Drug product:	SYMBICORT®	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Edition No.:	FINAL		
Study code:	D5899C00002		
Date:	5 November 2007		

A 6-Month Double-blind, Double-dummy, Randomized, Parallel group, Multicenter Efficacy & Safety Study of SYMBICORT® pMDI 2 x 160/4.5 µg & 80/4.5 µg bid Compared to Formoterol TBH, Budesonide pMDI (& the combination) & placebo in COPD Patients (SHINE)

Study site(s)

This study was conducted at a total of 194 sites in the US and 4 other countries, including Czech Republic, Netherlands, Poland, and South Africa.

Publications

None as of the completion date of this report

Study dates		**Phase of development**
First subject enrolled	04 April 2005	Therapeutic confirmatory (III)
Last subject completed	28 December 2006	

Objectives

The primary objectives of the study in hierarchical order were:

- To show that SYMBICORT pMDI 2x160/4.5 µg bid was effective in patients with COPD, when compared to formoterol TURBUHALER 2x4.5 µg bid with regard to their effect on predose FEV_1.

- To show that SYMBICORT pMDI 2x160/4.5 µg bid was effective in patients with COPD, when compared to budesonide HFA pMDI 2x160 µg bid with regard to their effect on 1 hour postdose FEV_1.

- To show that SYMBICORT pMDI 2x80/4.5 µg bid was effective in patients with COPD, when compared to formoterol TURBUHALER 2x4.5 µg bid with regard to their effect on predose FEV_1.

- To show that SYMBICORT pMDI 2x80/4.5 µg bid was effective in patients with COPD, when compared to budesonide HFA pMDI 2x160 µg bid with regard to their effect on 1 hour postdose FEV_1.[1]

The secondary objectives of the study were 1) to show that SYMBICORT pMDI 160/4.5 was effective in patients with COPD, when compared to placebo with regard to the effect on predose FEV_1; 2) to show that SYMBICORT pMDI 160/4.5 was effective in patients with COPD, when compared to placebo with regard to the effect on 1-hour postdose FEV_1; 3) to show that SYMBICORT pMDI 80/4.5 was effective in patients with COPD, when compared to placebo with regard to the effect on predose FEV_1; 4) to show that SYMBICORT pMDI 80/4.5 was effective in patients with COPD, when compared to placebo with regard to the effect on 1 hour postdose FEV_1; 5) to investigate the relative effects of SYMBICORT pMDI 160/4.5 and the free standing combination of the monoproducts (budesonide HFA pMDI 2x160 µg bid and formoterol TURBUHALER 2x4.5 µg bid)[2]; 6) to compare the efficacy of SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5, budesonide 160, formoterol 4.5, and placebo in patients with chronic obstructive pulmonary disease (COPD) for a number of secondary variables; 7) to assess the systemic exposure to budesonide and formoterol following administration of SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, budesonide 160, and formoterol 4.5 (when taken both together and separately) through measurement of plasma concentrations over 12 hours at steady state; 8) to compare the safety of SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5, budesonide 160, formoterol 4.5, and placebo in patients with COPD with regard to their effect on: adverse events (AEs); vital signs (including body mass index [BMI]), physical examination; hematology and clinical chemistry; urinalysis; 12-lead electrocardiogram (ECG) for assessment of intervals (eg, QTc) and rhythm; 24-hour urinary free cortisol (in a subgroup).

Key secondary variables were dyspnea, using the Breathlessness Diary, health-related quality of life using the St. George's Respiratory Questionnaire (SGRQ), and COPD exacerbations, ie, a course of oral steroids and/or hospitalization due to respiratory symptoms. Additional efficacy variables are described in results, below.

Study design: This was a randomized, double-dummy, parallel-group, multicenter study in patients with COPD, consisting of 6 months (26 weeks) of treatment with SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, budesonide 160, formoterol 4.5, the free combination of budes 160 plus form 4.5, or placebo. The primary outcome variables were FEV_1 predose and 1-hour postdose FEV_1.

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[1] Hereafter, these study medications are referred to as "SYMBICORT pMDI 160/4.5," "SYMBICORT pMDI 80/4.5," "budesonide 160," "formoterol 4.5," respectively.

[2] Hereafter, referred to as "budes 160+form 4.5" or the "free combination of budes 160 plus form 4.5."

Target subject population and sample size: The entry criteria were designed to recruit a representative population of patients with moderate to very severe COPD who were experiencing exacerbations. They were to be of either sex, ≥40 years of age with the following characteristics: prebronchodilator FEV_1 ≤50% of predicted normal value, prebronchodilator FEV_1/FVC <70%, a clinical diagnosis of COPD with symptoms for >2 years, current or previous smoker with a smoking history of ≥10 pack years, score of ≥2 on the Modified Medical Research Council (MMRC) dyspnea scale, a breathlessness-cough-sputum total symptom score (BCSS) of ≥2 per day for at least half of the run-in period, a history of at least 1 COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1-12 months before Visit 1, use of a short-acting inhaled bronchodilator (β_2-agonists or anticholinergics) as rescue medication, and no history of asthma or allergic rhinitis before 40 years of age. A sample size of approximately 250 subjects per treatment group was chosen to allow 90% power to detect a 0.10 L difference between treatments in predose FEV_1 and also allow for an estimated 25% withdrawal rate.

Investigational product and comparator(s): dosage, mode of administration and batch numbers: Treatments were given in double-dummy fashion because of the comparison of a pMDI device (SYMBICORT) and a TURBUHALER (TBH) dry powder device (formoterol 4.5). Subjects were randomly assigned to 1 of the 6 following treatment groups: (1) SYMBICORT pMDI 160/4.5 and placebo TBH; batch numbers of SYMBICORT pMDI 160/4.5 were 05-001638AZ, 04-000111AZ, 04-000136AZ, P6742; (2) SYMBICORT pMDI 80/4.5 and placebo TBH; batch numbers of SYMBICORT were 05-001479AZ, 05-000624AZ, 04-000135AZ, P6740; (3) budesonide 160 and placebo TBH; batch numbers of budesonide 160 were 05-001710AZ, 04-000137AZ, P6905; (4) formoterol 4.5 and placebo pMDI; batch numbers of formoterol 4.5 were 05-000786AZ, 04-000093AZ, P7028, P7067; (5) free combination of budesonide 160 plus formoterol 4.5; batch numbers of budesonide 160 were 05-001710AZ, 04-000137AZ, P6905 and of formoterol 4.5 were 05-000786AZ, 04-000093AZ, P7028, P7067; (6) placebo pMDI and placebo TBH; batch numbers for placebo pMDI were 04-000103AZ, 04-000146AZ, 05-001379AZ, P6856, P6985, and for placebo TBH, batch numbers were 04-000096AZ, 05-001073AZ, P7027, P7068.

Study rescue medication: Albuterol, delivered by pMDI (either CFC or HFA)(90 µg per inhalation), was used in US sites (batches ACM04A, ACV18A), while salbutamol, delivered by pMDI (HFA) (100 µg per inhalation), was used in non-US sites (batches X1560, 04-000147AZ, 05-000646AZ, 05-001701AZ, 05-002845AZ).

Duration of treatment: The study had a 2-week run-in period, a 6-month treatment period, and a follow-up telephone call 4-weeks after the last dose of study medication.

Efficacy and PRO variables: The co-primary efficacy variables were change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1. Key secondary variables were dyspnea, health-related quality of life (SGRQ total score), and COPD exacerbations. Other secondary variables: serial spirometry (FEV_1) – onset of effect, maintenance of effect at 12 hours, baseline-adjusted 12-hour FEV_1, and maximum FEV_1 (in a subgroup of subjects); inspiratory capacity (IC) (predose and 1-hour postdose in the serial spirometry subgroup of subjects); forced vital capacity (FVC); diary variables (including morning and evening peak expiratory flow [PEF], β_2-agonist rescue medication use, cough, sputum, night time awakenings; SGRQ domain scores [Symptoms, Activity, Impacts]); and COPD-related healthcare utilization.

Pharmacokinetic variables included $AUC_{(0-12)}$, C_{max}, T_{max}, for plasma budesonide and plasma formoterol, calculated from blood samples collected predose and at 9 timepoints over 12 hours postdose at Visit 6 in a subgroup of subjects.

Safety variables included AEs, vital signs (including BMI), physical examinations, hematology, clinical chemistry, urinalysis (including pregnancy testing), pre- and postdose 12-lead ECGs, and 24-hour urinary free cortisol (in a subgroup of subjects).

Statistical methods: The efficacy analysis set (EAS) included all randomized subjects who took at least 1 dose of randomized treatment and contributed sufficient data for at least 1 efficacy outcome variable. The co-primary outcome variables were each analyzed as a change from baseline to the average over the randomized treatment period using an analysis of covariance (ANCOVA) model, adjusting for treatment, country, and baseline predose FEV_1. Predose FEV_1 was used to compare SYMBICORT pMDI to formoterol. One-hour postdose FEV_1 was used to compare SYMBICORT pMDI to budesonide. For all secondary variables, the primary comparison was between SYMBICORT pMDI and placebo. Other continuous secondary variables were analyzed with methods similar to those used for the primary variables. Count data were analyzed using a Poisson regression model adjusting for treatment, country, time in study, and overdispersion. 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) and from whom any data after randomization were available.

Study Results:

Subject population: This study was conducted in the US and 4 other countries at 194 sites. The study population was representative of the target patient population with moderate to very severe COPD. Of 2381 screened subjects, 1704 were subsequently randomized. The US contributed 42% of randomized subjects. In general, demographic and key baseline characteristics were similar across geographic regions (US vs non-US countries). The randomized treatment groups were similar at baseline with respect to most demographic and disease severity characteristics (Table S1). The study population included a representative number of subjects with significant comorbid conditions. Subjects receiving anticholinergic treatment at study entry were to be converted to stable-dose ipratropium for the duration of the randomized treatment period; approximately 63% of subjects were prescribed ipratropium. Both SYMBICORT pMDI groups had significantly lower discontinuation rates compared with the monoproducts and placebo. The most common reason for discontinuation was an adverse event (143 subjects, 8%).

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group (µg)[a]						
	SYMB 160/4.5 (N=277)	SYMB 80/4.5 (N=281)	Budes 160+form 4.5 (N=287)	Budes 160 (N=275)	Form 4.5 (N=284)	Plac (N=300)	Total (N=1704)
Sex (n and % of subjects)							
Male	188 (67.9)	181 (64.4)	213 (74.2)	186 (67.6)	186 (65.5)	207 (69.0)	1161 (68.1)
Female	89 (32.1)	100 (35.6)	74 (25.8)	89 (32.4)	98 (34.5)	93 (31.0)	543 (31.9)
Age (yrs)							
Median	63	63	64	63	64	63	64
Range	41 to 86	40 to 90	40 to 84	40 to 90	42 to 89	40 to 86	40 to 90

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group (µg)[a]						
	SYMB 160/4.5 (N=277)	SYMB 80/4.5 (N=281)	Budes 160+form 4.5 (N=287)	Budes 160 (N=275)	Form 4.5 (N=284)	Plac (N=300)	Total (N=1704)
Age groups (yrs), (n and % of subjects)							
40 to <65	156 (56.3)	149 (53.0)	147 (51.2)	154 (56.0)	144 (50.7)	159 (53.0)	909 (53.3)
65 to <75	91 (32.9)	99 (35.2)	110 (38.3)	85 (30.9)	103 (36.3)	104 (34.7)	592 (34.7)
≥75	30 (10.8)	33 (11.7)	30 (10.5)	36 (13.1)	37 (13.0)	37 (12.3)	203 (11.9)
Country (n and % of subjects)							
US	114 (41.2)	118 (42.0)	127 (44.3)	112 (40.7)	120 (42.3)	129 (43.0)	720 (42.3)
Poland	84 (30.3)	81 (28.8)	80 (27.9)	83 (30.2)	84 (29.6)	85 (28.3)	497 (29.2)
Czech Republic	43 (15.5)	43 (15.3)	46 (16.0)	46 (16.7)	44 (15.5)	44 (14.7)	266 (15.6)
South Africa	22 (7.9)	21 (7.5)	21 (7.3)	21 (7.6)	21 (7.4)	23 (7.7)	129 (7.6)
Netherlands	14 (5.1)	18 (6.4)	13 (4.5)	13 (4.7)	15 (5.3)	19 (6.3)	92 (5.4)
Race, (n and % of subjects)							
Caucasian	261 (94.2)	262 (93.2)	264 (92.0)	259 (94.2)	262 (92.3)	284 (94.7)	1592 (93.4)
Black	9 (3.2)	14 (5.0)	14 (4.9)	8 (2.9)	11 (3.9)	8 (2.7)	64 (3.8)
Oriental	0	0	2 (0.7)	1 (0.4)	2 (0.7)	1 (0.3)	6 (0.4)
Other	7 (2.5)	5 (1.8)	7 (2.4)	7 (2.5)	9 (3.2)	7 (2.3)	42 (2.5)
Baseline FEV_1 (L) (predose at Visit 2)							
Mean (SD)	1.04 (0.415)	1.04 (0.396)	1.05 (0.362)	1.04 (0.404)	1.02 (0.399)	1.08 (0.379)	1.05 (0.392)
Baseline percent predicted FEV_1 (predose at Visit 2)							
Mean (SD)	33.70 (11.887)	34.16 (10.998)	33.55 (10.794)	33.54 (10.840)	33.64 (11.394)	34.65 (10.588)	33.88 (11.076)
Percent reversibility at Visit 1 (n and % of subjects)							
Mean (SD)	19.08 (19.675)	16.65 (14.992)	17.60 (20.846)	16.25 (19.081)	16.60 (17.716)	17.78 (18.358)	17.33 (18.535)
≥12% + change in FEV_1 ≥0.2L	103 (37.2)	91 (32.4)	99 (34.5)	85 (30.9)	95 (33.5)	120 (40.0)	593 (34.8)
MMRC score							
Mean (SD)	2.84 (0.79)	2.88 (0.81)	2.92 (0.79)	2.89 (0.81)	2.98 (0.83)	2.92 (0.77)	2.90 (0.80)
Range	2 to 5	2 to 5	2 to 5	2 to 5	1 to 5	2 to 5	1 to 5
Postbronchodilator % predicted FEV_1 at Visit 1 (screening) (n and % of subjects)[b]							
<30%	71 (25.6)	53 (18.9)	67 (23.3)	62 (22.5)	70 (24.6)	52 (17.3)	375 (22.0)
≥30 <50%	153 (55.2)	173 (61.6)	167 (58.2)	160 (58.2)	154 (54.2)	184 (61.3)	991 (58.2)
≥50-<80%	52 (18.8)	53 (18.9)	53 (18.5)	51 (18.5)	59 (20.8)	61 (20.3)	329 (19.3)
≥80%	0	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.7)	5 (0.3)
Missing	1 (0.4)	1 (0.4)	0	1 (0.4)	0	1 (0.3)	4 (0.2)
Smoking history (n and % of subjects)							
-Ex-smoker	154 (55.6)	155 (55.2)	168 (58.5)	157 (57.1)	165 (58.1)	181 (60.3)	980 (57.5)
-Habitual smoker	113 (40.8)	111 (39.5)	107 (37.3)	110 (40.0)	109 (38.4)	108 (36.0)	658 (38.6)
-Occasional smoker	10 (3.6)	15 (5.3)	12 (4.2)	8 (2.9)	10 (3.5)	11 (3.7)	66 (3.9)
Pack years							
N	277	281	287	275	284	300	1704
Median	40.0	40.0	42.0	41.0	40.0	40.0	40.0
Min, Max	10 to 184	10 to 196	10 to 188	10 to 171	10 to 144	10 to 200	10 to 200

[a] SYMB SYMBICORT pMDI; Budes budesonide; Form formoterol; Plac placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily.

[b] Categories are based on GOLD criteria categories for postbronchodilator percent predicted FEV_1 : ≥80%: mild; ≥50-<80%: moderate; ≥30-<50%: severe; <30%: very severe.

FEV_1 Forced expiratory volume in one second; MMRC Modified Medical Research Council.

Efficacy and pharmacokinetic results: Results of the primary analysis of the co-primary efficacy endpoints (predose FEV_1 and 1-hour postdose FEV_1) are summarized in Table S2 and Table S3, respectively.

Table S2 Predose FEV_1 (L): treatment comparisons for change from baseline to the average during the randomized treatment period (EAS)

	ANCOVA analysis		
Comparison[a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB 160/4.5 minus Plac	0.08 (0.02)	0.04, 0.11	<0.001
SYMB 160/4.5 minus Budes 160	0.08 (0.02)	0.04, 0.11	<0.001
SYMB 160/4.5 minus Form 4.5	**0.04 (0.02)**	**0.00, 0.07**	**0.026**
SYMB 160/4.5 minus Budes 160+Form 4.5	0.01 (0.02)	-0.02, 0.05	0.479
SYMB 80/4.5 minus Plac	0.05 (0.02)	0.02, 0.09	0.002
SYMB 80/4.5 minus Budes 160	0.06 (0.02)	0.02, 0.09	0.001
SYMB 80/4.5 minus Form 4.5	**0.02 (0.02)**	**-0.02, 0.05**	**0.335**
Budes 160 minus Plac	-0.00 (0.02)	-0.04, 0.03	0.902
Form 4.5 minus Plac	0.04 (0.02)	0.00, 0.07	0.037
SYMB 160/4.5 minus SYMB 80/4.5	0.02 (0.02)	-0.01, 0.06	0.198

[a] SYMB SYMBICORT pMDI; Budes budesonide; Form formoterol; Plac Placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily.

Note: Baseline is defined as the last predose FEV_1 value before the 1st dose of randomized treatment. The bolded comparison is the prespecified primary comparison for this variable.

EAS Efficacy analysis set.

Table S3 1-hour postdose FEV_1 (L): treatment comparisons for change from baseline to the average during the randomized treatment period (EAS)

	ANCOVA analysis		
Comparison[a]	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB 160/4.5 minus Plac	0.17 (0.02)	0.14, 0.20	<0.001
SYMB 160/4.5 minus Budes 160	**0.17 (0.02)**	**0.14, 0.21**	**<0.001**
SYMB 160/4.5 minus Form 4.5	0.04 (0.02)	0.00, 0.07	0.039
SYMB 160/4.5 minus Budes 160+Form 4.5	0.01 (0.02)	-0.02, 0.05	0.461
SYMB 80/4.5 minus Plac	0.16 (0.02)	0.13, 0.20	<0.001
SYMB 80/4.5 minus Budes 160	**0.16 (0.02)**	**0.13, 0.20**	**<0.001**
SYMB 80/4.5 minus Form 4.5	0.03 (0.02)	-0.01, 0.06	0.116
Budes 160 minus Plac	0.00 (0.02)	-0.03, 0.03	0.997
Form 4.5 minus Plac	0.14 (0.02)	0.10, 0.17	<0.001
SYMB 160/4.5 minus SYMB 80/4.5	0.01 (0.02)	-0.03, 0.04	0.615

[a] SYMB SYMBICORT pMDI; Budes budesonide; Form formoterol; Plac Placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily.

Note: Baseline is defined as the last predose FEV_1 value before the 1st dose of randomized treatment. The bolded comparison is the prespecified primary comparison for this variable.

EAS Efficacy analysis set.

Summary of findings for the co-primary variables, predose FEV_1 and 1-hour postdose FEV_1: SYMBICORT pMDI 160/4.5 demonstrated a statistically significantly greater increase from baseline in average predose FEV_1 compared with formoterol 4.5 and in average postdose FEV_1 compared with budesonide 160, with maintenance of effect for both comparisons over the 6-month treatment period. Additionally, SYMBICORT pMDI 160/4.5 demonstrated a significant increase from baseline for the average postdose FEV_1 compared with formoterol 4.5. These results demonstrate the contribution of both formoterol and budesonide to the efficacy of SYMBICORT pMDI 160/4.5. SYMBICORT pMDI 80/4.5 demonstrated a statistically significantly greater increase from baseline in average postdose FEV_1 compared with budesonide 160, with maintenance of effect over the course of the study. No difference was detected between SYMBICORT pMDI 80/4.5 and formoterol for predose FEV_1. Both dosage strengths of SYMBICORT pMDI demonstrated statistically significantly greater increases from baseline in average predose FEV_1 and 1-hour postdose FEV_1 compared to placebo. Formoterol 4.5 showed superiority over placebo for postdose FEV_1; however, no difference was detected between budesonide 160 and placebo for predose FEV_1.

Summary of findings for the 3 key secondary and other efficacy endpoints:

Dyspnea: Both doses of SYMBICORT pMDI significantly reduced dyspnea scores compared with placebo and the monoproducts budesonide 160 and formoterol 4.5. The LS means compared to placebo approached the validated minimal clinically important difference (MID). A responder analysis showed that a significantly greater proportion of subjects taking SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 achieved the MID for the dyspnea score compared with placebo.

SGRQ: SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 showed a highly significant reduction from baseline in SGRQ total scores compared with placebo, budesonide 160, and formoterol 4.5, indicating improvement. The LS means compared to placebo approached the validated MID. A responder analysis demonstrated that a significantly higher proportion of SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 subjects achieved the MID compared to placebo for each instrument.

COPD exacerbations: There were no statistically significant differences in the rate of exacerbations per subject-treatment year between treatment groups. SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 had a numerical 20-25% lower exacerbation rate compared with placebo and formoterol, driven by oral corticosteroid use. For the subset of hospitalized exacerbations, SYMBICORT pMDI 160/4.5, but not SYMBICORT pMDI 80/4.5, had a statistically significantly increased rate of hospitalization per subject treatment year compared to placebo. However, the hospitalization rate per treatment group was very low, preventing a robust comparison between treatments.

Serial spirometry: 12-hour serial FEV_1 assessments at the end of treatment demonstrated that SYMBICORT pMDI 160/4.5 produced rapid and sustained improvement in FEV_1 over 12 hours, with no diminution of effect over the 6-month treatment period, compared with placebo. SYMBICORT pMDI 80/4.5 also produced rapid and sustained improvement in FEV_1 over 12 hours; however, there was attentuation of effect during the treatment period.

Other secondary efficacy variables: In general, both dosage strengths of SYMBICORT showed efficacy across a broad range of secondary variables, such as PEF, cough, sleep, and use of rescue medication, compared with placebo. There were few significant differences between treatment groups for health resource utilization variables.

Pharmacokinetics results: $AUC_{(0-12)}$ values for budesonide were 7.243, 3.361, 6.715 and 6.492 nmol·h/L for SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, budes 160+form 4.5 and budes 160 treatments, respectively; and for formoterol were 172.5, 152.7, 148.4 and 132.6 pmol·h/L for SYMBICORT pMDI 160/4.5, SYMBICORT pMDI 80/4.5, budes 160+form 4.5 and form 4.5 treatments, respectively.

Safety results: All 1704 randomized subjects received at least 1 dose of study drug and were included in the safety analysis set. Mean exposure was shortest in the placebo group (150 days) and longest in the 2 SYMBICORT pMDI groups (both >166 days). SYMBICORT pMDI was well tolerated relative to placebo and the monoproducts across a wide range of age, gender, race, COPD severity, comorbid conditions, smoking status, geographic region, and concomitant medication use. Safety results were similar for the SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 groups with no consistent budesonide dose-ordered response for most safety variables. The percentage of subjects with any serious adverse events (SAEs) as well as COPD SAEs was slightly higher in the SYMBICORT groups compared to the monoproducts and placebo. The SYMBICORT groups had lower incidences of discontinuations due to adverse event (DAEs) compared to the monoproducts and placebo. Review of the incidences of known ICS and LABA class effects did not demonstrate clinically important differences between either SYMBICORT pMDI group and the relevant monoproduct group. The incidence of pneumonia was similar across all treatment arms. There was a higher percent of subjects reporting AEs with preferred terms that could potentially represent lung infections other than pneumonia, mainly under the bronchitis category, on SYMBICORT pMDI 160/4.5 compared to placebo. The overall number of deaths was very low considering the severity of the population, and no deaths were considered by the investigator to be drug-related. Eleven subjects died from an SAE with onset during the randomized treatment period: 3 in the SYMBICORT pMDI 160/4.5 group (metastatic lung cancer; cardiac failure; hip fracture and subsequent cardiopulmonary failure), 4 in the SYMBICORT pMDI 80/4.5 group (COPD, cardiac arrest, congestive cardiac failure and COPD; COPD), 2 in the budesonide 160 group (COPD; cerebrovascular accident), 1 in the formoterol 4.5 group (myocardial infarction), and 1 in the placebo group (subarachnoid hemorrhage), with none reported in the budes 160+form 4.5 group. Ten subjects died from an SAE with onset after the randomized treatment period: 1 in the SYMBICORT pMDI 160/4.5 group (COPD), 1 in the SYMBICORT pMDI 80/4.5 group (arrhythmia), 1 in the budesonide 160+form 4.5 group (cardiovascular disorder), 1 in the budesonide 160 group (congestive cardiac failure), 4 in the formoterol 4.5 group (scleroderma and dehydration; hypoxia; septic shock; cerebrovascular accident and ventricular fibrillation), and 2 in the placebo group (sudden death; myocardial infarction). Clinically significant changes in laboratory values (including 24 hour urinary free cortisol), vital signs, or ECG measures were rare with no clinically important differences between subjects treated with SYMBICORT pMDI compared to both placebo and the monoproducts. SYMBICORT pMDI was well tolerated relative to placebo and the monoproducts across a wide range of age, gender, race, COPD severity, comorbid conditions, smoking status, geographic region, and concomitant medication use. Safety results were similar for the SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 groups with no consistent budesonide dose-ordered response for most safety variables.

An overview of AEs that occurred during randomized treatment for the safety analysis set is presented in Table S4. AEs that occurred at an incidence of ≥3% in any treatment group during randomized treatment are presented by MedDRA preferred term in Table S5.

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

	Treatment group (µg) [b]					
AE category	**SYMB 160/4.5 (N=277)**	**SYMB 80/4.5 (N=281)**	**Budes 160+form 4.5 (N=287)**	**Budes 160 (N=275)**	**Form 4.5 (N=284)**	**Plac (N=300)**
Mean (SD) exposure, days	166.5 (41.29)	168.3 (37.73)	164.6 (40.28)	157.1 (51.31)	156.3 (53.22)	150.0 (60.15)
	Number (%) of subjects with at least 1 AE in the specified category [a]					
With at least 1 AE	159 (57.4)	147 (52.3)	142 (49.5)	158 (57.5)	161 (56.7)	152 (50.7)
With an SAE	33 (11.9)	34 (12.1)	26 (9.1)	28 (10.2)	24 (8.5)	26 (8.7)
SAE leading to death	3 (1.1)	4 (1.4)	0	2 (0.7)	1 (0.4)	1 (0.3)
SAE not leading to death	31 (11.2)	30 (10.7)	26 (9.1)	26 (9.5)	23 (8.1)	25 (8.3)
SAE leading to DAE	10 (3.6)	10 (3.6)	7 (2.4)	7 (2.5)	7 (2.5)	6 (2.0)
With an AE leading to DAE	19 (6.9)	19 (6.8)	13 (4.5)	25 (9.1)	32 (11.3)	25 (8.3)
With an SAE and/or DAE	42 (15.2)	42 (14.9)	31 (10.8)	46 (16.7)	48 (16.9)	44 (14.7)
With a study-drug related AE	24 (8.7)	24 (8.5)	17 (5.9)	22 (8.0)	22 (7.7)	18 (6.0)
SAE	1 (0.4)	2 (0.7)	0	0	1 (0.4)	0
AE leading to DAE	3 (1.1)	5 (1.8)	1 (0.3)	2 (0.7)	10 (3.5)	6 (2.0)
	Total number of adverse events					
AEs, by intensity	364	345	327	343	369	320
Mild, n (%)	187 (51.4)	172 (49.9)	183 (56.0)	155 (45.2)	198 (53.7)	167 (52.2)
Moderate, n (%)	131 (36.0)	126 (36.5)	107 (32.7)	145 (42.3)	120 (32.5)	117 (36.6)
Severe, n (%)	46 (12.6)	47 (13.6)	37 (11.3)	43 (12.5)	51 (13.8)	36 (11.3)
AEs per subject treatment year	2.9	2.7	2.5	2.9	3.0	2.6
SAEs	42	44	30	42	30	34
SAEs per subject treatment year	0.33	0.34	0.23	0.35	0.25	0.28
DAEs	19	25	14	29	36	30
DAEs per subject treatment year	0.15	0.19	0.11	0.24	0.30	0.24
Study-drug related AEs	39	36	25	34	38	28

[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.

[b] SYMB SYMBICORT pMDI; Budes budesonide; Form formoterol; Plac placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily.

AE Adverse event; SAE Serious adverse event; DAE Discontinuation due to adverse event.

Table S5 Most frequently reported adverse events (reported by at least 3% of subjects in any treatment group) by MedDRA preferred term, during randomized treatment (Safety analysis set)

	Treatment group (µg) [a]					
MedDRA preferred term [b]	**SYMB 160/4.5 (N=277)**	**SYMB 80/4.5 (N=281)**	**Budes 160+form 4.5 (N=287)**	**Budes 160 (N=275)**	**Form 4.5 (N=284)**	**Plac (N=300)**
Mean (SD) exposure, days	166.5 (41.29)	168.3 (37.73)	164.6 (40.27)	157.1 (51.31)	156.3 (53.22)	150.0 (60.15)
	Number (%) of subjects					
Subjects with at least 1 AE	159 (57.4)	147 (52.3)	142 (49.5)	158 (57.5)	161 (56.7)	152 (50.7)
COPD	37 (13.4)	34 (12.1)	30 (10.5)	34 (12.4)	50 (17.6)	35 (11.7)
Nasopharyngitis	21 (7.6)	11 (3.9)	12 (4.2)	9 (3.3)	15 (5.3)	16 (5.3)
Oral candidiasis	10 (3.6)	7 (2.5)	8 (2.8)	12 (4.4)	7 (2.5)	6 (2.0)
Bronchitis	10 (3.6)	4 (1.4)	10 (3.5)	8 (2.9)	8 (2.8)	6 (2.0)
Sinusitis	8 (2.9)	9 (3.2)	9 (3.1)	4 (1.5)	5 (1.8)	6 (2.0)
Diarrhea	3 (1.1)	5 (1.8)	4 (1.4)	3 (1.1)	9 (3.2)	1 (0.3)

[a] SYMB SYMBICORT pMDI; Budes budesonide; Form formoterol; Plac placebo pMDI and TBH. Each treatment was administered as 2 actuations/inhalations twice daily.

[b] Sorted by decreasing order of frequency for the total incidence across all treatment groups.

Note: This table uses a cut-off of 3.0% based on the AE incidence in any treatment group.
MedDRA Medical dictionary for regulatory activities (version 9.1).

Date of the report

5 November 2007