AstraZeneca

Drug product:	SYMBICORT®	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Edition No.:	FINAL		
Study code:	D5899C00001		
Date:	17 March 2008		

A 12-Month Double-blind, Double-dummy, Randomized, Parallel group, Multicenter Efficacy & Safety Study of SYMBICORT® pMDI 2 x 160/4.5 mcg bid and 2 x 80/4.5 mcg bid Compared to Formoterol TBH 2 x 4.5 mcg bid and Placebo in Patients with COPD

Study site(s)

This study was conducted at a total of 237 sites in the US and 8 other countries (Bulgaria, Denmark, Germany, Greece, Hungary, Iceland, Mexico, and Romania).

Publications

None as of the completion date of this report

Study dates

First subject enrolled   4 April 2005
Last subject completed   27 September 2007

Phase of development

Therapeutic confirmatory (IIIA)

Objectives

The primary objectives of the study were:

1.   To show that SYMBICORT pMDI 2 x 160/4.5 mcg bid is effective in patients with COPD, when compared to placebo and formoterol Turbuhaler (TBH®) 2 x 4.5 mcg bid with regard to its effect on predose FEV_1 and when compared to placebo with regard to its effect on 1-hour postdose FEV_1.

2.   To show that SYMBICORT pMDI 2 x 80/4.5 mcg bid is effective in patients with COPD, when compared to placebo and formoterol TBH 2 x 4.5 mcg bid with regard to its effect on predose FEV_1 and when compared to placebo with regard to its effect on 1-hour postdose FEV_1.

The secondary objectives were:

1.   To compare the efficacy of SYMBICORT pMDI 2 x 160/4.5 mcg bid and SYMBICORT pMDI 2 x 80/4.5 mcg bid in patients with COPD, with placebo and formoterol TBH 2 x 4.5 mcg bid for a number of secondary variables; the most important of-these (ie, the "key" secondary variables) were dyspnea using Breathlessness Diary; health-related quality of life ie, SGRQ total score; number of exacerbations ie, a course of oral steroids and/or hospitalization due to a worsening of COPD.

2.   To compare the safety of SYMBICORT pMDI 2 x 160/4.5 mcg bid and SYMBICORT pMDI 2 x 80/4.5 mcg bid in patients with COPD, with placebo and formoterol TBH 2 x 4.5 mcg bid.[1]

Study design: This was a randomized, double-blind, double-dummy, parallel-group, multicenter study in patients with COPD, consisting of 12 months (52 weeks) of treatment with SYMBICORT pMDI 2x 160/4.5 mcg bid, SYMBICORT pMDI 2x 80/4.5 mcg bid, formoterol TBH 2x 4.5 mcg bid, or placebo bid. The primary outcome variables were FEV_1 predose and 1-hour postdose.

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 had experienced exacerbations and were candidates for an inhaled corticosteroid (ICS) and long-acting β_2 adrenergic receptor agonist (LABA) combination product. 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 400 patients in each treatment group would allow 90% power to detect a reduction from 1.07 to 0.74 (about 30% reduction) in the number of exacerbations, adjusting for overdispersion (deviance) of 2.3, and >95% power to detect a 0.10 L difference in FEV_1 based on an estimated standard deviation of 0.3 L.

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 TBH dry powder device (formoterol 4.5). Subjects were randomly assigned to 1 of the 4 following treatment groups: (1) SYMBICORT 160/4.5 and placebo TBH; batch numbers of SYMBICORT 160/4.5 were: 05-001638AZ, 05-005538AZ, 04-000111AZ, 04-000136AZ, and P6742. (2) SYMBICORT 80/4.5 and placebo TBH; batch numbers of SYMBICORT 80/4.5 were: 05-001479AZ, 05-005495AZ, 05-000624AZ, 04-000135AZ, and P6740. (3) Formoterol 4.5 and placebo pMDI; batch numbers of formoterol 4.5 were: 05-000786AZ, 05-004205AZ, 06-009524AZ, 05-001385AZ, 04-000094AZ, P7028, and P7067, (4) placebo pMDI and placebo TBH; batch numbers for placebo pMDI were: 04-000146AZ, 05-001379AZ, P6856, and P6985; batch numbers for placebo TBH were: 04-000095AZ, 05-001073AZ, 05-004246AZ, 06-009525AZ, P7027, and P7068. Study rescue

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

medication: Albuterol, delivered by pMDI (either CFC or HFA) (90 µg per inhalation), was used in US sites (batches: ACM04A, ACV18A, FHC027A, FHC033A, GHB063A), while salbutamol, delivered by pMDI (HFA) (100 µg per inhalation), was used in non-US sites (04-000147AZ, 05-004635AZ, 06-009329AZ, 07-010583AZ, X1560).

Duration of treatment: The study had a 2-week run-in period, a 12-month treatment period, and a follow-up telephone call 4-weeks after the last dose of study medication.

Criteria for evaluation (main variables):

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 Breathlessness Diary Scores, health-related quality of life (SGRQ total score), and number of and time to first 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); inspiratory capacity (IC; predose and 1-hour postdose in the serial spirometry subgroup); forced vital capacity (FVC), diary variables (including morning and evening peak expiratory flow [PEF], study-provided β_2-agonist rescue medication use, cough, sputum, BCSS (the sum of the dyspnea, cough, and sputum scores), night time awakenings; SGRQ domain scores [Symptoms, Activity, Impacts]); and COPD-related healthcare utilization.

Safety variables: Safety variables included 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 Holter monitoring (in a subgroup); 24-hour urinary free cortisol (in a subgroup); ophthalmologic assessment, i.e., lenticular opacities and ocular pressure (in a subgroup); bone mineral density (BMD) (in a subgroup).

Statistical methods: To maintain the experiment-wise Type I error rate at no greater that 5%, a sequential approach to hypothesis testing and the interpretation of unadjusted p-values was taken. The higher dose, SYMBICORT pMDI 160/4.5, was first compared with placebo for 1-hour postdose and predose FEV_1 and then with formoterol 4.5 for predose FEV_1. If these tests were rejected at the 5% level, then sequential testing for Dyspnea, SGRQ, and number of exacerbations per subject treatment year for the higher dose would be completed comparing SYMBICORT pMDI 160/4.5 versus placebo. If these 3 comparisons were significant, then the same testing procedure was followed for SYMBICORT pMDI 80/4.5. All efficacy analyses were performed on an efficacy analysis set (EAS) population using 2-sided tests at the 5% level of significance. The 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, demonstrating the effect of budesonide. One-hour postdose FEV_1 was used to compare SYMBICORT pMDI to placebo. 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 and for whom any data were available after randomization (safety analysis set).

Results

Subject population:

This study was conducted at 237 sites in the US and 8 other countries. The study population was representative of the target patient population with moderate to very severe COPD. Of 2816 screened subjects, 1964 were subsequently randomized. The US contributed 45% 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 characteristics and disease severity (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 43% of subjects were prescribed ipratropium. Among randomized subjects, the discontinuation rate was lowest in the SYMBICORT pMDI 160/4.5 group (27%), followed by the SYMBICORT pMDI 80/4.5 (29%), formoterol 4.5 (32%), and placebo (36%) groups. The time to discontinuation was statistically significantly increased in each SYMBICORT pMDI group compared with the placebo group. The most common reason for discontinuation was an adverse event (255 subjects, 13%).

Table S1   Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group (mcg)[a]				
	SYMB 160/4.5 (N=494)	SYMB 80/4.5 (N=494)	Form 4.5 (N=495)	Plac (N=481)	Total (N=1964)
Sex (n and % of subjects)					
Male	308 (62.3)	310 (62.8)	323 (65.3)	314 (65.3)	1255 (63.9)
Female	186 (37.7)	184 (37.2)	172 (34.7)	167 (34.7)	709 (36.1)
Age (yrs)					
Median	64	64	63	63	63
Range	40 to 83	42 to 89	41 to 88	40 to 84	40 to 89
Age groups (yrs), (n and % of subjects)					
40 to <65	266 (53.8)	262 (53.0)	282 (57.0)	273 (56.8)	1083 (55.1)
65 to <75	185 (37.4)	165 (33.4)	161 (32.5)	150 (31.2)	661 (33.7)
≥75	43 (8.7)	67 (13.6)	52 (10.5)	58 (12.1)	220 (11.2)
Country (n and % of subjects)					
US	**224 (45.3)**	**225 (45.5)**	**224 (45.3)**	**211 (43.9)**	**884 (45.0)**
Non-US	**270 (54.7)**	**269 (54.5)**	**271 (54.7)**	**270 (56.1)**	**1080 (55.0)**
Hungary	76 (15.4)	81 (16.4)	79 (16.0)	81 (16.8)	317 (16.1)
Germany	57 (11.5)	51 (10.3)	57 (11.5)	52 (10.8)	217 (11.0)
Romania	37 (7.5)	38 (7.7)	38 (7.7)	37 (7.7)	150 (7.6)
Bulgaria	37 (7.5)	37 (7.5)	36 (7.3)	36 (7.5)	146 (7.4)
Denmark	24 (4.9)	24 (4.9)	21 (4.2)	25 (5.2)	94 (4.8)
Mexico	23 (4.7)	20 (4.0)	22 (4.4)	24 (5.0)	89 (4.5)

Table S1 **Demographic and key characteristics (safety analysis set)**

Demographic or key characteristic	Treatment group (mcg)[a]				
	SYMB 160/4.5 (N=494)	SYMB 80/4.5 (N=494)	Form 4.5 (N=495)	Plac (N=481)	Total (N=1964)
Greece	10 (2.0)	12 (2.4)	11 (2.2)	10 (2.1)	43 (2.2)
Iceland	6 (1.2)	6 (1.2)	7 (1.4)	5 (1.0)	24 (1.2)
Race, (n and % of subjects)					
Caucasian	457 (92.5)	460 (93.1)	457 (92.3)	441 (91.7)	1815 (92.4)
Black	13 (2.6)	13 (2.6)	10 (2.0)	11 (2.3)	47 (2.4)
Oriental	1 (0.2)	1 (0.2)	4 (0.8)	2 (0.4)	8 (0.4)
Other	23 (4.7)	20 (4.0)	24 (4.8)	27 (5.6)	94 (4.8)
Baseline FEV_1 (L) (predose at Visit 2)					
Mean (SD)	1.02 (0.391)	1.04 (0.388)	1.03 (0.401)	1.08 (0.419)	1.04 (0.400)
Baseline percent predicted FEV_1 (predose at Visit 2)					
Mean (SD)	33.84 (11.440)	34.51 (11.532)	33.73 (11.293)	35.52 (11.905)	34.39 (11.555)
Percent reversibility at Visit 1 (n and % of subjects)					
Mean (SD)	16.34 (16.049)	15.15 (16.125)	15.94 (15.924)	17.53 (20.560)	16.23 (17.259)
≥12% + change in FEV_1 ≥0.2L	150 (30.4)	144 (29.1)	158 (31.9)	153 (31.8)	605 (30.8)
MMRC score					
Mean (SD)	2.92 (0.82)	2.94 (0.79)	2.99 (0.79)	2.91 (0.76)	2.94 (0.79)
Range	2 to 5	2 to 5	2 to 5	2 to 5	2 to 5
Postbronchodilator % predicted FEV_1 at Visit 1 (screening) (n and % of subjects)[b]					
<30%	120 (24.3)	94 (19.0)	119 (24.0)	90 (18.7)	423 (21.5)
≥30 <50%	290 (58.7)	314 (63.6)	285 (57.6)	298 (62.0)	1187 (60.4)
≥50-<80%	84 (17.0)	85 (17.2)	89 (18.0)	91 (18.9)	349 (17.8)
≥80%	0	0	1 (0.2)	1 (0.2)	2 (0.1)
Missing	0	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Smoking history (n and % of subjects)					
-Ex-smoker	301 (60.9)	287 (58.1)	272 (54.9)	270 (56.1)	1130 (57.5)
-Habitual smoker	172 (34.8)	183 (37.0)	204 (41.2)	190 (39.5)	749 (38.1)
-Occasional smoker	21 (4.3)	24 (4.9)	19 (3.8)	21 (4.4)	85 (4.3)
Pack years					
Median	40	40	40	40	40
Min, Max	10 to 180	10 to 210	10 to 165	10 to 225	10 to 225

[a] SYMB SYMBICORT pMDI; 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 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		
Treatment group comparison[a]	LS mean (SEM)	95% CI	p-value
SYMB 160/4.5 minus Plac	0.09 (0.01)	0.06, 0.12	<0.001
SYMB 160/4.5 minus Form 4.5	0.04 (0.01)	0.01, 0.07	0.008
SYMB 80/4.5 minus Plac	0.07 (0.01)	0.05, 0.10	<0.001
SYMB 80/4.5 minus Form 4.5	0.02 (0.01)	-0.01, 0.05	0.161
Form 4.5 minus Plac	0.05 (0.01)	0.03, 0.08	<0.001
SYMB 160/4.5 minus SYMB 80/4.5	0.02 (0.01)	-0.01, 0.05	0.206

[a]   SYMB SYMBICORT pMDI; 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.

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	0.18 (0.01)	0.16, 0.21	<0.001
SYMB 160/4.5 minus Form 4.5	0.03 (0.01)	0.00, 0.06	0.023
SYMB 80/4.5 minus Plac	0.16 (0.01)	0.13, 0.19	<0.001
SYMB 80/4.5 minus Form 4.5	0.01 (0.01)	-0.02, 0.04	0.420
Form 4.5 minus Plac	0.15 (0.01)	0.12, 0.18	<0.001
SYMB 160/4.5 minus SYMB 80/4.5	0.02 (0.01)	-0.01, 0.05	0.144

[a]   SYMB SYMBICORT pMDI; 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

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 predose FEV_1 compared with formoterol 4.5 and placebo, with overall maintenance of effect over the 12-month treatment period. Additionally, SYMBICORT pMDI 160/4.5 demonstrated a significant increase from baseline for 1-hour postdose FEV_1 compared with placebo and also formoterol 4.5. Taken together, these results demonstrate the contribution of both monoproducts to efficacy of SYMBICORT 160/4.5.

SYMBICORT pMDI 80/4.5 did not demonstrate a significant difference from formoterol 4.5 for predose $FEV1$. However, a significant difference was seen for both predose FEV_1 and 1-hour postdose FEV_1 compared with placebo. Formoterol 4.5 showed superiority over placebo for 1-hour postdose FEV_1 and also predose FEV_1.

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

Dyspnea: SYMBICORT pMDI 160/4.5 showed statistically and clinically significant improvements in dyspnea scores via the Breathlessness Diary compared to placebo and achieved the MID. SYMBICORT pMDI 80/4.5 resulted in statistically significant improvement in dyspnea scores compared with placebo; however, the MID was not achieved.

SGRQ: SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 resulted in statistically significant improvements in the SGRQ total score compared with placebo; however, neither dose met the MID.

COPD exacerbations: In this 12-month study, SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 demonstrated statistically significant reductions of approximately 37 and 41% in exacerbation rate per subject-treatment year compared with placebo and also significant reductions compared with formoterol 4.5 (25% and 29% for the SYMBICORT pMDI 160/4.5 and SYMBICORT pMDI 80/4.5 groups, respectively), driven by the subset of the exacerbations treated with oral steroid treatment with or without hospitalization. Additionally, both SYMBICORT pMDI doses significantly increased the time to first exacerbation compared with placebo. However, for the subset of subjects who were hospitalized due to COPD exacerbation, SYMBICORT 160/4.5 and SYMBICORT 80/4.5 showed small numerical increases in the rate per subject treatment year compared with placebo.

Serial spirometry: 12-hour serial FEV_1 assessments at the end of treatment demonstrated that both SYMBICORT pMDI 160/4.5 and 80/4.5 produced rapid and sustained improvement in FEV_1 over 12 hours, with no decrease of effect over the 12-month treatment period, compared with placebo.

Other secondary efficacy variables: In general, both dosage strengths of SYMBICORT pMDI showed efficacy across a broad range of secondary variables, such as BCSS, IC, cough, sputum, AM and PM PEF, sleep scores, awakening free nights, and total rescue medication use, compared with placebo. There were few significant differences between treatment groups for health resource utilization variables. Although there were few statistically significant differences between the 2 SYMBICORT pMDI doses for efficacy, PRO, or health economics variables, there was numerical dose separation between the 2 dosage strengths for predose FEV_1 and also in the serial FEV_1 profiles.

Safety results:

All 1964 randomized subjects received at least 1 dose of study drug and were included in the safety analysis set. Subgroups of subjects were evaluated for BMD, ophthalmology, and 24-hour urine cortisol and Holter variables. Mean exposure was shortest in the placebo group (270 days) and longest in the SYMBICORT 160/4.5 pMDI group (305 days). Mean exposure was also shorter in the US (255 days) versus non-US region (320 days).

SYMBICORT pMDI was well tolerated relative to placebo and formoterol 4.5 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. There was a slight increase in AEs in all active treatment groups compared to placebo, which may be related to a greater and earlier discontinuation in the placebo group, but may also be attributable to ICS and/or β_2 class effects. The percentage of subjects with any serious adverse event (SAE) was also slightly higher in the three active treatment groups compared to placebo. The incidence of discontinuations due to adverse event (DAEs) was similar across treatment groups and ranged from 11.3% (SYMBICORT pMDI 160/4.5) to 12.5% (placebo), with an overall incidence of 12.1%. However, the time to discontinuation was statistically significantly prolonged in each SYMBICORT pMDI group compared with the placebo group (see Table 11.1.2.9).

Review of the incidences of known inhaled corticosteroid (ICS) and long-acting β_2 adrenergic receptor agonist (LABA) class effects did not demonstrate clinically important differences between either of the SYMBICORT pMDI groups and the formoterol 4.5 group. The incidence of pneumonia was similar across all treatment groups, but was highest in the placebo group.

Clinically significant changes in laboratory values (including 24-hour urinary free cortisol), vital signs, ECG measures, 24-hour Holter, BMD, and ophthalmologic assessments were rare with no clinically important differences between subjects treated with SYMBICORT pMDI compared to both placebo and formoterol 4.5.

The overall number of deaths that occurred during the study (N=32) was low considering the severity of the population, and no deaths were considered by the investigator to be drug-related. A total of 15 subjects died from an SAE with onset during the randomized treatment period, and an analysis of all fatal events did not show a particular pattern across or within treatment groups.

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)

AE category	Treatment group (mcg)[a]			
	SYMB 160/4.5 (N=495)	SYMB 80/4.5 (N=494)	Form 4.5 (N=494)	Plac (N=481)
Mean (SD) exposure, days	**305 (115)**	**299 (118)**	**289 (127)**	**270 (139)**
Number (%) of subjects with at least 1 AE in the specified category[b]				
With at least 1 AE	322 (65.2	323 (65.4)	299 (60.4)	268 (55.7)
With an SAE	79 (16.0)	69 (14.0)	89 (18.0)	62 (12.9)
SAE leading to death	3 (0.6)	6 (1.2)	2 (0.4)	4 (0.8)
SAE not leading to death	77 (15.6)	67 (13.6)	88 (17.8)	58 (12.1)
SAE leading to DAE	23 (4.7)	22 (4.5)	34 (6.9)	19 (4.0)

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

	Treatment group (mcg)[a]			
With an AE leading to DAE	56 (11.3)	61 (12.3)	61 (12.3)	60 (12.5)
With an SAE and/or DAE	107 (21.7)	107 (21.7)	112 (22.6)	103 (21.4)
With a study-drug related AE	63 (12.8)	51 (10.3)	42 (8.5)	30 (6.2)
SAE	5 (1.0)	3 (0.6)	7 (1.4)	0
AE leading to DAE	13 (2.6)	18 (3.6)	14 (2.8)	15 (3.1)
Total number of adverse events				
AEs, by intensity	1061	976	898	733
Mild, n (%)	556 (52.4)	475 (48.7)	446 (49.7)	359 (49.0)
Moderate, n (%)	381 (35.9)	389 (39.9)	343 (38.2)	302 (41.2)
Severe, n (%)	124 (11.7)	112 (11.5)	109 (12.1)	72 (9.8)
AEs per subject treatment year	2.6	2.4	2.3	2.1
SAEs	113	110	117	88
SAEs per subject treatment year	0.27	0.27	0.3	0.25
DAEs	75	71	72	72
DAEs per subject treatment year	0.18	0.18	0.18	0.2
Study-drug related AEs	96	81	58	53

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

[b]   Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

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

Data derived from Tables 11.3.2.2.1 and 11.3.2.1.5.

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 (mcg)[a]			
MedDRA preferred term[b]	**SYMB 160/4.5 (N=495)**	**SYMB 80/4.5 (N=494)**	**Form 4.5 (N=494)**	**Plac (N=481)**
Mean (SD) exposure, days	305 (115)	299 (118)	289 (127)	270 (139)
Number (%) of subjects				
Subjects with ≥1 AE	322 (65.2)	323 (65.4)	299 (60.4)	268 (55.7)
COPD	66 (13.4)	93 (18.8)	83 (16.8)	77 (16.0)

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 (mcg)[a]			
MedDRA preferred term[b]	**SYMB 160/4.5** **(N=495)**	**SYMB 80/4.5** **(N=494)**	**Form 4.5** **(N=494)**	**Plac** **(N=481)**
Nasopharyngitis	35 (7.1)	44 (8.9)	30 (6.1)	22 (4.6)
Bronchitis	24 (4.9)	22 (4.5)	24 (4.8)	18 (3.7)
Viral upper respiratory tract infection	21 (4.3)	22 (4.5)	22 (4.4)	17 (3.5)
Pneumonia	15 (3.0)	15 (3.0)	17 (3.4)	23 (4.8)
Oral candidiasis	36 (7.3)	21 (4.3)	2 (0.4)	8 (1.7)
Sinusitis	19 (3.8)	19 (3.8)	19 (3.8)	8 (1.7)
Back pain	18 (3.6)	5 (1.0)	14 (2.8)	11 (2.3)
Upper respiratory tract invection	14 (2.8)	16 (3.2)	10 (2.0)	5 (1.0)
Muscle spasms	16 (3.2)	16 (3.2)	4 (0.8)	6 (1.2)
Dysphonia	16 (3.2)	6 (1.2)	1 (0.2)	4 (0.8)

[a] SYMB SYMBICORT pMDI; 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 10.0).

Data derived from Tables 11.3.2.4.8.

Date of the report

17 March 2008