Clinical Study Report Synopsis	
Drug Substance	budesonide/formoterol
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A 52-Week, Randomized, Double-Blind, Parallel-Group, Multi-Center, Phase IIIB Study Comparing the Long Term Safety of SYMBICORT®pMDI 160/4.5 µg x 2 Actuations Twice Daily to Budesonide HFA pMDI 160 µg x 2 Actuations Twice Daily in Adult and Adolescent (≥12 years) African-American Subjects with Asthma

Study dates: First patient enrolled: 8 February 2007
Last patient completed: 30 November 2009

Phase of development: Phase IIIB

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

Study centers

The study was conducted in 172 sites in the Unites States

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	
To assess the long-term safety profile of SYMBICORT pressurized metered-dose inhaler (pMDI) 160/4.5 µg x 2 actuations twice a day (BID) compared to that of budesonide hydrofluoroalkane (HFA) pMDI 160 µg x 2 actuations BID, in African-American (self-reported) patients with moderate to severe asthma, over a 52-week treatment period.	The safety variables for this objective included asthma exacerbations, adverse events (AEs), laboratory parameters, electrocardiograms (ECGs), 24-hour Holter monitor assessments, physical exams, and vital signs over the 52-week treatment period. The objective was met by comparing the 2 treatment groups for the variables listed above.
Secondary	
To assess Patient Reported Outcomes (PROs) and resource utilization data for patients treated with SYMBICORT pMDI 160/4.5 µg x 2 actuations BID compared to that of budesonide HFA pMDI 160 µg x 2 actuations BID, over a 52-week treatment period.	The variables for this objective included the number and percentage of symptom-free days, the number and percentage of rescue medication-free days, the number and percentage of asthma-control days over the randomized treatment period, the number and percentage of days missed from work/school due to asthma over the randomized treatment period, the number and percentage of days of interrupted activities due to asthma, the number of inhalations and number of days on which adjunctive medications (other than rescue) were required due to worsening asthma, the number and total duration of hospitalizations for asthma, the number of emergency room visits for asthma, the number of urgent care center visits for asthma, the number of unscheduled physician visits for asthma, and the number of unscheduled phone calls to physicians for asthma. The objective was met by comparing the 2 treatment groups for the variables above.
To assess patient satisfaction, using the Asthma Treatment Satisfaction Measure (ATSM) and patient perception of onset of effect using the Onset of Effect Questionnaire (OEQ).	Responses to the ATSM instrument and OEQ. The objective was met by comparing the 2 treatment groups for the variables listed above.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
To assess pre-dose forced expiratory volume in 1 second (FEV_1) and morning Peak expiratory flow (AM PEF).	Variables for this objective include changes from pre-dose FEV_1 at Baseline (defined as the last available measurement prior to the first dose of study medication) to the randomized treatment period (to each visit, to the average over all visits, and to last observation carried forward [LOCF]) and the change from baseline (average of all days before randomization) to the average over the randomized treatment period in AM PEF. The objective was met by comparing the 2 treatment groups for the variables listed above.
Collection of a blood sample for use in future retrospective pharmacogenetic analyses.	

Study design

This was a 52-week, randomized, double-blind, parallel-group, multi-center, Phase IIIB study comparing the 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) African-American (self-reported) patients with moderate to severe asthma who required medium to high dose inhaled corticosteroids (ICS) therapy.

Target patient population and sample size

Approximately 720 male and female African-American patients ≥12 years of age with a documented clinical diagnosis of moderate-to-severe asthma for at least 6 months prior to Visit 2 and were in stable condition were targeted for the study. Patients were to have received maintenance asthma treatment with a stable daily dose of ICS (in medium dose range) for at least 30 days prior to Visit 2. Patients were also required to have a pre-bronchodilator FEV_1 of ≥50% of predicted normal. Patients had to have a documented history, within one year of Visit 2, of reversibility of FEV_1 of ≥12% and ≥0.20 liters (L) from baseline or demonstrated reversibility of FEV_1 of ≥12% and ≥0.20 L following a standard dose of albuterol prior to receiving run-in medication.

According to International Conference on Harmonisation guidelines, the safety evaluation of a chronic treatment requires at least 300 patients to be treated for 6 months and 100 patients for 12 months. A sample size of 360 patients per treatment arm accommodated a withdrawal rate of 17% by Month 6. In addition, as it is desirable to have approximately 200 patients with usable pharmacogenetic data complete 12 months of treatment in each treatment group, a 1:1 design facilitated meaningful pharmacogenetic analyses of data within this single study.

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

Dosage, mode of administration and batch numbers: Treatments were given in a double dummy fashion because of the difference in devices. During the run-in period, patients received budesonide HFA pMDI 160 µg x 2 actuations BID. Patients were then randomly assigned to 1 of the 2 following treatment groups: (1) SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg x 2 actuations BID. Batch numbers of SYMBICORT pMDI 160/4.5 µg were 2000102132, 2000107560, 2000107697, 2000107699, 2000109877, 2000114337, 2000115206, 2000115208, BN2000104795, BN2000107559, BN2000107562, WK70007.032, WK70007.033, and WK70007.037; (2) Budesonide HFA pMDI 160 µg x 2 actuations BID. Batch numbers of budesonide TBH were 2000102130, 2000102131, 2000107561, 2000107698, 2000107700, 2000109878, 2000112022, 2000114338, 2000115207, BN2000107563, WK7007.031, WK70007.034, and WK70007.038.

Duration of treatment

The study consisted of an initial screening visit, a 2-week single-blind run-in period, a 12-month randomized treatment period, and a follow-up telephone call 2 weeks after the last dose of study medication.

Statistical methods

No single variable was considered to be the primary variable. During the finalization of the Clinical Study Report, it was recognized that a primary outcome variable had to be identified for this study to be compliant with the reporting requirements for Clinicaltrials.gov. Therefore, it was decided by AstraZeneca, post-hoc, to designate asthma exacerbations as the primary outcome variable when reporting the study results to Clinicaltrials.gov. It should be emphasized that this designation is not specified in the Clinical Study Protocol, is not included in the Clinical Study Report itself, and in no way influences the interpretation of the study's results or the conclusions drawn from the study. No explicit hypotheses were being tested with this protocol. Given the high number of patients who deviated from the protocol for this study, the study statistics were generated with 2 analysis sets: 1) all patients in safety analysis set and 2) all patients meeting eligibility criteria. Patients who met the eligibility criteria specifically excluded patients in the safety analysis set who violated inclusion criterions 4, 5, 7, and 14. The data were summarized primarily with descriptive statistics. Two-sided p-values and 95% confidence intervals (CIs), unadjusted for multiplicity, were presented for several variables. However, these were considered descriptive in nature to aid in data interpretation and were not associated with any formal hypothesis testings or statistical inferences.

Changes from baseline in values of laboratory assessments, physical examinations, ECGs, and Holter monitoring were summarized with descriptive statistics and analysis of covariance (ANCOVA) techniques, using treatment as a fixed factor and baseline as a covariate. Summary statistics were reported by treatment group. Time to first exacerbation was compared between treatments with a log rank test. These data are displayed graphically using Kaplan-Meier survival curves. The numbers of exacerbations were compared between

treatments using a Poisson regression model. Changes from baseline in pre-dose FEV_1 were summarized using descriptive statistics and analyzed with an ANCOVA model using treatment as a fixed factor and baseline as a covariate. Variables derived from the electronic diary data (ie, symptom-free days, asthma-control days, interrupted-activity days, rescue medication use, and AM PEF) were summarized descriptively and were compared between treatments with the ANCOVA model described above. The ATSM was compared between treatments using an analysis of variance (ANOVA) model. No adjustments were made for baseline ATSM. The patient perception of onset of effect data collected in the electronic diary was transformed to binary variables. For the binary scale, treatments were compared using Fisher's exact test. For the original scale, treatments were compared using a Cochran-Mantel-Haenszel test on modified ridit scores. For AEs with the preferred term occurring in ≥3% of patients in any treatment group, treatment comparisons among each pair of treatments were made using odds ratios, 95% CIs for the odds ratio, and p-values using a Fisher's Exact test in the cumulative incidence of AEs. Here, the p-value was meant to serve as a "flagging device" for events that required additional investigation and was not associated with a decision rule regarding statistical significance.

Subject population

A total of 1643 patients were screened for possible study participation from 121 sites in the United States. Of these 1643 patients, 899 subsequently entered the run-in period and received at least 1 dose of budesonide. Overall, the screen failure rate was 54.8% (901 patients). The most common reason patients were not randomized to the study was incorrect enrollment or eligibility criteria not fulfilled (741 [82.2%] patients). A total of 157 (9.6%) patients received run-in medication, but were not randomized. At Visit 3, a total of 742 patients were randomized to 1 of 2 treatment groups (377 patients in the SYMBICORT pMDI treatment group and 365 patients in the budesonide treatment group). All randomized patients received at least 1 dose of the study medication, with the exception of 1 patient in the budesonide treatment group (patient E0035004). Among randomized patients, the overall discontinuation rate was 39.5% (149 patients) in the SYMBICORT pMDI treatment group and 34.2% (125 patients) in the budesonide treatment group.

Table S2 Demographic and key characteristics (all randomized patients)

	Treatment group[a]	
Demographic or baseline characteristic	**SYM 160/4.5 x 2 BID (N=377)**	**BUD 160 x 2 BID (N=365)**
Demographic characteristics		
Sex (n and % of patients)		
Male	128 (34.0)	133 (36.4)
Female	249 (66.0)	232 (63.6)
Age (years)		
Mean (SD)	36.19 (15.67)	38.35 (15.22)
Median	37.00	41.00

Table S2 Demographic and key characteristics (all randomized patients)

Demographic or baseline characteristic	Treatment group[a] SYM 160/4.5 x 2 BID (N=377)	BUD 160 x 2 BID (N=365)
Range	12 to 82	12 to 82
Age group (n and % of patients)		
12 to <16	48 (12.7)	42 (11.5)
16 to <65	318 (84.4)	310 (84.9)
≥65	11 (2.9)	13 (3.6)
Key characteristics		
Years since asthma diagnosis		
Mean (SD)	17.93 (13.79)	19.27 (15.51)
Median	13.77	14.51
Range	0.51 to 61.37	0.48 to 62.96
Total daily ICS dose at entry (mcg)		
N	370	358
Mean (SD)	512.29 (237.62)	543.62 (260.59)
Median	440.00	440.00
Range	80 to 2000	160 to 2000

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; BUD 160 x 2 BID: budesonide HFA pMDI 160/4.5 µg x 2 actuations BID.
Abbreviations: ICS: inhaled corticosteroids; N, n: number; SD: standard deviation.

Summary of efficacy results

There were no efficacy objectives in this safety study. Treatment comparisons for key secondary efficacy variables are presented in the following tables.

Table S3 ANCOVA summary of treatment comparisons for rescue-free days, symptom-free days, and asthma-control days (safety analysis set)

Domain Time point Comparison[a]	ANCOVA LS Mean (SE)	95% CI	P-value
Percentage of rescue-free days			
Treatment period average			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	5.26 (1.79)	1.75, 8.77	0.003
Percentage of symptom-free days			
Treatment period average			

Table S3 ANCOVA summary of treatment comparisons for rescue-free days, symptom-free days, and asthma-control days (safety analysis set)

Domain Time point Comparison[a]	ANCOVA		
	LS Mean (SE)	95% CI	P-value
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	1.88 (1.39)	-0.86, 4.61	0.178
Percentage of asthma-control days			
Treatment period average			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	5.06 (1.84)	1.45, 8.68	0.006

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

Factors in the Analysis of Covariance model include: treatment and baseline value.

Note: Baseline is defined as the mean of the run-in period values; Treatment period average is defined as the mean of the double-blind period values.

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; LS: least squares; SE: standard error.

Data derived from Table 11.2.3.2.3, Section 11.2.

Table S4 Onset of Effect Questionnaire at the end of Week 1: number (%) of patients and treatment group comparisons (age ≥ 18) (safety analysis set)

Parameter	Treatment[a]	N	Positive response[b]	P-value[c]
Response to Item 2 of the OEQ: "During the past week, you could feel your study medication begin to work right away."	SYM 160/4.5 x 2 BID	377	172 (74.8)	
	BUD 160 x 2 BID	364	158 (65.6)	
	SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID			0.034
Response to Item 5 of the OEQ: "During the past week, you were satisfied with how quickly you felt your study medication begin to work."	SYM 160/4.5 x 2 BID	377	165 (71.7)	
	BUD 160 x 2 BID	364	157 (65.1)	
	SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID			0.137

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

[b] Positive response: strongly agree and somewhat agree.

[c] P-value is from Fisher's exact test.

Note: Only patients who were ≥18 years of age took the questionnaire. The denominator of the percentage was the patients who took the questionnaire at each time point.

Abbreviations: N, n: number; OEQ: Onset of Effect Questionnaire; vs: versus.

Data derived from Table 11.2.3.4.2, Section 11.2.

Table S5 Onset of Effect Questionnaire at the end of Week 12: number (%) of patients and treatment group comparisons (age ≥ 18) (safety analysis set)

Parameter	Treatment[a]	N	Positive response[b]	P-value[c]
Response to Item 2 of the OEQ: "During the past week, you could feel your study medication begin to work right away."	SYM 160/4.5 x 2 BID	377	135 (73.4)	
	BUD 160 x 2 BID	364	135 (68.5)	
	SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID			0.312
Response to Item 5 of the OEQ: "During the past week, you were satisfied with how quickly you felt your study medication begin to work."	SYM 160/4.5 x 2 BID	377	145 (78.8)	
	BUD 160 x 2 BID	364	140 (71.1)	
	SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID			0.098

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; BUD 160 x 2 BID: budesonide HFA pMDI 160/4.5 µg x 2 actuations BID.
[b] Positive response: strongly agree and somewhat agree.
[c] P-value is from Fisher's exact test.
Note: Only patients who were ≥18 years of age took the questionnaire. The denominator of the percentage was the patients who took the questionnaire at each time point.
Abbreviations: N: number; OEQ: Onset of Effect Questionnaire; vs: versus.
Data derived from Table 11.2.3.4.2, Section 11.2.

Table S6 ANCOVA summary of treatment comparisons for AM PEF (L/min) (safety analysis set)

Time point Comparison[a]	ANCOVA		
	LS Mean (SE)	95% CI	P-value
Treatment period average			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	10.40 (4.18)	2.19, 18.61	0.013

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; BUD 160 x 2 BID: budesonide HFA pMDI 160/4.5 µg x 2 actuations BID.
Factors in the Analysis of Covariance model include: treatment and baseline value.
Note: Baseline is defined as the mean of the run-in period values; Treatment period average is defined as the mean of the double-blind period values.
Abbreviations: ANCOVA: analysis of covariance; AM PEF: morning peak expiratory flow; CI: confidence interval; N, n: number; SE: standard error.
Data derived from Table 11.2.3.1.3, Section 11.2.

Table S7 ANCOVA summary of treatment comparisons for pre-dose FEV_1 (L) (safety analysis set)

Time point Comparison[a]	ANCOVA		
	LS Mean (SE)	95% CI	P-value
Treatment period average			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	0.09 (0.02)	0.05, 0.13	<0.001

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; BUD 160 x 2 BID: budesonide HFA pMDI 160/4.5 µg x 2 actuations BID.
Factors in the ANCOVA model include: treatment, and baseline value.
Note: Treatment period average is defined as the mean of all available valid values after randomization.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; LS: least squares; N: number; SE: standard error.
Data derived from Table 11.2.1.2.2, Section 11.2.

Summary of safety results

A lower percentage of patients in the SYMBICORT pMDI treatment group experienced an asthma exacerbation compared to patients in the budesonide treatment group. Patients in the SYMBICORT pMDI treatment group also had fewer asthma exacerbations per-patient treatment year and a longer time to first exacerbation than patients in the budesonide treatment group.

Table S8 Asthma exacerbations: treatment comparisons (safety analysis set)

Comparison[a]	Estimate[b]	95% CI	P-value
Number of patients with at least 1 asthma exacerbation[c]			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	0.511	0.316, 0.827	0.006
Estimated number of asthma exacerbations per patient-treatment year[d]			
SYM 160/4.5 x 2 BID vs BUD 160 x 2 BID	0.615	0.448, 0.843	0.002

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; BUD 160 x 2 BID: budesonide HFA pMDI 160/4.5 µg x 2 actuations BID.
[b] Comparison of SYMBICORT pMDI to budesonide
[c] P-values are from chi-square test.
[d] Statistics are based on Poisson regression adjusted for differential treatment exposure by using person years as an offset variable.
Abbreviations: CI: confidence interval; N: number.

In addition, patients in the SYMBICORT pMDI treatment group had fewer asthma exacerbations that required oral steroid use, systemic steroid use, or resulted in

hospitalizations or emergency room or urgent care visits for their asthma compared to patients in the budesonide treatment group.

The number of patients with at least 1 AE during the randomized treatment period was similar between the 2 treatment groups, and the majority of the AEs were mild or moderate in intensity. For severe AEs, no notable trends in terms of individual AEs or differences between the 2 treatment groups were identified. The number of patients experiencing an AE during the randomized treatment period that was considered to be drug-related by the investigator was similar between the 2 treatment groups. The number of patients experiencing serious adverse events (SAEs) during the randomized treatment period was low and similar between the 2 treatment groups. One patient in each treatment group experienced an SAE that led to death. There were no drug-related SAEs reported in either treatment group. The number of patients experiencing an AE that lead to study discontinuation was low and similar between the 2 treatment groups.

Table S9 Overview of AEs with onset during the randomized treatment period (safety analysis set)

	SYM 160/4.5 x 2 BID (N= 377)	**BUD 160 x 2 BID (N= 364)**
Mean (SD) duration of exposure (days)	266.21 (134.95)	287.14 (123.24)
Category	**Number (%) of patients who had an AE in each category[a]**	
Any adverse event (AE)	193 (51.2)	174 (47.8)
Any drug-related AE	10 (2.7)	7 (1.9)
Serious Adverse events (SAEs)	12 (3.2)	15 (4.1)
SAEs leading to death	1 (0.3)	1 (0.3)
SAEs not leading to death	11 (2.9)	14 (3.8)
SAEs leading to discontinuation	3 (0.8)	3 (0.8)
AEs leading to discontinuation (DAEs)	10 (2.7)	8 (2.2)
Other significant adverse events (OAEs)	0 (0.0)	0 (0.0)
	Total number of AEs	
AEs	681	663
SAEs	15	16
DAEs	11	9
OAEs	0	0

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

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

Abbreviations: AE: adverse event; DAE: adverse event leading to discontinuation; N: number; OAE: other significant adverse event; SAE: serious adverse event; SD: standard deviation.

Table S10 System organ class (SOC) categories with at least 1 AE reported during the randomized treatment period (safety analysis set)

	Treatment group[a]	
	SYM 160/4.5 x 2 BID (N= 319)	**BUD 160 x 2 BID (N= 299)**
Mean (SD) duration of exposure (days)	266.21 (134.95)	287.14 (123.24)
	n (%) of patients	
Number of patients with any AE[b]	**193 (51.2)**	**174 (47.8)**
Infections and infestations	116 (30.8)	112 (30.8)
Respiratory, thoracic, and mediastinal disorders	55 (14.6)	64 (17.6)
Musculoskeletal and connective tissue disorders	45 (11.9)	35 (9.6)
Nervous system disorders	44 (11.7)	33 (9.1)
Gastrointestinal disorders	36 (9.5)	36 (9.9)
Injury, poisoning, and procedural complications	22 (5.8)	23 (6.3)
General disorders and administrative site conditions	13 (3.4)	19 (5.2)
Investigations	15 (4.0)	13 (3.6)
Reproductive system and breast disorders	16 (4.2)	7 (1.9)
Skin and subcutaneous tissue disorders	9 (2.4)	12 (3.3)
Psychiatric disorders	9 (2.4)	8 (2.2)
Vascular disorders	8 (2.1)	9 (2.5)
Eye disorders	3 (0.8)	10 (2.7)
Immune system disorders	8 (2.1)	5 (1.4)
Blood and lymphatic system disorders	6 (1.6)	4 (1.1)
Cardiac disorders	6 (1.6)	4 (1.1)
Metabolism and nutrition disorders	1 (0.3)	7 (1.9)
Renal and urinary disorders	5 (1.3)	2 (0.5)
Ear and labyrinth disorders	2 (0.5)	4 (1.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4 (1.1)	2 (0.5)
Endocrine disorders	1 (0.3)	3 (0.8)
Hepatobiliary disorders	0 (0.0)	1 (0.3)
Social circumstances	1 (0.3)	0 (0.0)

[a] SYM 160/4.5 x 2 BID: SYMBICORT pMDI 160/4.5 µg x 2 BID; BUD 160 x 2 BID: Budesonide HFA pMDI 160 µg x 2 BID.
[b] Based on MedDRA Version 12.0; sorted by decreasing order of frequency in the total population.
Note: Patients with multiple events in the same category are counted only once in that category.

Abbreviations: AE: adverse event; BID: twice daily; N, n: number; SOC: system organ class.

No clinically important findings in hematology, clinical chemistry, vital signs, or physical examination findings were noted between patients in the 2 treatment groups. Differences between the SYMBICORT pMDI and budesonide treatment groups were observed for some ECG and Holter parameters; however these were small and similar between the 2 treatment groups and are consistent with the known profile of beta-agonists.

Date of report

15 November 2010