AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D589BL00003
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A 12-week, randomized, double-blind, double-dummy, multi-center, phase IV study comparing the efficacy and safety of SYMBICORT® pMDI 160/4.5 µg × 2 actuations twice daily versus budesonide inhalation powder DPI 180 µg × 2 inhalations twice daily, in adult and adolescent (≥12 years) African American subjects with asthma

Study dates: First subject enrolled: 5 June 2008
Last subject last visit: 10 September 2009

Phase of development: Therapeutic use (IV)

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

Study center(s)

The study was conducted in 46 centers in the United States (US).

Publications

None, at the time of writing this report.

Objectives and criteria for evaluation

Objectives and criteria for evaluation are outlined in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the efficacy of SYMBICORT® pressurized metered dose inhaler (pMDI) to that of budesonide dry powder inhaler (DPI) in African American (self-reported) subjects with inhaled corticosteroid (ICS)-dependent asthma	Pre-dose FEV_1	Efficacy
Secondary	**Secondary**	
To compare the morning effects on lung function of SYMBICORT pMDI compared to budesonide DPI in African American subjects with ICS-dependent asthma	AM PEF	Efficacy
To compare the evening effects on lung function of SYMBICORT pMDI compared to budesonide DPI in African American subjects with ICS-dependent asthma	PM PEF	Efficacy
To compare the effects on lung function spirometry measures of SYMBICORT pMDI compared to budesonide DPI in African American subjects with ICS-dependent asthma	FVC	Efficacy
To compare the effects on lung function spirometry measures of SYMBICORT pMDI compared to budesonide DPI in African American subjects with ICS-dependent asthma	$FEF_{25\%-75\%}$	Efficacy
To compare the time to first predefined asthma event in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Predefined asthma event	Efficacy

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare the time to withdrawal due to first predefined asthma event in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Withdrawal due to predefined asthma event	Efficacy
To rate nighttime and daytime asthma symptoms in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Asthma symptom score (nighttime and daytime)	Efficacy
To assess whether asthma caused nighttime awakenings, and whether subsequent albuterol use was required, in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Nighttime awakenings due to asthma	Efficacy
To compare rescue medication use for relief of asthma in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Rescue medication use	Efficacy
To compare rescue medication-free days for relief of asthma in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Rescue-free days	Efficacy
To compare asthma symptom-free days in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Symptom-free days	Efficacy
To compare asthma-free (symptom-free and rescue-free) days in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	Asthma-control days	Efficacy
To compare subject's perception of onset of medication effect in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	OEQ	Efficacy
To compare the emotional and functional impairment in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	AQLQ(S)	PRO

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare asthma control at the individual level in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	ACT	PRO
To compare the effect of asthma, its symptoms, and its treatment on social status, role functional status, and well being in African American subjects with ICS-dependent asthma treated with SYMBICORT pMDI or budesonide DPI	AIS	PRO
To evaluate the safety of SYMBICORT pMDI compared to budesonide DPI	AEs, vital signs, physical examination, ECG	Safety
To collect peripheral blood samples for future pharmacogenetic research to be conducted outside the scope of the CSR	Pharmacogenetic assessments and analysis	Pharmaco-genetic

AE = adverse event; AM = morning; AQLQ(S) = Asthma Quality of Life Questionnaire-Standardized; ACT = Asthma Control Test; AIS = Asthma Impact Survey; DPI = Dry Powder Inhaler; ECG = electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; OEQ = Onset of Effect Questionnaire; PEF = peak expiratory flow; PM = evening; pMDI = Pressurized Metered Dose Inhaler; PRO = patient reported outcome.

Study design

This was a 12-week, randomized, double-blind, double-dummy, Phase IV study comparing the efficacy and safety of SYMBICORT pressurized metered dose inhaler (pMDI) 160/4.5 µg × 2 actuations twice daily (BID) to budesonide inhalation powder dry powder inhaler (DPI) 180 µg × 2 inhalations BID in adult and adolescent (≥12 years) African American (self-reported) subjects with asthma who required a medium to high dose of inhaled corticosteroid (ICS) therapy. Randomization was stratified by asthma severity, based on the daily dosage of ICS at Screening (Visit 1).

Target subject population and sample size

African American (self-reported) subjects with asthma who required a medium to high dose of ICS therapy.

The primary efficacy variable for the determination of efficacy was the change from baseline (Visit 3) in pre-dose forced expiratory volume in 1 second (FEV_1) averaged over the treatment period. The sample size for this study was based on numerous studies conducted with combination ICS and long-acting beta 2 agonist (LABA) products. In order to detect a true difference in means between SYMBICORT pMDI and budesonide for the average treatment

period pre-dose FEV_1 of 0.15 L (estimated standard deviation of 0.40 L), a sample size of 151 subjects in each group was required for 90% power, assuming a test with a 0.05 two-sided significance level. A number of other scenarios were considered relative to the treatment difference and standard deviation and, based on these, 150 subjects randomized per treatment group was recommended. An important consideration was the requirement to have appropriate power for testing diary variables, such as rescue medication use, at the end of the treatment period. Variability for these variables tends to be higher at the end of the treatment period, especially when averaging values over a shorter period of time, 7 days, compared to the 84-day total treatment period. The sample size of 150 per treatment group was appropriate (power ~90%) for these important secondary variables based on results from previous studies. A total of 301 patients (153 SYMBICORT pMDI; 148 budesonide) were included in the efficacy full analysis set (FAS).

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

Patients were randomly assigned to 1 of the 2 following treatment groups. Treatments were given in a double-dummy fashion because of the difference in delivery devices.

SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg, 2 actuations administered BID, and placebo DPI, 2 actuations BID. Batch numbers of SYMBICORT pMDI were WK80047.003, WK80047.006, and WK80047.010.

Budesonide DPI 180 µg, 2 inhalations BID, and placebo pMDI, 2 inhalations BID. Batch numbers of budesonide DPI were WK80047.004, WK80047.007, and WK80047.13.

Run-in medication (budesonide DPI 90 µg × 2 inhalations) batch numbers were WK80047.002, WK80047.008, and WK80047.009.

All study medications (with the exception of commercially available albuterol rescue medication) were manufactured by AstraZeneca.

Duration of treatment

Study treatment was administered over a 12-week, randomized, double-blind, double-dummy, treatment period.

Statistical methods

The primary efficacy variable for the determination of efficacy was the change from baseline (Visit 3) in pre-dose FEV_1 averaged over the treatment period. FEV_1 was analyzed with an analysis of covariance (ANCOVA) model with terms for treatment and baseline ICS strata, using baseline FEV_1 as a covariate. Treatment comparisons were made within the context of this model. Standard diagnostic approaches were used to verify that the key statistical assumptions required by the model appeared to have been reasonably satisfied. Analyses were performed on the subject's change from baseline to their average value over the treatment period, as well as for the change to the end of treatment, which was secondary to the average over the treatment period. A qualitative assessment of the consistency of treatment

effects across centers was made. Randomization was stratified by asthma severity, based on the subject's daily dosage of ICS at Visit 1.

In order to deal with multiplicity issues, a step-down procedure was used. If the treatment difference for the primary variable was statistically significant ($p < 0.05$), then the secondary variables were tested in a predefined order at the 0.05 level of significance as long as the significance level was met. Once a p-value greater than 0.05 was observed, subsequent nominal p-values were calculated, but were viewed as descriptive in nature. The order of testing after the primary variable was: morning (AM) peak expiratory flow (PEF), evening (PM) PEF, total rescue medication use, total daily asthma symptom score and predefined asthma events. For all variables other then these, nominal p-values were reported.

Secondary diary variables included recordings of AM and PM PEF, rescue medication use (number of puffs of rescue medication), rescue-free days, nighttime awakenings due to asthma, nighttime and daytime asthma symptom scores (total daily asthma symptom score), symptom-free days, and asthma-control days. These individual diary variables were analyzed as continuous data, comparing mean changes from baseline to the average of the double-blind treatment period between treatments.

The time to the first predefined asthma event and time to withdrawal due to predefined asthma events was analyzed. Time to the first predefined asthma event and time to withdrawal was described using Kaplan-Meier plots. For these variables, the primary comparison between treatment groups was accomplished via a Wilcoxon log-rank test. Additional sensitivity analyses of these variables were performed using a stratified (by asthma severity) log-rank test. A supportive analysis comparing the number of patients with predefined asthma events between treatment groups, irrespective of the time of occurrence of events, was also conducted using the Cochran -Mantel-Haenszel Test adjusted for ICS dose.

Patient Reported Outcomes (PROs)

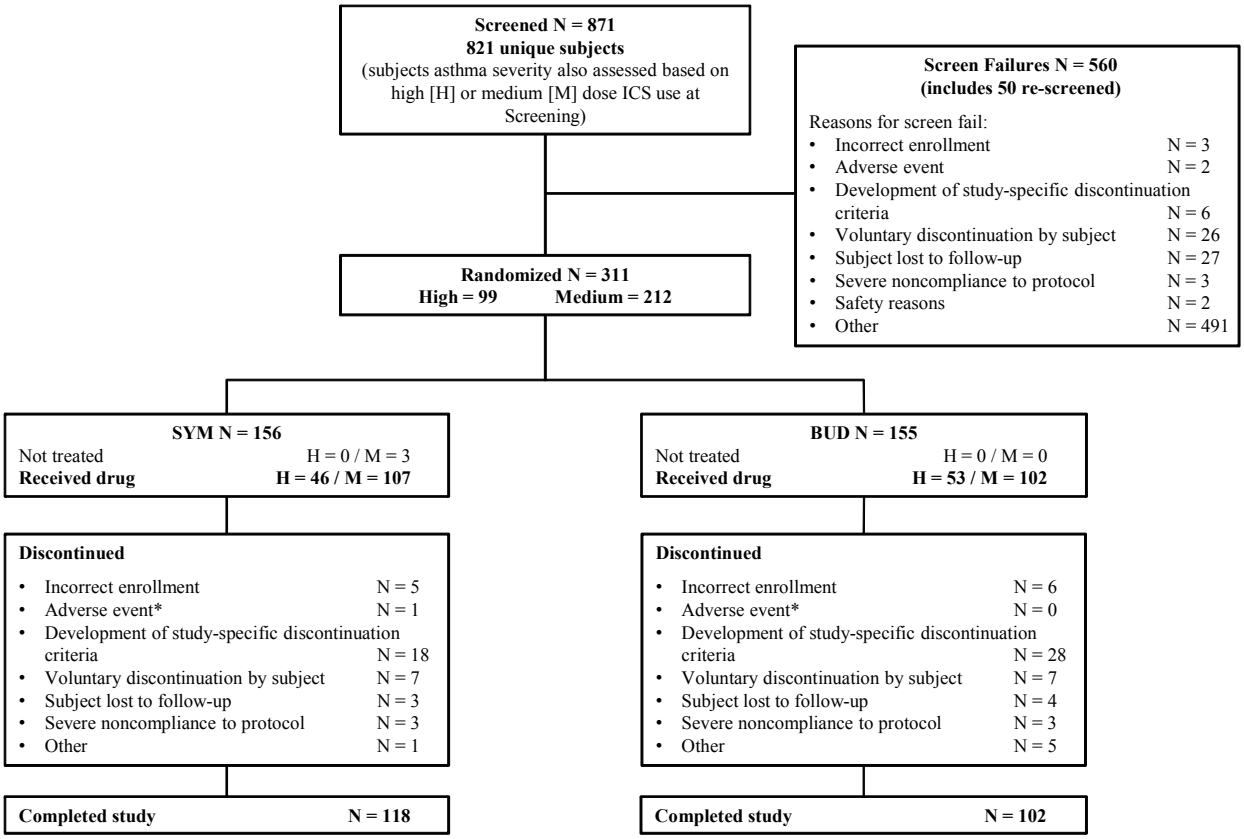
The Asthma Quality of Life Questionnaire Standardized (AQLQ[S]) was administered to subjects ≥17 years of age at Visits 3 and 6. Each of the 4 domain scores were summarized with descriptive statistics for each treatment group. The AQLQ(S) domains were analyzed at the end of treatment (Visit 6) using an ANCOVA model similar to the primary variables with the Visit 3 value as a covariate.

The Asthma Control Test (ACT) was analyzed by comparing the proportion of subjects whose asthma was controlled (score >19) at baseline to the proportion whose asthma was controlled at Visit 5 and at the end of treatment (Visit 6). A Mantel-Haenszel test was used. As a supplemental analysis, the change in the score from baseline was analyzed via an ANCOVA with the baseline score as the covariate.

The Asthma Impact Survey (AIS) was administered to subjects ≥17 years at the time of randomization and analyzed as the change in the score from baseline at Visits 5 and 6 (end of treatment), using an ANCOVA with the baseline score as the covariate.

Subject population

This study was conducted at 46 study centers in the US. Study disposition is presented below.



* Patients whose primary reason for study discontinuation was listed as an adverse event are included in this category. There was an additional 1 patient each in the SYMBICORT pMDI and budesonide groups who had an AE that contributed to but was not the primary reason for their discontinuation, and these 2 patients are thus accounted for in other reason for discontinued categories.

The treatment groups were well balanced in terms of demographic and baseline data.

Of the 301 patients included in the FAS, there was a slightly greater percentage of female than male patients (65.1% versus 34.9%, respectively), which is generally consistent with the disease prevalence among adults and adolescents. There was a slightly higher percentage of female patients in the SYMBICORT pMDI 160/4.5 × 2 BID treatment group than the budesonide DPI 180 × 2 BID treatment group, (71.2% versus 58.8%, respectively).

Patient ages within the FAS ranged from 12.0 to 79.0 years of age, with an overall mean of 39.2 years. The majority of patients (89.7%) were 16 to <65 years of age. Patients who were 12 to <16 years of age comprised 9.0% of the population. All patients were Black, and the majority (93.0%) were African American. At entry, 67.8% of patients received a medium ICS dose and 32.2% received a high ICS dose.

Years since asthma diagnosis ranged from 0.0 to 58.0 years, with an overall mean of 21.4 years. The distribution of patients by age, age category, race, ethnicity, and years since asthma diagnosis was similar between the SYMBICORT pMDI 160/4.5 × 2 BID and budesonide DPI 180 × 2 BID treatment groups. In the safety analysis set, mean (SD) weight was 92.6 (25.28) kg and mean (SD) height was 168.2 (9.30) cm. Mean body mass index (BMI) was 32.7 kg/m^2, which qualified the mean BMI in this population as obese.

Summary of efficacy results

Results of the primary efficacy variable, change from baseline in the pre-dose FEV_1 averaged over the randomized treatment period for the FAS, are presented in Table S2.

Table S2 Treatment means for pre-dose FEV_1 (FAS)

Time Point	Comparison	LS Mean (SE)	95% CI	P-value
Treatment average	SYM minus BUD	0.09 (0.03)	(0.02, 0.16)	0.008

BUD = Budesonide DPI 180 µg × 2 BID; CI = Confidence interval; FAS = Full analysis set; LS = Least squares; SE = Standard error; SYM = SYMBICORT pMDI 160/4.5 µg × 2 BID.

Results for the primary efficacy endpoint were as follows:

- The difference between treatment groups for the primary variable, the treatment period average FEV_1, was statistically significant (p = 0.008) in favor of SYMBICORT pMDI.
- Results of the sensitivity analysis according to the calculated ICS dose at study entry (ie, medium [p = 0.056] or high [p = 0.148]) and the per-protocol categories were generally consistent with the primary analysis.

For the secondary endpoints, results are summarized in Table S3.

Table S3 Secondary efficacy parameter summary

Variable	SYM minus BUD	P-value	95% CI
AM PEF (L/min)	22.90	<0.001[a]	(14.03, 31.76)
PM PEF (L/min)	19.27	<0.001[a]	(9.56, 28.97)
Average daily asthma symptom score	-0.10	0.039[a]	(-0.20, -0.01)
Rescue medication use (puffs/day)	-0.34	0.029[a]	(-0.65, -0.04)
FVC (L)	0.08	0.035[a]	(0.01, 0.15)
$FEF_{25\%-75\%}$ (L/sec)	0.09	0.135[a]	(-0.03, 0.20)
Predefined asthma event by ICS dose	0.73	0.189	(0.46, 1.17)
Withdrawals due to asthma events	0.58	0.097	(0.31, 1.11)
Nighttime asthma symptom score	-0.09	0.077[a]	(-0.19, 0.01)
Daytime asthma symptom score	-0.09	0.091[a]	(-0.19, 0.01)
Awakening free nights	2.16	0.181[a]	(-1.01, 5.33)
Nighttime rescue medication use (puffs/day)	-0.23	0.007[a]	(-0.39, -0.06)
Daytime rescue medication use (puffs/day)	-0.10	0.210[a]	(-0.26, 0.06)
Rescue-free days	6.78	0.054[a]	(-0.11, 13.68)
Symptom-free days	5.41	0.137[a]	(-1.74, 12.55)
Asthma-control days	5.65	0.110[a]	(-1.28, 12.59)
OEQ	--	NS	--
AQLQ(S)	0.14	0.268[b]	(-0.11, 0.38)
ACT	1.03	0.913[b]	(0.64, 1.64)
AIS	-0.43	0.676[b]	(-2.46, 1.60)

[a] = treatment average; [b] = end of treatment
ACT = Asthma control test; AIS = Asthma impact survey; AQLQ(S) = Asthma quality of life questionnaire standardized; FEF = forced expiratory flow; FEV = forced expiratory volume; ICS = Inhaled corticosteroid; L = Liters; min = minutes; NS = not significant; OEQ = Onset of effect questionnaire; sec = seconds.

Secondary efficacy parameters which reached statistical significance between treatment groups in favor of SYMBICORT pMDI were AM and PM PEF, total asthma symptom score, rescue medication use, pre-dose FVC, and nighttime rescue medication use.

For morning PEF, there was a difference in mean change from baseline to the entire treatment period of 22.90 L/min in favor of SYMBICORT and this difference was statistically significant ($p < 0.001$). For evening PEF, there was a difference in mean change from baseline to the entire treatment period of 19.27 L/min in favor of SYMBICORT and this difference was statistically significant ($p < 0.001$). The treatment group difference for the average of the last 7 days indicates that the effect was maintained through the 12 weeks of treatment.

For forced vital capacity (FVC), a difference in mean change from baseline favoring SYMBICORT pMDI was observed at all measured timepoints. This difference was statistically significant when comparing the change from baseline averaged over the treatment period.

For predefined asthma events for all patients, there were fewer asthma events in the SYMBICORT pMDI treatment group compared with the budesonide treatment group. Case Report Form (CRF), Diary, Spirometry (CDS)-defined events were similar. The percentage of patients who withdrew due to a pre-defined asthma event was lower in the SYMBICORT pMDI treatment group (11.8%) than in the budesonide treatment group (18.9%), but the difference was not statistically significant.

For total, nighttime and daytime asthma symptom scores and for the average daily score for the treatment average, there was a statistically significant difference in favor of SYMBICORT pMDI.

For total and nighttime rescue medication use, there was a statistically significantly greater reduction from baseline in total rescue medication use in favor of SYMBICORT pMDI. The direction of differences for changes from baseline in daytime rescue medication use and rescue-free days were in favor of SYMBICORT pMDI, but were not statistically significant. For symptom-free days and nighttime awakenings due to asthma averaged over the treatment period, the direction of differences favored SYMBICORT pMDI, but were not statistically significant.

The increase from baseline in the percentage of asthma-control days averaged over the treatment period was not statistically significant. However, there was a significantly greater increase from baseline with SYMBICORT pMDI compared with budesonide at the last 7 days average.

For the Onset of Effect Questionnaire (OEQ) for both patients aged ≥12 years and ≥18 years, patients in both treatment groups reported a high percentage of patients who could feel that their study medication was working right away and that they were satisfied with how quickly their study medication worked. A slightly higher percentage of patients in the SYMBICORT pMDI 160/4.5 group treatment group than in the budesonide treatment group reported that they could feel that their medication was working right away and that they were satisfied with how quickly the medication began to work. This difference in favor of SYMBICORT pMDI was not statistically significant. For the AQLQ(S), SYMBICORT pMDI achieved the MID (0.5 units) in overall score, but budesonide did not. The small differences in mean change from baseline in favor of SYMBICORT pMDI compared with budesonide for the overall score and the individual domain scores on the AQLQ(S) were not statistically significant.

For the ACT at baseline, the SYMBICORT pMDI treatment group contained significantly more patients who reported that their asthma was not controlled compared with the budesonide treatment group. At the last week of treatment, the SYMBICORT pMDI treatment group had 52.4% of patients who reported that their asthma was controlled

compared with 51.8% in the budesonide treatment group. The direction of difference in favor of SYMBICORT pMDI was not statistically significant.

For the AIS across both treatment groups, there was no difference in changes recorded in the AIS.

Summary of pharmacogenetic results

Peripheral blood samples were collected for future pharmacogenetic research to be conducted outside the scope of the Clinical Study Report (CSR).

Summary of safety results

Mean treatment exposure during double-blind treatment was 10 weeks with a median of 83 days (slightly longer for SYMBICORT pMDI). A total of 70.5% of patients had at least 10 weeks of treatment.

The overall percentage of patients with at least 1 adverse event (AE) during double-blind treatment was 30.3% in the budesonide treatment group and 41.2% in the SYMBICORT pMDI treatment group. The majority of AEs were mild or moderate in intensity. There were no deaths or other [significant] AEs (OAEs) during the double-blind treatment period.

Three patients in the safety analysis set experienced serious adverse events (SAEs) during the double-blind treatment period; 2 in the budesonide treatment group (events of pyrexia and asthma exacerbation) and 1 patient in the SYMBICORT pMDI treatment group (event of ruptured ovarian cyst). No patient discontinued from treatment due to an SAE. No SAEs were considered study medication related. An overview of AEs is presented in Table S4.

The most commonly reported AEs (occurring at an incidence of ≥3% in any randomized treatment group) are summarized by preferred term in Table S5. The overall percentage of patients reporting AEs during the randomized treatment period was generally low and similar between the 2 treatment groups.

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

	Number (%) of subjects with an AE[a]	
	SYM N = 153	**BUD N = 155**
Category of adverse event	**n (%)**	**n (%)**
Number of AEs	129	78
Subjects with at least 1 AE	63 (41.2)	47 (30.3)
Number of SAEs	1	2
Subjects with at least 1 SAE	1 (0.7)	2 (1.3)
Subjects with SAE leading to death	0	0
Subjects with SAEs not leading to death	1 (0.7)	2 (1.3)
Subjects with SAEs leading to discontinuation	0	0
Number of AEs leading to discontinuation	2	1
Subjects with at least 1 AE leading to discontinuation	2 (1.3)	1 (0.6)
Number of study drug-related AEs	2	1
Subjects with at least 1 study drug-related AE	2 (1.3)	1 (0.6)
Subjects with study drug-related SAE	0	0
Subjects with study drug-related AE leading to discontinuation	0	0
Number of OAEs	0	0
Number of subjects with OAEs	0	0

[a] Subjects with multiple events in the same category are counted only once in that category.

AE = Adverse event; BUD = Budesonide DPI 180 µg × 2 BID; N = Number of patients in treatment group; n = Number of patients; OAE = Other significant AE; SAE = Serious adverse event; SYM = SYMBICORT pMDI 160/4.5 µg × 2 BID.

Table S5 Number (%) of subjects with at least 3% incidence of adverse events during the randomized treatment period (safety analysis set)

Preferred Term	SYM N = 153	BUD N = 155	Total N = 308
Adverse event	**n (%)**	**n (%)**	**n (%)**
Headache	10 (6.5)	8 (5.2)	18 (5.8)
Nasopharyngitis	8 (5.2)	4 (2.6)	12 (3.9)
Upper respiratory tract infection	4 (2.6)	6 (3.9)	10 (3.2)

Note: This table uses a cut-off of ≥3% based on the AE incidence in any treatment group.
BUD = Budesonide DPI 180 µg × 2 BID; N = Number of subjects; SYM = SYMBICORT pMDI 160/4.5 µg × 2 BID.

The overall percentage of patients with drug-related AEs as judged by the investigator during treatment was low (1.0%) and slightly higher in the SYMBICORT pMDI treatment group (1.3%) compared to the budesonide treatment group (0.6%). There were no drug-related SAEs or drug-related AEs that lead to discontinuation during the study.

There were statistically significant increases in mean changes from baseline to the end of treatment in sitting SBP for patients receiving SYMBICORT pMDI, which reflected a small increase in SBP in the SYMBICORT pMDI arm versus a small decrement in SBP in the budesonide arm. At the end of treatment, there were few shifts from normal to high overall. During the treatment period, a greater number of SYMBICORT pMDI patients than budesonide patients had clinically important abnormalities in SBP and DBP, but shifts to high values were infrequent, and the majority of patients exhibiting shifts in both arms had a previous history of hypertension. The overall incidence of AEs of hypertension was low in both SYMBICORT pMDI and budesonide treatment groups (2 and 1 patient, respectively). There were no other significant changes observed in clinical laboratory findings.

Overall, SYMBICORT pMDI was well-tolerated for use in the treatment of asthma in adult and adolescent African American patients, with an AE profile similar to budesonide. SYMBICORT pMDI demonstrated few clinically significant physical examination or vital sign findings.