Drug product	SYMBICORT® pMDI 160/4.5 µg per actuation	**SYNOPSIS**	
Drug substance(s)	Budesopinde/For,oterol		
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A Six-Month, Randomized, Open-Label Safety Study of SYMBICORT® (160/4.5 µg) Compared to PULMICORT Turbuhaler® in Asthmatic Children Aged 6 to 11 Years.

International coordinating investigator

None appointed for this study

Study centers

This study was conducted in the United States (29 centers)

Publications

None at the time of this report

Study dates		**Phase of development**
First subject enrolled	22 July 2002	Phase III
Last subject completed	06 October 2003	

Objectives

Primary: The primary objective of this study was to compare the long-term safety profile of SYMBICORT®, a fixed combination of 160 µg budesonide and 4.5 µg formoterol (per puff[1]) in a single metered-dose inhaler product, administered as 2 puffs twice daily, to that of PULMICORT®, 200 µg per inhalation, administered as 2 inhalations twice daily, in asthmatic children aged 6 to 11 years over a period of 26 weeks.

Secondary: The secondary objective was to compare measurements of health economics and health-related quality of life (HRQOL[2]) between the same 2 treatment groups.

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

[2] Hereafter referred to as patient-reported outcomes (PRO).

Study design

This was a 26-week, randomized, open-label, safety study of SYMBICORT® pressurized metered-dose inhaler (SYMBICORT pMDI) compared with PULMICORT Turbuhaler® (PULMICORT TBH) in children 6 to <12 years of age with asthma. Randomized, open-label treatment was preceded by a 1-week baseline period during which time subjects continued to use their normally prescribed inhaled corticosteroid (ICS) therapy. Additional study visits were scheduled after 2, 12, and 26 weeks of treatment.

Target subject population and sample size

The subject population comprised male and female subjects 6 to <12 years of age with ICS-dependent asthma. Subjects must have demonstrated forced expiratory volume in 1 second (FEV_1) ≥50% of predicted normal and documented historic peak expiratory flow (PEF) or FEV_1 reversibility ≥12% from a pre-albuterol value within 15 to 30 minutes after administration of a standard dose of fast-acting β_2-agonist. Subjects without a documented history of reversibility must have demonstrated FEV_1 reversibility as above at any time before Visit 2.

Approximately 175 to 180 children were to be randomized into this study in a 2:1 ratio (SYMBICORT pMDI/PULMICORT TBH). It was planned that at least 100 children randomized to SYMBICORT pMDI and approximately 50 children randomized to PULMICORT TBH would complete 26 weeks of treatment. The sample size for this study was not based on any formal statistical criteria. Rather, it was chosen to achieve at least 100 study completers in the SYMBICORT pMDI treatment group, assuming a 15% early withdrawal rate.

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

Subjects were randomly assigned to 1 of the 2 following open-label treatment groups: SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg per actuation, 2 actuations administered twice daily. Batch numbers of SYMBICORT pMDI were P6040 and P6502A.

PULMICORT TBH 200 µg budesonide (approximately 160 µg budesonide delivered) per inhalation, 2 inhalations administered twice daily. Batch numbers of PULMICORT pMDI were P6478, P6583, X1447, and DE1682.

Albuterol, delivered by pMDI, was used as rescue medication on an as-needed (prn) basis during both the 1-week baseline period and the randomized treatment period. Batch numbers for albuterol were ABL97A and ABLP33A. EMLA®[3] Cream was provided for topical analgesia prior to venipuncture as directed by the investigator. Batch numbers for EMLA cream were 203083, 211051, 301148, and 302074.

[3] EMLA is a registered trademark of the AstraZeneca group of companies.

Duration of treatment

A 26-week randomized treatment period preceded by a 1-week baseline period.

Criteria for evaluation (main variables)

No single variable was considered to be primary. The primary objective of the study was to assess long-term safety.

Efficacy, PRO, health economic outcomes, and pharmacokinetics

There was no efficacy objective in this safety study. However, spirometry was conducted at each study visit to detect any untoward decreases in lung function over the 26-week period. Spirometry assessments included forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory flow (volume) expired during the middle half of exhalation ($FEF_{25-75\%}$), and peak expiratory flow (PEF). Physician and caregiver Global Assessments of overall control of asthma symptoms were conducted independently at the final study visit to support health economics and outcomes research objectives.

Health economic outcomes were assessed through measures of the following direct medical and indirect resource utilization:

Direct medical resource utilization

- Emergency Room (ER) visits (all cause)
- ER visits due to asthma or breathing problems
- Hospital admissions and number of nights in the hospital (all cause)
- Hospital admissions and number of nights in the hospital due to asthma or breathing problems. This included direct admissions and admissions through the ER.
- Urgent care visits due to child's asthma or breathing problems
- Unscheduled healthcare provider visits due to child's asthma or breathing problems
- Unscheduled telephone calls to healthcare provider due to child's asthma or breathing problems

Indirect resource utilization

- Days child was unable to participate in normal daily activities such as school, playschool, daycare, or camp because of asthma or breathing problems

- Days caregiver (or household member) had usual daily routine interrupted because of child's asthma or breathing problems

- Days caregiver (or household member) missed work (at least one-half day) because of child's asthma or breathing problems

Subject health-related quality of life was assessed using the standardized version of the Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]; validated in subjects 7 to 17 years of age). Caregiver quality of life was evaluated through the Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ; validated in caregivers of subjects 7 to 17 years of age).

All subjects who consented to pharmacokinetics (PK) testing were to undergo PK sampling at Visit 3, approximately 2 weeks after beginning treatment with study medication. Testing was performed for plasma concentrations of budesonide and formoterol in appropriate specimens (ie, samples from subjects treated with PULMICORT TBH were not analyzed for formoterol concentrations). The following parameters were evaluated: C_{max} (maximum plasma concentration), T_{max} (time to C_{max}), and AUC_{0-6} (area under the curve from time 0 to 6 hours).

Safety

Adverse events, clinical laboratory data including 24-hour urinary cortisol, 12-lead electrocardiograms (ECGs), and physical examination and vital signs were used to evaluate safety.

Statistical methods

The safety analysis set was defined as all randomized subjects who took at least 1 dose of study medication. The safety analysis set was used for the analyses of efficacy, health economic, and safety variables. The PK analysis set included all subjects who consented to PK testing and who had at least 1 blood draw for PK testing performed during treatment. The PRO analysis set contained all subjects who were ≥7 years of age. Predose FEV_1 was analyzed by formulating contrasts within an analysis of covariance (ANCOVA) model, adjusting for fixed factors of center and treatment and for the covariate of baseline FEV_1. PRO variables were compared between treatment groups using analyses similar to those specified for predose FEV_1.

Data from Global Assessments were analyzed using chi-square tests; positive responses were pooled in the primary method.

For measures of direct medical and indirect resource utilization, event rate data were analyzed with Poisson regression and numbers of subjects were compared using Fisher's exact test.

Pharmacokinetic parameters for budesonide and formoterol were summarized with descriptive statistics. C_{max} and AUC_{0-6} for budesonide were compared between treatment groups using a multiplicative ANOVA model.

Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models.

Subject population

A total of 252 subjects were screened, of whom 187 subjects from 28 centers were subsequently randomized. All but 1 randomized subject (randomized to SYMBICORT pMDI but who subsequently withdrew consent) received study medication and were included in the safety analysis set.

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 withdrawal rate was low (12.3%) and slightly lower in the SYMBICORT pMDI group (10.5%, 13/124) compared with the PULMICORT TBH group (15.9%, 10/63). The most common reason for discontinuation was withdrawal of consent (4.8% overall). A total of 164 (87.7%) subjects completed the study.

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or baseline characteristic		Treatment group[a]					
		SYMB (N=123)		PULM (N=63)		Total (N=186)	
Demographic characteristics							
Sex (n and % of subjects)	Male	79	(64.2)	40	(63.5)	119	(64.0)
	Female	44	(35.8)	23	(36.5)	67	(36.0)
Age (years)	Mean (SD)	9.03	(1.639)	8.94	(1.605)	9.00	(1.624)
	Range	6 to 11		6 to 11		6 to 11	
Race (n and % of subjects)	Caucasian	109	(88.6)	58	(92.1)	167	(89.8)
	Black	11	(8.9)	3	(4.8)	14	(7.5)
	Oriental	1	(0.8)	1	(1.6)	2	(1.1)
	Other	2	(1.6)	1	(1.6)	3	(1.6)
Baseline characteristics							
Years since asthma diagnosis							
Mean (SD)		6.04	(3.002)	6.02	(2.916)	6.03	(2.966)
Min, Max		0.6, 11.9		0.8, 11.5		0.6, 11.9	
ICS use at entry (µg/day)							
Mean (SD)		306.10	(214.161)	308.95	(212.615)	307.6	(213.038)
Min, Max		50.0, 1000.0		44.0, 1000.0		44.0, 1000.0	

Table S1 Demographic and key characteristics (safety analysis set)

Demographic or baseline characteristic	Treatment group[a]					
	SYMB (N=123)		PULM (N=63)		Total (N=186)	
FEV_1 at screening (Visit 1, pre-bronchodilator)						
(L), Mean (SD)	1.75	(0.435)	1.75	(0.398)	1.75	(0.421)
% Predicted, Mean (SD)	84.60	(13.242)	83.54	(12.115)	84.24	(12.850)
FEV_1 at baseline (predose at Visit 2)						
(L), Mean (SD)	1.75	(0.447)	1.73	(0.400)	1.74	(0.431)
% Predicted, Mean (SD)	84.01	(13.516)	82.90	(13.296)	83.64	(13.416)

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation ×2 actuations bid, PULM PULMICORT TBH 200 µg metered (approximately 160 µg delivered) per inhalation ×2 inhalations bid.

Efficacy, PRO, health economic outcomes, and pharmacokinetics results

Compared with baseline, both SYMBICORT pMDI 160/4.5 µg per actuation ×2 actuations bid and PULMICORT TBH 200 µg metered (approximately 160 µg delivered) per inhalation ×2 inhalations bid improved the lung function and quality of life of pediatric subjects with asthma. Mean improvements from baseline in predose FEV_1 were significantly greater for SYMBICORT pMDI compared with PULMICORT TBH for the average of all FEV_1 values across all on-treatment visits as well as at the end of treatment ($p \leq 0.009$ and $p < 0.001$, respectively). Primary analysis of the physician Global Assessment indicated no statistically significant differences between treatment groups. Analysis of the caregiver Global Assessment indicated a significantly ($p \leq 0.048$ for both questions) higher rate of positive responses for SYMBICORT pMDI subjects compared with PULMICORT TBH subjects at end of treatment.

Improvements from baseline for all PAQLQ(S) scores were significantly ($p \leq 0.012$ for overall score and each domain score) greater for SYMBICORT pMDI versus PULMICORT TBH, but the differences between groups did not reach a minimally important difference (defined as a mean difference between groups of ≥0.5 point). Improvements from baseline in PACQLQ were significantly greater for SYMBICORT pMDI versus PULMICORT TBH for overall ($p=0.006$) and emotional function ($p=0.001$) scores.

Results obtained from measures of direct medical resource utilization indicated the following. There were fewer visits to urgent care facilities made by subjects in the SYMBICORT pMDI group (0.069 visits per subject-treatment year) compared with the PULMICORT TBH group (0.314 visits per subject-treatment year; $p=0.012$ for the difference between groups). There were no differences between treatment groups in the number of either unscheduled health care provider visits or phone calls to health care providers due to asthma or breathing problems. Discrepancies were found between SAE narratives and IVRS data for ER visits and hospital admissions. Therefore, no formal treatment comparisons were performed for these direct medical resources because the data were deemed to be unreliable.

Results obtained from measures of indirect resource utilization indicated the following. There were fewer days that the caregiver was absent from work due to the subject's asthma or breathing problems for the SYMBICORT pMDI group (0.503 days per subject-treatment year) compared with the PULMICORT TBH group (1.011 days per subject-treatment year; p=0.008 for the difference between groups). However, there was no difference between treatment groups in the percentage of subjects with caregivers who reported at least 1 such day. There were fewer days (p<0.001 for the difference between groups) that the child was unable to participate in daily activities due to asthma or breathing problems and fewer children (p=0.050 for the difference between groups) reporting at least 1 such day for the SYMBICORT pMDI group (1.752 days per subject-treatment year, 29.3% of subjects) compared with the PULMICORT TBH group (3.662 days per subject-treatment year, 44.4% of subjects). There was no difference between treatment groups in the number of days the caregiver's usual daily routine was interrupted due to the subject's asthma or breathing problems or in the percentage of subjects with caregivers who had at least 1 such day.

Systemic exposure to budesonide was comparable between the SYMBICORT pMDI and PULMICORT TBH treatment groups, as indicated by AUC_{0-6} and C_{max} mean (90% confidence interval) treatment ratios of 1.080 (0.442, 2.641) and 0.956 (0.368, 2.481), respectively. However, it should be noted that this comparison is based on a relatively small amount of data (11 subjects in total). For SYMBICORT pMDI, geometric mean values for formoterol AUC_{0-6} and C_{max} were 109.77 pmol h/L and 26.988 pmol, respectively, and the median value for T_{max} was 0.701 h. Plasma concentration profiles for formoterol tended to be relatively flat in some subjects in this study compared with what was previously observed in healthy subjects.

Safety results

Overall, SYMBICORT pMDI had a similar adverse event (AE) profile compared with PULMICORT TBH in children. The overall percentage of subjects with at least 1 AE was similar between the SYMBICORT pMDI and PULMICORT TBH groups (Table S2). The majority of AEs were mild or moderate in intensity. Two serious adverse events (SAE; asthma, pneumonia) reported during the randomized treatment period occurred in the SYMBICORT pMDI group and 1 SAE (sickle cell anemia) occurred in the PULMICORT TBH group; none of the 3 SAEs led to the discontinuation of the subjects from treatment. These SAEs were determined to not be study drug-related by the investigator. Four subjects (2 in each treatment group) experienced AEs leading to discontinuation from study treatment (DAEs) during the randomized treatment period. Asthma DAEs occurred in 2 subjects, 1 in each treatment group. There were no deaths or other significant adverse events (OAEs) at any time during the study.

Table S2 **Number (%) of subjects who had at least 1 adverse event during randomized treatment in any category, and total numbers of adverse events (safety population)**

Category of adverse event	Number (%) of subjects who had an adverse event in each category[a]		
	SYMB (n=123)	PULM (n=63)	Total (n=186)
Any adverse events	104 (84.6)	54 (85.7)	158 (84.9)
Serious adverse events	2 (1.6)	1 (1.6)	3 (1.6)
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	2 (1.6)	1 (1.6)	3 (1.6)
Discontinuations of study treatment due to adverse events	2 (1.6)	2 (3.2)	4 (2.2)
Other significant adverse event	0	0	0
	Total number of adverse events		
Any adverse events	431	244	675
Serious adverse events	2	1	3
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 160/4.5 µg per actuation x 2 actuations bid; PULM PULMICORT TBH 200 µg metered (approximately 160 µg delivered) per inhalation x 2 inhalations bid.

The most common AEs (≥3% incidence overall) are shown in Table S3. Overall, the percentage of subjects reporting AEs during the randomized treatment period was similar between treatment groups. The most frequently occurring AEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term were headache, upper respiratory tract infection, nasopharyngitis, upper abdominal pain, asthma, pharyngolaryngeal pain, and cough. While the incidence of these events was generally similar across treatment groups, the percentages of subjects with asthma, pharyngolaryngeal pain, and cough were slightly higher in the SYMBICORT pMDI group. The incidence of potentially asthma-related AEs, defined as disease under study (DUS; wheezing, cough, chest discomfort, dyspnea, dyspnea exacerbated, throat secretions increased, increased bronchial secretions, and increased viscosity of bronchial secretions), was generally low and similar across the 2 treatment groups, although the incidence of cough was slightly higher in the SYMBICORT pMDI group, as previously described. The incidence of cardiac-related AEs was low and similar between treatment groups. The musculoskeletal and connective tissue disorders SOC revealed a slightly higher incidence of AEs in the SYMBICORT pMDI group (due mostly to slightly higher incidences of myalgia, extremity pain, and arthralgia AEs).

There was an overall trend in both treatment groups for a slightly higher incidence of individual AEs to be reported in the 1st month of the initial 3-month period. The type and incidence of AEs reported were similar during the 1st and last 3-month periods of the

study, with no notable difference in patterns of onset between treatment groups. Increased duration of exposure to SYMBICORT pMDI or PULMICORT TBH was not associated with a change in the profile of adverse events reported.

Table S3 Number (%) of subjects with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)

	Treatment group[a]		
Preferred term	**SYMB (n=123)**	**PULM (n=63)**	**Total (n=186)**
Total number of subjects with any adverse event	104 (84.6)	54 (85.7)	158 (84.9)
Headache	26 (21.1)	14 (22.2)	40 (21.5)
Upper respiratory tract infection	24 (19.5)	15 (23.8)	39 (21.0)
Nasopharyngitis	20 (16.3)	10 (15.9)	30 (16.1)
Abdominal pain upper	15 (12.2)	8 (12.7)	23 (12.4)
Asthma	16 (13.0)	6 (9.5)	22 (11.8)
Pharyngolaryngeal pain	15 (12.2)	6 (9.5)	21 (11.3)
Cough	15 (12.2)	5 (7.9)	20 (10.8)
Pyrexia	13 (10.6)	4 (6.3)	17 (9.1)
Dyspepsia	12 (9.8)	4 (6.3)	16 (8.6)
Nasal congestion	10 (8.1)	3 (4.8)	13 (7.0)
Sinusitis	8 (6.5)	4 (6.3)	12 (6.5)
Pharyngitis streptococcal	8 (6.5)	2 (3.2)	10 (5.4)
Viral infection	5 (4.1)	5 (7.9)	10 (5.4)
Vomiting	6 (4.9)	4 (6.3)	10 (5.4)
Bronchitis	6 (4.9)	3 (4.8)	9 (4.8)
Influenza	6 (4.9)	3 (4.8)	9 (4.8)
Otitis media	5 (4.1)	4 (6.3)	9 (4.8)
Ear pain	5 (4.1)	2 (3.2)	7 (3.8)
Epistaxis	5 (4.1)	1 (1.6)	6 (3.2)
Gastroenteritis viral	4 (3.3)	2 (3.2)	6 (3.2)

[a] SYMB SYMBICORT pMDI 160/4.5 µg per actuation x 2 actuations bid; PULM PULMICORT TBH 200 µg metered (approximately 160 µg delivered) per inhalation x 2 inhalations bid.

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

Glucose and potassium assessments timed to coincide with peak sustained pharmacodynamic activity of the formoterol component of SYMBICORT pMDI generally did not reveal meaningful differences in mean changes over time between treatment groups. Similarly timed 12-lead ECGs demonstrated small differences in ECG

heart rate and QTc (Baz and Frid) means between the SYMBICORT pMDI and PULMICORT TBH treatment groups that were generally not clinically meaningful. Overall percentages of subjects experiencing QT, QTc (Baz), and QTc (Frid) changes from baseline >30 msec were similar between the 2 groups. The incidence of changes from baseline ≥60 msec in QTc (Baz) and QTc (Frid) was low and slightly higher in the SYMBICORT pMDI group. There were slightly more SYMBICORT pMDI subjects with shifts to ≥450 msec in QTc (Baz). There were no shifts to ≥500 msec in QT, QTc (Baz), and QTc (Frid) in either treatment group. The number of subjects manifesting new clinically notable ECG findings or shifts in overall ECG evaluation was low, but slightly higher in the SYMBICORT pMDI treatment group. Overall, none of these new findings resulted in subject withdrawal from the study. Similarly, the number of AEs reported for cardiac findings was very low. Close inspection of these data does not suggest the presence of significant cardiac issues related to the use of SYMBICORT pMDI in children. No consistent association was seen between individual clinically important changes in glucose or potassium and changes in ECG parameters.

Overall, the effect of SYMBICORT pMDI on hypothalamus-pituitary-adrenal (HPA) axis function as assessed by 24-hour urinary cortisol measurements was similar to PULMICORT TBH. Both treatment groups showed mean decreases at all timepoints during treatment in 24-hour urinary cortisol and cortisol/creatinine ratio compared with baseline; the SYMBICORT pMDI group generally manifested numerically smaller decreases across visits compared with the PULMICORT TBH group. The percentage of subjects with shifts below the normal 24-hour urinary cortisol range was small, with a slightly smaller percentage of SYMBICORT pMDI subjects identified as having notable urinary cortisol findings compared with the PULMICORT TBH group. Throughout the study, there was only 1 subject (PULMICORT TBH group) who experienced an AE that was related to abnormal urine cortisol (cortisol urine decreased; creatinine urine decreased). There were no DAEs or SAEs related to urinary cortisol findings.

There were no important findings in other clinical chemistry and hematology parameters, physical examination, or vital signs noted between treatment groups.

Date of the report

11 January 2005