoterol and placebo subjects, no significant findings in clinical chemistry and hematology parameters, physical examination, or vital signs were noted among active treatment groups.

Date of the report

30 April 2004