Drug product	SYMBICORT® pMDI 160/4.5 µg	**SYNOPSIS**	
Drug substance(s)	Budesonide/formoterol		
Document No.			
Edition No.			
Study code	SD-039-0717		
Date	16 December 2004		

A Twelve-Week, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial of SYMBICORT® (160/4.5 µg) versus its Mono-Products (budesonide and formoterol) in Adolescents (≥12 Years of Age) and Adults with Asthma.

International Co-ordinating investigator

None for this study.

Study center(s)

This study was conducted in the United States (84 centers). A subset of 23 study centers conducted 24-hour Holter monitoring.

Publications

Noonan M, Rosenwasser L, Martin P, O'Brien C, O'Dowd L. Efficacy and Safety of Budesonide and Formoterol in One Pressurised Metered-Dose Inhaler in Adults and Adolescents with Moderate to Severe Asthma: A Randomised Clinical Trial. Drugs 2006; 66(17):2235-2254.

Study dates		**Phase of development**
First subject enrolled	9 July 2002	Phase III
Last subject completed	29 January 2004	

Objectives

Primary: To compare the safety and efficacy (including health-related quality of life [HRQOL] and patient satisfaction variables) of SYMBICORT®, a fixed-combination metered-dose inhaler product containing budesonide and formoterol (160/4.5 µg per puff[1] respectively) administered as 2 actuations twice daily, to that of budesonide (160 µg per actuation) alone in a metered-dose inhaler and to that of formoterol (4.5 µg per inhalation) alone in a dry powder inhaler, both administered as 2 inhalations twice daily, in subjects with asthma.

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

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

Tertiary: To compare the relative safety and efficacy of the free combination of budesonide and formoterol versus the fixed combination, as SYMBICORT.

Although pharmacokinetic testing was not included as a specific objective in the clinical study protocol, the pharmacokinetic properties of budesonide and formoterol were examined as planned in a subset of subjects. For subjects consenting to pharmacokinetic testing, plasma concentrations of budesonide and/or formoterol were measured in blood samples collected predose and at 7 timepoints during the 6-hour postdose period at Visit 3 (ie, 2 weeks after start of randomized treatment).

In addition, subjects ≥18 years of age were given the option to sign a separate informed consent form permitting storage of, and future molecular genetic studies on, DNA extracted from their blood. Molecular genetic studies may not commence for 2 or more years following completion of this clinical study. Thus, the information derived from the genetic studies will not appear in this clinical study report.

Study design

This was a randomized, double-blind, double-dummy, placebo-controlled study comparing the safety and efficacy of SYMBICORT® pMDI (pressured metered-dose inhaler) with those of its monoproducts (budesonide pMDI and formoterol Turbuhaler® [TBH]) and with the free combination of the monoproducts in adolescents and adults (≥12 years of age) with asthma. Randomization was stratified by asthma severity, based on the consistent, total daily dosage (moderate versus high dose) of inhaled corticosteroid (ICS) prior to screening, to ensure an equal distribution of subjects across treatment groups within each of these 2 strata; the primary analysis included subjects from both strata. The study comprised a screening visit, a 2-week (±1 week) single-blind budesonide 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, who were chronically treated with a medium to high dose[2] of ICS; and whose forced expiratory volume in the first second (FEV_1) on ICS therapy was within the entrance range (45% to 85% of predicted normal) were eligible for enrollment. In addition, subjects had to demonstrate reversibility of FEV_1 of at least 12% and ≥0.20 L from the prealbuterol 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). Qualification for randomization was based on lung function and asthma symptom scores during the run-in period.

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

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 per treatment group were required. Allowing for up to 5% of randomized subjects to be unevaluable for efficacy, 112 randomized subjects per treatment group (560 subjects overall) were sought to meet the primary objective.

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

Subjects were randomly assigned to 1 of the 5 following treatment groups. Treatments were given in double-dummy fashion because of the difference in devices.

- SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg (delivered dose) per actuation, 2 actuations administered twice daily (bid), and placebo TBH, 2 inhalations bid. Batch numbers of SYMBICORT pMDI were P6040, P6041A, P6502A.
- Budesonide pMDI 160 µg (delivered dose) per actuation, 2 actuations administered bid, and placebo TBH, 2 inhalations administered bid. Batch numbers of budesonide pMDI were P6363, P6364, P6388, P6495, P6611.
- 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, P6550, P6624.
- Budesonide pMDI 160 µg (delivered dose) per actuation, 2 actuations administered bid in combination with formoterol TBH 4.5 µg (delivered dose) per inhalation, 2 inhalations administered bid.[3] Batch numbers of budesonide were P6363, P6364, P6388, P6495, P6611, and of formoterol were P6474, P6508, P6550, P6624.
- Placebo pMDI, 2 actuations administered bid, and placebo TBH, 2 inhalations administered bid. Batch numbers were P6254, P6349, P6351, P6490, P6491 for placebo pMDI and P6476, P6512, P6623, P6625, P6677 for placebo TBH.

Budesonide pMDI (80 µg per actuation, 2 actuations administered bid) was used during the single-blind run-in period (batch numbers P6361, P6494). Albuterol, delivered by pMDI, was used as rescue medication on an as-needed basis, during both the run-in and treatment periods (batch numbers ABL97A and ABZ93A). Batch numbers for EMLA Cream, used as needed for local anesthesia prior to phlebotomy, were 203083, 211051, 301148, and 302074.

[3] This treatment group will henceforth be referred to as the *budesonide+formoterol* group.

Duration of treatment

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

Criteria for evaluation

Efficacy (including HRQOL assessments) and pharmacokinetics

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

1. Predefined asthma events and withdrawals due to predefined asthma events
2. Other spirometry or spirometry-related variables (2-hour postdose FEV_1, maximum FEV_1, onset of effect [15% improvement in FEV_1] and subject perception of onset of effect [POE])
3. Diary variables (morning and evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings due to asthma, rescue medication use, and subject perception of onset of effect using the Onset of Effect Questionnaire [OEQ])
4. Global assessments (patient global assessment and physician's global assessment)
5. HRQOL (hereafter referred to as Patient Reported Outcomes [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], and Medical Outcome Study [MOS] Sleep Scale)

- Pharmacokinetic (PK) parameters (AUC_{0-6}, C_{max}, and T_{max}) for plasma budesonide and plasma formoterol were calculated for subjects who chose to provide blood samples for this purpose. Blood samples were collected predose and at 7 timepoints over 6 hours postdose at Visit 3 (ie, 2 weeks after start of randomized treatment).

Safety

Adverse events, clinical laboratory data, 12-lead ECGs, 24-hour Holter monitoring (for subjects at a subset of centers), physical examination, and vital signs were used to evaluate safety.

Statistical methods

The efficacy analysis set (EAS) was defined as all randomized subjects, irrespective of asthma severity strata, who took at least 1 dose of randomized treatment and contributed

sufficient data for at least 1 co-primary endpoint. Secondary efficacy analyses were performed using the per-protocol (PP) analysis set.

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, ICS dose strata at entry, and treatment, and for the covariate of baseline FEV_1. Baseline-adjusted average 12-hour FEV_1 was analyzed at Week 2 LOCF WV Pre-CF (last observation carried forward, within-visit predose FEV_1 value carried forward imputational method), 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 primarily, 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 predefined 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 standardized 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 either chi-square or Cochran-Mantel-Haenszel tests and also with survival analysis methodology when appropriate.

Pharmacokinetic parameters for formoterol and budesonide were analyzed with descriptive statistics and ANOVA models using subjects in the PK analysis set.
Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models using all subjects who received at least 1 dose of randomized treatment (safety analysis set).

Subject population

A total of 1373 subjects were screened for possible study participation, 596 of whom were subsequently randomized. Study recruitment was stopped when the target enrollment was reached. All randomized subjects received randomized treatment and provided at least 1 efficacy observation; therefore, the population of all randomized subjects, the safety analysis set, and the efficacy analysis set (EAS) are the same in this study.
Treatment groups were similar at baseline with respect to most demographic and disease severity characteristics (see Table S1). Expected differences between ICS dose strata were seen in terms of disease severity characteristics.

Among randomized subjects, the overall withdrawal rate was highest in the placebo treatment group (60.0%), followed by the formoterol group (51.2%). The percentage of

subjects withdrawn in the SYMBICORT pMDI, budesonide, and budesonide+formoterol groups was notably lower (21.8%, 28.4%, and 25.2% respectively). The most common reason for withdrawal was due to study-specific discontinuation criteria (ie, withdrawals due to predefined asthma events). The percentages of subjects who withdrew because of a predefined asthma event were lower in the SYMBICORT pMDI (10.5%) and budesonide+formoterol (11.3%) groups than in the budesonide (20.2%), formoterol (35.8%), and placebo (49.6%) groups.

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]					
	SYMB (N=124)	Budes (N=109)	Form (N=123)	Budes+Form (N=115)	Plac (N=125)	Total (N=596)
Sex (n and % of subjects)						
Male	44 (35.5)	38 (34.9)	43 (35.0)	50 (43.5)	53 (42.4)	228 (38.3)
Female	80 (64.5)	71 (65.1)	80 (65.0)	65 (56.5)	72 (57.6)	368 (61.7)
Age (yr)						
Mean (SD)	41.8 (15.45)	40.7 (14.20)	40.0 (16.40)	40.3 (14.65)	41.9 (15.19)	40.9 (15.20)
Median	41.5	42.0	41.0	40.0	43.0	41.0
Range	12 to 74	12 to 80	12 to 87	13 to 75	12 to 75	12 to 87
Age groups (yr), (n and % of subjects)						
12 to <16	6 (4.8)	3 (2.8)	12 (9.8)	5 (4.3)	6 (4.8)	32 (5.4)
16 to <65	107 (86.3)	102 (93.6)	102 (82.9)	104 (90.4)	112 (89.6)	527 (88.4)
65 to <75	11 (8.9)	3 (2.8)	8 (6.5)	5 (4.3)	6 (4.8)	33 (5.5)
≥75	0	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	4 (0.7)
Race, (n and % of subjects)						
Caucasian	98 (79.0)	84 (77.1)	91 (74.0)	89 (77.4)	101 (80.8)	463 (77.7)
Black	18 (14.5)	17 (15.6)	21 (17.1)	20 (17.4)	20 (16.0)	96 (16.1)
Oriental	0	3 (2.8)	3 (2.4)	2 (1.7)	1 (0.8)	9 (1.5)
Other	8 (6.5)	5 (4.6)	8 (6.5)	4 (3.5)	3 (2.4)	28 (4.7)
Years since asthma diagnosis						
Mean (SD)	23.1 (15.09)	23.2 (16.03)	21.7 (15.32)	21.7 (13.36)	23.3 (15.01)	22.6 (14.95)
Min, Max	1.0, 56.7	0.6, 78.6	0.7, 65.0	0.5, 61.6	0.6, 64.6	0.5, 78.6
ICS dose at entry (all, µg/day)						
Mean (SD)	570.3 (225.08)	589.7 (252.40)	593.4 (236.57)	587.6 (244.56)	606.8 (269.35)	589.6 (245.43)
Min, Max	160, 1200	160, 1600	220, 1320	160, 1200	160, 1600	160, 1600
ICS dose at entry (moderate-dose stratum, µg/day)						
N	91	81	86	82	87	427
Mean (SD)	465.9 (119.62)	490.6 (201.87)	480.2 (145.63)	462.1 (135.58)	460.9 (131.69)	471.7 (148.44)
Min, Max	160, 1000	160, 1600	220, 1000	160, 1200	160, 1000	160, 1600
ICS dose at entry (high-dose stratum, µg/day)						
N	33	28	37	33	38	169
Mean (SD)	858.2 (194.96)	876.4 (139.21)	856.5 (194.48)	899.4 (160.97)	941.1 (194.96)	887.5 (181.23)
Min, Max	320, 1200	320, 1000	320, 1320	320, 1200	660, 1600	320, 1600
FEV_1 (L) at screening (Visit 1, prebronchodilator)						
Mean (SD)	2.2 (0.69)	2.3 (0.61)	2.1 (0.57)	2.2 (0.57)	2.2 (0.63)	2.2 (0.62)

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]					
	SYMB (N=124)	Budes (N=109)	Form (N=123)	Budes+Form (N=115)	Plac (N=125)	Total (N=596)
Baseline FEV_1 (L) (predose at Visit 2)						
Mean (SD)	2.2 (0.72)	2.3 (0.63)	2.2 (0.60)	2.2 (0.61)	2.3 (0.68)	2.2 (0.65)
Percent predicted FEV_1 at screening (Visit 1, prebronchodilator)						
Mean (SD)	67.9 (10.48)	68.7 (10.74)	65.1 (10.30)	65.4 (10.16)	67.5 (10.73)	66.9 (10.54)
Baseline percent predicted FEV_1 (predose at Visit 2)						
Mean (SD)	67.5 (11.50)	70.0 (10.45)	67.5 (11.51)	66.9 (10.86)	68.7 (11.07)	68.1 (11.12)
Percent reversibility in FEV_1 at screening (Visit 1)						
Mean (SD)	20.5 (11.79)	22.7 (13.25)	24.4 (12.86)	22.6 (10.95)	21.1 (11.46)	22.2 (12.12)
Median	17.2	18.4	20.1	18.4	18.2	18.3
Min, Max	-0.4, 86.4	10.3, 92.0	11.2, 97.7	10.6, 71.2	9.1, 92.1	-0.4, 97.7

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

Efficacy, PRO, and pharmacokinetic 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, WV Pre-CF imputational method), 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 at the primary timepoint (Week 2 LOCF, WV Pre-CF imputational method) was significantly greater for SYMBICORT pMDI compared with 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 with 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. Results of sensitivity analyses were consistent across the 2 asthma severity strata.

- A significantly greater mean increase from baseline to the average over the treatment period 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. Results of sensitivity analyses were consistent across the 2 asthma severity strata.
- For the co-primary variables at every protocol-specified timepoint, there were no clinically relevant or statistically significant differences between the fixed combination of budesonide and formoterol administered as SYMBICORT pMDI and the free combination of budesonide administered with a pMDI device plus formoterol administered with a TBH device.

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

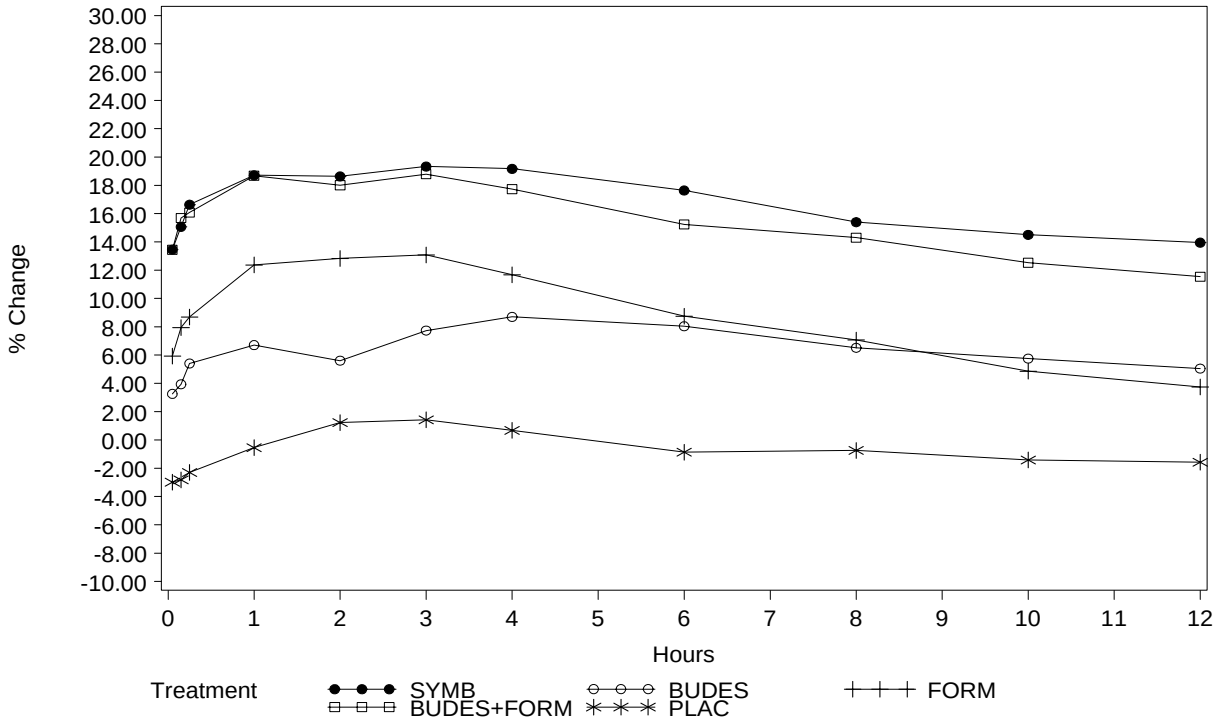
	ANCOVA analysis		
Comparison[a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB minus Plac	0.37 (0.04)	(0.29, 0.45)	<0.001
SYMB minus Budes	**0.20 (0.04)**	**(0.11, 0.28)**	**<0.001**
SYMB minus Form	0.15 (0.04)	(0.07, 0.23)	<0.001
SYMB minus Budes+Form	0.01 (0.04)	(-0.07, 0.09)	0.739
Budes minus Plac	0.17 (0.04)	(0.09, 0.25)	<0.001
Form minus Plac	0.22 (0.04)	(0.14, 0.30)	<0.001

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus 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)



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 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo 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)

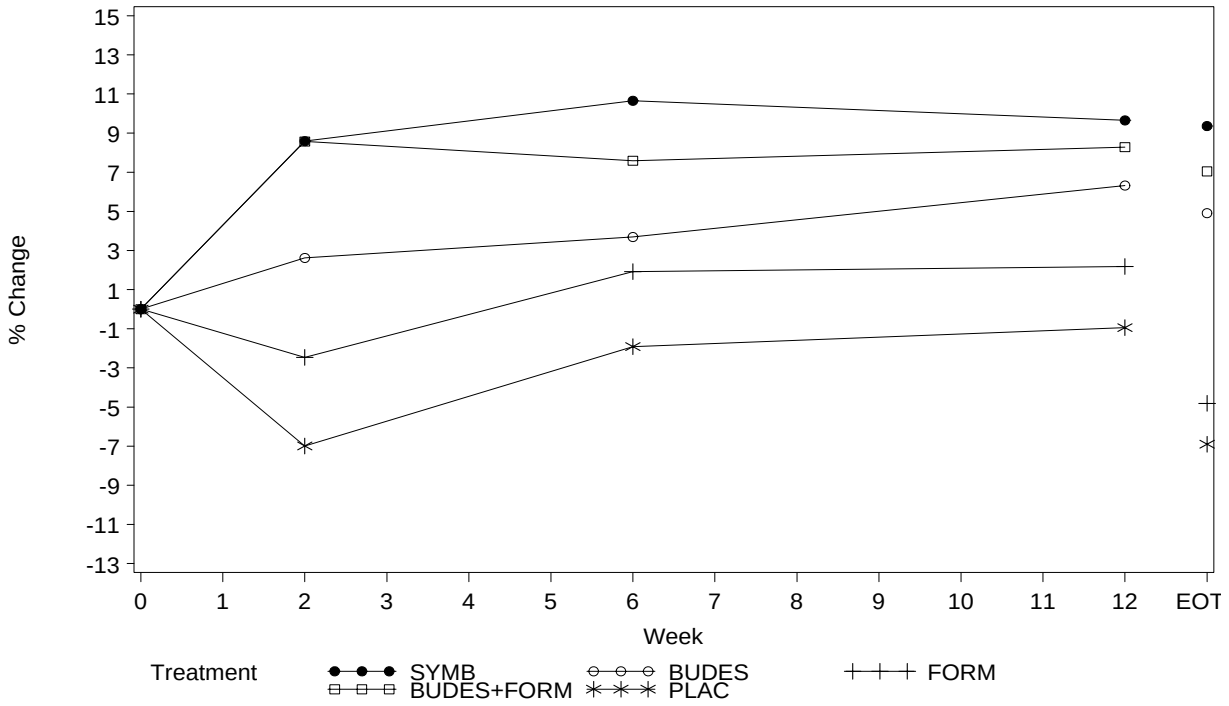
	ANCOVA analysis		
Comparison [a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB minus Plac	0.37 (0.04)	(0.28, 0.45)	<0.001
SYMB minus Budes	0.12 (0.04)	(0.04, 0.21)	0.006
SYMB minus Form	**0.26 (0.04)**	**(0.17, 0.35)**	**<0.001**
SYMB minus Budes+Form	0.04 (0.04)	(-0.05, 0.12)	0.399
Budes minus Plac	0.25 (0.04)	(0.16, 0.33)	<0.001
Form minus Plac	0.11 (0.04)	(0.02, 0.19)	0.012

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide MDI 160 µg per actuation x 2 actuations bid plus 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 study week (EAS)



	Week 2 N	Week 6 N	Week 12 N	EOT N
SYMB	117	107	100	117
Budes	108	90	79	108
Form	114	83	68	114
Budes+Form	111	102	92	111
Plac	116	70	56	116

SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus 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 (percentage of subjects who had a predefined asthma event; asthma symptoms as measured by percentage of symptom-free days; and overall AQLQ[S] score), SYMBICORT pMDI was statistically superior to placebo ($p<0.001$ for all endpoints). The percentages of subjects with at least 1 predefined asthma event were lower in the SYMBICORT pMDI (30%) and budesonide+formoterol (21%) groups than in the budesonide (44%), formoterol (55%), and placebo (67%) groups. Subjects taking SYMBICORT pMDI reported a higher percentage of symptom-free days during the study, compared with placebo (LS mean difference: 20.56% symptom-free days, 95% CI: 14.08% to 27.04%, $p<0.001$). The percentage of subjects with symptom-free days was greater for SYMBICORT pMDI than for placebo, starting 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 with placebo (LS mean difference 0.70, 95% CI: 0.468, 0.929, p<0.001). For all 3 key secondary endpoints, SYMBICORT pMDI also demonstrated a significant difference over each of its monoproducts.

For all additional secondary spirometry, diary, and global assessment efficacy endpoints, SYMBICORT pMDI showed superiority over placebo. For most of these secondary endpoints, SYMBICORT pMDI was also more efficacious than both formoterol and budesonide (delivered as monoproducts). In addition, subjects perceived the onset of effect faster following SYMBICORT pMDI than following placebo or budesonide, based on results of the Onset of Effect Questionnaire (OEQ), a diary variable. These results were consistent with the results of the Perception of Onset of Effect Question (POE), which was asked during spirometry.

Results of other PRO assessments conducted at the end of treatment, including the subdomains of the AQLQ and the Patient Satisfaction with Asthma Medication questionnaire (PSAM), demonstrated statistically significant improvement for SYMBICORT pMDI relative to placebo with respect to asthma-specific health-related quality of life and treatment satisfaction. The only PRO assessment for which a significant difference from placebo was not demonstrated was the MOS Sleep scale. The pediatric assessment instrument, ie, the PAQLQ(S), was not planned to be subjected to formal analysis.

For all secondary variables at every protocol-specified timepoint, there were no clinically relevant or statistically significant differences between the fixed combination of budesonide and formoterol administered as SYMBICORT pMDI and the free combination of budesonide administered with a pMDI device plus formoterol administered with a TBH device.

Secondary variables in this study also included pharmacokinetic parameters (AUC_{0-6}, C_{max}, and T_{max}) for plasma budesonide and plasma formoterol. Systemic exposure to budesonide was comparable between the SYMBICORT pMDI and budesonide treatment groups, as indicated by AUC_{0-6} and C_{max} mean treatment ratios (90% CI) of 0.955 (0.768, 1.187) and 1.008 (0.773, 1.315), respectively, and between the SYMBICORT pMDI and budesonide+formoterol treatment groups, as indicated by AUC_{0-6} and C_{max} mean treatment ratios (90% CI) of 0.899 (0.740, 1.092) and 0.958 (0.774, 1.185), respectively. T_{max} values were also similar between treatments. Systemic exposure to formoterol was comparable between the SYMBICORT pMDI and formoterol treatment groups, as indicated by AUC_{0-6} and C_{max} mean treatment ratios (90% CI) of 0.992 (0.736, 1.337) and 0.924 (0.671, 1.273), respectively, and between the SYMBICORT pMDI and budesonide+formoterol treatment groups, as indicated by AUC_{0-6} and C_{max} mean treatment ratios (90% CI) of 0.946 (0.752, 1.190) and 0.796 (0.633, 1.001), respectively. T_{max} for SYMBICORT pMDI (1.039 hr) was delayed relative to the formoterol (0.300 hr) and budesonide+formoterol (0.212 hr) treatment groups. In all formoterol-containing treatment groups, many subjects had plasma concentrations that were low and relatively unchanged across the sampling interval, which is an unexpected pattern for formoterol plasma concentration-time curves, based on previous results in healthy subjects, where the typical plasma concentration-time profile demonstrates a peak plasma concentration

at the first timepoint postdose followed by a rapid decline in concentration over the first hour postdose.

Safety results

Overall, the mean duration of exposure was lowest in the placebo group, followed by the formoterol group. Duration of exposure was comparable for the SYMBICORT pMDI, budesonide, and budesonide+formoterol groups. Differences in exposure between treatment groups must be taken into consideration when interpreting safety findings. The overall percentage of subjects with at least 1 AE during double-blind treatment was slightly lower in the placebo group than in the active treatment groups (see Table S4). Nine subjects had SAEs during double-blind treatment: 4 in the SYMBICORT pMDI group (asthma [2]; upper respiratory tract infection; ECG T wave inversion), 2 in the formoterol group (muscle rupture; angina pectoris), and 3 in the budesonide+formoterol group (small intestine obstruction; abdominal injury; pneumonia). One SAE in the SYMBICORT pMDI group (ECG T wave inversion) was considered to be study drug-related as judged by the investigator. A total of 30 subjects had AEs leading to discontinuation (DAE) during the treatment period, with a slightly higher incidence in the SYMBICORT pMDI and budesonide+formoterol groups compared with the other groups. Across treatment groups, asthma was the most commonly observed DAE (8 subjects total: SYMBICORT pMDI [3], budesonide [1], formoterol [3], budesonide+formoterol [0], and placebo [1]). All asthma SAEs and DAEs met predefined asthma event criteria and therefore do not represent additional cases of asthma exacerbation. 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=124)	**Budes (N=109)**	**Form (N=123)**	**Budes+Form (N=115)**	**Plac (N=125)**
Mean duration of exposure (days)	73.8	71.4	57.9	74.5	49.4
Any adverse events (AEs)	76 (61.3)	64 (58.7)	77 (62.6)	73 (63.5)	54 (43.2)
Serious adverse events (SAEs)	4 (3.2)	0	2 (1.6)	3 (2.6)	0
SAEs leading to death	0	0	0	0	0
SAEs not leading to death	4 (3.2)	0	2 (1.6)	3 (2.6)	0
SAEs leading to discontinuation	4 (3.2)	0	0	2 (1.7)	0
Subjects discontinued due to AEs	8 (6.5)	4 (3.7)	5 (4.1)	9 (7.8)	4 (3.2)
	Total number of adverse events				
Any AEs	231	182	226	185	144
SAEs	4	0	2	3	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 SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus 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 the active treatment groups, although the percentage of subjects with pharyngolaryngeal pain was slightly higher in the SYMBICORT pMDI, budesonide, and budesonide+formoterol groups than in the formoterol or placebo groups, and the percentage of subjects with stomach discomfort was slightly higher in the SYMBICORT pMDI group compared with other treatment groups. The incidence of oral candidiasis was low and occurred only in the SYMBICORT pMDI and budesonide+formoterol groups. The majority of AEs were mild or moderate in intensity. The incidence of asthma and potentially asthma-related AEs and of cardiac and cardiac-related investigational AEs was generally low and similar across treatment groups.

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

Preferred term	Treatment group[a], n (%) of subjects				
	SYMB (N=124)	Budes (N=109)	Form (N=123)	Budes+Form (N=115)	Plac (N=125)
Mean duration of exposure (days)	73.8	71.4	57.9	74.5	49.4
Number of subjects with any AE	76 (61.3)	64 (58.7)	77 (62.6)	73 (63.5)	54 (43.2)
Headache	14 (11.3)	14 (12.8)	13 (10.6)	11 (9.6)	10 (8.0)
Upper respiratory tract infection	13 (10.5)	10 (9.2)	10 (8.1)	10 (8.7)	14 (11.2)
Nasopharyngitis	12 (9.7)	12 (11.0)	8 (6.5)	9 (7.8)	9 (7.2)
Pharyngolaryngeal pain	11 (8.9)	8 (7.3)	4 (3.3)	10 (8.7)	3 (2.4)
Sinusitis	6 (4.8)	3 (2.8)	9 (7.3)	6 (5.2)	5 (4.0)
Cough	3 (2.4)	3 (2.8)	8 (6.5)	8 (7.0)	4 (3.2)
Stomach discomfort	8 (6.5)	5 (4.6)	3 (2.4)	1 (0.9)	2 (1.6)
Asthma	3 (2.4)	3 (2.8)	4 (3.3)	0	4 (3.2)
Vomiting	4 (3.2)	3 (2.8)	3 (2.4)	1 (0.9)	3 (2.4)
Diarrhea	3 (2.4)	3 (2.8)	4 (3.3)	1 (0.9)	2 (1.6)
Pyrexia	3 (2.4)	2 (1.8)	1 (0.8)	4 (3.5)	3 (2.4)
Back pain	2 (1.6)	6 (5.5)	2 (1.6)	1 (0.9)	0
Chest discomfort	1 (0.8)	2 (1.8)	5 (4.1)	1 (0.9)	1 (0.8)
Influenza	3 (2.4)	1 (0.9)	4 (3.3)	2 (1.7)	0
Nasal congestion	4 (3.2)	4 (3.7)	1 (0.8)	1 (0.9)	0
Nausea	3 (2.4)	1 (0.9)	5 (4.1)	0	1 (0.8)
Oral candidiasis	4 (3.2)	0	0	3 (2.6)	0

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 160 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Budes+Form budesonide pMDI 160 µg per actuation x 2 actuations bid plus formoterol TBH 4.5 µg per inhalation x 2 inhalations bid; Plac placebo x 2 actuations bid.

- Twelve-lead ECG and chemistry (glucose and potassium) assessments timed to coincide with peak sustained pharmacodynamic activity generally did not reveal meaningful differences between treatment groups. While there were small numerical differences between groups for mean changes from baseline in QT and QTc intervals, there were no clinically relevant differences. There were no relevant differences between treatment groups in individual clinically important QT and QTc data, although a slightly higher number of SYMBICORT pMDI subjects were noted to have ST-T wave changes on ECG. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters. Twenty-four hour Holter monitoring did not reveal significant differences in findings between treatment groups. The overall similarity of ECG and Holter findings across groups suggests no increased risk of atrial or ventricular dysrhythmia or the presence of significant cardiac issues related to SYMBICORT pMDI. 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

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