

Efficacy of budesonide/formoterol pressurized metered-dose inhaler versus budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial

James Zangrilli, MD*; Lyndon E. Mansfield, MD†; Tom Uryniak, MS*; and Christopher D. O'Brien, MD, PhD*

Background: Few clinical trials in asthma have focused on Hispanic populations.

Objective: To compare the efficacy and safety of budesonide/formoterol (BUD/FM) with BUD in an ethnically diverse group of Hispanic participants with asthma previously treated with inhaled corticosteroids (ICS).

Methods: This 12-week, randomized, double-blind, active-controlled study (NCT00419757) was designed to enroll Hispanic participants (self-reported) (≥ 12 years of age) with moderate to severe asthma requiring medium- to high-dose ICS. After a 2-week run-in period (low-dose BUD pressurized metered-dose inhaler [pMDI] $80\text{ }\mu\text{g} \times 2$ inhalations [$160\text{ }\mu\text{g}$] twice daily), participants with a symptom score greater than 0 (scale: 0–3) on 3 or more of 7 run-in days and forced expiratory volume in 1 second (FEV_1) 45%–85% predicted were randomized to BUD/FM pMDI $160/4.5\text{ }\mu\text{g} \times 2$ inhalations ($320/9\text{ }\mu\text{g}$) twice daily or BUD pMDI $160\text{ }\mu\text{g} \times 2$ inhalations ($320\text{ }\mu\text{g}$) twice daily.

Results: Randomized participants ($n = 127$ BUD/FM; $n = 123$ BUD) were predominately Mexican (51%) or Puerto Rican (21%). During low-dose ICS run-in, the mean symptom score was 1.0; however, mean predose FEV_1 improved ($2.10\text{--}2.21\text{ L}$). During randomized treatment, small, but not statistically significant, improvements favored BUD/FM vs BUD (AM peak expiratory flow [PEF; primary efficacy variable] 25.4 vs 19.9 L/min ; PM PEF 20.6 vs 15.8 L/min ; predose FEV_1 0.16 vs 0.11 L ; rescue medication use -0.7 vs -0.6 inhalations/d). Most adverse events were mild or moderate in intensity.

Conclusions: Improvement in clinically relevant control end points occurred in both BUD/FM and BUD groups; both treatments were well tolerated in this Hispanic asthma population but were not significantly differentiated.

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INTRODUCTION

Evidence suggests that Hispanic asthma patients have greater asthma-related mortality and barriers to asthma management than do non-Hispanic asthma patients.^{1–3} Disparities in asthma control indicators have been reported between subgroups of Hispanic asthma patients, including less bronchodilator responsiveness and reduced pulmonary function in patients of Puerto Rican descent vs those of Mexican descent.⁴

Despite evidence for poor asthma control and asthma-related mortality in Hispanic patients, few targeted studies of Hispanic asthma patients have been published.⁵ Combination treatment with an inhaled corticosteroid (ICS) and a long-acting β_2 -adrenergic agonist (LABA) is recommended for patients with moderate to severe persistent asthma not well controlled on ICS. Randomized, controlled studies in predominantly white populations with asthma have previously demonstrated the benefits of budesonide (BUD)/formoterol (FM) pressurized metered-dose inhaler (pMDI)^{6–9} and of BUD alone.^{6,7} The aim of the current study was to evaluate the efficacy and safety of BUD/FM pMDI compared with BUD pMDI in Hispanic asthma patients.

METHODS

Participants

Male and female Hispanic (self-reported) adults and adolescents (aged ≥ 12 years) with asthma for at least 6 months (American Thoracic Society definition)¹⁰ were qualified to participate. Inclusion and exclusion criteria and ICS run-in were designed to select participants with moderate to severe

Affiliation: * AstraZeneca LP, Wilmington, Delaware; † Texas Tech University, El Paso, Texas.

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asthma¹¹ based on historical daily dosing of medium- to high-dose ICS alone or in combination with a LABA for 30 days or more before enrollment. Participants had pre-bronchodilator forced expiratory volume in 1 second (FEV₁) of 45% to 85% of predicted normal and reversibility of 12% or greater and 0.20 L or greater within 15 to 30 minutes after albuterol inhalation (pMDI with or without a spacer: 180 μ g to 360 μ g; nebulized: up to 2.5 mg). The percentage of predicted normal FEV₁ values was assessed based on established Crapo et al¹² and Polgar and Promadhat¹³ reference equations for participants aged older than 18 and 12 to 17 years, respectively. Randomized participants had documented daytime or nighttime asthma symptom scores of greater than 0 on 3 or more days within 7 consecutive days during a 2-week run-in period on BUD pMDI 160 μ g twice daily. Participants were excluded if they had required hospitalization once or emergency treatment more than once in the preceding 6 months, used systemic corticosteroids within the previous 30 days, or had a 10-pack-year or more smoking history.

The protocol was approved by institutional review boards at each study center. Participants provided written informed consent and assent. 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.

Study Design and Treatment

This was a 12-week, multicenter, randomized, double-blind, active-controlled US study (NCT 00419757). After meeting screening criteria, participants discontinued their previous asthma therapy and received BUD pMDI 160 μ g twice daily for 2 weeks (± 7 days). Albuterol pMDI (90 μ g $\times$ 2 inhalations) was used for rescue medication, as needed. Mini-Wright peak flow meters (Clement Clark, Columbus, Ohio) and hand-held electronic diaries (LogPad, PHT Corporation, Massachusetts) were dispensed at screening. Participants used the electronic diary twice daily to record peak expiratory flow (PEF), asthma symptoms, nighttime asthma awakenings, and rescue medication use. Adverse events and concomitant medication use were recorded in paper diaries.

Randomization used a computer-generated allocation schedule. The participants were stratified by asthma severity, based on the ICS daily dose at study entry according to 1997 National Asthma Education and Prevention Program guidelines.¹¹ Participants meeting entry criteria were randomized 1:1 within the appropriate ICS dose stratum (medium or high) to receive twice-daily BUD/FM pMDI 160/4.5 μ g $\times$ 2 inhalations (320/9 μ g) or BUD pMDI 160 μ g $\times$ 2 inhalations (320 μ g). Additional study design information is described in the e-Methods supplement.

Efficacy Evaluations

The primary outcome was the mean change from baseline in morning (AM) PEF. The PEF measurements were assessed

before taking study medication, when possible 6 or more hours after the last dose of rescue medication. Secondary outcomes included predefined asthma events and withdrawals caused by these events, pulmonary function assessments, and diary-based measures of asthma control. Other secondary outcomes, including participant perception of onset of effect, participant and physician global assessments of overall control of asthma symptoms, and participant satisfaction with asthma medication, are described in the e-Methods.

Predose FEV₁ and forced vital capacity (FVC) were performed before run-in, at randomization, and at weeks 2, 6, and 12. Daytime and nighttime asthma symptom scores, nighttime awakenings attributable to asthma, and daytime and nighttime rescue medication use were recorded daily by participants. A predefined asthma event was any of the following: decreased FEV₁ 20% or more from randomization or FEV₁ less than 40% of predicted normal, albuterol use 12 or more inhalations per day or decreased morning PEF 20% or more from baseline (mean from 7-day period before randomization) on 3 or more of 7 consecutive days after randomization, 2 or more nocturnal asthma awakenings requiring rescue medication within 7 consecutive days after randomization, or a clinical exacerbation requiring emergency treatment, hospitalization, or use of an excluded asthma medication. Participants who experienced any predefined asthma event, except nighttime awakenings, were withdrawn from the study. Participants who met the criterion for nighttime awakenings remained in the study if they were considered clinically stable by the investigator.

Safety Evaluations

Participants recorded adverse events (AEs) daily (see e-Methods for additional details). Investigators determined whether the reported AEs were related to the study drug. Participants assessed events as mild, moderate, or severe. Serious AEs were those that resulted in death, were immediately life-threatening, required hospitalization, resulted in significant disability or incapacity, were a congenital abnormality or birth defect, or required intervention to prevent one of these outcomes and were reported, regardless of whether they were considered causally related to the study drug. Asthma symptoms or signs were recorded as AEs if the event was serious, new to the patient (ie, not consistent with the patient's pre-existing asthma history), or resulted in discontinuation. Safety studies of chemistry and hematology were collected at screening and at final visit. Twelve-lead electrocardiogram (ECG) measurements were performed at screening and at weeks 2, 6, and 12 before the morning dose of study medication (see e-Methods for additional details).

Statistical Analyses

Efficacy analyses included participants who received 1 or more doses of study medication and contributed sufficient data for at least 1 efficacy end point. A sample size of 126 participants per group was estimated to provide 90% power to detect a true difference in mean AM PEF of 15 L/min (stan-

dard deviation, 35 L/min). The safety analysis set included all randomized participants who took at least 1 dose of study medication and had postrandomization data. The patient-reported outcomes analysis set included all participants from the safety analysis aged 18 years or older.

Differences between treatment groups in adjusted (least squares) mean changes from baseline to the mean during the 12-week treatment period in diary variables and predose FEV₁ were assessed using analysis of covariance with treatment and center as fixed factors and the baseline value as a covariate. Differences between treatment groups in mean changes from baseline to the end of week 12 in predose FVC were summarized descriptively. Mean FEV₁/FVC ratio at the end of 12 weeks also was assessed. Baseline value was the mean of all values during the 7 days before randomization for diary variables and the predose FEV₁, FVC, and FEV₁/FVC at randomization. A sensitivity analysis was performed, and asthma severity stratum was added to the analysis of covariance model. Time to first predefined asthma event and time to withdrawal were described using Kaplan-Meier plots. Differences between treatment groups were analyzed using a log-rank test. Exploratory post hoc analyses investigated the effect of outlier data on pulmonary function variables, assessed the effect of treatment in participants with stable or decreasing FEV₁ during the run-in period, and stratified data for AM PEF and predose FEV₁ by self-reported region of descent (Puerto Rican, South or Central America and Mexican, Cuban and Caribbean, or Mixed descent).

RESULTS

Participants

Thirty-six centers participated in the study. Participant disposition is shown in Figure 1. Demographic and key baseline characteristics were balanced among treatment groups (Table 1); 50.8% of participants were of self-reported Mexican descent; and 21.2% were of self-reported Puerto Rican descent. At study entry, 91.2% of participants (*n* = 228) reported taking an ICS, most commonly BUD (33.6%), fluticasone (24.0%), and beclomethasone (18.4%); 39.2% (*n* = 98) reported taking ICS/LABA combination therapy. A similar proportion of participants in the BUD/FM and BUD groups reported use of ICS (92.1% and 90.2%, respectively) and ICS/LABA combination (38.6% and 39.8%, respectively) therapy.

Among randomized participants, mean daily ICS dose at study entry (screening) was similar in the BUD/FM (583 µg/day) and BUD groups (607 µg/day).

Efficacy

Pulmonary function. The AM PEF value increased from baseline during randomized treatment, with no statistically significant differences between the BUD/FM and BUD groups (Fig 2). Improvements occurred within 1 day with BUD/FM, which did not occur with BUD monotherapy. Results of sensitivity analyses based on ICS dose at entry (medium or high) and the per-protocol analysis set were consistent with the primary analysis. Improvements in PM

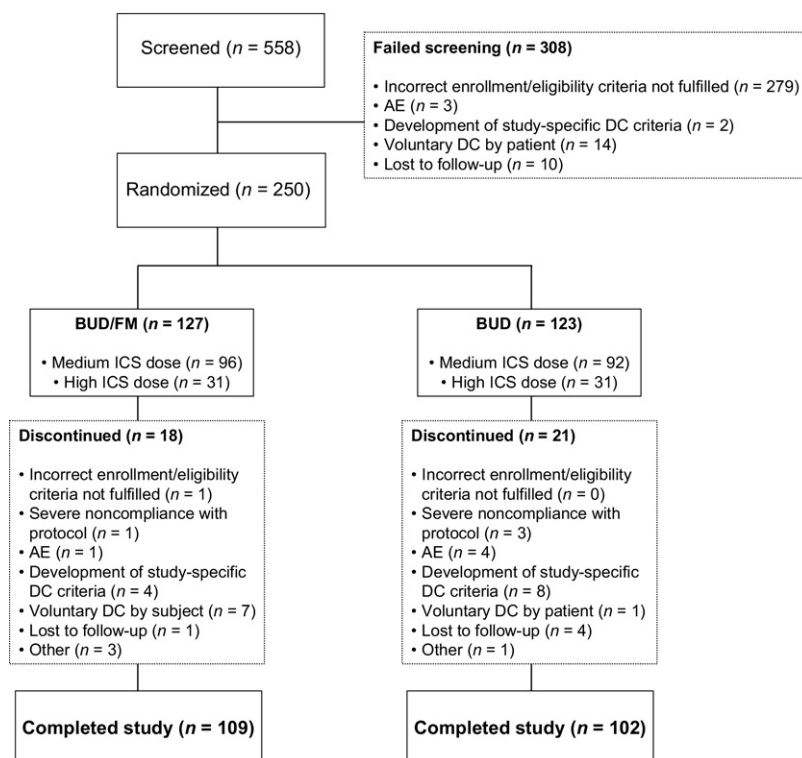


Figure 1. Patient disposition. Abbreviations: AE, adverse event; BUD, budesonide; DC, discontinuation; FM, formoterol; ICS, inhaled corticosteroid.

Table 1. Demographic and Key Baseline Characteristics for the Overall Population

Characteristic ^a	BUD/FM 320/9 µg n = 127	BUD 320 µg n = 123
Sex, n (%)		
Male	43 (33.9)	43 (35.0)
Female	84 (66.1)	80 (65.0)
Age, y	39.8 (16.6)	37.0 (14.9)
Body mass index, kg/m ²	31.4 (8.3)	31.1 (8.4)
Self-reported descent, n (%)		
Mexican	67 (52.8)	60 (48.8)
Puerto Rican	26 (20.5)	27 (22.0)
Cuban	17 (13.4)	16 (13.0)
South or Central American	13 (10.2)	18 (14.6)
Caribbean	2 (1.6)	1 (0.8)
Mixed Hispanic	2 (1.6)	1 (0.8)
Total ICS dose at entry, µg/d	582.5 (282.4)	607.0 (294.5)
Range	80–2000	80–1600
Predose FEV ₁ at screening		
L	2.07 (0.57)	2.12 (0.54)
% Predicted	68.3 (10.6)	68.0 (12.2)
Predose FEV ₁ at randomization		
L	2.20 (0.59)	2.22 (0.59)
% Predicted	72.6 (10.2)	70.9 (12.8)
Predose FVC (L)		
At screening	2.74 (0.89)	2.79 (0.77)
At randomization	2.82 (0.82)	2.88 (0.79)
Predose FEV ₁ /FVC		
At screening	0.77	0.76
At randomization	0.78	0.77
Postdose FEV ₁ /FVC at screening	0.81	0.80
% Reversibility in FEV ₁ at screening, L	27.7 (18.9)	25.3 (14.7)
PEF at baseline, L/min		
Morning	330.0 (90.0)	321.6 (83.6)
Evening	340.6 (92.6)	331.3 (83.8)

Abbreviations: BUD, budesonide; FEV₁, forced expiratory volume in 1 second; FM, formoterol; FVC, forced vital capacity; ICS, inhaled corticosteroid; PEF, peak expiratory flow.

^a Values are presented as mean (standard deviation) unless otherwise indicated.

PEF were similar with BUD/FM and BUD (Fig 2). Mean improvements from baseline predose FEV₁ to the mean during the randomized treatment period were not significantly different between treatments (0.16 L, BUD/FM vs 0.11 L, BUD). Mean predose FEV₁ was improved by week 2 and continued through to the end of treatment (0.17 L, BUD/FM vs 0.12 L, BUD), with no statistically significant differences. Mean FVC also improved from baseline to week 12 in both treatment groups (0.16 L, BUD/FM and 0.11 L, BUD). Mean FEV₁/FVC ratio at the end of 12 weeks was 0.80 and 0.78 in the BUD/FM and BUD groups, respectively.

Predefined asthma events. Fewer participants receiving BUD/FM vs BUD had worsening asthma based on the predefined criteria (25.2% vs 31.7%) or were withdrawn (3.1%

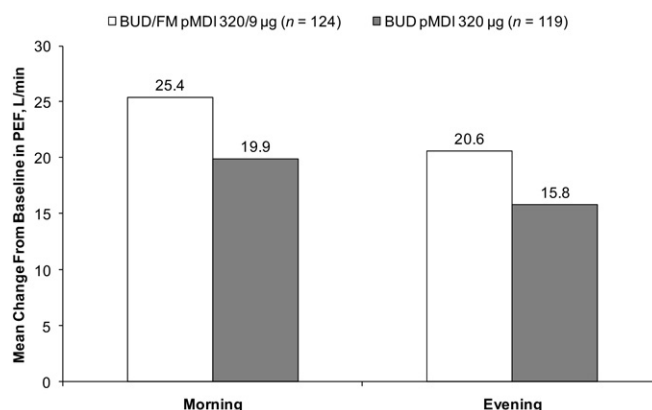


Figure 2. Mean change from baseline PEF to the mean during the randomized treatment period for the overall population. Baseline was defined as the mean of all values obtained from the 7-day period before randomization. Differences between treatment groups were not statistically significant ($P \geq .428$). Abbreviations: BUD, budesonide; FM, formoterol; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler.

vs 6.5%); the differences were not statistically significant. Time to first predefined asthma events occurred later with BUD/FM, but differences between the groups were not statistically significant (Fig 3).

Diary assessments. Symptom scores and rescue medication use decreased, and the percentage of symptom-free days, awakening-free nights, and rescue medication-free days increased with both treatments without statistically significant differences between groups (Table 2). Other outcomes are described in the e-Results.

Post hoc analyses. Potential reasons for the absence of statistical significance between the BUD/FM and BUD groups for the primary efficacy variable (AM PEF) were explored. An outlier analysis identified 1 male participant of Mexican descent in the BUD/FM group with an improbable baseline AM PEF of 900 L/min. Reanalysis of the primary variable after removing the outlier did not alter the overall result (AM PEF increased from 25.4 L/min to 27.4 L/min in the BUD/FM group). No obvious outliers were identified with regard to predose FEV₁.

Mean predose FEV₁ unexpectedly improved (2.10–2.21 L) after a “step-down” to low-dose ICS during the run-in. Therefore, a post hoc analysis was conducted in participants who did not have an improved FEV₁ after stepping down to low-dose ICS (33.2% of the total population; BUD/FM, $n = 43$; BUD, $n = 40$). In this subgroup, the size of improvement in AM and PM PEF in the BUD/FM group relative to BUD was substantially larger (13.7 vs -0.4 and 18.6 vs 1.2 L/min, respectively) than in the overall population (Fig 2). Total rescue medication use was reduced during the treatment period with BUD/FM (-0.5 inhalations/day) relative to BUD (0.1 inhalations/day); however, this difference was not significant.

Further analysis of run-in pulmonary function data stratified by region of descent showed that participants of Puerto

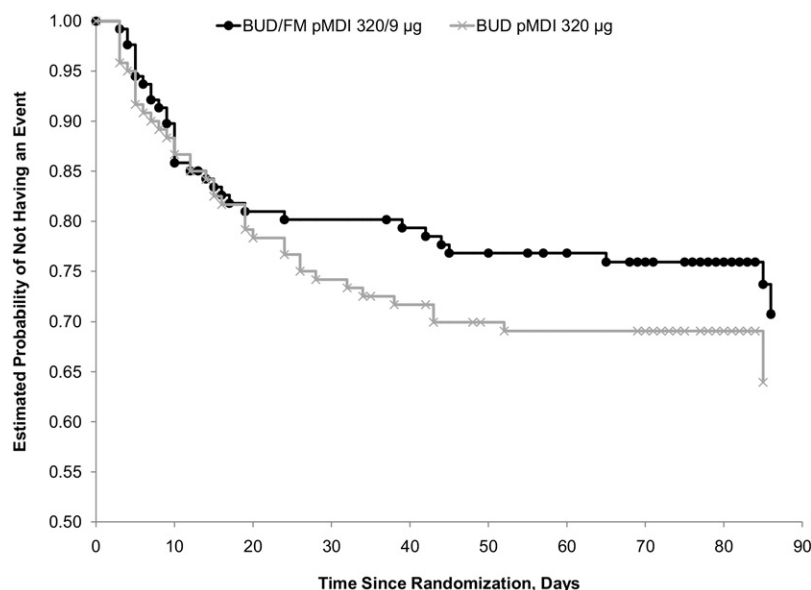


Figure 3. Kaplan-Meier probability curve for the time to first predefined event of asthma worsening. Data symbols represent the days on which censored observations occurred. Abbreviations: BUD, budesonide; FM, formoterol; pMDI, pressurized metered-dose inhaler.

Rican descent ($n = 47$) had lower predose screening FEV₁ and percent predicted FEV₁ (1.94 L and 62.9%, respectively) than those of Mexican descent (2.16 L and 70.6%; $n = 105$, respectively). However, after the 2-week low-dose BUD run-in, predose pulmonary function improved substantially in Puerto Ricans (Puerto Ricans, 10.4%; Mexicans, 2.8%). Accordingly, the differences in pulmonary function between the Puerto Rican and Mexican subpopulations were decreased vs screening values (predose FEV₁ = 2.14 L vs 2.22 L; % predicted FEV₁ = 69.4% vs 72.5%, respectively).

Stratification of data by region of descent showed numerically greater improvements from baseline in AM PEF to the mean over the randomized treatment period with BUD/FM vs BUD for all ethnic subpopulations except Puerto Rican, in which the magnitude of response was slightly higher for BUD (Fig 4A). Changes from baseline in mean predose FEV₁ to week 12 were consistently greater with BUD/FM vs BUD across ethnicities; however, the magnitude of response was lower in participants of Puerto Rican or South/Central American descent than in participants of Mexican or Cuban descent (Fig 4B). Relative values for BUD/FM vs BUD for AM PEF and predose FEV₁ were similar for men and women within each ethnic subgroup (data not shown). Percent reversibility in FEV₁ was greatest in participants of Cuban descent (31.7%), followed by those of Puerto Rican (27.1%), Mexican (25.8%), and South/Central American (25.0%) descent.

Safety

The percentage of participants with at least 1 AE during randomized treatment was similar in the BUD/FM and BUD groups (40.9% and 37.4%, respectively). Most AEs were of mild or moderate intensity. AEs judged by the investigator to

be related to study medication occurred in 4 participants treated with BUD/FM and 1 participant treated with BUD (e-Table 1); all were judged to be of mild or moderate intensity. Four participants experienced serious adverse events (e-Table 1) during the randomized treatment period in the BUD/FM group; none was considered related to study medication, and only 1 (gastrointestinal hemorrhage) led to discontinuation. AEs leading to discontinuation during randomized treatment occurred in 1 BUD/FM participant (dysphagia and gastrointestinal hemorrhage) and 2 BUD participants (1, pharyngolaryngeal pain; 1, viral upper respiratory infection). No deaths occurred during the randomized treatment period. No clinically meaningful findings or differences were found between the 2 treatment groups in changes from baseline for serum glucose and potassium levels. No clinically significant changes in ECG results were seen for participants treated with BUD/FM vs those treated with BUD.

DISCUSSION

Research suggests that possible differences in response to asthma treatment related to ethnicity may exist,^{14,15} underscoring the importance of specific clinical data on medication response in these populations. The current study was designed primarily to evaluate the efficacy of adding a LABA to an ICS maintenance therapy in a heterogeneous Hispanic (self-reported) population with moderate to severe asthma. Results from overall and exploratory analyses show improvement in clinically relevant control end points for both the BUD/FM combination therapy and BUD monotherapy groups. Although results numerically favored BUD/FM over BUD in this population, no statistically significant between-

Table 2. Asthma Symptoms and Rescue Medication Use During Randomized Treatment

Variable ^a	BUD/FM 320/9 µg n = 125	BUD 320 µg n = 119
Daily symptom score ^b		
Baseline ^c	1.0 (0.6)	1.0 (0.5)
Change from baseline to treatment mean	−0.3 (0.4)	−0.3 (0.4)
Daytime symptom score ^b		
Baseline ^c	0.9 (0.6)	1.0 (0.5)
Change from baseline to treatment mean	−0.3 (0.5)	−0.3 (0.4)
Nighttime symptom score ^b		
Baseline ^c	1.0 (0.6)	1.0 (0.5)
Change from baseline to treatment mean	−0.3 (0.5)	−0.3 (0.5)
Symptom-free days (% of days) ^d		
Baseline ^c	17.2 (26.5)	11.8 (21.0)
Change from baseline to treatment mean	18.5 (30.9)	17.9 (31.0)
Awakening-free nights (% of nights)		
Baseline ^c	78.8 (19.9)	75.8 (22.8)
Change from baseline to treatment mean	7.3 (24.0)	9.9 (22.8)
Rescue medication use, inhalations/day		
Baseline ^c	2.0 (2.0)	2.0 (1.9)
Change from baseline to treatment mean	−0.7 (1.2)	−0.6 (1.9)
Rescue medication-free days (% of days)		
Baseline ^c	37.3 (37.4)	35.9 (36.8)
Change from baseline to treatment mean	17.6 (32.9)	16.7 (33.5)

Abbreviations: BUD, budesonide; FM, formoterol.

Differences between treatment groups were not statistically significant ($P \geq .181$).

^a Values are presented as mean (standard deviation) unless otherwise indicated.

^b Based on a 4-point scale where 0 = no symptoms and 3 = severe symptoms.

^c Defined as the mean of all values obtained from the 7-day period before randomization.

^d Defined as no morning or evening symptoms and no awakenings attributable to asthma.

group differences in pulmonary function and measures of asthma symptoms were observed.

One possible interpretation of the current study findings is that the addition of a LABA to an ICS does not result in treatment benefit beyond that of an ICS alone in Hispanic patients with moderate to severe asthma. The inclusion criteria of this study were designed to identify a population of moderate to severe asthma participants requiring medium- to high-dose ICS therapy, either alone or in combination with a

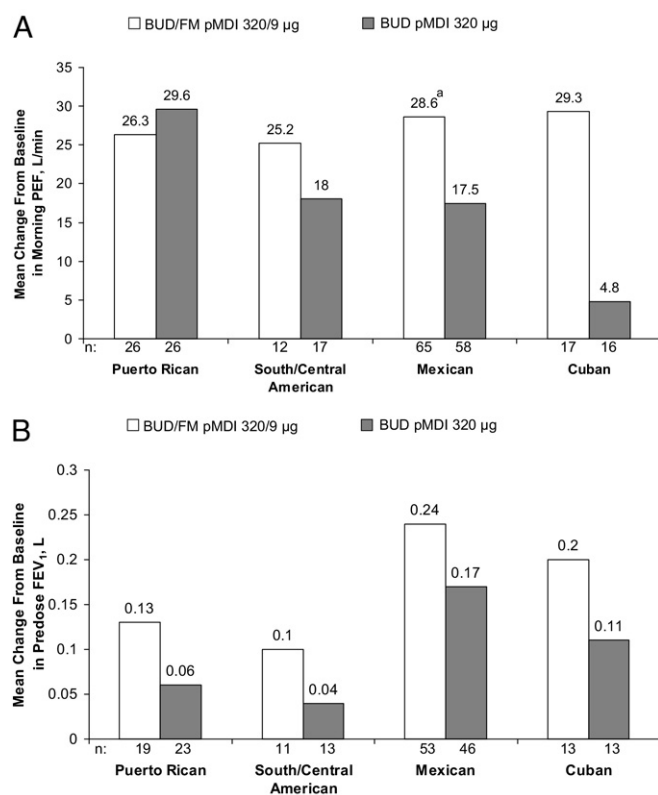


Figure 4. Post hoc analysis of data stratified by region for (A) mean changes from baseline to the mean during the randomized treatment period for morning PEF and (B) mean change from baseline to 12 weeks for predose FEV₁. Abbreviations: BUD, budesonide; FEV₁, forced expiratory volume in 1 second; FM, formoterol; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler. ^a Outlier data removed for 1 patient with baseline PEF value of 900 L/min in the BUD/FM group (value with outlier included = 20.4 L/min).

LABA, similar to the design of a study conducted in a predominately white population reported by Noonan et al.⁷ However, results from the current study suggested that this participant population may have had milder disease than was originally intended for the study, as evidenced by the notable and unexpected improvement in mean lung function after step-down to low-dose BUD over the run-in period. The reasons for failure to exclude mild or steroid-naïve participants from randomization in the current study remain speculative but may relate to study conduct issues, including inaccurate reporting of baseline ICS use at the time of screening (participant's historical ICS requirement not formally corroborated) and permitting rescreening of study applicants (if their disease severity warranted) after initiating therapy. These results contrast with the Noonan et al study in moderate to severe asthma patients⁷ and studies in patients with milder disease (OPTIMA,¹⁶ Corren et al⁶) in which larger and significant differences in improvements in pulmonary function variables were observed between the BUD/FM and BUD

groups. These studies also demonstrated the efficacy of BUD alone relative to placebo for pulmonary function and asthma control measures in a first controller population (OPTIMA A),¹⁶ and in patients with mild to moderate⁶ and moderate to severe⁷ asthma, a result that was presumed for the current trial. Because the current study did not include a placebo comparator arm to anchor relative efficacy, conclusions regarding asthma control end points are limited to improvements from baseline.

One explanation for the inconsistencies observed between the current study and other studies could be the inclusion of several different Hispanic ethnicities in this study. Differences in treatment response between racial subgroups have been noted in the literature, including differences in bronchodilator response and baseline pulmonary function between Mexican and Puerto Rican participants with asthma.⁴ Similar to the current study, Burchard et al⁴ reported significantly lower baseline pulmonary function in Puerto Rican vs Mexican participants. Stratification by severity in that study showed a statistically significant difference in baseline percentage predicted FEV₁ for participants with moderate to severe ($P = .004$) and mild asthma ($P = .007$).⁴ In the current study, baseline pulmonary function was lower in participants of Puerto Rican vs Mexican descent. However, this disparity decreased after the low-dose BUD run-in period, suggesting that both populations had a capacity for improved pulmonary function after ICS treatment in this study. These results complement findings from a previous report showing improved bronchodilator response after albuterol in Mexican American and Puerto Rican participants receiving ICS treatment.¹⁴ In participants of Puerto Rican descent in this study, the observed improvement in AM PEF was unusually high with BUD alone and of a magnitude typically seen with the BUD/FM combination treatment. These results contrast with those for all other ethnic subpopulations assessed in the exploratory post hoc analysis of AM PEF in this study. In the exploratory analysis of predose FEV₁ by region, results consistently favored BUD/FM over BUD in all ethnic subpopulations; however, the magnitude of improvement was lower with both treatments in participants of Puerto Rican or South/Central American descent vs Mexican or Cuban descent. Although the current study was not designed or powered to assess pulmonary function by ethnicity, these data, along with the Burchard et al⁴ data, suggest differences in baseline characteristics or barriers to asthma treatment between subpopulations of Hispanic participants.

Overall, the results from this study are consistent with current National Asthma Education and Prevention Program guidelines recommending ICS monotherapy for long-term control of mild persistent asthma and addition of a LABA to ICS therapy for patients with asthma that is inadequately controlled with ICS alone.¹⁷ Both BUD/FM and BUD treatments were well tolerated, with a safety profile consistent with that previously reported.^{6,7} The results from the overall and subgroup populations in the current study show improve-

ments from baseline in clinical outcomes in both the BUD/FM and BUD groups in a Hispanic asthma population.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anai.2011.05.024.

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Requests for reprints should be sent to:

James Zangrilli, MD
AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19803
E-mail: James.Zangrilli@astrazeneca.com

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1. a
2. b
3. b
4. c
5. d
6. d
7. a
8. c
9. c
10. d

e-METHODS

Study Design and Treatment

Participants were stratified by asthma severity, based on the daily dose of their inhaled corticosteroid (ICS) at study entry and 1997 National Asthma Education and Prevention Program guidelines.¹ The specified daily dose ranges for the medium-dose ICS group were beclomethasone dipropionate chlorofluorocarbon: 504–840 μg ; beclomethasone dipropionate hydrofluoroalkane: 160–280 μg ; budesonide (BUD): 400–600 μg ; BUD/formoterol (FM) pressurized metered-dose inhaler (pMDI): 160–320 μg ; flunisolide: 1,000–1,999 μg ; fluticasone chlorofluorocarbon: 264–440 μg , fluticasone hydrofluoroalkane: 264–460 μg ; fluticasone: 300–500 μg ; triamcinolone acetonide: 800–1,999 μg ; or mometasone: 440–559 μg . The high ICS-dose group included participants receiving daily doses above the medium-dose stratum upper limit of the previously mentioned ICSs. Participants with abnormal laboratory or ECG findings were allowed to participate, at the investigator's discretion. Electrocardiograms suggesting ischemia, QT interval (QTc) greater than 500 m/sec, uncontrolled atrial fibrillation, third-degree or type II second-degree atrioventricular block, or Wolff-Parkinson-White syndrome excluded participation.

Concomitant Medications

Any asthma medication other than study medication was disallowed, including other ICS, long-acting β_2 -adrenergic agonists, short-acting β_2 -adrenergic agonists other than supplied albuterol, anticholinergics, omalizumab (or any other monoclonal or polyclonal antibody therapy), leukotriene antagonists, and systemic corticosteroids (taken for any indication). Additional disallowed medication included hydroxyzine and β -adrenoceptor antagonists (β -blockers), including eyedrops. Medications allowed included antitussives (not containing ephedrine or other bronchodilators) as needed, mucolytics (not containing ephedrine), and nasal corticosteroids. Under most circumstances, use of a disallowed medication resulted in discontinuation from the study.

Other Efficacy Evaluations and Statistical Analysis

Other secondary outcome variables included participant perception of onset of effect, participant and physician global assessments of overall control of asthma symptoms, and the Patient Satisfaction with Asthma Medication Questionnaire (PSAM). Participant perception of onset of effect was assessed using the Onset of Effect Questionnaire (OEQ) as described previously.² Participant and physician global assessments of overall asthma control were collected by electronic case report forms at week 12 or on early withdrawal. Participants 18 years of age or older completed the PSAM as described previously.³

The patient-reported outcomes analysis set included all participants from the safety analysis set who were 18 years of age or older. Responses on the OEQ were transformed to a dichotomous (yes/no) variable and compared between treatment groups using Fisher exact test.² No baseline values were avail-

able for PSAM scores, and data were analyzed at weeks 2, 6, and 12 and at the end of treatment by analysis of variance.

Safety Evaluations

Participants recorded adverse events (AEs) daily. Beginning at enrollment, participants recorded "Yes" or "No" to the question, "Have you experienced any new medical problems today?" in a notebook diary. Participants also recorded whether they had used any nonstudy medications to treat such conditions. The participants' electronic diary reminded them to record the events at the end of each day.

e-RESULTS

Participant/Physician-Reported Outcomes

Based on the OEQ, a statistically significantly higher percentage of participants treated with BUD/FM perceived their medication working right away and were satisfied with how quickly they felt the medication work (88.8% and 91.8%, respectively) compared with participants treated with BUD (77.0% and 75.9%, respectively) at the end of week 1 ($P = .048$ and $P = .004$, respectively). At treatment's end, between-group differences in responses to the perception and satisfaction questions were not statistically different.

Global assessments were made by all participants and physicians at the end of treatment. Participant global assessments for questions of health status ("Compared with the start of the study, how would you rate your health now?") and asthma management ("Since the start of the study, how would you evaluate your ability to manage your asthma?") were similar, with 88.7% and 86.3% of participants treated with BUD/FM and 89.6% and 89.7% of participants treated with BUD, respectively, responding positively. At the end of treatment, 85% to 92% of physicians provided positive responses to questions regarding symptoms ("Since the start of the study, how would you evaluate the subject's asthma symptoms?") and their ability to manage the participant's asthma ("Since the start of the study, how would you evaluate your ability to manage the subject's asthma?"), regardless of treatment.

At the end of treatment, participants rated BUD/FM significantly ($P = .044$) higher for the Control Relief Index and significantly ($P = .005$) higher for the Comparison with Other Medications Index of the PSAM versus BUD. Ratings for the Perception of Medication Index were higher, but not statistically different, for BUD/FM vs BUD.

Safety

AEs judged by the investigator to be related to study medication occurred in 4 participants treated with BUD/FM and 1 participant treated with BUD (e-Table 1); all were judged to be of mild or moderate intensity. Four participants experienced serious adverse events (e-Table 1) during the randomized treatment period in the BUD/FM group; none was considered related to study medication, and only 1 (gastrointestinal hemorrhage) led to discontinuation.

e-Table 1. Treatment-Related and Serious Adverse Events During Randomized Treatment

Category	Number (%) of participants, treatment group	
	BUD/FM 320/9 µg n = 127	BUD 320 µg n = 123
≥1 Treatment-related AE ^a	4 (3.1)	1 (0.8)
Jittery	1 (0.8)	0
Nasal congestion	1 (0.8)	0
Oral candidiasis	1 (0.8)	0
Palpitations (cardiac)	1 (0.8)	0
Pharyngolaryngeal pain	1 (0.8)	0
Rash	1 (0.8)	0
Throat irritation	1 (0.8)	0
Upper respiratory tract infection	0	1 (0.8)
Upper respiratory tract infection, viral	1 (0.8)	0
≥1 Serious AE	4 (3.1)	0
Cellulitis	1 (0.8)	0
Cholecystitis	1 (0.8)	0
Gastrointestinal hemorrhage ^b	1 (0.8)	0
Status asthmaticus	1 (0.8)	0

Abbreviations: AE, adverse event. BUD, budesonide; FM, formoterol.

^a No treatment-related AE led to study discontinuation.

^b Led to study discontinuation.

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