Drug product:	SYMBICORT® pMDI 160/4.5 µg	**SYNOPSIS**	
Drug substance(s):	Budesonide/Formoterol		
Edition No.:			
Study code:	D5896C00005		
Date:	23 May 2006		

A two-stage randomized, open-label, parallel group, phase III, multicenter, 7-month study to assess the efficacy and safety of SYMBICORT® pMDI administered either as fixed or as an adjustable regimen versus a fixed regimen of Advair™ in subjects 12 years of age and older with asthma

International co-ordinating investigator

None appointed for this study

Study center(s)

This study was conducted in the United States (145 centers enrolled subjects and received study medication).

Publications

WW Busse, SR Shah, L Somerville, P Martin, M Goldman. Comparison of Asthma Exacerbations and Lung Function With Adjustable-Dose Budesonide/Formoterol Pressurized Metered-Dose Inhaler (BUD/FM pMDI), Fixed-Dose BUD/FM pMDI, and Fixed-Dose Fluticasone/Salmeterol Dry Powder Inhaler (FP/SM DPI). Am J Respir Crit Care Med. 2007;175:A191 (abstract).

L Somerville, WW Busse, SR Shah, P Martin, M Goldman. Safety of Adjustable-Dose Budesonide (BUD)/Formoterol (FM) Pressurized Metered-Dose Inhaler (pMDI), Fixed-Dose BUD/FM pMDI, and Fixed-Dose Fluticasone (FP)/Salmeterol (SM) Dry Powder Inhaler (DPI) in Asthma Patients. Am J Respir Crit Care Med. 2007;175:A191 (abstract).

Study dates		**Phase of development**
First subject enrolled	03 November 2003	Therapeutic confirmatory (III)
Last subject completed	05 January 2005	

Objectives

Primary: The primary objective of the study was to compare the efficacy of SYMBICORT pMDI given as an adjustable regimen with that of a fixed regimen of Advair Diskus®[1] in subjects 12 years of age and older with asthma. In addition, the efficacy of SYMBICORT® pMDI given as a fixed regimen was compared with that of a fixed regimen of Advair. The primary variable in this study was asthma control as assessed by exacerbations. The number of asthma exacerbations, time to first asthma exacerbation and the number (%) of subjects with at least 1 exacerbation were analyzed.

Secondary:

(a) To assess the use of rescue medication in the SYMBICORT pMDI adjustable regimen, SYMBICORT pMDI fixed regimen and Advair fixed regimen.

(b) To demonstrate the efficacy of SYMBICORT pMDI adjustable and fixed regimens compared to Advair fixed regimen.

(c) To demonstrate health-related quality of life, patient-reported asthma control, and patient satisfaction of SYMBICORT pMDI adjustable and fixed regimens compared to Advair fixed regimen.

(d) To demonstrate reduced resource utilization (medication and overall healthcare) for subjects receiving SYMBICORT pMDI adjustable and fixed regimen compared to Advair fixed regimen.

(e) To demonstrate better patient perception of onset of effect during the first 2 months after randomization in subjects receiving SYMBICORT pMDI compared to Advair.

(f) To demonstrate the safety of SYMBICORT pMDI adjustable and fixed regimens compared to Advair fixed regimen.

Study design

This was a 7-month, multi-center, randomized, open-label, Phase III study comparing the efficacy and safety of SYMBICORT pMDI given either as a fixed-dose regimen or as an adjustable-dose regimen versus fixed-dose Advair regimen in subjects with asthma requiring inhaled corticosteroids (ICS) or combination therapy with long-acting beta-agonist (LABA). This study had 3 phases: Screening/Run-in (10-14 days), Treatment Period 1 (1 month), and Treatment Period 2 (6 months). At Screening/Run-in, eligible subjects remained on their current asthma therapy for a period of 10-14 days. If eligible at the end of run-in, subjects entered Treatment Period 1 and received either fixed-dose SYMBICORT pMDI or Advair in a 2:1 randomization scheme. After subjects had completed Treatment Period 1, subjects on SYMBICORT pMDI were randomized again

[1] Hereafter referred to as "Advair."

(Randomization 2) to either fixed- or adjustable-dose SYMBICORT pMDI in a 1:1 randomization scheme. Subjects randomized to Advair during Treatment Period 1 remained on Advair throughout the course of the study. At the beginning of Treatment Period 2, subjects randomized to adjustable-dose SYMBICORT pMDI whose asthma was controlled (as judged by their use of short-acting β_2-agonist and number of nighttime awakenings) had their SYMBICORT dose "stepped down" from 2 actuations twice daily (bid) to 2 actuations once daily (qd). Those subjects in the adjustable-dose group not meeting step-down criteria were to remain at 2 actuations bid for the first 3 months of Treatment Period 2, after which time, those who met step-down criteria were to have their SYMBICORT dose adjusted from 2 actuations bid to 2 actuations qd. Subjects still not meeting step-down criteria were to remain on 2 actuations bid for the duration of the study. During times of asthma deterioration, all subjects in the adjustable-dose SYMBICORT pMDI group were to use 4 actuations bid for 7-14 days and then return to their previous regimen.

Target subject population and sample size

The target subject population included male and female subjects ≥12 years of age, with a documented clinical diagnosis of asthma for at least 6 months prior to screening, and who were in stable condition. Subjects should have received maintenance asthma treatment with ICS or ICS/LABA combination therapy for ≥12 weeks prior to the screening visit. Subjects were also required to have an FEV_1 ≥50% of predicted normal, measured at least 24 hours after the last dose of LABA and 6 hours after the last dose of short-acting β_2-agonist. Approximately 1200 subjects (400/treatment group) were targeted for randomization.

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

- Fixed-dose SYMBICORT pMDI 160/4.5 µg (2 actuations bid) and adjustable-dose SYMBICORT pMDI 160/4.5 µg (2 actuations qd, 2 actuations bid, or 4 actuations bid); batches P6675 and P6722.

- Fixed-dose Advair 250/50 µg (1 inhalation bid); batches B118484, B124490, and X1492.

Albuterol, delivered by pMDI (90 µg per inhalation), was used as rescue medication on an as-needed basis during both the run-in and treatment periods (batch numbers ACC11A and ACF35A).

Duration of treatment

This study consisted of a 10-14 day run-in period during which all subjects remained on their current asthma therapy. All qualifying subjects were then randomized to 1 of 2 investigational treatment groups for 1 month (Treatment Period 1). At the end of

Treatment Period 1, a second randomization occurred for subjects on fixed-dose SYMBICORT pMDI. These subjects were randomized to either fixed- or adjustable-dose SYMBICORT pMDI, while subjects on Advair remained on Advair. The second randomized treatment period lasted 6 months (Treatment Period 2).

Criteria for evaluation (main variables)

Efficacy, patient-reported outcomes, and health economics

Primary variable:

The primary efficacy endpoint was asthma control as measured by asthma exacerbations. Asthma exacerbations were defined as worsening asthma, requiring treatment with oral steroids. Exacerbations were assessed using time to first exacerbation, the number of exacerbations in each treatment group, and number (%) of subjects with at least 1 exacerbation.

Secondary outcome variables:

- Spirometry variable: predose FEV_1
- Diary variables: morning PEF, nighttime and daytime asthma symptom scores, nighttime awakenings due to asthma symptoms, daytime and nighttime rescue medication use, total daily rescue medication use
- *Derivatives of diary variables:* average daily symptom score, symptom-free days, asthma control days, rescue medication-free days.
- Global Assessments: physician's global assessment; patient's global assessment.
- Patient reported outcomes (PROs): health-related quality of life using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]) for subjects 18 and older and the standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]) for subjects 12-17; patient-reported asthma control as measured by the Asthma Control Questionnaire (ACQ) for subjects 17 and older; Asthma Treatment Satisfaction Measure (ATSM) for subjects 18 and older; patient perception of onset of effect questionnaire (OEQ).
- Health Economics (measures of direct and indirect resource utilization): numbers of hospital admissions, emergency room or urgent care center visits, and unscheduled visits to healthcare providers due to asthma; use of rescue medication, use of additional asthma medication, days of interrupted activities, hours missed from work/school, study medication use by adjustable-dose SYMBICORT pMDI subjects during Treatment Period 2.

Pharmacokinetic: Not applicable.

Pharmacodynamic: Not applicable.

Safety: Adverse events, vital signs, and physical examination were used to evaluate safety.

Statistical methods

The efficacy analysis set was defined as all subjects who had 1 randomization code, took at least 1 dose of randomized treatment, and contributed data for at least 1 efficacy endpoint.

The primary variable was asthma exacerbations, measured by time to first exacerbation, the number and percentage of subjects with at least 1 asthma exacerbation, and the total number of exacerbations. Time (in days) from the first dose of randomized treatment to the first exacerbation was presented as the primary derivation of this variable, because it was used to power the study. It was analyzed using a log-rank test and also described using a Kaplan-Meier plot. Additionally, a Cox proportional hazards model was used to estimate hazard ratios. The number and percentage of subjects with at least 1 asthma exacerbation during randomized treatment was analyzed using a chi-square test. The number of exacerbations was expressed as the number per subject-treatment year and analyzed using a Poisson regression model adjusting for subject exposure. Exacerbation data were additionally analyzed using the per-protocol analysis set.

Nominal p-values were reported for all comparisons involving secondary variables. When appropriate, continuous variables were analyzed as changes from baseline using an analysis of covariance model including treatment and site as factors and baseline value as a covariate. If a change from baseline was not used, data were analyzed using an analysis of variance model with treatment and site as factors. Analyses of number and percentage of subjects used a Cochran-Mantel-Haenszel test adjusting for site. Event data were analyzed using a Poisson regression model adjusting for subject exposure.

All subjects who received at least 1 dose of study treatment were included in the safety analysis set. Adverse events (AEs), serious adverse events (SAEs), and discontinuation of treatment with investigational product due to adverse events (DAEs) were summarized by treatment group. Clinically significant findings in vital signs and physical examination were summarized by treatment group. Summary statistics and treatment group comparisons were provided for vital signs.

Presentation of results

In the following sections, results are presented in tabular and graphic representations for the overall randomized treatment period (ie, Treatment Periods 1 and 2, combined). Important differences in results between the treatment periods are discussed in-text.

Subject population

At Visit 1, a total of 2080 subjects were screened for possible study participation, 1225 of whom were subsequently randomized at Visit 2 to enter Treatment Period 1 (817 fixed-dose SYMBICORT pMDI; 408 Advair). At Visit 3, the 778 subjects remaining in the

fixed-dose SYMBICORT pMDI group were randomized into Treatment Period 2: 389 subjects in each of the adjustable-dose SYMBICORT pMDI and fixed-dose SYMBICORT pMDI groups. The 391 subjects remaining in the Advair group continued on the same dose and regimen during Treatment Period 2. Demographic and baseline characteristics were generally well balanced across treatment groups. Table S1 summarizes demographic and key baseline characteristics for the safety analysis set. The discontinuation rate during Treatment Period 1 was similar for the fixed-dose SYMBICORT pMDI and Advair groups (14.6% and 13.2%, respectively). During Treatment Period 2, 11.2% of the adjustable-dose SYMBICORT pMDI group, and 9.5% of each of the fixed-dose SYMBICORT pMDI and Advair groups discontinued. The most common reasons for discontinuation among randomized subjects were loss to follow-up and unwillingness to continue the study.

Table S1 Demographic and key baseline characteristics for the overall randomized treatment period (safety analysis set)

	Treatment group[a]			
	SYMB pMDI FD N=427	**SYMB pMDI AD N=389**	**Advair N=406**	**Total (N=1222)**
Sex (n and % of subjects)				
Male	146 (34.2)	170 (43.7)	174 (42.9)	490 (40.1)
Female	281 (65.8)	219 (56.3)	232 (57.1)	732 (59.9)
Age (yr)				
Mean (SD)	39.4 (15.93)	38.4 (15.79)	38.8 (15.89)	38.9 (15.87)
Median	41	40	40	40
Min, Max	12, 79	12, 87	12, 82	12, 87
Race (n and % of subjects)				
Caucasian	350 (82.0)	320 (82.3)	341 (84.0)	1011 (82.7)
Black	59 (13.8)	48 (12.3)	50 (12.3)	157 (12.8)
Oriental	4 (0.9)	3 (0.8)	3 (0.7)	10 (0.8)
Other	14 (3.3)	18 (4.6)	12 (3.0)	44 (3.6)
Years since asthma diagnosis				
Mean (SD)	19.6 (15.57)	18.7 (14.6)	19.1 (14.52)	19.1 (14.92)
Min, Max	0.5, 67	0.5, 63.6	0.2, 68.9	0.2, 68.9
Total daily ICS dose at study entry (μg)				
N	425	388	406	1219
Mean (SD)	555.7 (210.05)	538.9 (200.28)	542.8 (181.09)	546.1 (197.63)
Min, Max	200, 2880	200, 2000	360, 2000	200, 2880
FEV_1 (L) at screening (Visit 1)				
N	426	387	405	1218
Mean (SD)	2.5 (0.74)	2.6 (0.78)	2.6 (0.73)	2.6 (0.75)
Percent predicted FEV_1 at screening (Visit 1)				
N	426	387	405	1218
Mean (SD)	79.3 (15.36)	78.9 (16.79)	77.9 (14.19)	78.7 (15.46)
Baseline FEV_1 (L) (predose at Visit 2)				
N	426	389	406	1221
Mean (SD)	2.5 (0.72)	2.7 (0.77)	2.6 (0.74)	2.6 (0.75)
Baseline percent predicted FEV_1 (predose at Visit 2)				

Table S1 **Demographic and key baseline characteristics for the overall randomized treatment period (safety analysis set)**

	Treatment group[a]			
	SYMB pMDI FD N=427	**SYMB pMDI AD N=389**	**Advair N=406**	**Total (N=1222)**
N	426	389	406	1221
Mean (SD)	79.6 (15.22)	79.4 (16.11)	78.1 (14.33)	79 (15.22)

[a] SYMB pMDI FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; SYMB pMDI AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily; Advair Advair Diskus 250/50 x 1 inhalation twice daily.

Note: The overall randomized treatment period included both Treatment Period 1 and Treatment Period 2.

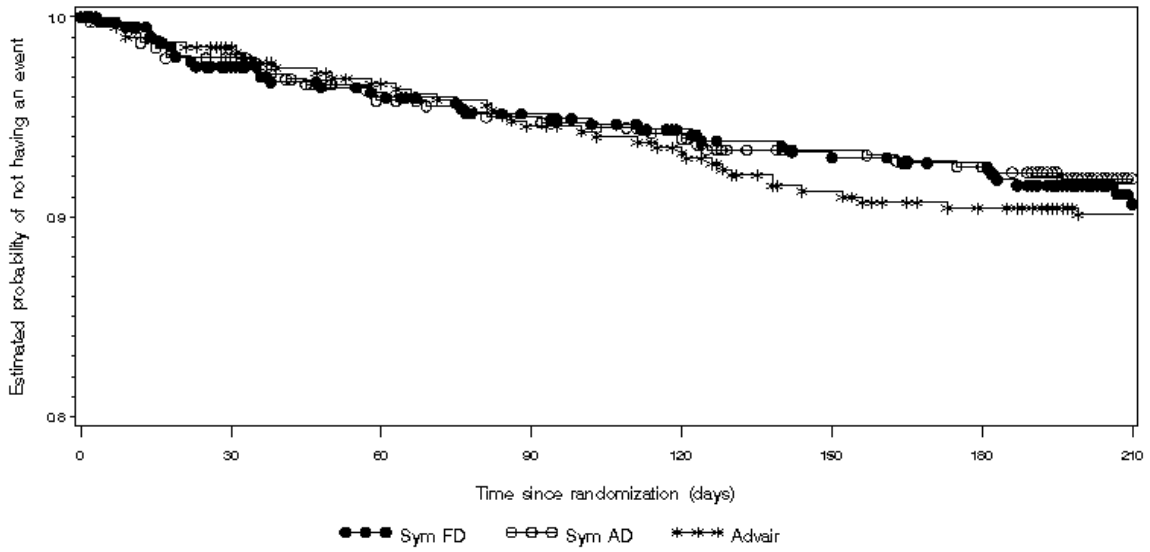
Note: The fixed-dose SYMBICORT pMDI total includes 38 subjects who discontinued during Treatment Period 1.

Efficacy results

Primary variable: There were no statistically significant differences between treatment groups for any measure of asthma exacerbation, including time to first asthma exacerbation, the number and percentage of subjects who had at least 1 asthma exacerbation, and the total number of asthma exacerbations per subject-treatment year during the overall randomized treatment period.

Time from the first dose of randomized treatment to the first asthma exacerbation was analyzed as the primary derivation of this variable. Figure S1 presents Kaplan-Meier probability curves for time in days to first asthma exacerbation during the overall randomized treatment period. Table S2 presents the survival analysis of time to first asthma exacerbation for the overall randomized treatment period.

Figure S1 **Time (days) to first asthma exacerbation during the overall randomized treatment period: Kaplan-Meier probability curves (efficacy analysis set)**



Sym FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; Sym AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily; Advair Advair Diskus 250/50 x 1 inhalation twice daily.
Note: The first 30 days on this figure represents Treatment Period 1; this was approximately the timeframe during which subjects in the SYMBICORT pMDI AD group received fixed-dose SYMBICORT pMDI.

Table S2 Survival analysis of time to first asthma exacerbation during the overall randomized treatment period (efficacy analysis set)

Treatment[a]/ treatment comparison	N	Had event, n (%)	Log-rank test	
			Chi-square	p-value
Treatment				
SYMB FD	422	37 (8.8)		
SYMB pMDI AD[b]	389	31 (8.0)		
Advair	404	37 (9.2)		
Treatment comparison				
SYMB FD vs Advair			0.003	0.958
SYMB FD vs SYMB AD			0.389	0.533
SYMB pMDI AD vs Advair			0.467	0.494

[a] SYMB pMDI FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; SYMB pMDI AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily.
[b] Subjects in the adjustable-dose group received approximately 1 month of fixed-dose SYMBICORT pMDI during Treatment Period 1.
Note: The overall randomized treatment period included both Treatment Period 1 and Treatment Period 2.

Secondary variables

Approximately 68% of subjects randomized to adjustable-dose SYMBICORT pMDI were able to "step down" to 2 inhalations once daily. Approximately 18% of subjects in this treatment group "stepped up" to 4 inhalations twice daily during asthma exacerbation.

Table S3 summarizes the results for the analyses of the secondary efficacy, PRO, and Health Economics variables, as expressed by level of statistical significance.

Table S3 Summary of secondary efficacy, patient-reported outcomes, and health economics results for the overall randomized treatment period

	Treatment group comparisons[a]		
Variable	SYMB pMDI AD vs Advair	SYMB pMDI FD vs SYMB pMDI AD	SYMB pMDI FD vs Advair
Secondary efficacy variables			
Predose FEV_1	ns	ns	ns
Morning PEF	ns	ns	ns
Daytime asthma symptom score	ns	ns	ns
Nighttime asthma symptom score	ns	ns	ns
Average daily asthma symptom score	ns	ns	ns
Symptom-free days (%)	ns	ns	ns

Table S3 Summary of secondary efficacy, patient-reported outcomes, and health economics results for the overall randomized treatment period

	Treatment group comparisons[a]		
Awakening-free nights (%)	ns	ns	ns
Asthma control days (%)	ns	ns	ns
Total rescue medication use	ns	ns	ns
Rescue medication-free days (%)	ns	ns	ns
Variable	**SYMB pMDI AD vs Advair**	**SYMB pMDI FD vs SYMB pMDI AD**	**SYMB pMDI FD vs Advair**
Physician global assessment	ns/***(SYMB AD)	ns/ns	ns/*(SYMB FD)
Patient global assessment	ns/ns	ns/ns	ns/ns
Patient-reported outcomes (PRO) variables			
AQLQ(S) overall score	* (SYMB AD)	* (SYMB AD)	ns
Change ≥MID	no	no	no
PAQLQ(S) overall score	ns	ns	ns
ACQ overall score	ns	ns	ns
ATSM overall score	* (SYMB AD)	ns	ns
OEQ overall score[b]			
Question 2 - Week 1/Week 8	ns/***(SYMB AD)	ns/ns	ns/***(SYMB FD)
Question 5 - Week 1/Week 8	ns/* (SYMB AD)	ns/ns	ns/ns
Health economics variables			
Resource utilization (asthma-related)			
Hospitalizations	ns	ns	ns
Emergency room visits	ns	ns	ns
Urgent care clinic visits	ns	ns	ns
Unscheduled healthcare provider visits	ns	ns	ns
Days of interrupted activities	ns	* (SYMB AD)	*** (Advair)
Hours missed from work/school	ns	* (SYMB AD)	ns
Asthma-related concomitant medication use			
Oral/parenteral corticosteroids	ns	ns	ns
All other asthma-related concomitant medication use[c]	ns	ns	ns
Study medication use, SYMB FD vs SYMB AD			
Number of puffs/day of study medication	NA	*** (SYMB AD)	NA

Key: ns not statistically significant (p>0.050); * p>0.010 and ≤0.050; ** p>0.001 and ≤0.010; *** p≤0.001; NA Not applicable. The treatment group with significantly better results is shown in parentheses for each comparison, when applicable.

[a] SYMB pMDI FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; SYMB pMDI AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily; Advair Advair Diskus 250/50 x 1 inhalation twice daily. The treatment group with better results is shown in parentheses for each comparison, when applicable.

[b] For subjects ≥18 years of age.

[c] Other than study-provided rescue medication.

AQLQ(S) Asthma quality of life questionnaire (standardized); MID minimal important difference (≥0.5); PAQLQ(S) Pediatric asthma quality of life questionnaire (standardized); ACQ Asthma control questionnaire; ATSM Asthma treatment satisfaction measure; OEQ Onset of effect questionnaire; NA not applicable.

Safety results

The mean exposure to study medication during Treatment Period 1 was approximately 29 days in each treatment group. During Treatment Period 2, mean exposure for all subjects was approximately 168 days, with similar exposure across treatment groups. For the overall treatment period, the mean exposure was approximately 190 days and was similar across treatment groups.

Overall, fixed-dose and adjustable-dose SYMBICORT pMDI and Advair were well tolerated when used in the treatment of asthma in adolescent and adult subjects 12 years of age and older. No new safety concerns were identified. The percentage of subjects with AEs during the overall randomized treatment period was similar across treatment groups (see Table S4). The percentage of subjects with SAEs was low and similar across treatment groups. Preferred terms (PTs) for individual SAEs were diverse, with no discernible pattern identified. The percentage of subjects with DAEs was low overall and slightly higher in the fixed-dose SYMBICORT pMDI group compared with the adjustable-dose SYMBICORT pMDI group and Advair groups. The most commonly observed DAEs were in the Respiratory, Thoracic and Mediastinal Disorders system organ class. Headache was the most commonly reported DAE; it occurred only in the fixed-dose SYMBICORT pMDI group (4 [0.9%]) and in the adjustable-dose SYMBICORT pMDI group (1 [0.3%]). There were 3 DAEs of asthma: 2 (0.5%) in the Advair group and 1 (0.2%) in the fixed-dose SYMBICORT pMDI group. There were no deaths reported or other significant adverse events (OAEs) identified.
An overview of AEs that occurred during the overall randomized treatment period is presented in Table S4.

Table S4 Overview of AEs during the overall randomized treatment period (safety analysis set)

Category	Treatment group[a], n (%) of subjects		
	SYMB pMDI FD (N=427)	SYMB pMDI AD (N=389)	Advair (N=406)
Mean exposure (days)	**182.0**	**196.1**	**191.3**
Number (%) of subjects with an AE[b]			
Any AE	263 (61.6)	225 (57.8)	238 (58.6)
SAEs	9 (2.1)	7 (1.8)	9 (2.2)
Deaths	0	0	0
Non-fatal SAEs[c]	9 (2.1)	7 (1.8)	9 (2.2)
SAEs leading to discontinuation[c]	0	2 (0.5)	3 (0.7)
DAEs[d]	18 (4.2)	8 (2.1)	8 (2.0)
OAEs	0	0	0
Any drug-related AEs	45 (10.5)	22 (5.7)	19 (4.7)
Total number of AEs			
All AEs	893	690	747

Table S4 Overview of AEs during the overall randomized treatment period (safety analysis set)

Category	Treatment group[a], n (%) of subjects		
	SYMB pMDI FD (N=427)	SYMB pMDI AD (N=389)	Advair (N=406)
AE intensity			
Mild, number of AEs (% of total)	519 (58.1)	382 (55.4)	405 (54.2)
Moderate, number of AEs (% of total)	316 (35.4)	273 (39.6)	305 (40.8)
Severe, number of AEs (% of total)	58 (6.5)	35 (5.1)	37 (5.0)
SAEs	10	8	10
DAEs	30	8	12
OAEs	0	0	0

[a] SYMB pMDI FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; SYMB pMDI AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily; Advair Advair Diskus 250/50 x 1 inhalation 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.

[c] In addition, there was 1 subject in the SYMB pMDI FD group who had an SAE/DAE with onset during run-in and another subject who had an SAE with onset after the last dose of randomized treatment.

[d] In addition, there was 1 subject in the SYMB pMDI FD group, described in footnote c, who had an SAE/DAE with onset during run-in, and there were 2 subjects (1 SYMB pMDI FD subject and 1 Advair subject) who had DAEs with onset after the last dose of randomized treatment.

Note: The overall randomized treatment period includes both Treatment Periods 1 and 2.

Note: The SYMBICORT pMDI AD group received approx. 1 month of SYMBICORT pMDI FD during Treatment Period 1.

AE adverse event; SAE serious adverse event, DAE discontinuation of treatment with investigational product due to adverse event; OAE other significant adverse event.

The majority of AEs were mild or moderate in intensity. The incidence of asthma and potentially asthma-related AEs and of cardiac AEs was generally low and similar across treatment groups. The incidence of subjects with AEs by MedDRA PT during the overall randomized treatment period is shown in Table S5.

Table S5 Number (%) of subjects with the most commonly reported adverse events by preferred term during the overall randomized treatment period (safety analysis set)

Preferred term[b]	Treatment group[a], n (%) of subjects		
	SYMB pMDI FD (N=427)	SYMB pMDI AD (N=389)	Advair (N=406)
Mean duration of exposure (days)	**182.0**	**196.1**	**191.3**
Total number of subjects with any AE, n (%)	**263 (61.6)**	**225 (57.8)**	**238 (58.6)**
Headache	51 (11.9)	45 (11.6)	39 (9.6)
Nasopharyngitis	35 (8.2)	33 (8.5)	33 (8.1)
Sinusitis	37 (8.7)	28 (7.2)	31 (7.6)
Upper respiratory tract infection.	31 (7.3)	31 (8.0)	34 (8.4)

Table S5 Number (%) of subjects with the most commonly reported adverse events by preferred term during the overall randomized treatment period (safety analysis set)

Preferred term[b]	Treatment group[a], n (%) of subjects		
	SYMB pMDI FD (N=427)	SYMB pMDI AD (N=389)	Advair (N=406)
Pharyngolaryngeal pain	29 (6.8)	22 (5.7)	24 (5.9)
Asthma	18 (4.2)	19 (4.9)	23 (5.7)
Bronchitis	14 (3.3)	10 (2.6)	16 (3.9)
Cough	21 (4.9)	7 (1.8)	11 (2.7)
Nasal congestion	14 (3.3)	10 (2.6)	8 (2.0)
Dysphonia	14 (3.3)	7 (1.8)	3 (0.7)

[a] SYMB pMDI FD SYMBICORT pMDI (fixed-dose) 160/4.5 µg x 2 actuations twice daily; SYMB pMDI AD SYMBICORT pMDI (adjustable-dose) 160/4.5 µg x 2 actuations once daily, 160/4.5 µg x 2 actuations twice daily, 160/4.5 µg x 4 actuations twice daily; Advair Advair Diskus 250/50 x 1 inhalation twice daily.

[b] Based on MedDRA Version 8.0.

Note: "Most commonly reported" refers to AEs reported by at least 3% of subjects in any treatment group, sorted by decreasing order of frequency across all treatment groups (total).

Note: The overall randomized treatment period includes both Treatment Periods 1 and 2.

Note: The SYMB pMDI AD group received approximately 1 month of SYMBICORT pMDI FD during Treatment Period 1.

No clinically meaningful changes or treatment group differences were observed in vital signs or physical exam findings during the conduct of the study.

Date of the report

23 May 2006