

Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: A randomized controlled trial

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Background: Information surrounding the long-term safety of combination inhaled corticosteroid/long-acting β_2 -adrenergic agonist medications in African American asthmatic patients is limited.

Objective: We sought to assess safety and asthma control with a budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide over 1 year in African American patients.

Methods: This 52-week, randomized, double-blind, parallel-group, multicenter, phase 3B safety study (NCT00419952) was conducted in 742 self-reported African American patients 12 years or older with moderate-to-severe asthma previously receiving medium- to high-dose inhaled corticosteroids. After 2 weeks using a 320 μ g twice-daily budesonide pMDI, patients were randomized 1:1 to 320/9 μ g twice-daily budesonide/formoterol pMDI or 320 μ g twice-daily budesonide pMDI.

Results: Both treatments were well tolerated. Asthma exacerbation incidence and rate (per patient-treatment year) were lower with budesonide/formoterol versus budesonide (incidence, 7.7% vs 14.0% [$P = .006$]; rate ratio, 0.615 [$P = .002$]). Time to first asthma exacerbation was longer ($P = .018$) with budesonide/formoterol versus budesonide. The most common adverse events, regardless of study drug relationship, were headache (9.5% and 7.7%), nasopharyngitis (6.9% and 8.0%), sinusitis (4.0% and 6.3%), and viral upper respiratory tract infection (5.8% and 4.4%) for budesonide/formoterol and budesonide, respectively. Serious adverse events occurred in 12 and 15 patients, respectively; none were considered drug related. No substantial or unexpected patterns of abnormalities were observed in laboratory, electrocardiographic, or Holter monitoring assessments. Hospitalization caused by asthma

exacerbation occurred in 0 and 4 patients in the budesonide/formoterol and budesonide groups, respectively. Pulmonary function and asthma control measures generally favored budesonide/formoterol.

Conclusions: In this population budesonide/formoterol pMDI was well tolerated over 12 months, with a safety profile similar to that of budesonide; the asthma exacerbation rate was reduced by 38.5% versus budesonide. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Budesonide, formoterol, asthma, randomized controlled trial, safety, African American

The prevalence¹ and burden^{2,3} of asthma in the United States is greater in black versus white patients; however, it is unclear whether the response to asthma medications differs between these populations.⁴⁻⁸ The Salmeterol Multicenter Asthma Research Trial suggested that African American patients receiving the long-acting β_2 -adrenergic agonist (LABA) salmeterol had a significantly increased risk of combined respiratory-related death or life-threatening events.⁶ Whether patients were taking inhaled corticosteroids (ICSs) concomitantly during that study is unclear, but baseline ICS use was reported by a smaller percentage of African American (38%) versus white (49%) patients.⁶ A 1-year efficacy study in an African American population showed neither an increased risk nor a significantly decreased risk of asthma exacerbations with the ICS/LABA combination of fluticasone/salmeterol versus fluticasone alone.⁷ More recently, a retrospective analysis of pooled data from 10 Asthma Clinical Research Network trials showed a 2-fold increased risk of treatment failure (driven primarily by increased rescue medication use) in African American ($n = 233$) versus white ($n = 795$) patients receiving LABA therapy, regardless of concomitant asthma therapy.⁸ These findings suggest a need for additional prospective studies evaluating the safety and efficacy of ICS/LABA therapy in African Americans.⁹

The short-term efficacy and safety of the ICS/LABA budesonide/formoterol administered through a pressurized metered-dose inhaler (pMDI) have been shown relative to budesonide in a 12-week efficacy study in an African American asthmatic population.¹⁰ The present study is the first to assess the long-term safety profile of the ICS/LABA budesonide/formoterol pMDI versus budesonide pMDI over 1 year in African American patients with moderate-to-severe asthma, contributing valuable information regarding the safety of this treatment in a population

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Abbreviations used

AE: Adverse event
 ATSM: Asthma Treatment Satisfaction Measure
 ECG: Electrocardiogram
 ICS: Inhaled corticosteroid
 LABA: Long-acting β_2 -adrenergic agonist
 pMDI: Pressurized metered-dose inhaler
 SAE: Serious adverse event

with high morbidity that is generally underrepresented and understudied in asthma clinical trials.

METHODS**Study design and patients**

This randomized, double-blind, parallel-group, multicenter, 52-week, phase 3B study (NCT00419952) was conducted from February 8, 2007, to November 30, 2009. Eligible patients were aged 12 years or older, self-reported race as African American (same for both parents), had stable asthma for 6 or more months (American Thoracic Society definition¹¹), had a prebronchodilator FEV₁ of 50% or greater of predicted normal value at screening and randomization, demonstrated reversibility of FEV₁ of 12% or greater and 0.20 L or greater, and had consistent treatment with daily medium- to high-dose ICSs (with or without LABAs) for 30 days or more before screening. See the Methods section in this article's Online Repository at www.jacionline.org for ICS dose ranges (see Table E1) and additional details.

Patients discontinued asthma therapy and entered a 2-week, single-blind, run-in period of budesonide pMDI, 160 $\mu\text{g} \times 2$ inhalations (320 μg) twice daily. Eligible patients were randomized 1:1 to receive twice-daily budesonide/formoterol pMDI, 160/4.5 $\mu\text{g} \times 2$ inhalations (320/9 μg), or budesonide pMDI, 160 $\mu\text{g} \times 2$ inhalations (320 μg). Albuterol pMDI, 90 $\mu\text{g} \times 2$ inhalations, was permitted for as-needed use during the run-in and randomization periods. See the Methods section in this article's Online Repository for randomization details, allocation concealment procedures, and allowed and disallowed medications.

The study was performed in accordance with ethical principles based on the Declaration of Helsinki and consistent with the International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. The final study protocol was approved in writing by the institutional review board or independent ethics committee at each study center. Written informed consent was obtained from patients before any study procedures were initiated.

Assessments

Asthma exacerbations were defined as requirement of oral/parenteral corticosteroids and/or emergency department visit and/or urgent care visit and/or hospitalization for asthma. Patients who experienced more than 2 exacerbations within 3 months or more than 5 exacerbations within 1 year during randomized treatment were discontinued from the study.

Adverse events (AEs) were recorded in electronic diaries and assessed by investigators for a causal relationship to the study medication. Serious adverse events (SAEs) were those that were immediately life-threatening or resulted in hospitalization or prolongation of existing hospitalization, significant disability, or death.

Designed as a safety study, no single efficacy variable was considered primary. Spirometric variables, including predose FEV₁ and forced vital capacity, were performed according to American Thoracic Society guidelines¹² (at screening; randomization; days 14 and 45; and months 3, 6, 9, and 12) at least 6 hours after albuterol use and approximately 12 hours after study medication use. Daily diary-based measures of asthma control included morning peak expiratory flow (in liters per minute), rescue medication use (administered through an inhaler or nebulizer), rescue medication-free days,

symptom-free days, and asthma control days (no asthma symptoms or rescue medication use).

Statistical analysis

Descriptions of the study population and population size are shown in the Methods section in this article's Online Repository. The percentage of patients with 1 or more asthma exacerbations and the number of asthma exacerbations per patient-treatment year were compared between groups by using the Fisher exact test and Poisson regression (adjusting for differential treatment exposure). Time to first asthma exacerbation was described by using a Kaplan-Meier plot and analyzed through log-rank testing. Laboratory assessments, vital signs, electrocardiograms (ECGs), Holter monitoring, predose FEV₁, and diary variables were analyzed by using descriptive statistics and analysis of covariance. Additional details of these analyses, safety assessments, resource use variables, and patient-reported questionnaires (Onset of Effect Questionnaire¹³ and Asthma Treatment Satisfaction Measure [ATSM]¹⁴) are described in the Methods section in this article's Online Repository. Because there were no prespecified hypotheses in this study, all reported *P* values are nominal, without adjustment for multiple comparisons.

RESULTS**Patients**

Patient disposition is shown in Fig 1. Demographic and baseline asthma characteristics generally were similar in both groups (Table I). The per-protocol analysis set included 319 and 299 patients in the budesonide/formoterol and budesonide groups, respectively; the most common reason for exclusion from the per-protocol analysis set was lack of ICS treatment based on inclusion criteria. The percentages of patients receiving concomitant asthma medications other than study medication were similar in both treatment groups (see Table E2 in this article's Online Repository at www.jacionline.org).

Asthma exacerbations

Asthma exacerbations totaled 36 and 61 in the budesonide/formoterol and budesonide groups, respectively. The percentage of patients with 1 or more asthma exacerbations was lower (*P* = .006) and the rate of asthma exacerbations was reduced by 38.5% with budesonide/formoterol versus budesonide (rate ratio, 0.615; *P* = .002). Most exacerbation events were based on oral prednisone use, the rate of which was reduced by 49.9% with budesonide/formoterol versus budesonide (rate ratio, 0.501; *P* < .001; Table II). The rate per patient-treatment year of less-frequent asthma exacerbation components also generally favored budesonide/formoterol (Table II). No patients in the budesonide/formoterol group experienced an exacerbation resulting in hospitalization compared with 4 patients in the budesonide group. No patients in either group met prespecified study withdrawal exacerbation criteria. Patients treated with budesonide/formoterol showed a longer time to first asthma exacerbation versus those treated with budesonide (*P* = .018; Fig 2).

Safety

Mean treatment exposure was 266 and 287 days in the budesonide/formoterol and budesonide groups, respectively. In the safety population, 51.2% and 47.8% of patients in the budesonide/formoterol and budesonide groups, respectively, experienced 1 or more AEs during randomized treatment. Most AEs were mild to moderate in intensity. AEs reported by 5% or greater

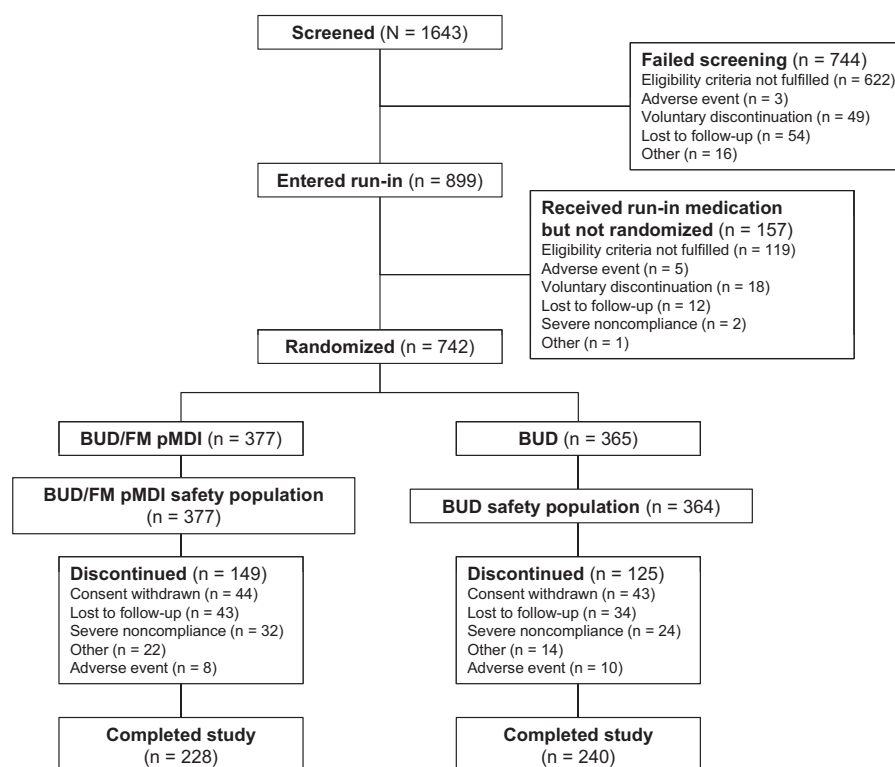


FIG 1. Patient disposition. BUD, Budesonide; FM, formoterol.

TABLE I. Patients' demographic and baseline disease characteristics

	BUD/FM pMDI, 320/9 µg twice daily	BUD pMDI, 320 µg twice daily
Sex, no. (%)	n = 377	n = 365
Male	128 (34.0)	133 (36.4)
Female	249 (66.0)	232 (63.6)
Age (y)	n = 377	n = 365
Mean (SD)	36.2 (15.7)	38.4 (15.2)
Range	12.0-82.0	12.0-82.0
Duration of asthma (y)	n = 377	n = 365
Mean (SD)	17.9 (13.8)	19.3 (15.5)
Range	0.5-61.4	0.5-63.0
ICS dose at entry (µg)	n = 370	n = 358
Mean (SD)	512.3 (237.6)	543.6 (260.6)
FEV ₁ at randomization (baseline)	n = 376	n = 364
Mean (L [SD])	2.3 (0.7)	2.3 (0.6)
% Predicted, mean (SD)	77.0 (15.1)	78.2 (16.0)

BUD, Budesonide; FM, formoterol.

of all patients were headache (8.6%), nasopharyngitis (7.4%), sinusitis (5.1%), and viral upper respiratory tract infection (5.1%; see Table E3 in this article's Online Repository at www.jacionline.org for additional details). In the budesonide/formoterol and budesonide groups, respectively, 2.7% and 2.2% discontinued for AEs, 3.2% and 4.1% experienced SAEs (fatal and nonfatal events), and 2.9% and 3.8% experienced nonfatal SAEs. No SAE was judged by the investigator to be treatment related. Two deaths occurred during randomized treatment: 1 cerebrovascular accident (budesonide/formoterol) and 1 homicide

(budesonide); both were considered unrelated to study medication. Treatment-related AEs as judged by the investigator occurred in 10 (2.7%) patients receiving budesonide/formoterol and 7 (1.9%) patients receiving budesonide, with 1 discontinuation in each group for a treatment-related AE (tachycardia, budesonide/formoterol pMDI; heart palpitations, budesonide).

No clinically meaningful changes from baseline or differences between treatment groups in laboratory assessments or vital sign findings occurred at any time point; small increases from baseline in heart rate were observed with budesonide/formoterol versus budesonide at the end of treatment. No clinically significant mean changes occurred from baseline to treatment maximum or end of treatment in QTc (QT interval corrected for heart rate using the Bazett or Fridericia correction formula, $P \geq .05$). Statistically significant differences in mean ECG parameters generally were small and reflective of the precision around the point estimates but were not considered clinically meaningful. Additional data can be found in the Results section in this article's Online Repository at www.jacionline.org and Tables E4 and E5 in this article's Online Repository at www.jacionline.org for ECG assessments, Holter monitoring, and shift-table analyses.

Efficacy

Improvements in predose FEV₁, forced vital capacity, and morning peak expiratory flow were greater with budesonide/formoterol versus budesonide ($P \leq .013$; Table III). Improvements also were higher for budesonide/formoterol versus budesonide for the percentage of rescue medication-free days ($P = .003$) and asthma control days ($P = .006$; Table III) but not for symptom-free days. Reductions in rescue albuterol pMDI use

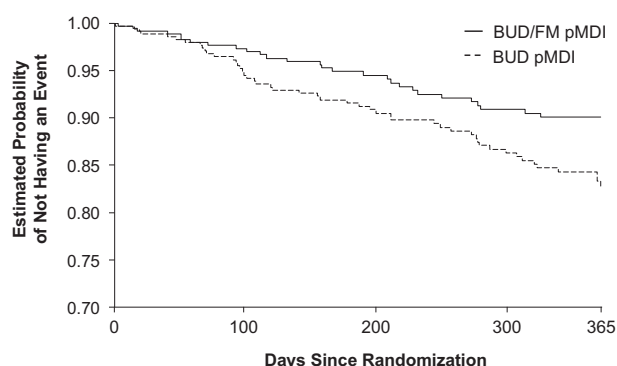
TABLE II. Incidence of asthma exacerbations and predefined asthma exacerbation criteria

	BUD/FM pMDI, 320/9 µg twice daily (n = 377)	BUD pMDI, 320 µg twice daily (n = 364)	Ratio estimate (95% CI between groups)
Overall (any predefined criteria met)			
Patients with ≥1 asthma exacerbation, no. (%)	29 (7.7)	51 (14.0)	0.511 (0.316 to 0.827)*
No. per patient-treatment year	0.131	0.213	0.615 (0.448 to 0.843)*
Individual predefined criteria			
Use of oral corticosteroids			
Patients with ≥1 event, no. (%)	24 (6.4)	44 (12.1)	0.494 (0.294 to 0.832)*
No. per patient-treatment year	0.109	0.189	0.579 (0.417 to 0.803)*
Use of parenteral corticosteroids			
Patients with ≥1 event, no. (%)	7 (1.9)	9 (2.5)	0.746 (0.275 to 2.025)
No. per patient-treatment year	0.029	0.031	0.926 (0.621 to 1.381)
Hospitalization			
Patients with ≥1 event, no. (%)	0	4 (1.1)	0.106 (0.006 to 1.978)
No. per patient-treatment year	0	0.017	NA†
Emergency department visits			
Patients with ≥1 event, no. (%)	12 (3.2)	12 (3.3)	0.964 (0.428 to 2.175)
Visits per patient-treatment year	0.047	0.049	0.967 (0.661 to 1.416)
Urgent care visits			
Patients with ≥1 event, no. (%)	1 (0.3)	8 (2.2)	0.118 (0.015 to 0.951)*
Visits per patient-treatment year	0.004	0.028	0.130 (0.068 to 0.250)*

BUD, Budesonide; FM, formoterol; NA, not analyzed.

* $P \leq .019$ compared with budesonide pMDI.

† P value and rate ratio could not be calculated because no patients in the budesonide/formoterol pMDI group were hospitalized during the randomized treatment period.

**FIG 2.** Kaplan-Meier probability curve for time to first overall asthma exacerbation (safety population). BUD, Budesonide; FM, formoterol.

were higher with budesonide/formoterol versus budesonide (-0.52 vs -0.29 inhalations per day, respectively; $P = .003$). Reductions in albuterol nebulizations were similar in the budesonide/formoterol (-0.12 inhalations per day) and budesonide (-0.10 inhalations per day) groups over the 52-week study. Similar results were observed in the per-protocol population. Results for resource use variables, patient-reported questionnaires, and ATSM scores (Table E6) are included in the Results section in this article's Online Repository.

DISCUSSION

The present study is the first to investigate the long-term safety of budesonide/formoterol pMDI in African American patients with moderate-to-severe persistent asthma previously treated with medium- to high-dose ICS therapy and is the largest long-term study evaluating ICS/LABA therapy versus ICS therapy conducted in this population to date. Treatment with budesonide/formoterol, 320/9 µg twice daily, resulted in a 39% reduction in the rate of

asthma exacerbations and a longer time to first asthma exacerbation compared with budesonide alone. No treatment-related deaths or treatment-related SAEs were reported during 52 weeks of treatment. These findings are consistent with results from studies in general populations of asthmatic patients evaluating the effect of budesonide/formoterol pMDI on asthma exacerbations.^{15,16}

Concerns surrounding the safety of LABAs in patients with asthma^{6,17,18} have prompted the US Food and Drug Administration to issue boxed warnings for LABAs and to require LABA manufacturers to conduct controlled clinical trials assessing the safety of LABAs plus ICSs versus ICSs alone.¹⁹ The Salmeterol Multicenter Asthma Research Trial suggested a possible increased risk for respiratory-related death or life-threatening events with salmeterol in African American patients compared with white patients.⁶ A subsequent long-term efficacy study reported by Bailey et al⁷ allayed some concerns regarding the safety of the LABA salmeterol when administered in combination with the ICS fluticasone in a population of 475 African American patients, with a numeric reduction in exacerbation rate of 15% observed with salmeterol/fluticasone dry powder inhaler versus fluticasone alone. Although not designed to assess the end points evaluated in the Salmeterol Multicenter Asthma Research Trial,⁶ the present long-term safety study extends the findings of Bailey et al⁷ to a larger population of 742 African American patients and to the ICS/LABA budesonide/formoterol combination, showing a 39% reduction in the rate of asthma exacerbations relative to budesonide alone and an acceptable safety profile based on extensive safety evaluations. These findings are consistent with those of recent analyses of formoterol in general populations, showing no evidence of an increased risk of serious asthma events when formoterol is used in conjunction with an ICS either as a fixed-dose combination or as separate devices.²⁰⁻²²

In this study budesonide/formoterol was well tolerated in African American patients, with a safety profile similar to that of budesonide alone. Across AE, clinical laboratory, and cardiac

TABLE III. Summary of efficacy results over the randomized treatment period

Variable	BUD/FM pMDI, 320/9 μ g twice daily	BUD pMDI, 320 μ g twice daily	Difference (95% CI between groups)*
Predose FEV ₁ (L)			
No. of patients	359	354	
Baseline,† mean (SD)	2.31 (0.66)	2.31 (0.64)	
Mean (SD) change from baseline	0.08 (0.26)	−0.01 (0.29)	0.09 (0.05 to 0.13)‡
Predose FVC (L)			
No. of patients	359	354	
Baseline,† mean (SD)	3.05 (0.85)	3.07 (0.86)	
Mean (SD) change from baseline	0.08 (0.31)	0 (0.34)	0.07 (0.03 to 0.12)‡
Morning PEF (L/min)			
No. of patients	364	349	
Baseline,§ mean (SD)	343.46 (105.21)	335.70 (99.28)	
Mean (SD) change from baseline	29.39 (63.15)	20.49 (54.74)	10.40 (2.19 to 18.61)‡
Rescue medication-free days (%)			
No. of patients	369	353	
Baseline,§ mean (SD)	61.51 (36.47)	62.18 (37.11)	
Mean (SD) change from baseline	16.02 (29.39)	10.48 (27.41)	5.26 (1.75 to 8.77)‡
Symptom-free days (%)			
No. of patients	369	353	
Baseline,§ mean (SD)	78.15 (30.24)	73.45 (32.78)	
Mean (SD) change from baseline	8.50 (22.72)	8.57 (22.84)	1.88 (−0.86 to 4.61)
Asthma control days (%)			
No. of patients	369	353	
Baseline,§ mean (SD)	56.90 (36.66)	56.51 (38.03)	
Mean (SD) change from baseline	16.61 (28.24)	11.70 (28.93)	5.06 (1.45 to 8.68)‡

BUD, Budesonide; FM, formoterol; FVC, forced vital capacity; PEF, peak expiratory flow.

*Least-squares mean differences between groups and 95% CIs from analysis of covariance were used for all variables.

†Defined as the last predose value before the first dose of randomized treatment.

‡ $P < .05$.

§Defined as the mean of all values obtained during the run-in period.

safety parameters, no substantial or unexpected abnormal patterns were observed with budesonide/formoterol or budesonide for up to 1 year of treatment. Safety findings were consistent with the known safety profiles of ICSs²³ and LABAs^{24,25} and with findings from the previously reported studies of budesonide/formoterol pMDI in predominantly white populations of asthmatic patients over 12 weeks,^{26,27} predominantly white²⁸ or racially undefined international²⁹ populations of asthmatic patients over 52 weeks, and an African American population with moderate-to-severe asthma over 12 weeks.¹⁰ Additional information on resource use is included in the Discussion section in this article's Online Repository.

One limitation of this study is that it was not designed as a direct comparison of African American versus white patients. However, the consistency of safety and efficacy measures with earlier studies is reassuring. Another possible limitation of the present study is the inclusion of patients who deviated from the study protocol in the primary safety analysis; however, similar results were observed after exclusion of patients who deviated from the protocol, providing reassurance that patients with protocol deviations did not bias results.

In summary, results of this long-term safety study show that budesonide/formoterol has a tolerability profile similar to that of budesonide and consistent with findings from studies in predominantly white populations with asthma.^{26,27} A lower incidence of asthma exacerbations was shown with budesonide/formoterol pMDI versus budesonide pMDI. With regard to other safety outcomes, no substantial or unexpected patterns of abnormalities of safety measures were observed for up to 1 year of treatment. Greater improvements in pulmonary function and asthma control

were observed with budesonide/formoterol pMDI, 320/9 μ g twice daily, versus budesonide pMDI, 320 μ g twice daily. Overall, the results support the use of a budesonide/formoterol pMDI in African American patients aged 12 years or older with moderate-to-severe persistent asthma whose symptoms are not adequately controlled with an ICS alone.

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Clinical implications: Findings support the safety of the budesonide/formoterol pMDI in African American adolescents and adults with moderate-to-severe persistent asthma whose symptoms are not adequately controlled with an ICS alone.

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METHODS

Patients

Patients were required to have demonstrated reversibility of FEV₁ of 12% or greater and 0.20 L or greater from baseline within 15 to 30 minutes after administration of a short-acting β_2 -adrenergic agonist at screening or documented history (within 1 year of the study) of reversibility of FEV₁ of 12% or greater and 0.20 L or greater from baseline within 15 to 30 minutes after administration of a fast-acting β_2 -adrenergic agonist while undergoing maintenance ICS regimens. When considering the patient's FEV₁ at screening and randomization, Crapo-predicted healthy subjects incorporated a 12% reduction for African Americans aged 18 years or older. Polgar-predicted healthy subjects were used for patients aged 12 to 17 years.

Patients were required to have a smoking history of less than 10 pack-years and to have had treatment with a consistent daily dose of ICS for at least 30 days before screening with the total daily ICS dosage for either single therapy or combination therapy (combination therapy was defined as using an ICS and a LABA), as defined in Table E1. If patients were receiving immunotherapy, the regimen must have been stable for 4 weeks before screening.

Patients were excluded if they received treatment with oral corticosteroids within 30 days before screening, omalizumab or any other antibody therapy within 90 days before screening, or a β -blocker (including eye drops) during the study. Patients also were excluded from the study if they were pregnant or breast-feeding or if they had a malignancy within the last 5 years or other disease that the investigator believed might compromise the patient's safety or influence study results, a known or suspected hypersensitivity to study therapy or excipients of the investigational products, or clinically relevant abnormal findings on laboratory tests, physical examinations, or electrocardiography. Patients also were excluded if they had or were recovering from a respiratory tract infection or other viral/bacterial illness at the time of the randomization visit that, in the investigator's opinion, would have interfered with the patient's lung function, ability to perform spirometry, or both.

Study design and treatments

Patients were provided with Mini-Wright peak flow meters (Clement Clark, Columbus, Ohio) and hand-held electronic diaries (LogPad; PHT Corp, Charlestown, Mass) at screening. They were instructed to enter electronic diary data every morning. Randomization occurred by using computer-generated sequential allocation; approximately equal distribution of patients per treatment group at each site was ensured by using balanced blocks. Allocation concealment was maintained by packaging the study medications identically, with the exception of the computer-generated randomization number.

Concomitant medications

Standard clinical practice for treating asthma exacerbations usually involves treatment with a burst of systemic corticosteroids and possibly nebulized albuterol. Leukotriene receptor antagonists or methylxanthines were allowed as add-on therapy for adjunctive treatment of an asthma exacerbation or for additional asthma controller therapy to prevent withdrawal from the study. Use of alternate rescue medications was limited or eliminated as symptoms improved.

Asthma medication other than study medication and albuterol pMDI was disallowed, including systemic corticosteroids, short-acting β_2 -adrenergic agonist, LABAs, leukotriene receptor antagonists (except as noted above), anticholinergics, and 5-lipoxygenase inhibitors. Additional medications disallowed during run-in or randomized treatment included hydroxyzine, β -blockers (including eye drops), xanthines, ephedrine, mAb or polyclonal antibody therapy, topical corticosteroids, and potent cytochrome P450 (CYP) 3A4 inhibitors.

Safety evaluations

AEs were recorded in response to the study site-administered question "Have you/Has your child had any health problems since the previous visit?" at all study visits and during a follow-up telephone call with the patient or legal guardian after the final study visit. Asthma symptoms or signs were recorded

as AEs if the event was serious, led to study discontinuation, was new to the patient, or was not consistent with the patient's preexisting asthma history (defined as within 1 year of screening). Patients using 12 or more inhalations per day of albuterol on 3 or more days within a 7-day period were contacted for an unscheduled physician's office visit, although this was not considered an exacerbation unless oral or parenteral corticosteroids were prescribed. Other safety assessments included laboratory evaluations, vital signs, physical examinations, and 12-lead ECGs collected at each visit. Twenty-four-hour Holter monitoring was performed before randomization (baseline) and at week 2 in a subset of patients.

Resource use evaluations

Resource use was evaluated based on the incidence of asthma-related hospitalizations, emergency department visits, urgent care center visits, unscheduled physician's visits, and unscheduled telephone calls to physicians. Additionally, use of adjunctive asthma medications for asthma worsening, missed work or school days, and days of interrupted activities were recorded in patients' diaries.

Efficacy evaluations

Onset of effect questionnaire. Patients aged 18 years or older completed the validated 5-item Onset of Effect Questionnaire^{E1} at the end of weeks 1 to 12. The 5 items were as follows: (1) "During the past week, you could tell your study medication was working"; (2) "During the past week, you could feel your study medication begin to work right away"; (3) "During the past week, you felt physical sensations shortly after taking your study medication that reassured you that it was working"; (4) "During the past week, your study medication worked as quickly as albuterol"; and (5) "During the past week, you were satisfied with how quickly you felt your study medication begin to work." Each item was assessed on a 5-point Likert scale as follows: 1, strongly disagree; 2, somewhat disagree; 3, neither agree nor disagree; 4, somewhat agree; and 5, strongly agree. Results from items 2 and 5 were presented based on previous identification of these items as the best approach for capturing patient-perceived onset of effect during the development and validation study.^{E1}

ATSM. Patients aged 18 years or older completed the ATSM^{E2} at randomization and months 3, 6, and 12, which comprised 11 predefined attributes of asthma treatment. The overall satisfaction score and scores for the 11 predefined attributes were scored on a 0- to 100-point scale, with higher scores representing greater satisfaction with treatment.

Statistical analysis

The safety population comprised all randomized patients who received 1 or more study medication doses. A secondary analysis included only randomized patients who met the eligibility criteria (per-protocol population). The sample size met International Conference on Harmonization guidelines for evaluating the safety of a chronic treatment.^{E3} The final population size was driven by the need to have 200 or more patients per treatment group for meaningful pharmacogenetic analyses of alleles. A sample size of 360 patients per treatment arm allowed a withdrawal rate of 17% by month 6.

A secondary analysis specifically excluded patients who violated the following inclusion criteria: prebronchodilator FEV₁ of 50% of predicted normal value or greater at screening, randomization, or both; demonstrated reversibility of FEV₁ of 12% or greater and greater than 0.20 L from baseline; and/or treatment with a stable medium-to-high dose of ICS for 30 days or more before screening.

Results of laboratory assessments, vital signs, ECGs, and Holter monitoring were analyzed by using descriptive statistics and analysis of covariance, with treatment as a fixed effect and baseline values as covariates. Shift-table analyses for clinically relevant abnormalities were performed. Clinic predose FEV₁ and diary variables were analyzed descriptively and with analysis of covariance. Baseline values were defined as the last value before the first dose of randomized treatment for vital signs, Holter monitor readings, and spirometric variables; the mean of values from ECG recordings before the first dose of randomized treatment; and the mean of all run-in data (excluding the first day of randomized treatment) for diary variables.

Resource use variables were compared between treatment groups based on incidence by using the Cochran-Mantel-Haenszel test and events per patient-treatment year by using a Poisson regression model with the fixed factor of treatment adjusting for differential treatment exposure. Rate ratios for asthma exacerbations and resource use variables were based on the ratio of events per patient-treatment year for budesonide/formoterol versus budesonide, with ratios of less than 1 favoring budesonide/formoterol.

The distribution of responses to items 2 and 5 in the Onset of Effect Questionnaire was assessed at the end of weeks 1 and 12, and a responder analysis was conducted, with patient responses of “strongly agree” and “somewhat agree” prespecified as a positive response; treatment group differences were analyzed by using the Fisher exact test. Overall ATSM scores were compared between treatments by using ANOVA with treatment as a fixed factor and no adjustments for baseline ATSM scores.

RESULTS

Patients

The percentages of patients receiving concomitant asthma medications other than study medication were similar in both treatment groups (Table E2).

Safety

Common AEs are presented in Table E3. No clinically meaningful changes from baseline or differences between treatment groups in laboratory assessments or vital sign findings were found at any time point; small increases from baseline in heart rate were observed with budesonide/formoterol versus budesonide at the end of treatment (Table E4). Patients in the budesonide/formoterol group experienced decreases from baseline in PR ($P = .024$) and RR ($P = .025$) intervals at the end of treatment compared with those seen in patients in the budesonide pMDI group. No clinically significant mean changes occurred from baseline to treatment maximum or end of treatment in QTc (QT interval corrected for heart rate using the Bazett or Fridericia correction formula, $P \geq .05$). Statistically significant differences in mean ECG parameters generally were small and reflective of the precision around the point estimates but were not considered clinically meaningful. Overall, 133 patients (budesonide/formoterol, $n = 65$; budesonide, $n = 68$) had on-treatment Holter measurements at the end of week 2 with 16 or more hours analyzed. No clinically meaningful differences were observed between the treatment groups for mean and minimum heart rate. Maximum heart rate increased from baseline in the budesonide/formoterol group (2.80 beats/min) and decreased in the budesonide group (-3.59 beats/min; $P = .007$).

The percentages of patients who met the criteria for a clinically important abnormality (values crossing prespecified extended threshold limit or changes from baseline meeting reference criteria) in vital signs, laboratory assessments, ECG variables, and Holter monitoring are shown in Table E5. Overall, chemistry and ECG findings were consistent with the established safety profile of β_2 -adrenergic agonists. The percentage of patients who met the criteria for a clinically important abnormality in heart rate (value >100 beats/min or ≥ 20 beats/min increase) was higher in the budesonide/formoterol group than in the budesonide group, which is consistent with the known effects of β -agonists. One patient had a QTc (Bazett) value of 500 ms or greater (budesonide/formoterol pMDI group), and no patients had a QT or QTc (Fridericia) value of 500 ms or greater during randomized treatment. The numbers and percentages of patients with abnormalities in key Holter variables in the budesonide/

formoterol and budesonide groups were low and similar in both treatment groups.

Resource use

Four (1.1%) patients in the budesonide group were hospitalized as part of an asthma exacerbation. No hospitalizations for asthma were recorded in the budesonide/formoterol group, and therefore rate ratios for the incidence of hospitalizations caused by asthma exacerbation could not be calculated. The number of events per patient-treatment year of unscheduled physician's office visits (rate ratio, 0.619; $P = .014$), days of adjunctive asthma medication use (rate ratio, 0.209; $P < .001$), emergency department visits (rate ratio, 0.397; $P < .001$), and urgent care clinic visits (rate ratio, 0.312; $P < .001$) was lower in the budesonide/formoterol versus budesonide group. There was no difference in unscheduled telephone calls to physicians between treatment groups (rate ratio, 0.881; $P = .461$). With regard to indirect resource use variables, reductions from baseline in the numbers of missed work/school days and days of interrupted activities during the randomized treatment period were similar in the budesonide/formoterol and budesonide groups (missed work/school: -1.31 vs -2.58 ; $P = .318$; interrupted activities: -4.85 vs -6.21 ; $P = .208$). Resource use results for the per-protocol population were similar to those in the safety analysis set.

Efficacy

Onset of effect questionnaire. At the end of week 1, the percentage of patients who indicated that they could feel their study medication begin to work right away during the past week (ie, reported positive responses on item 2 of the Onset of Effect Questionnaire) was higher in the budesonide/formoterol group than in the budesonide group (74.8% vs 65.6%, respectively; $P = .034$). The percentages of patients reporting positive responses were not substantially different ($P \geq .098$) between the budesonide/formoterol and budesonide pMDI groups for item 5 (“During the past week, you were satisfied with how quickly you felt your study medication begin to work”) at week 1 (71.7% vs 65.1%, respectively) or for item 2 (73.4% vs 68.5%, respectively) and item 5 (78.8% vs 71.1%, respectively) at the end of week 12. The minimally important difference for onset-of-effect responses (defined as 50% to 75% minimum active treatment response with a placebo response no larger than 26% to 40%^{E4}) was not met for these questions at any time point. Results were similar in the per-protocol population for responses to items 2 and 5 after 1 and 12 weeks of treatment.

ATSM. After 12 months of treatment, patients 18 years of age or older treated with budesonide/formoterol had numerically higher adjusted mean scores for overall satisfaction and for each of the 11 ATSM attributes compared with patients treated with budesonide, with a P value of less than .05 observed only for the attributes of timely relief of symptoms and rescue medication use (Table E6). Similar results were observed in the per-protocol population.

DISCUSSION

During assessments of direct resource use, patients treated with budesonide/formoterol had less frequent visits to the emergency department, urgent care clinic, and other health care providers because of asthma. Overall use of these resources was low; in particular, no patients in the budesonide/formoterol group were hospitalized for asthma during randomized treatment. Conclusions from these data are limited because many of these events

occurred with low frequency. Budesonide/formoterol pMDI also was more effective than budesonide in improving measures of pulmonary function and asthma control. These results are consistent with previous 12-week efficacy studies of budesonide/formoterol in predominately white populations of patients with mild-to-moderate^{E5} or moderate-to-severe^{E6} asthma and in a subsequent 12-week study conducted in African American patients with moderate-to-severe asthma.^{E7}

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TABLE E1. Allowed ICS dosage range for study entry*

	Daily dose ($\mu\text{g}/\text{d}$)	
	Single	Combination
Beclomethasone dipropionate (CFC)	>1000 to 1640	≥ 504 to 1008
Beclomethasone dipropionate (HFA)	>240 to 320	≥ 120 to 240
Budesonide	>600 to 1200	≥ 400 to 800
Budesonide (Symbicort pMDI)	Not applicable	≥ 320 to 640
Flunisolide	>1000 to 2000	≥ 500 to 1000
Fluticasone (HFA or CFC)	>344 to 880	≥ 172 to 690
Fluticasone (Diskus)	>500 to 1000	≥ 200 to 750
Triamcinolone acetonide	>1000 to 2000	≥ 500 to 1000
Mometasone	>440 to 880	≥ 220 to 440

BUD, Budesonide; *CFC*, chlorofluorocarbon; *FM*, formoterol; *HFA*, hydrofluoroalkane.

*After providing written informed consent for withdrawal of medication 48 hours or more before spirometry testing, potential patients maintained on a fixed combination of an ICS and a LABA were switched to a comparable dose of an ICS without the addition of a LABA. This change was not considered a change in the dose of maintenance ICS.

TABLE E2. Concomitant asthma medications other than study medication

Medication class	BUD/FM pMDI, 320/9 µg twice daily (n = 377), no. (%)	BUD pMDI, 320 µg twice daily (n = 364), no. (%)
Corticosteroids (nasal, oral, injected, topical)	26 (6.9)	43 (11.8)
Selective β_2 -adrenergic receptor agonists	33 (8.8)	36 (9.9)
Adrenergics/other drugs for obstructive airway diseases*	17 (4.5)	22 (6.0)
ICSs	10 (2.7)	10 (2.7)
LTRAs	6 (1.6)	7 (1.9)
Anticholinergics	1 (0.3)	3 (0.8)
α - and β -Adrenergic receptor agonists	1 (0.3)	1 (0.3)

BUD, Budesonide; *FM*, formoterol; *LTRA*, leukotriene receptor antagonist.

*Includes fluticasone plus salmeterol, budesonide plus formoterol, and ipratropium plus albuterol.

TABLE E3. Overall AEs reported by $\geq 3\%$ of patients in both treatment groups

AE	BUD/FM pMDI, 320/9 μg twice daily (n = 377), no. (%)	BUD pMDI, 320 μg twice daily (n = 364), no. (%)
Headache	36 (9.5)	28 (7.7)
Nasopharyngitis	26 (6.9)	29 (8.0)
Sinusitis	15 (4.0)	23 (6.3)
Viral upper respiratory tract infection	22 (5.8)	16 (4.4)
Cough	14 (3.7)	15 (4.1)
Asthma	9 (2.4)	19 (5.2)
Oropharyngeal pain	19 (5.0)	9 (2.5)
Back pain	12 (3.2)	10 (2.7)
Bronchitis	13 (3.4)	9 (2.5)
Toothache	10 (2.7)	12 (3.3)
Bacterial upper respiratory tract infection	2 (0.5)	14 (3.8)

BUD, Budesonide; *FM*, formoterol.

TABLE E4. Summary of safety variables (safety population)

Variable	BUD/FM pMDI, 320/9 µg twice daily	BUD pMDI, 320 µg twice daily	Difference (95% CI between groups)*
Laboratory assessments			
Serum glucose (mmol/L)			
No. of patients	321	322	
Baseline, mean (SD)	5.43 (1.90)	5.60 (1.89)	
Change from baseline to end of treatment, mean (SD)	0.10 (1.85)	0.02 (1.69)	0.01 (−0.22 to 0.25)
Serum potassium (mmol/L)			
No. of patients	323	323	
Baseline, mean (SD)	4.20 (0.4)	4.09 (0.41)	
Change from baseline to end of treatment, mean (SD)	−0.05 (0.42)	0.02 (0.42)	−0.00 (−0.06 to 0.05)
Vital sign assessments			
Sitting pulse rate (beats/min)			
No. of patients	362	354	
Baseline, mean (SD)	74.46 (10.47)	73.80 (10.49)	
Change from baseline to end of treatment, mean (SD)	0.55 (11.20)	0.51 (11.14)	0.38 (−1.07 to 1.82)
Sitting systolic blood pressure (mm Hg)			
No. of patients	361	354	
Baseline, mean (SD)	122.31 (15.26)	124.12 (15.38)	
Change from baseline to end of treatment, mean (SD)	1.33 (15.45)	1.32 (13.78)	−0.80 (−2.71 to 1.10)
Sitting diastolic blood pressure (mm Hg)			
No. of patients	361	354	
Baseline, mean (SD)	77.45 (10.97)	78.42 (11.03)	
Change from baseline to end of treatment, mean (SD)	0.24 (10.70)	0.05 (11.03)	−0.30 (−1.67 to 1.07)
ECG assessments			
Heart rate (beats/min)			
No. of patients	362	354	
Baseline, mean (SD)	70.29 (10.93)	70.54 (10.49)	
Change from baseline to end of treatment, mean (SD)	1.40 (9.90)	−0.44 (10.22)	1.77 (0.36 to 3.18)†
QRS interval (ms)			
No. of patients	362	354	
Baseline, mean (SD)	88.78 (8.75)	87.86 (7.14)	
Change from baseline to end of treatment, mean (SD)	0.76 (6.46)	0.55 (6.43)	0.36 (0.57 to 1.29)
PR interval (ms)			
No. of patients	361	354	
Baseline, mean (SD)	158.85 (20.28)	159.55 (21.29)	
Change from baseline to end of treatment, mean (SD)	−0.13 (12.35)	1.81 (12.52)	−2.04 (−3.81 to −0.27)†
RR interval (ms)			
No. of patients	362	354	
Baseline, mean (SD)	878.66 (139.75)	873.26 (128.18)	
Change from baseline to end of treatment, mean (SD)	−14.26 (123.25)	7.05 (123.82)	−19.83 (−37.16 to −2.51)†
QT interval (ms)			
No. of patients	362	354	
Baseline, mean (SD)	383.92 (26.84)	383.63 (25.34)	
Change from baseline to end of treatment, mean (SD)	−1.79 (21.20)	1.84 (23.05)	−3.56 (−6.70 to −0.43)†
QTc (Bazett) interval (ms)			
No. of patients	362	354	
Baseline, mean (SD)	412.53 (24.33)	413.06 (22.95)	
Change from baseline‡ to end of treatment, mean (SD)	1.70 (20.34)	0.53 (20.53)	1.06 (−1.84 to 3.95)
QTc (Fridericia) interval (ms)			
No. of patients	362	354	
Baseline, mean (SD)	402.42 (20.64)	402.70 (19.60)	
Change from baseline‡ to end of treatment, mean (SD)	0.47 (15.84)	1.02 (16.82)	−0.60 (−2.93 to 1.72)

BUD, Budesonide; FM, formoterol.

*Adjusted mean difference between groups and 95% CIs from analysis of covariance were used for all variables.

† $P < .05$.

‡Baseline was defined as the average of values from electrocardiographic recordings performed before randomization.

TABLE E5. Clinically important changes in safety variables during randomized treatment

Variable	No. (%) of patients	
	BUD/FM pMDI, 320/9 µg twice daily (n = 377)	BUD pMDI, 320 µg twice daily (n = 364)
Laboratory assessments		
Serum glucose		
>9.0 mmol/L*	21 (5.6)	20 (5.5)
2.8-mmol/L increase from baseline†	34 (9.0)	31 (8.5)
Serum potassium		
<3.0 mmol/L*	7 (1.9)	9 (2.5)
1.0-mmol/L decrease from baseline†	19 (5.0)	9 (2.5)
Vital sign assessments		
Pulse rate (beats/min)		
>100 beats/min	17 (4.5)	8 (2.2)
20-beats/min increase from baseline	55 (14.6)	42 (11.5)
Systolic blood pressure (mm Hg)		
>160 mm Hg	16 (4.2)	20 (5.5)
30-mm Hg increase from baseline	37 (9.8)	23 (6.3)
Diastolic blood pressure (mm Hg)		
>100 mm Hg	15 (4.0)	10 (2.7)
15-mm Hg increase from baseline	58 (15.4)	58 (15.9)
ECG assessments		
Heart rate		
(A) >100 beats/min*	11 (2.9)	7 (1.9)
(B) ≥20 beats/min increase from baseline†	38 (10.1)	27 (7.4)
QRS duration		
(A) >120 ms*	2 (0.5)	2 (0.5)
(B) >30-ms increase from baseline†	0	1 (0.3)
PR interval		
(A) >220 ms*	6 (1.6)	13 (3.6)
(B) >40-ms increase from baseline†	4 (1.1)	4 (1.1)
QT interval (uncorrected)		
Potentially significant or high		
(A) ≥450 ms*	15 (4.0)	17 (4.7)
(B) ≥30-ms increase from baseline†	61 (16.2)	77 (21.2)
Significant or extremely high		
(C) ≥500 ms*	0	0
(D) ≥60-ms increase from baseline†	5 (1.3)	7 (1.9)
QTc interval (Bazett)		
Potentially significant or high		
(A) ≥450 ms*	63 (16.7)	68 (18.7)
(B) ≥30-ms increase from baseline†	75 (19.9)	75 (20.6)
Significant or extremely high		
(C) ≥500 ms*	1 (0.3)	0
(D) ≥60-ms increase from baseline†	8 (2.1)	4 (1.1)
QTc interval (Fridericia)		
Potentially significant or high		
(A) ≥450 ms*	14 (3.7)	28 (7.7)
(B) ≥30-ms increase from baseline†	35 (9.3)	46 (12.6)
Significant or extremely high		
(C) ≥500 ms*	0	0
(D) ≥60-ms increase from baseline†	1 (0.3)	1 (0.3)

(Continued)

TABLE E5. (Continued)

Variable	No. (%) of patients	
	BUD/FM pMDI, 320/9 µg twice daily (n = 377)	BUD pMDI, 320 µg twice daily (n = 364)
Holter assessments		
(A) ≥50 Ventricular ectopic beats	4/59 (6.8%)	3/63 (4.8)
(B) ≥50 Total supraventricular ectopic beats	4/60 (6.7)	3/67 (4.5)
(C) ≥1 Total ventricular runs	2/63 (3.2)	1/74 (1.4)

BUD, Budesonide; FM, formoterol.

*Clinically important abnormalities are defined as values that crossed extended reference ranges (high or low).

†Clinically important abnormalities are defined as changes from baseline values that met the reference criteria (increase or decrease).

TABLE E6. Mean ATSM scores* for patients aged 18 years or older at the end of month 12 of treatment

Attribute	BUD/FM pMDI, 320/9 µg twice daily	BUD pMDI, 320 µg twice daily
Overall		
No. of patients	203	232
Adjusted mean (SE)	48.0 (0.9)	45.6 (0.9)
Timely relief of symptoms		
No. of patients	203	229
Adjusted mean (SE)	54.0 (1.4) [†]	49.4 (1.3)
Level of symptom relief		
No. of patients	203	231
Adjusted mean (SE)	54.9 (1.3)	52.0 (1.2)
Rescue medication use		
No. of patients	203	229
Adjusted mean (SE)	52.9 (1.3) [†]	49.1 (1.2)
Asthma attack frequency		
No. of patients	203	232
Adjusted mean (SE)	56.4 (1.3)	53.6 (1.3)
Medication worked		
No. of patients	203	230
Adjusted mean (SE)	46.0 (1.1)	43.1 (1.0)
Feel medication working		
No. of patients	202	230
Adjusted mean (SE)	38.2 (1.3)	37.4 (1.2)
Daily activity		
No. of patients	202	230
Adjusted mean (SE)	47.0 (1.0)	45.1 (1.0)
Leisure activity		
No. of patients	201	230
Adjusted mean (SE)	46.3 (1.0)	43.7 (1.0)
Dosing management		
No. of patients	203	230
Adjusted mean (SE)	42.4 (1.1)	40.4 (1.1)
Medication convenience		
No. of patients	203	231
Adjusted mean (SE)	44.8 (1.0)	43.3 (1.0)
Side effects		
No. of patients	203	228
Adjusted mean (SE)	45.2 (1.2)	44.7 (1.1)

*Scale is 0 to 100, with higher scores representing greater satisfaction.

[†]*P* < .05.