AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D5896C00021
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A 12-week, randomized, double-blind, active-controlled, multi-center, phase IIIB study comparing the efficacy and evaluating the safety of SYMBICORT® pMDI 160/4.5 µg x 2 actuations twice daily versus budesonide HFA pMDI 160 µg x 2 actuations twice daily, in adult and adolescent (≥12 years) Hispanic subjects with asthma

Study dates: First subject randomized: 13 February 2007
Last subject completed: 20 May 2008

Phase of development: IIIB

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centers

The study was conducted at 36 centers in the United States at which subjects were randomized. An additional 15 centers received drug but did not enroll any subjects.

Publications

None at the time of writing this report.

Objectives

Primary:

To compare the efficacy of SYMBICORT pMDI 160/4.5 μg x 2 actuations bid to that of budesonide HFA pMDI 160 μg x 2 actuations bid, in Hispanic (self-reported) subjects with inhaled corticosteroid (ICS) dependent asthma. The primary efficacy variable was morning Peak Expiratory Flow (AM PEF).

Secondary:

- To evaluate the safety of SYMBICORT pMDI compared to budesonide.
- To collect a peripheral blood sample for pharmacogenetic testing in consenting subjects for future pharmacogenetic analyses to be conducted outside the scope of the clinical study report.

Study design

This was a 12-week, randomized, double-blind, active-controlled, Phase IIIB study comparing the efficacy and safety of SYMBICORT® pMDI 160/4.5 μg x 2 actuations BID to budesonide HFA pMDI 160 μg x 2 actuations BID in adult and adolescent (≥12 years) Hispanic (self-reported) subjects with asthma who required a medium to high dose of ICS therapy. Randomized treatment was preceded by a 2-week (±1 week) single-blind run-in period beginning at Visit 2. All enrolled subjects were treated with budesonide HFA pMDI 80 μg x 2 actuations BID, as well as study provided albuterol pMDI administered as 90 μg, 2 actuations as needed, for use as rescue medication.

Target subject population and sample size

Subjects eligible for enrollment were self-identified as being of Puerto Rican, South or Central American/Mexican, Cuban/Caribbean, or mixed descent with both parents identified as Hispanic. The inclusion criteria, exclusion criteria and ICS run-in were designed to select a population of moderate to severe asthmatics who required ICS therapy and were symptomatic after a run-in period of approximately 2 weeks on budesonide HFA pMDI 80 μg x 2 actuations BID.

The targeted population included male and female subjects with asthma who were at least 12 years of age, who were chronically treated with a medium to high dose[1] of ICS, and whose pre-bronchodilator forced expiratory volume in the first second (FEV_1) on ICS therapy was within the entrance range (45% to 85% of predicted normal), were eligible for enrollment. In addition, subjects had to demonstrate reversibility of FEV_1 of at least 12% and ≥0.20 L from the pre-albuterol baseline value within 15 to 30 minutes after administration of a standard dose of fast-acting beta$_2$-agonist (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 if required). Qualification for randomization was based on lung function and asthma symptom scores during the run-in period.

Run-in, dosage and mode of administration

- Budesonide HFA pMDI 80 µg x 2 actuations bid (run-in period)

Investigational product, dosage and mode of administration

- SYMBICORT pMDI 160/4.5 µg x 2 actuations bid (randomized treatment)

Comparator, dosage and mode of administration

- Budesonide HFA pMDI 160 µg x 2 actuations bid (randomized treatment)

Rescue therapy (for oral inhalation)

- Albuterol pMDI (90 µg per actuation) taken as needed (PRN), as rescue medication for relief of bronchospasm.

Duration of treatment

This study consisted of a 2 week (± 1 week) single-blind run-in period during which all subjects received budesonide HFA 80 µg x 2 actuations bid as treatment for asthma.

Qualifying subjects were randomly assigned to 1 of 2 possible treatment arms and entered a 12-week double-blind treatment period. At the end of the treatment period or early termination, subjects resumed appropriate asthma maintenance therapy.

Criteria for evaluation – efficacy, pharmacokinetics, safety, and genetics (main variables)

Efficacy

Primary efficacy variable:

- AM PEF

[1] Consistent with National Asthma Education and Prevention Program Guidelines (1997).

Secondary efficacy variables: Predefined asthma event

- Predefined asthma events
- Withdrawals due to predefined asthma events

Secondary efficacy variables: Lung function assessments

- Pre-dose FEV_1
- Evening PEF

Secondary efficacy variables: Diary assessments

- Nighttime and daytime asthma symptom scores
- Nighttime awakenings due to asthma
- Rescue medication use
- Rescue-free days
- Symptom-free days
- Asthma control days
- Onset of Effect Questionnaire (OEQ)

Secondary efficacy variables: Global assessments

- Patient global assessment
- Physician global assessment

Patient reported outcomes (PROs)

- Patient Satisfaction with Asthma Medication Questionnaire (PSAM) for subjects 18 years of age or older (Mathias et. al, 2000).

Health economics

- Not applicable

Pharmacokinetic

- Not applicable.

Pharmacodynamic

- Not applicable.

Safety

- Adverse events, serious adverse events, discontinuation of study treatment due to adverse events, clinical lab data, ECGs, vital signs, physical examination.

Genetics

- A single peripheral blood sample was collected in all subjects who consented/assented to pharmacogenetic testing to assess genetic markers related to asthma.

Statistical methods

The primary statistical analyses of efficacy was based on the full analysis set, which included data from all randomized subjects who contributed data sufficient for the calculation of the efficacy variables as defined in the CSP.

The primary variable, the change in AM PEF from the average over the baseline period to the average over the double-blind treatment period, was analyzed using the analysis of covariance (ANCOVA) model with treatment and center as fixed factors and the baseline value as a covariate. A sensitivity analysis was performed in which the asthma severity stratum was added to the ANCOVA model.

For all secondary variables, including patient questionnaires (OEQ and PSAM) and global assessments, nominal p-values were presented for treatment comparisons without adjustment for multiple comparisons. The continuous secondary efficacy and health-related quality of life variables were compared between the treatments using the analysis method described for the primary variable.

Pre-defined asthma events and withdrawals due to pre-defined asthma events were analyzed and summarized by 2 different methods. Time to first pre-defined asthma events and time to withdrawal due to a pre-defined asthma event was described using Kaplan-Meier plots.

The observation in the overall population of mean improvements in lung function during budesonide run-in and an unexpectedly large budesonide response during randomized treatment prompted a post-hoc analysis to be performed as a second sensitivity analysis. Post-hoc analysis included, for some efficacy variables, a subset analysis of subjects whose pre-dose FEV_1 did not increase from Visit 2 (run-in) to Visit 3 (randomization). Statistical analysis methods were the same as those used for the pre-defined analysis.

Subject population

The study population represented a subset of adult and adolescent (≥12 years) Hispanic subjects with asthma (as defined by ICS use at entry). Overall the screen failure rate was approximately 55.2% (308 of 558 subjects). Demographic and baseline characteristics were

generally well-balanced across the 2 treatment groups (Table S1). There was a greater proportion of female than male subjects (65.6% versus 34.4%) as consistent with the disease prevalence in adults and adolescents. Most subjects (50.8%) were Mexican, with Puerto Rican subjects comprising of 21.2% of the population. Approximately 14.8% of subjects in the efficacy analysis set were excluded from the PP analysis set; reasons for exclusion were similar in the 2 treatment groups.

Table S1 Demographic and key characteristics (safety analysis set)

	Treatment group[a]		
Demographic or key characteristic	**SYM 160/4.5 BID (N=127)**	**BUD 160 BID (N=123)**	**Total (N=250)**
Sex (N and % of subjects)			
Male	43 (33.9)	43 (35.0)	86 (34.4)
Female	84 (66.1)	80 (65.0)	164 (65.6)
Age (years)			
Mean (SD)	39.8 (16.63)	37.0 (14.87)	38.4 (15.81)
Median	40	40	40
Range	12 – 83	12 – 77	12 – 83
Region (N and % of subjects)			
Caribbean	2 (1.6)	1 (0.8)	3 (1.2)
Cuban	17 (13.4)	16 (13.0)	33 (13.2)
Mexican	67 (52.8)	60 (48.8)	127 (50.8)
Mixed Hispanic Descent	2 (1.6)	1 (0.8)	3 (1.2)
Puerto Rican	26 (20.5)	27 (22.0)	53 (21.2)
South or Central America	13 (10.2)	18 (14.6)	31 (12.4)
Any relevant medical conditions			
No	12 (9.4)	13 (10.6)	25 (10.0)
Yes	115 (90.6)	110 (89.4)	225 (90.0)
Any relevant surgery			
No	54 (42.5)	60 (48.8)	114 (45.6)
Yes	73 (57.5)	63 (51.2)	136 (54.4)
ICS dose at entry (all, µg/day)			
Mean (SD)	582.5 (282.41)	607.0 (294.47)	594.6 (288.23)
Min, Max	80, 2000	80, 1600	80, 2000
Baseline FEV_1 (L) (pre-dose at Visit 2)			

Demographic or key characteristic	Treatment group[a] SYM 160/4.5 BID (N=127)	BUD 160 BID (N=123)	Total (N=250)
Mean (SD)	2.07 (0.57)	2.12 (0.54)	2.10 (0.56)
Percent predicted FEV_1			
Mean (SD)	68.32 (10.64)	67.96 (12.25)	68.14 (11.44)
Percent reversibility in FEV_1 at Visit 2			
Mean (SD)	27.71 (18.92)	25.31 (14.70)	26.53 (16.98)
Median	21.89	20.83	21.41
Min, Max	11.83, 135.94	8.61, 82.64	8.61, 135.94

[a] SYM 160/4.5 BID: SYMBICORT pMDI 160/4.5 µg x 2 BID; BUD 160 BID: Budesonide HFA pMDI 160 µg x 2 BID

BID: twice daily; ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in one second; N: number; SD: standard deviation.

Summary of efficacy results

Table S2 and Table S3 summarize the results of the primary efficacy analysis in the treatment means and treatment comparisons, respectively, for change from baseline to the average during double-blind treatment for AM PEF.

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

			Double-blind treatment period			
		Baseline value	Observed value	Change from baseline	From ANCOVA on change from baseline	
Treatment	N	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SEM)	95% CI
SYMBICORT	124	329.5 (90.3)	352.4 (79.1)	22.9 (63.0)	25.4 (6.0)	13.5, 37.3
Budesonide	119	321.5 (84.4)	340.9 (91.2)	19.3 (43.7)	19.9 (6.5)	7.1, 32.8

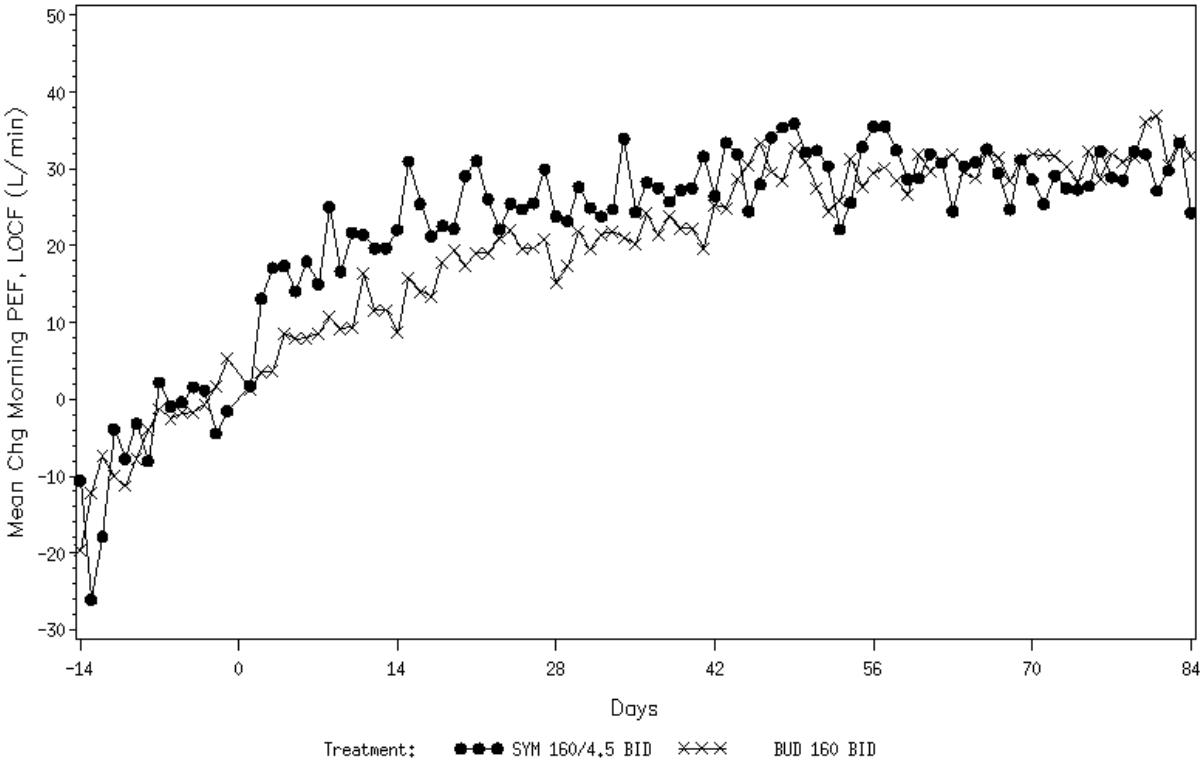
SYMBICORT: SYMBICORT pMDI 160/4.5 µg x 2 BID; Budesonide: Budesonide HFA pMDI 160 µg x 2 BID.
ANCOVA: analysis of covariance; CI: confidence interval; BID: twice daily; LS: least squares; N: number; SEM: standard error of the mean; SD: standard deviation.

Table S3 Morning PEF (L/min): treatment comparison during double-blind treatment (efficacy analysis set)

		ANCOVA analysis	
Comparison	**LS mean (SEM)**	**95% CI**	**p-value**
SYMB minus Budesonide	5.44 (6.85)	-8.06, 18.95	0.428

SYMB: SYMBICORT pMDI 160/4.5 µg x 2 BID; Budesonide: Budesonide HFA pMDI 160 µg x 2 BID
ANCOVA: analysis of covariance; CI: confidence interval; BID: twice daily; LS: least squares; N: number; SEM: standard error of the mean; SD: standard deviation.

Figure S1 Mean change from baseline in morning PEF by study day, LOCF (efficacy analysis set)



SYMB 160/4.5 BID: SYMBICORT pMDI 160/4.5 µg x 2 BID; BUD 160 BID: Budesonide HFA pMDI 160 µg x 2 BID.
Chg: change; LOCF: last observation carried forward; PEF: peak expiratory flow

Key findings for the primary efficacy variable are as follows:

- The small difference in mean change from baseline in favor of SYMBICORT pMDI was not statistically significant.

- Improvements in AM PEF were observed within 1 day of the first dose in the SYMBICORT pMDI treatment group, but not in the budesonide treatment group. Improvements from baseline in both treatment groups were evident during the remainder of the study.

Secondary variables (percentage of subjects who had a pre-defined asthma event; withdrawals due to predefined asthma events; lung function assessments [pre-dose FEV_1, PM PEF]; diary assessments [daytime symptom score, nighttime symptom score, percentage of symptom-free days, and percentage of awakening-free nights]; global assessments; and patient reported outcomes) consistently numerically favored SYMBICORT pMDI, but were not statistically significantly different from budesonide monotherapy for the efficacy analysis set.

For the efficacy analysis set, the percentage of subjects with at least 1 pre-defined asthma event (as defined on the ASTEXAC eCRF) was 25.2% in the SYMBICORT pMDI treatment group and 31.7% in the budesonide treatment group. This difference was not statistically significant (p=0.256). The percentage of subjects who withdrew due to a pre-defined asthma event was 2.1% in the SYMBICORT pMDI treatment group and 6.5% in the budesonide treatment group. This difference was not statistically significant (p=0.218).

For the OEQ, at the end of Week 1, a higher percentage of subjects in the SYMBICORT pMDI treatment group than in the budesonide treatment group agreed with Item 2 (88.8% versus 77.0%) and Item 5 (91.8% versus 75.9%). Despite the high rate of positive responses in the budesonide treatment group, the differences for both Item 2 (p=0.048) and Item 5 (p=0.004) were nominally statistically significant. At the end of treatment, differences between SYMBICORT pMDI and budesonide treatment groups for Items 2 and 5 were not statistically significant (p=0.286 and 0.208, respectively). PSAM results at the end of treatment significantly favored SYMBICORT pMDI over budesonide for the Control Relief Index ($p \leq 0.044$) and Comparison with Other Medications ($p \leq 0.005$). For the Perception of Medication domain, the score numerically favored SYMBICORT pMDI treatment group.

A post-hoc analysis of subjects whose pre-dose FEV_1 did not increase from Visit 2 (run-in) to Visit 3 (randomization) was performed. By imposing a requirement for stable or declining FEV_1 during treatment with low dose budesonide during run-in, subjects that more closely represent the intended moderate to severe asthma population were selected. In this subpopulation, treatment differences between SYMBICORT pMDI and budesonide treatment groups for certain efficacy endpoints were substantially larger than those observed for the total efficacy population. Specifically, the absolute mean treatment average change from baseline AM PEF was 23.5 L/min for SYMBICORT pMDI treatment subgroup and 11.9 L/min for budesonide treatment subgroup, representing 7.3% and 3.9% improvements over baseline, respectively. Similarly, for reduction in the treatment average mean number of total inhalations of rescue medication, a difference of -0.7 and -0.3 inhalations for SYMBICORT pMDI and budesonide treatment subgroups were observed, which correspond to 41% and 17% reductions from baseline, respectively. These findings in Hispanic subjects appropriate for combination therapy (i.e., not well controlled on low dose ICS) are consistent with what has been observed for the general population in previous studies.

Summary of pharmacokinetic results

Not applicable

Summary of pharmacodynamic results

Not applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of pharmacogenetic results

Not applicable

Summary of safety results

SYMBICORT pMDI was well tolerated for use in the treatment of asthma in adult and adolescent Hispanic subjects, with an AE profile similar to budesonide. SYMBICORT pMDI demonstrated no clinically significant findings in glucose, potassium, and other clinical laboratory findings, physical examination, ECG, or vital signs compared with budesonide.

Table S4 Overview of adverse events during the double-blind treatment period (safety analysis set)

	Treatment group[a], n (%) of subjects	
Category	**SYM 160/4.5 BID (N=127)**	**BUD 160 BID (N=123)**
Any adverse event (AE)	52 (40.9)	46 (37.4)
Serious adverse events (SAE)	4 (3.1)	0
SAEs leading to death	0	0
SAEs not leading to death	4 (3.1)	0
SAEs leading to discontinuation	1 (0.8)	0
Subjects discontinued due to AEs	1 (0.8)	2 (1.6)
	Total number of adverse events	
Any AEs	117	102
SAEs	4	0
Other significant adverse events (OAEs)	0	0

[a] SYM 160/4.5 BID: SYMBICORT pMDI 160/4.5 µg x 2 BID; BUD 160 BID: Budesonide HFA pMDI 160 µg x 2 BID

Note: 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; BID: twice daily; OAE: other significant adverse event; SAE: serious adverse event.

The most commonly reported AEs for the safety analysis set were within the SOC categories of infections and infestations; respiratory, thoracic and mediastinal disorders; musculoskeletal and connective tissue disorders; and gastrointestinal (GI) disorders.

Table S5 Summary of system organ class categories with at least 1 adverse event reported during the randomization period, sorted by decreasing order of frequency across all treatment groups (>3% incidence in either group) (safety analysis set)

	Treatment group[a], n (%) of subjects		
System organ class	**SYM 160/4.5 BID (N=127)**	**BUD 160 BID (N=123)**	**Total (N=250)**
Number of subjects with any AE	**52 (40.9)**	**46 (37.4)**	**98 (39.2)**
Infection and infestations	29 (22.8)	22 (17.9)	51 (20.4)
Nervous system disorders	12 (9.4)	15 (12.2)	27 (10.8)
Respiratory, thoracic and mediastinal disorders	12 (9.4)	11 (8.9)	23 (9.2)
Musculoskeletal and connective tissue disorders	9 (7.1)	11 (8.9)	20 (8.0)
Gastrointestinal disorders	11 (8.7)	5 (4.1)	16 (6.4)
General disorders and administration center conditions	4 (3.1)	3 (2.4)	7 (2.8)
Injury, poisoning and procedural complications	4 (3.1)	3 (2.4)	7 (2.8)

[a] SYM 160/4.5 BID: SYMBICORT pMDI 160/4.5 µg x 2 BID; BUD 160 BID: Budesonide HFA pMDI 160 µg x 2 BID

Note: Subjects with multiple events in the same category are counted only once in that category.
AE: adverse event; BID: twice daily; N: number.

SYMBICORT pMDI demonstrated no clinically significant findings in clinical laboratory findings, physical examination, or vital signs compared with budesonide. SYMBICORT pMDI also demonstrated no clinically significant changes in ECG findings compared with budesonide.