Drug product:	SYMBICORT® pMDI 40/4.5 µg per actuation	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Document No.:			
Edition No.:			
Study code:	SD-039-718		
Date:	23 April 2004		

A Twelve-Week, Randomized, Double-Blind, Double-Dummy Trial of Symbicort® (40/4.5 mcg) versus its Mono-Products (budesonide and formoterol) in Asthmatic Children Aged Six to Fifteen Years.

International coordinating investigator

None appointed for this study

Study center(s)

This study was conducted in the United States (52 centers).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	24 July 2002	Phase III
Last subject completed	14 October 2003	

Objectives

The primary objective of the study is to compare the safety and efficacy, including health-related quality of life (HRQOL) and onset of effect, of SYMBICORT, a fixed-combination metered-dose inhaler product, containing budesonide and formoterol (40/4.5 µg per puff, respectively) administered as two puffs[1] twice daily to that of budesonide (40 µg per puff) alone in a metered-dose inhaler and formoterol (4.5 µg per inhalation) alone in a dry powder inhaler, both administered as two inhalations twice daily, in asthmatic children aged 6 to 15 years.

No secondary objectives were set forth in the clinical trial protocol. However, in order to examine the pharmacokinetic properties of the study medications, plasma levels of budesonide and formoterol were to be measured in blood samples collected predose and

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

at 10±3, 40±3, 120±5 and 360±5 minutes postdose at Visit 3 (ie, 2 weeks after start of randomized treatment).

Study design

This was a 12-week, randomized, double-blind, double-dummy, active-controlled trial comparing the efficacy and safety of SYMBICORT® pMDI with its monoproducts, budesonide and formoterol, in children aged 6 through 15 years with mild to moderate asthma. Randomization was stratified by age group (children under 8 years of age versus children 8 years and older).

Target subject population and sample size

Male and female pediatric subjects with asthma who were 6 through 15 years of age; who were chronically treated with a low to medium dose of inhaled corticosteroid (ICS); and whose forced expiratory volume in the first second (FEV_1) on ICS therapy was within the entrance range (≥50% of predicted normal), were eligible for enrollment.

Subjects ≥12 years of age had to demonstrate reversibility of FEV_1 of ≥12% and ≥0.20 L from the pre-albuterol value within 15-30 minutes after administration of a standard dose of a fast-acting 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). Subjects <12 years of age needed to show only reversibility of ≥12%. Alternatively, reversibility of PEF of at least 15%, but not more than 50%, could be used by any subject to meet the reversibility criterion. Qualification for randomization was also based on lung function and asthma symptom scores during the run-in period.

It was determined that a sample size of 133 subjects per treatment group would provide 90% power to detect a mean difference in change in morning PEF of 12 L/min between the SYMBICORT pMDI group and either of the other two groups, assuming that the common standard deviation was 30 L/min, based on results of AstraZeneca Study SD-039-0353.

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

Subjects were randomly assigned to 1 of the 3 following treatment groups. Treatments were given in double-dummy fashion because of the difference in devices.

- SYMBICORT pMDI (budesonide/formoterol) 40/4.5 µg (delivered dose) per actuation, 2 actuations administered bid. Batch numbers for SYMBICORT pMDI were P6350, P6352.
- Budesonide pMDI 40 µg (delivered dose) per actuation, 2 actuations administered bid. Batch numbers for budesonide pMDI were P6360, P6493.
- Formoterol TBH 4.5 µg (delivered dose) per inhalation, 2 inhalations administered bid. Batch numbers for formoterol TBH were P6474, P6508, P6624.

Batch numbers for placebo pMDI (2 actuations administered bid used to treat subjects in a double-dummy fashion) were P6204, P6351, P6491. Batch numbers for placebo TBH (2 inhalations administered bid used to treat subjects in a double-dummy fashion) were P6476, P6512, P6677. Albuterol, delivered by pMDI, was used as rescue medication on an as-needed basis during both the run-in and treatment periods. Batch numbers for albuterol were ABL97A and ABP33A. Batch numbers for the single-blind budesonide pMDI used during run-in (40 µg per actuation, 2 actuations administered bid) were P6360, P6584. Batch numbers for Emla Cream, used as needed for local anesthesia prior to phlebotomy, were 203083, 211051, 301148, and 302074.

Duration of treatment

This study comprised a 12-week randomized treatment period preceded by a 2-week (±1 week) single-blinded budesonide pMDI run-in period.

Criteria for evaluation (main variables)

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

- Primary efficacy variable: morning peak expiratory flow (PEF)
- Secondary efficacy variables:
  - Pre-defined asthma events and withdrawals due to pre-defined asthma events
  - Spirometry measurements (predose and 90-minute postdose FEV_1)
  - Diary variables: evening PEF, nighttime and daytime asthma symptom scores, nighttime awakenings due to asthma symptoms, daytime and nighttime rescue medication use.
  - PRO variables (standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]), Pediatric Asthma Caregivers Quality of Life Questionnaire (PACQLQ)) and Global Assessments

Pharmacokinetics

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 4 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, physical examination and vital signs were used to evaluate safety.

Statistical methods

The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed at least 1 PEF value to the primary endpoint. Primary efficacy analyses were based on subjects from the EAS population. Sensitivity analyses for the primary endpoint were performed using the per protocol (PP) analysis set.
The primary variable, morning PEF, was analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for the fixed factors of center, age strata, and treatment and for the covariate of baseline morning PEF. Morning PEF was analyzed as the change from baseline to the average over the treatment period as the primary endpoint and was used to compare SYMBICORT pMDI to budesonide and SYMBICORT pMDI to formoterol.

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 primarily with Cochran Mantel Haenszel test (stratified by age) 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 one dose of study medication.

Subject population

A total of 696 subjects were screened, of whom 411 subjects from 47 centers were subsequently randomized. Study recruitment was stopped when the study population target number was reached. All randomized subjects received study treatment and provided at least one efficacy observation; therefore, the population of all randomized subjects, the safety analysis set, and EAS are the same in this study.

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

Among randomized subjects, the overall discontinuation rate was lowest in the SYMBICORT pMDI group (28%). The percentage of subjects who discontinued in budesonide and formoterol groups was similar and slightly higher (35%). The most common reason for discontinuation was due to study-specific discontinuation criteria (ie, withdrawals due to pre-defined asthma events), which was similar across treatment groups (20% for SYMBICORT pMDI, 24% for budesonide, 23% for formoterol).

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic		Treatment group[a]			
		SYMB N=128	Budes N=145	Form N=138	Total N=411
Sex (n and % of subjects)					
	Male	80 (62.5)	111 (76.6)	90 (65.2)	281 (68.4)
	Female	48 (37.5)	34 (23.4)	48 (34.8)	130 (31.6)
Age (yr)					
	Mean (SD)	10.16 (2.711)	10.46 (2.606)	10.54 (2.742)	10.39 (2.683)
	Median	10.0	11.0	11.0	11.0
	Range	6 to 15	6 to 15	6 to 15	6 to 15
Age strata (yr), (n and % of subjects)					
	<8	26 (20.3)	27 (18.6)	22 (15.9)	75 (18.2)
	≥8 to <16	102 (79.7)	118 (81.4)	116 (84.1)	336 (81.8)
Age group (yr), (n and % of subjects)					
	<12	86 (67.2)	89 (61.4)	81 (58.7)	256 (62.3)
	≥12 to <16	42 (32.8)	56 (38.6)	57 (41.3)	155 (37.7)
Race (n and % of subjects)					
	Caucasian	86 (67.2)	109 (75.2)	112 (81.2)	307 (74.7)
	Black	29 (22.7)	22 (15.2)	20 (14.5)	71 (17.3)
	Oriental	2 (1.6)	1 (0.7)	0	3 (0.7)
	Other	11 (8.6)	13 (9.0)	6 (4.3)	30 (7.3)
Years since asthma diagnosis					
	Mean (SD)	6.77 (3.399)	7.01 (3.404)	6.68 (3.543)	6.82 (3.444)
	Median	6.0	7.0	6.0	7.0
	Min, Max	1, 15	0, 14	0, 14	0, 15
ICS use at entry (µg/day)					
	Mean (SD)	235.19 (120.270)	235.68 (107.541)	232.58 (144.046)	234.49 (124.409)
	Min, Max	80, 1000	80, 800	88, 1250	80, 1250
FEV_1 at screening (L) (Visit 1, pre-bronchodilator)					
	Mean (SD)	1.92 (0.648)	2.04 (0.640)	2.04 (0.730)	2.00 (0.675)
FEV_1 at baseline (L) (predose at Visit 2)					
	Mean (SD)	1.96 (0.684)	2.10 (0.664)	2.08 (0.728)	2.05 (0.694)
FEV_1 % predicted at screening (Visit 1, pre-bronchodilator)					
	Mean (SD)	81.73 (13.484)	82.44 (13.048)	82.48 (12.704)	82.24 (13.044)
FEV_1 % predicted at baseline (predose at Visit 2)					
	Mean (SD)	82.59 (12.926)	84.71 (12.775)	84.38 (12.672)	83.94 (12.790)

[a] SYMB SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 40 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

Efficacy and pharmacokinetic results

Change from baseline in morning PEF to the average over the double-blind treatment period was chosen as the primary efficacy variable in this study to demonstrate the superiority of SYMBICORT pMDI over its monoproducts. A significantly greater increase from baseline in morning PEF was seen for SYMBICORT pMDI compared with budesonide and with formoterol during the double-blind treatment period ($p<0.001$ for each), thereby demonstrating the contribution of each monoproduct to the efficacy of SYMBICORT pMDI (Tables S2 and S3). Significant improvements in morning PEF with SYMBICORT pMDI were seen within 1 day of the first dose ($p<0.001$) in

comparison with budesonide, and within 2 days of the first dose (p=0.043) in comparison with formoterol, with no diminution of effect over the 12-week treatment period. The effects of SYMBICORT pMDI on the primary variable were robust when examined across age strata (<8 years versus ≥8 to <16 years) and age group (<12 years versus ≥12 to <16 years). In addition, there was no evidence of differential effects of SYMBICORT pMDI on morning PEF across sex or race.

Figure S1 shows mean changes from baseline over time in morning PEF.

Table S2 Morning PEF (L/min): treatment means during double-blind treatment (EAS)

			Double-blind treatment period[a]			
			Observed value	Change from baseline	From ANCOVA on change from baseline	
Treatment[b]	N	Baseline value[c] Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SEM)	95% CI
SYMB	128	267.11 (83.151)	290.67 (85.858)	23.56 (32.782)	24.49 (3.283)	(18.03, 30.94)
Budes	145	277.99 (80.184)	285.94 (84.328)	7.95 (26.722)	8.28 (2.997)	(2.39, 14.17)
Form	138	281.69 (85.403)	290.24 (82.528)	8.55 (30.282)	8.68 (3.126)	(2.54, 14.83)

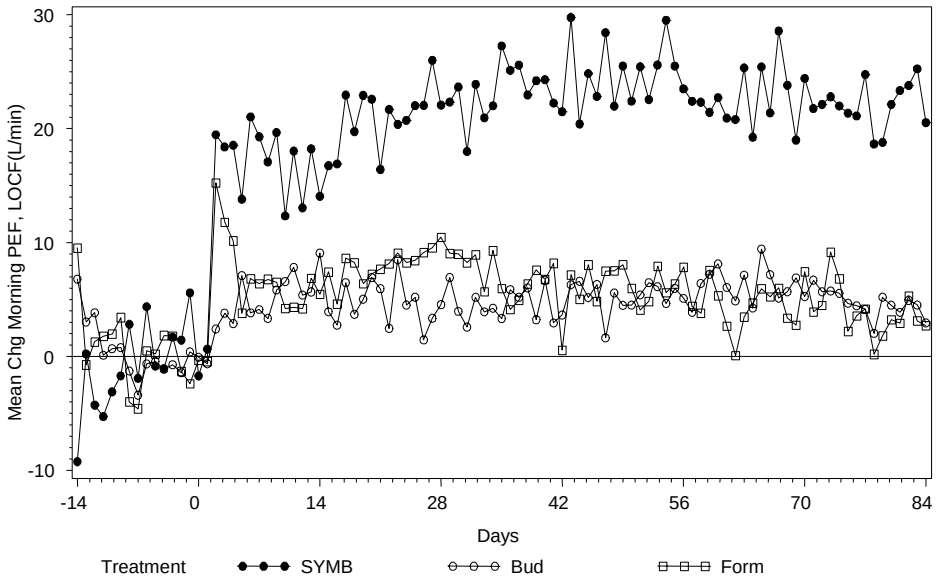
[a] Defined as the mean of all data collected during the double-blind treatment period.
[b] SYMB SYMBICORT 40/4.5 µg ×2 bid, Budes budesonide 40 µg ×2 bid, Form formoterol 4.5 µg ×2 bid.
[c] Baseline is defined as the mean of all values obtained during the run-in period.
EAS Efficacy analysis set.

Table S3 Morning PEF (L/min): treatment comparisons for change from baseline during the double-blind treatment period (EAS)

	ANCOVA analysis		
Comparisons[a]	LS mean (SEM)	95% CI	p-value
SYMB minus Budes	16.21 (3.506)	(9.31, 23.10)	<0.001
SYMB minus Form	15.80 (3.547)	(8.83, 22.78)	<0.001

[a] SYMB SYMBICORT 40/4.5 µg ×2 bid, Budes budesonide 40 µg ×2 bid, Form formoterol 4.5 µg ×2 bid.
EAS Efficacy analysis set.
Note: Double-blind treatment period is defined as the mean of data collected during the double-blind treatment period.

Figure S1 Mean change from baseline over time in morning PEF (EAS)



SYMB SYMBICORT 40/4.5 µg ×2 bid, Budes budesonide 40 µg ×2 bid, Form formoterol 4.5 µg ×2 bid.
EAS Efficacy Analysis Set.

Consistent with these findings for morning PEF, additionally the measurement of PEF in the evening showed similar results. A significantly greater increase from baseline in evening PEF was seen for SYMBICORT pMDI compared with budesonide and with formoterol during the double-blind treatment period ($p<0.001$ for each). For other secondary variables, SYMBICORT pMDI and budesonide generally had similar effects and showed greater improvements in measures of symptom control compared to formoterol alone; whereas SYMBICORT pMDI showed greater effects on lung function measures than did budesonide alone. In particular, a significantly greater increase from baseline in predose FEV_1 was seen for SYMBICORT pMDI compared with budesonide during the double-blind treatment period ($p=0.038$); no significant treatment difference was observed for SYMBICORT pMDI compared with formoterol. There were no statistically significant treatment differences observed with regard to PRO, as assessed by PAQLQ(S) and PACQLQ; however, improvements from baseline in these measures were seen in all treatment groups.

Secondary variables in this study also included pharmacokinetic parameters (AUC_{0-6} and C_{max}) for plasma budesonide and plasma formoterol. Systemic exposure to budesonide was comparable between the SYMBICORT pMDI and budesonide groups, as indicated by AUC_{0-6} and C_{max} mean treatment ratios of 0.88 (90% CI 0.680, 1.146) and 0.90 (90% CI 0.603, 1.332), respectively. Analysis of formoterol data indicated that systemic exposure to formoterol (AUC_{0-6}) was comparable in the 2 treatment groups as indicated by a mean treatment ratio of 0.875 (90% CI 0.692, 1.107). However, C_{max} was significantly lower in the SYMBICORT pMDI treatment group as indicated by a mean treatment ratio of 0.611 (90% CI 0.466, 0.801). Plasma concentration profiles for

formoterol tended to be relatively flat in many subjects in this study compared with what was previously observed in healthy subjects.

Safety results

Adverse events

Overall, SYMBICORT pMDI appears to have a similar AE profile compared to both of its monoproducts in children. The overall percentage of subjects with at least one AE was similar in the SYMBICORT pMDI and formoterol groups and slightly lower in the budesonide group (Table S4). The majority of AEs were mild or moderate in intensity. The only serious adverse event (SAE; asthma) reported during the double-blind treatment period occurred in the formoterol group and led to the discontinuation of the subject from treatment. This SAE was considered not study drug-related as judged by the investigator. The incidence of discontinuations due to adverse events (DAEs) was slightly lower in the SYMBICORT pMDI group than in the budesonide and formoterol groups. Asthma was the most commonly observed individual DAE and had a slightly higher incidence in the budesonide group compared to the SYMBICORT pMDI and formoterol groups. There were no deaths or other significant adverse events (OAEs) at any time during the study.

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

Category of adverse event	Number (%) of subjects with an adverse event[a]		
	SYMB N=128	Budes N=145	Form N=138
Mean duration of exposure (days)	**70.8**	**69.8**	**70.0**
Any adverse events	90 (70.3)	92 (63.4)	97 (70.3)
Serious adverse events	0	0	1 (0.7)
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	0	0	1 (0.7)
Serious adverse events leading to discontinuation	0	0	1 (0.7)
Subjects discontinued due to adverse events	4 (3.1)	10 (6.9)	11 (8.0)
	Total number of adverse events		
Any adverse events	272	277	311
Serious adverse events	0	0	1
Other significant adverse events	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 40/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 40 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

The most common AEs (≥3% incidence in any treatment group) are shown in Table S5. The incidence of each of these events was generally similar across treatment groups. The overall incidence of asthma reported as an AE was low, with a numerically lower

incidence in the SYMBICORT pMDI group compared to the budesonide or formoterol groups. The percentage of subjects with potentially asthma-related AEs was also low and was 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)

	Treatment group[a], n (%) of subjects		
Preferred Term	**SYMB N=128**	**Budes N=145**	**Form N=138**
Mean duration of exposure (days)	**70.8**	**69.8**	**70.0**
Total number of subjects with any adverse event	**90 (70.3)**	**92 (63.4)**	**97 (70.3)**
Headache	19 (14.8)	20 (13.8)	24 (17.4)
Pharyngolaryngeal pain	17 (13.3)	14 (9.7)	19 (13.8)
Nasopharyngitis	14 (10.9)	14 (9.7)	13 (9.4)
Pyrexia	15 (11.7)	7 (4.8)	11 (8.0)
Upper respiratory tract infection	6 (4.7)	9 (6.2)	12 (8.7)
Sinusitis	6 (4.7)	11 (7.6)	9 (6.5)
Abdominal pain upper	9 (7.0)	8 (5.5)	8 (5.8)
Cough	7 (5.5)	9 (6.2)	8 (5.8)
Dyspepsia	8 (6.3)	9 (6.2)	6 (4.3)
Vomiting	9 (7.0)	5 (3.4)	5 (3.6)
Nasal congestion	9 (7.0)	5 (3.4)	4 (2.9)
Asthma	2 (1.6)	7 (4.8)	7 (5.1)
Influenza	7 (5.5)	2 (1.4)	5 (3.6)
Lymphadenopathy	4 (3.1)	4 (2.8)	2 (1.4)
Pain in extremity	4 (3.1)	1 (0.7)	4 (2.9)
Diarrhea	1 (0.8)	5 (3.4)	2 (1.4)
Ear infection	4 (3.1)	2 (1.4)	1 (0.7)
Pharyngitis streptococcal	4 (3.1)	0	3 (2.2)

[a] SYMB SYMBICORT pMDI 40/4.5 µg per actuation x 2 actuations bid; Budes budesonide pMDI 40 µg per actuation x 2 actuations bid; Form formoterol TBH 4.5 µg per inhalation x 2 inhalations bid.

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

Hematology and chemistry assessments, including glucose and potassium timed to coincide with peak sustained pharmacodynamic activity, did not generally reveal meaningful differences in mean changes from baseline within or between treatment groups. Individual clinically important findings in chemistry and hematology variables were infrequent with no meaningful differences between treatment groups. Twelve-lead ECGs timed to coincide with peak sustained pharmacodynamic activity did not reveal meaningful differences in mean changes from baseline between treatment groups. Mean

changes from baseline in heart rate and in QTc (Bazett's and Fridericia's correction) noted in SYMBICORT pMDI and formoterol groups compared to the budesonide group were small and not clinically meaningful. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters. No significant physical examination or vital sign findings were noted among treatment groups.

Date of the report

23 April 2004