

Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients

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Background: The adjustable-dose budesonide/formoterol dry powder inhaler (DPI) has demonstrated similar or greater asthma control with less inhaled corticosteroid compared with the fixed-dose budesonide/formoterol DPI.

Objective: We sought to evaluate the efficacy, tolerability, and resource use of maintenance therapy with the adjustable-dose budesonide/formoterol pressurized metered-dose inhaler versus the fixed-dose budesonide/formoterol pressurized metered-dose inhaler and the fixed-dose fluticasone propionate/salmeterol DPI. **Methods:** This was a randomized, open-label, multicenter study of patients (N = 1225) 12 years and older with moderate-to-severe persistent asthma. After 10 to 14 days of current therapy, patients were randomized 2:1 to fixed-dose budesonide/formoterol (160/4.5 $\mu\text{g} \times 2$ inhalations [320/9 μg] twice daily) or fixed-dose fluticasone propionate/salmeterol (250/50 $\mu\text{g} \times 1$ inhalation twice daily) for 1 month (treatment period 1), after which, the fixed-dose fluticasone propionate/salmeterol group continued therapy and the fixed-dose budesonide/formoterol group was randomized 1:1 to fixed-dose budesonide/formoterol or adjustable-dose budesonide/formoterol (adjustable from 2 inhalations [320/9 μg] twice daily to 2 inhalations [320/9 μg] once daily or 4 inhalations [640/18 μg] twice daily) for 6 months (treatment period 2).

Results: There were no significant between-group differences in asthma exacerbations (primary variable), asthma symptoms, or lung function during the 7-month treatment period. Less study drug (inhalations per day, $P < .001$) was used with adjustable-dose versus fixed-dose budesonide/formoterol. All treatments were well tolerated.

Conclusions: Adjustable-dose and fixed-dose budesonide/formoterol showed no differences in asthma control or tolerability versus fixed-dose fluticasone propionate/salmeterol. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Budesonide, formoterol, fluticasone propionate, salmeterol, adjustable dosing, asthma

The combination of inhaled corticosteroids (ICSs) and long-acting β_2 -adrenergic agonists (LABAs) is recommended by the National Asthma Education and Prevention Program asthma guidelines for patients whose symptoms are not adequately controlled with low- to medium-dose ICSs alone.¹ Administering the ICS/LABA combination with 1 inhaler simplifies treatment, which might be important, because multiple medications can make adherence to treatment difficult.^{2,3}

Fixed-dose budesonide/formoterol dry-powder inhaler (DPI; 160/4.5 $\mu\text{g} \times 2$ inhalations twice daily or 200/6 $\mu\text{g} \times 2$ inhalations twice daily) and fixed-dose fluticasone propionate/salmeterol DPI (250/50 $\mu\text{g} \times 1$ inhalation twice daily) have demonstrated similar clinical efficacy.^{4,5} However, the adjustable-dose budesonide/formoterol DPI has demonstrated similar or greater improvements in asthma control with lower ICS use and economic costs versus the fixed-dose budesonide/formoterol DPI.^{4,6-9} Comparable safety and efficacy have been observed with the fixed-dose budesonide/formoterol DPI and pressurized metered-dose inhaler (pMDI).¹⁰

This study evaluated the efficacy, tolerability, and resource use of maintenance therapy with the adjustable-dose budesonide/formoterol pMDI after stabilization with a fixed-dose budesonide/formoterol pMDI compared with the fixed-dose budesonide/formoterol pMDI and the fixed-dose fluticasone propionate/salmeterol DPI in a large population (n = 1222) of adults and adolescents with moderate-to-severe asthma.

METHODS

Patients

Patients aged 12 years and older with a documented diagnosis of asthma, as defined by the American Thoracic Society,¹¹ for 6 months or more before

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Abbreviations used

AE:	Adverse event
DPI:	Dry powder inhaler
ICS:	Inhaled corticosteroid
LABA:	Long-acting β_2 -adrenergic agonist
PEF:	Peak expiratory flow
pMDI:	Pressurized metered-dose inhaler

screening and who were in stable condition were qualified to participate. Study procedures at screening are detailed in the Methods section of the Online Repository at www.jacionline.org. Patients were required to have a prebronchodilator FEV₁ of 50% or greater of predicted normal value and to have been maintained on a daily medium-dose ICS or ICS/LABA combination (allowed doses based on individual product dose ranges¹) for 12 weeks or longer before screening. Exclusion criteria included systemic corticosteroid use within 30 days before screening, a 20-pack-year or longer smoking history at screening, or a significant disease, respiratory tract infection, or illness that might interfere with the patient's lung function or participation in the study.

Study design and treatment

This was a randomized, open-label, 7-month, phase 3 US study (D5896C00005) conducted at 145 centers. The study comprised 3 phases: run-in (10–14 days), treatment period 1 (1 month, fixed-dose regimens), and treatment period 2 (6 months, adjustable-dose or fixed-dose regimens; Fig 1). During the run-in period, eligible patients remained on their current asthma therapy and were provided rescue albuterol. Patients with an FEV₁ of 50% or more of predicted value 6 or more hours after short-acting β_2 -adrenergic agonist use and 24 or more hours after LABA use who received 8 or more inhalations of albuterol during the last 10 days of the run-in period and demonstrated a mean morning peak expiratory flow (PEF) of between 50% and 85% of the PEF value obtained 15 minutes after albuterol pMDI (2–4 inhalations [90 μ g per inhalation]) during the last 7 days of the run-in period were eligible for randomization.

At visit 2 (first randomization and beginning of treatment period 1), eligible patients were randomized 2:1 to receive a fixed-dose budesonide/formoterol pMDI (160/4.5 μ g $\times$ 2 inhalations [320/9 μ g] twice daily) or a fixed-dose fluticasone propionate/salmeterol DPI (250/50 μ g $\times$ 1 inhalation twice daily) for 1 month (treatment period 1). Eligible patients who completed treatment period 1 (fixed-dose regimens) entered treatment period 2 (adjustable-dose or fixed-dose regimens) at visit 3 (Fig 1). Patients receiving a budesonide/formoterol pMDI during treatment period 1 were randomized to receive 6 months of fixed-dose budesonide/formoterol pMDI or adjustable-dose budesonide/formoterol pMDI (treatment period 2). Patients receiving a fixed-dose fluticasone propionate/salmeterol DPI during treatment period 1 continued the same treatment for the 6-month treatment period 2. Details of treatment adjustments in the adjustable-dose budesonide/formoterol pMDI arm are summarized in Fig 2. An albuterol pMDI was supplied to all patients for as-needed use. Disallowed medications and details of compliance assessments are included in the Methods section of the Online Repository.

The study protocol was approved by an institutional review board at each study center and conducted in conformance with guidelines for ethical treatment of human subjects, good clinical practice, and applicable local regulations. Patients or guardians provided written informed consent; minor patients provided written assent.

Efficacy evaluations

The primary efficacy variable was asthma control, as assessed by asthma exacerbations. An asthma exacerbation was defined as worsening asthma requiring oral corticosteroid treatment; if a second course of corticosteroids was required, it was considered a second exacerbation. The time from the first

dose of randomized treatment to the first exacerbation, the number of exacerbations per patient-treatment year, and the number (percentage) of patients with 1 or more exacerbations were assessed.

Secondary variables included predose FEV₁ (performed at clinic visits 1–5); morning PEF, daytime and nighttime asthma symptom scores (4-point scale: 0, none; 1, mild; 2, moderate; 3, severe; recorded on awakening and before going to bed), nighttime awakenings caused by asthma, and daily rescue medication use (all recorded daily by patients in a paper diary after visit 1); and average daily symptom scores, symptom-free days (24-hour period with no asthma symptoms and no nighttime awakenings due to asthma), awakening-free nights, rescue medication-free days (24-hour period with no rescue medication use), and asthma control days (24-hour period with no asthma symptoms, no nighttime awakenings caused by asthma, and no rescue medication use). When possible, the PEF measurement was to be taken 6 or more hours after rescue medication and always before the morning dose of study medication.

Health care resource use evaluations

During the randomized treatment period (beginning at visit 2), patients recorded direct resource use in their diaries. Study medication use was assessed in all treatment groups during the randomized treatment period; the number of patients with a step up (8 puffs per day) or step down (2 puffs per day) in therapy in the adjustable-dose budesonide/formoterol pMDI group was assessed during treatment period 2. Details of direct health care resource use variables are described in the Methods section of the Online Repository.

Safety evaluations

Safety evaluations were based on adverse events (AEs), serious AEs, and discontinuations caused by AEs. Further details of AE assessments are provided in the Methods section of the Online Repository. Vital signs were assessed at baseline (visit 1) and at study visits 2 to 5. Comprehensive physical examinations were conducted at visits 1 and 5; brief physical examinations were conducted at visits 2 through 4.

Statistical analyses

Efficacy analyses included randomized patients who received 1 or more doses of randomized study medication and contributed data sufficient to calculate 1 or more primary or secondary efficacy end points. Safety analyses included all patients who received 1 or more doses of study medication. A sample size of 400 patients per treatment group was estimated to provide 90% or greater power for a hazard ratio of 1.4 or more for the primary efficacy variable and to detect a 0.15-L difference in FEV₁. This study was designed as a superiority trial to demonstrate statistically significant differences between treatment groups. All statistical comparisons were conducted as 2-sided tests; statistical significance was defined as a *P* value of .05 or less.

Efficacy data were analyzed for 3 periods: first month (treatment period 1; fixed-dose regimens), last 6 months (treatment period 2; adjustable-dose or fixed-dose regimens), and all 7 months of treatment (overall randomized treatment period [considered primary]). Time to first asthma exacerbation was described by using a Kaplan-Meier plot and presented with the log-rank test; a Cox proportional hazard model with treatment as a factor was used to estimate hazard ratios and 95% CIs for treatment group comparisons. The number of patients with 1 or more exacerbations was compared between groups by using a χ^2 test. The number of exacerbations per patient-treatment year was analyzed by using a Poisson regression model with exposure as an offset variable. Spirometric and diary data were analyzed as the change from baseline to the average over the randomized treatment period by using analysis of covariance models. Baseline for spirometric data was defined as the predose measurement for each variable on the day of randomization. Baseline for PEF and diary variables was defined as the mean of all available days of the run-in period. Daily study medication use (average inhalations per day) was compared between groups by using ANOVA.

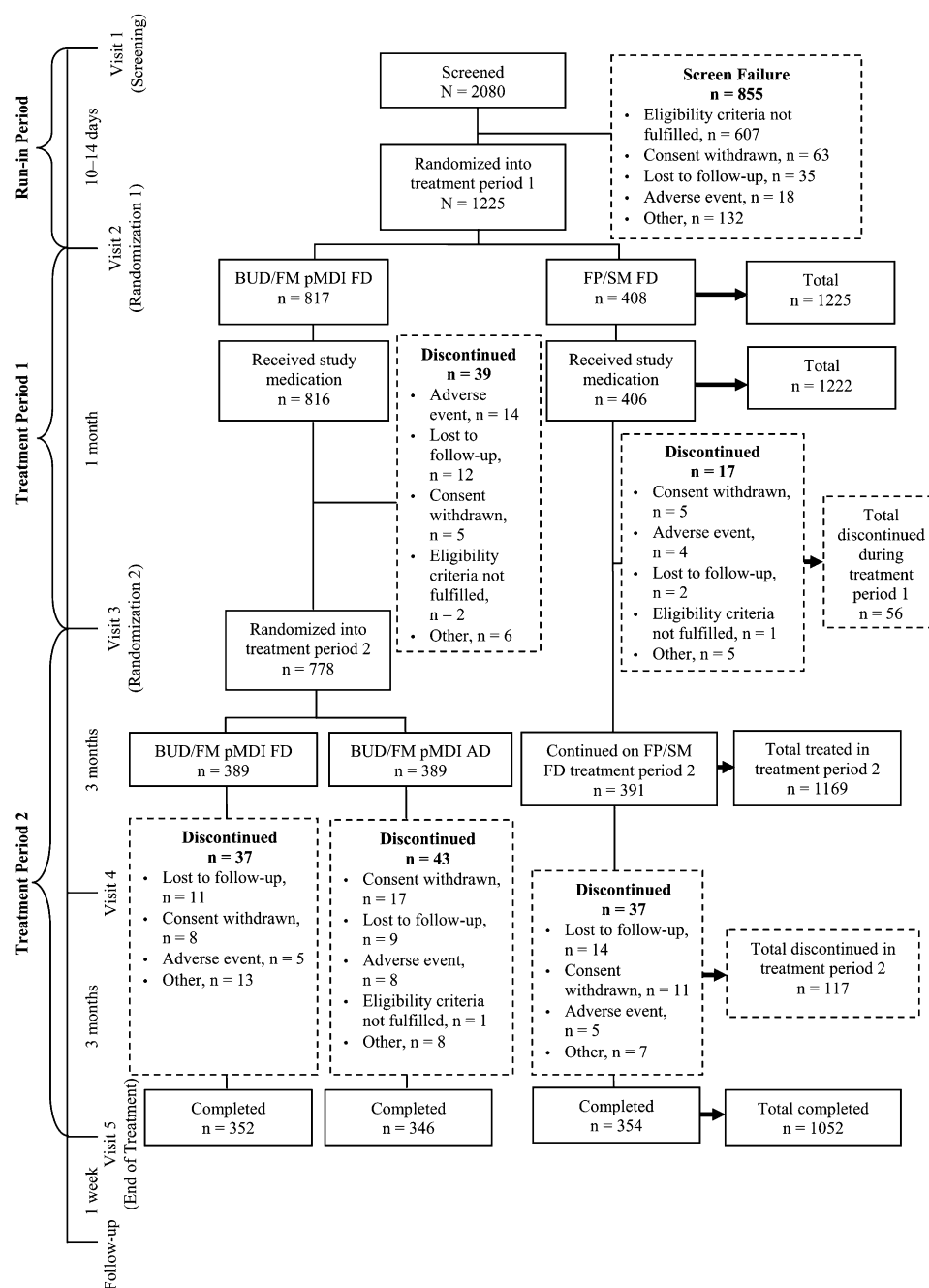


FIG 1. Study design and patient disposition. AD, Adjustable dose; BUD, budesonide; FD, fixed dose; FM, formoterol; FP, fluticasone propionate; SM, salmeterol.

Safety variables were summarized descriptively. Changes from baseline in vital signs to each visit and to the average for each treatment period were analyzed by using analysis of covariance models.

RESULTS

Patients

Patient disposition is shown in Fig 1. Baseline characteristics were generally similar across the 3 treatment groups (Table I). More than 99% of patients were using ICSs at study entry, the most common of which were fluticasone (either as a monoproduct or as a fluticasone propionate/salmeterol DPI) or budesonide.

Compliance data are presented in the Results section in the Online Repository at www.jacionline.org.

Efficacy

There were no significant differences between the treatment groups in time to first exacerbation (Fig 3) during the overall randomized treatment period, which is defined as the combination of treatment periods 1 and 2. No significant differences were observed for hazard ratios for the time to first asthma exacerbation during the overall randomized treatment period. Additionally, no significant between-group differences were observed in the

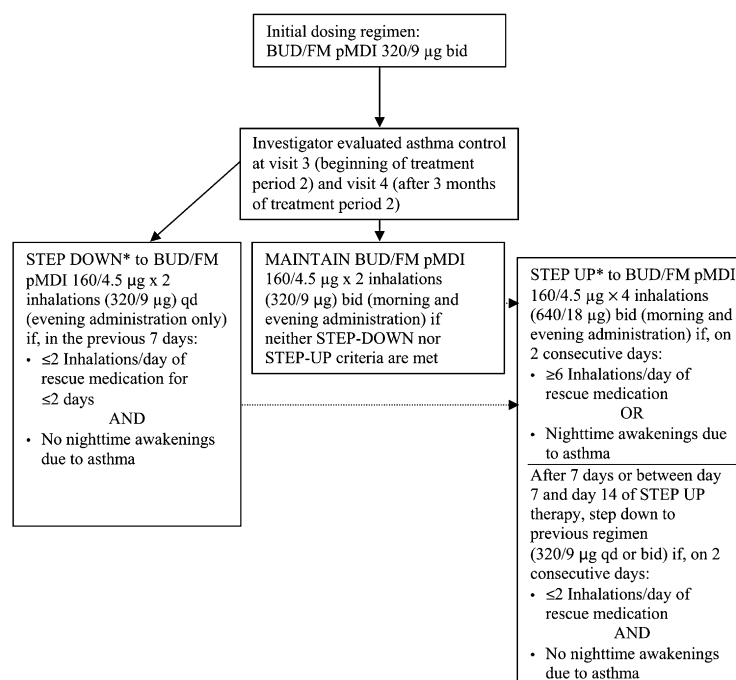


FIG 2. Criteria for dose adjustments in patients receiving adjustable-dose budesonide/formoterol. *Initial step ups and step downs were evaluated by the investigator. During the periods between visits, step ups and step downs to previous therapy were evaluated by the patient, with input from the investigator if needed. *BUD*, Budesonide; *FM*, formoterol; *bid*, twice daily; *qd*, once daily.

percentage of patients with 1 or more exacerbations or the total number of exacerbations per patient-treatment year during the overall randomized treatment period (Table II). Similar to the overall randomized treatment period, analyses for the time to first exacerbation, the percentage of patients with 1 or more exacerbations, and the total number of exacerbations per patient-treatment year during treatment period 1 or during treatment period 2 were not significantly different between treatment groups (data not shown).

Improvements from baseline to the average of the overall randomized treatment period were observed in all spirometric and diary variables in all treatment groups, with no statistically significant between-group differences observed for these variables or for symptom-free days, awakening-free nights, rescue medication-free days, and asthma control days (Table III).

Over treatment period 1, improvements from baseline in the percentage of patients with rescue medication-free days were significantly ($P = .009$) greater for the fixed-dose budesonide/formoterol pMDI versus the fixed-dose fluticasone propionate/salmeterol DPI, although significant differences were not observed for this measure over treatment period 2. Results for all other secondary efficacy variables over treatment periods 1 and 2 were similar to those from the overall randomized treatment period.

Health care resource use

Of the 389 patients receiving the budesonide/formoterol pMDI (320/9 µg twice daily) in treatment period 1 and the adjustable-dose budesonide/formoterol pMDI in treatment period 2, 77% were able to step down from 2 inhalations twice daily to 2 inhalations once daily, whereas 22% needed to step up from 2 inhalations once or twice daily to 4 inhalations twice daily.

Approximately one fourth of the patients in the adjustable-dose arm continued to receive the budesonide/formoterol pMDI (160/4.5 µg × 2 inhalations [320/9 µg] once daily) throughout treatment period 2; only 8% received the budesonide/formoterol pMDI (160/4.5 µg × 4 inhalations [640/18 µg] twice daily) for 2 or more weeks. The numbers and percentages of patients able to step down therapy or who needed to step up therapy are summarized in Table E1 (available in the Online Repository at www.jacionline.org). Patients in the adjustable-dose budesonide/formoterol pMDI group used, on average, significantly ($P < .001$) fewer inhalations of study medication per day (mean, 3.0 inhalations per day) than the patients in the fixed-dose budesonide/formoterol pMDI group (mean, 4.0 inhalations per day) during treatment period 2. Results of direct health care resource use variables are presented in the Results section and Table E2 of the Online Repository.

Safety

All treatments were well tolerated. AEs were mostly mild (56.1%) or moderate (38.4%) in intensity, with a similar distribution in each treatment group. No clinically important differences in the percentages of patients reporting AEs were observed in subgroups divided according to age or race. No study medication-related AEs were considered serious. Further details are provided in Table E3 and the Results section of the Online Repository at www.jacionline.org.

DISCUSSION

This is the first study to compare clinical outcomes with the US-approved fixed-dose regimen of budesonide/formoterol

TABLE I. Demographic and key baseline characteristics of all randomized patients

Characteristic	Adjustable-dose BUD/FM (n = 389)	Fixed-dose BUD/FM (n = 427)	Fixed-dose FP/SM (n = 406)
Sex, no. (%)			
Male	170 (43.7)	146 (34.2)	174 (42.9)
Female	219 (56.3)	281 (65.8)	232 (57.1)
Race, no. (%)			
White	320 (82.3)	350 (82.0)	341 (84.0)
Black	48 (12.3)	59 (13.8)	50 (12.3)
Other	21 (5.4)	18 (4.2)	15 (3.7)
Age (y)			
Mean (SD)	38.4 (15.8)	39.4 (15.9)	38.8 (15.9)
Range	12-87	12-79	12-82
Age groups, n (%)			
12 to <16 y	43 (11.1)	42 (9.8)	43 (10.6)
16 to <65 y	330 (84.8)	357 (83.6)	339 (83.5)
≥65 y	16 (4.1)	28 (6.6)	24 (5.9)
Duration of asthma (y)			
Mean (SD)	18.7 (14.6)	19.6 (15.6)	19.1 (14.5)
Range	0.5-63.6	0.5-67.0	0.2-68.9
Mean total daily ICS dose at study entry, $\mu\text{g}/\text{d}$ (SD)	538.9 (200.3)	555.7 (210.1)	542.8 (181.1)
Mean total FP/SM DPI dose at study entry, $\mu\text{g}/\text{d}$ (SD)	561.1 (206.2)	560.7 (220.5)	565.9 (187.2)
Mean total fluticasone dose at study entry, $\mu\text{g}/\text{d}$ (SD)	482.0 (140.7)	502.3 (165.4)	484.0 (130.9)
Mean total budesonide dose at study entry, $\mu\text{g}/\text{d}$ (SD)	503.7 (189.3)	561.7 (198.4)	535.2 (204.8)
Mean rescue medication use, inhalations/day (SD)	2.5 (2.1)	2.4 (1.7)	2.5 (1.8)
FEV ₁ at screening			
Mean (SD), L	2.6 (0.8)	2.5 (0.7)	2.6 (0.7)
% Predicted, mean (SD)	78.9 (16.8)	79.3 (15.4)	77.9 (14.2)
Predose FEV ₁ at randomization			
Mean (SD), L	2.7 (0.8)	2.5 (0.7)	2.6 (0.7)
% Predicted, mean (SD)	79.4 (16.1)	79.6 (15.2)	78.1 (14.3)

BUD, Budesonide; FM, formoterol; FP, fluticasone propionate; SM, salmeterol.

pMDI with that of the fixed-dose fluticasone propionate/salmeterol DPI. In this study, measures of pulmonary function and asthma control, including the primary efficacy variable asthma exacerbations, were not significantly different in patients receiving the adjustable-dose budesonide/formoterol pMDI, the fixed-dose budesonide/formoterol pMDI, and the fixed-dose fluticasone propionate/salmeterol DPI. However, the adjustable-dose budesonide/formoterol pMDI group required significantly ($P < .001$) less study medication versus the fixed-dose budesonide/formoterol pMDI group (mean, 3.0 vs 4.0 inhalations per day, respectively) during treatment period 2. The clinical significance of this reduction in study medication use is not known.

The lack of significant differences in the rates of asthma exacerbations between the fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI groups are consistent with results reported in previous studies comparing the fixed-dose budesonide/formoterol DPI and the fixed-dose fluticasone propionate/salmeterol DPI at the same dosage regimens used in the present study.^{4,5} In addition, a recent study by Kuna et al¹² demonstrated a similar time to first severe exacerbation and total number of severe exacerbations between the fixed-dose budesonide/formoterol DPI and fixed-dose fluticasone propionate/salmeterol pMDI.

The rate of exacerbations also was not significantly different between the fixed-dose budesonide/formoterol pMDI and adjustable-dose budesonide/formoterol pMDI arms in the present study, which is consistent with the results reported by Aalbers et al.⁴ However, other studies with step-up criteria similar to those used in the Aalbers et al study demonstrated a significant ($P < .05$)

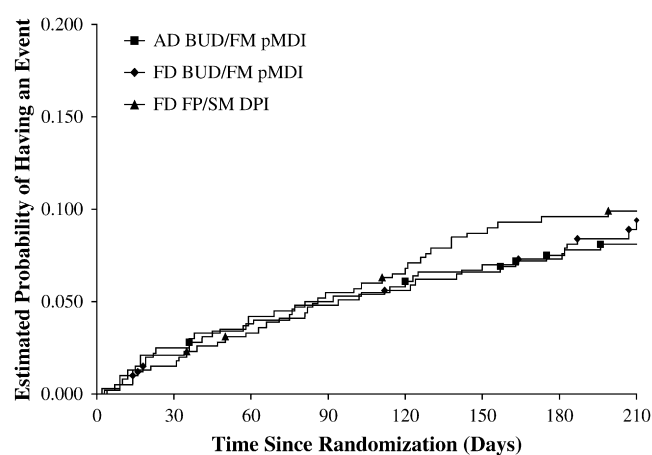


FIG 3. Kaplan-Meier curve for the time to first asthma exacerbation during the overall randomized treatment period. The estimated probability of having an asthma exacerbation at each time point is shown. Data symbols represent the days on which censored observations occurred. Hazard ratios (95% CIs) for treatment comparisons are as follows: adjustable-dose budesonide/formoterol pMDI versus fixed-dose fluticasone propionate/salmeterol DPI (0.847 [95% CI, 0.526–1.366; $P = .496$]), fixed-dose budesonide/formoterol pMDI versus adjustable-dose budesonide/formoterol (1.163 [95% CI, 0.722–1.875; $P = .535$]), and fixed-dose budesonide/formoterol pMDI versus fixed-dose fluticasone propionate/salmeterol (0.994 [95% CI, 0.791–1.248; $P = .958$]). AD, Adjustable dose; BUD, budesonide; FM, formoterol; FD, fixed dose; FP, fluticasone propionate; SM, salmeterol.

reduction in asthma exacerbation rates in the adjustable-dose versus fixed-dose budesonide/formoterol DPI groups.^{8,9}

TABLE II. Summary of asthma exacerbation results during the overall randomized treatment period (treatment periods 1 and 2)

	Adjustable-dose BUD/FM (n = 389)	Fixed-dose BUD/FM (n = 422)	Fixed-dose FP/SM (n = 404)	Comparisons between group estimate (95% CI)		
				Adjustable-dose BUD/FM vs fixed-dose FP/SM	Fixed-dose BUD/FM vs fixed-dose FP/SM	Fixed-dose BUD/FM vs adjustable-dose BUD/FM
Patients with ≥1 exacerbation,* no. (%)	31 (8.0)	37 (8.8)	37 (9.2)	0.859 (0.522-1.415)	0.953 (0.591-1.537)	1.110 (0.674-1.827)
Exacerbations per patient- treatment year†	0.196	0.240	0.189	1.041 (0.673-1.609)	1.272 (0.841-1.925)	1.222 (0.810-1.844)

BUD, Budesonide; FM, formoterol; FP, fluticasone propionate; SM, salmeterol.

*Estimates are odds ratios; *P* values are derived from χ^2 tests.

†Estimates are rate ratios; *P* values are derived from Poisson regression analysis.

The similar asthma exacerbation rates in the adjustable-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI groups in this study differed from the results reported by Aalbers et al⁴ and FitzGerald et al,¹³ in which a lower and higher rate of exacerbations, respectively, was observed with the adjustable-dose budesonide/formoterol DPI versus that with the fixed-dose fluticasone propionate/salmeterol DPI. The discrepancy in results might be due to methodological differences among the studies. For example, less stringent criteria for step-down dosing and more stringent criteria for step-up dosing were used in the present study compared with the Aalbers et al⁴ study, with step-down therapy only possible at the end of the double-blind treatment period in the Aalbers et al study. In the study by FitzGerald et al,¹³ the step-down dose was lower (budesonide/formoterol DPI, 200/6 μ g [metered-dose equivalent to 160/4.5 μ g delivered dose] $\times$ 1 inhalation once daily) compared with the present study (budesonide/formoterol pMDI, 160/4.5 μ g $\times$ 2 inhalations [320/9 μ g] once daily) and compared with all other studies investigating adjustable dosing with the budesonide/formoterol DPI.^{4,8,9,13} The doses of budesonide/formoterol pMDI (160/4.5 μ g $\times$ 2 inhalations twice daily) and fluticasone propionate/salmeterol DPI (250/50 μ g $\times$ 1 inhalation twice daily) used in this study are the recommended dosing regimens for patients with moderate-to-severe asthma.^{14,15}

Improvements in secondary measures of pulmonary function and asthma symptoms were similar among the treatment groups. These results are consistent with those of 2 previous studies, in which measures of lung function (FEV₁ and PEF) and asthma symptoms were similar among the fixed-dose budesonide/formoterol DPI and fluticasone propionate/salmeterol DPI groups.^{5,12} However, the results of the present study differ from those reported by Aalbers et al,⁴ in which small but significantly greater improvements in FEV₁ were observed in the fixed-dose budesonide/formoterol DPI group versus the fixed-dose fluticasone propionate/salmeterol DPI group.

Study medication use (inhalations per day) in the present study was lower with the adjustable-dose budesonide/formoterol pMDI versus the fixed-dose budesonide/formoterol pMDI, which is similar to that seen in other studies comparing the adjustable-dose budesonide/formoterol DPI with the fixed-dose budesonide/formoterol DPI.^{4,7,9,16,17} Study medication use between the adjustable-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI arms in this study was not informative because 2 inhalations were required to deliver a full dose of the budesonide/formoterol pMDI, whereas 1 inhalation was required to deliver a full dose of the fluticasone propionate/salmeterol DPI. However, there was no difference in efficacy observed between the fixed-dose fluticasone propionate/salmeterol

DPI and adjustable-dose budesonide/formoterol pMDI treatments. These results are consistent with the results of health economic analyses that demonstrated that lower health care costs and medication use are achievable with no loss of asthma control with adjustable- versus fixed-dose budesonide/formoterol DPI.^{6,16}

Overall, the adjustable-dose budesonide/formoterol pMDI, fixed-dose budesonide/formoterol pMDI, and fixed-dose fluticasone propionate/salmeterol treatments in this study were well tolerated, with no new safety concerns identified. These results are similar to those reported in other studies evaluating fixed- or adjustable-dose budesonide/formoterol DPI and fixed-dose fluticasone propionate/salmeterol DPI.^{4,5}

Certain aspects of the study design must be considered when interpreting the results from this study. A limitation of the present study is its open-label design; knowledge of the treatment assignment might have influenced more subjective measures, such as rescue medication use or asthma symptoms. However, it is unlikely that the incidence of asthma exacerbations or other clinical measures were influenced by the lack of blinding. The lack of inclusion of a placebo arm might have limited a complete evaluation of how well asthma control was maintained in patients switched to the adjustable-dose budesonide/formoterol pMDI arm because their asthma was stabilized before beginning adjustable-dose therapy. Also, the addition of a once-daily fluticasone propionate/salmeterol DPI arm would have allowed for more informative comparisons between the fixed-dose fluticasone propionate/salmeterol DPI and the adjustable-dose budesonide/formoterol pMDI.

Recent data have suggested that in patients with mild-to-moderate asthma that is controlled with twice-daily dosing with the budesonide/formoterol pMDI, continuation of this regimen generally is more effective than taking the same dose once daily (ie, half the total daily dose).¹⁸ In the present study, 26% of patients continued taking the budesonide/formoterol pMDI once daily over 6 months during treatment period 2. Identification of the population of patients who were able to continue with half the total daily dose of budesonide/formoterol pMDI in the present study is not possible without empiric testing. Also, because asthma control varies over time, it is not clear how long any one patient would continue this reduced dosing regimen without meeting the step-up criteria in this study. The present study, which used a more flexible dosing regimen in patients with moderate-to-severe asthma, provides some insight as to asthma control with the budesonide/formoterol pMDI in patients who might not be fully adherent and might transiently reduce their prescribed daily medication dose by half.

In conclusion, the results of this study suggest no differences in asthma control and tolerability between adjustable dosing of the

TABLE III. Summary of secondary variables during the overall randomized treatment period (treatment periods 1 and 2)

Variable	Differences between groups (95% CI)*†					
	Adjustable-dose BUD/FM	Fixed-dose BUD/FM	Fixed-dose FP/SM	Adjustable-dose BUD/FM minus fixed-dose FP/SM	Fixed-dose BUD/FM minus fixed-dose FP/SM	Fixed-dose BUD/FM minus adjustable-dose BUD/FM
Predose FEV ₁ (L)						
No. of patients	387	396	391			
Baseline, mean (SD)	2.66 (0.77)	2.52 (0.72)	2.60 (0.74)			
Mean change (SD)	0.13 (0.25)	0.15 (0.28)	0.16 (0.31)	−0.03 (−0.07 to 0.01)	−0.02 (−0.06 to 0.02)	0.01 (−0.03 to 0.06)
Morning PEF (L/min)						
No. of patients	388	405	397			
Baseline, mean (SD)	358.52 (100.66)	348.42 (91.17)	350.39 (93.73)			
Mean change (SD)	34.73 (47.01)	30.86 (42.11)	33.59 (44.02)	1.75 (−4.75 to 8.26)	−4.34 (−10.73 to 2.05)	−6.10 (−12.65 to 0.46)
Daytime symptom score						
No. of patients	385	402	395			
Baseline, mean (SD)	1.01 (0.56)	1.02 (0.61)	1.03 (0.57)			
Mean change (SD)	−0.40 (0.55)	−0.37 (0.59)	−0.35 (0.56)	−0.03 (−0.10 to 0.04)	−0.02 (−0.09 to 0.05)	0.01 (−0.06 to 0.08)
Nighttime symptom score						
No. of patients	379	396	390			
Baseline, mean (SD)	1.01 (0.56)	1.01 (0.59)	1.03 (0.53)			
Mean change (SD)	−0.40 (0.54)	−0.36 (0.55)	−0.36 (0.54)	−0.03 (−0.10 to 0.04)	0.00 (−0.07 to 0.07)	0.03 (−0.04 to 0.10)
Average daily symptom score‡						
No. of patients	386	403	395			
Baseline, mean (SD)	1.00 (0.53)	1.02 (0.57)	1.04 (0.52)			
Mean change (SD)	−0.39 (0.51)	−0.37 (0.54)	−0.35 (0.53)	−0.3 (−0.09 to 0.04)	−0.01 (−0.08 to 0.06)	0.02 (−0.05 to 0.09)
Symptom-free days (%)						
No. of patients	385	404	395			
Baseline, mean (SD)	15.71 (24.65)	14.77 (24.78)	13.23 (22.60)			
Mean change (SD)	26.59 (34.93)	25.80 (34.26)	25.39 (33.41)	1.04 (−3.92 to 5.99)	−0.18 (−5.05 to 4.68)	−1.22 (−6.20 to 3.77)
Awakening-free nights (%)						
No. of patients	385	406	397			
Baseline, mean (SD)	85.22 (23.64)	83.88 (26.11)	86.75 (21.71)			
Mean change (SD)	10.03 (21.50)	10.02 (23.27)	7.73 (18.58)	1.10 (−0.47 to 2.66)	0.02 (−1.51 to 1.55)	−1.08 (−2.65 to 0.49)
Rescue medication use (puffs/d)						
No. of patients	387	406	396			
Baseline, mean (SD)	2.51 (2.11)	2.41 (1.71)	2.52 (1.81)			
Mean change (SD)	−1.42 (2.06)	−1.32 (1.60)	−1.30 (1.62)	−0.08 (−0.26 to 0.10)	−0.07 (−0.24 to 0.10)	0.01 (−0.17 to 0.19)
Rescue medication-free days (%)						
No. of patients	387	406	396			
Baseline, mean (SD)	18.99 (23.25)	19.21 (22.61)	17.86 (22.72)			
Mean change (SD)	41.84 (34.81)	41.24 (35.34)	38.85 (35.50)	2.15 (−2.67 to 6.97)	1.87 (−2.85 to 6.60)	−0.27 (−5.11 to 4.56)
Asthma control days (%)						
No. of patients	387	408	397			
Baseline, mean (SD)	8.12 (15.88)	7.71 (15.84)	5.99 (13.65)			
Mean change (SD)	28.43 (33.65)	28.14 (33.83)	26.36 (33.53)	1.56 (−3.34 to 6.45)	1.38 (−3.41 to 6.18)	−0.17 (−5.08 to 4.74)

BUD, budesonide; FM, formoterol; FP, fluticasone propionate; SM, salmeterol.

*Adjusted mean differences between groups, 95% CIs, and *P* values from analysis of covariance.†*P* values were nonsignificant for all comparisons.

‡Average of daytime and nighttime symptom scores measured on the same day.

budesonide/formoterol pMDI and fixed dosing of the budesonide/formoterol pMDI (320/9 µg twice daily) or the fluticasone propionate/salmeterol DPI (250/50 µg twice daily) in a large population of patients with moderate-to-severe persistent asthma. The results also suggest that an adjustable-dose budesonide/formoterol pMDI regimen might expose patients to lower levels of medication versus a fixed-dose regimen.

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Clinical implications: This study provides information about controlling asthma with the budesonide/formoterol pMDI by using dosing regimens adjusted according to asthma control.

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METHODS

Study design and treatment

At screening, patients were given a Mini-Wright peak flowmeter (Clement Clarke, Columbus, Ohio) to measure PEF and paper diary cards in which they were instructed to record data in the morning, evening, or both for several variables, including morning PEF (morning only), daytime and nighttime asthma symptom scores (morning and evening), use of rescue medication (evening only), and nighttime awakenings caused by asthma (morning only). Asthma symptoms were assessed on a 4-point scale (0 = none to 3 = severe). Additionally, patients recorded any AEs and use of concomitant medications.

Concomitant medications

After the screening visit, any asthma medication other than study medication was disallowed, including other ICSs, LABAs, leukotriene antagonists, nebulized albuterol, and systemic corticosteroids. Additional disallowed medications included hydroxyzine and β -blockers (including eye drops). Under most circumstances, use of disallowed medication was to result in discontinuation from the study. If patients were receiving a stable regimen of nasal corticosteroids or immunotherapy before screening, they were permitted to continue and were expected to continue the same regimen throughout the study.

Compliance with study medication was assessed based on the number of inhalations of study medication recorded in the diary relative to the expected number of inhalations of study medication based on the duration of the randomized treatment period for each patient. Compliance could not be assessed for patients receiving adjustable-dose budesonide/formoterol pMDI during treatment period 2 because of the nature of the adjustable-dosing regimen.

Health care resource use evaluations

Direct resource use included hospitalizations, emergency department visits, and urgent care clinic visits caused by an exacerbation; unscheduled office visits; and use of additional asthma-related medications, including oral and parenteral corticosteroids.

Safety

AEs were recorded by the patient in a daily diary and reviewed by the investigator at each study visit. AEs also were collected at clinic visits 2 through 5 and during a follow-up telephone call approximately 1 week after the last study visit. AEs also were collected when patients were asked a standard question ("Have you had any health problems since the previous visit?") at visits 2 through 5 and during a follow-up telephone call approximately 1 week after the last study visit. AEs were rated by the patient on the following scale: mild, an awareness of symptoms but easily tolerated; moderate, symptoms interfering with daily activities; severe, incapacitating with inability to perform normal daily activities. Each investigator evaluated all AEs regarding their causal relationship to study medication. AEs were considered serious if they resulted in death, were immediately life-threatening, required hospitalization, or resulted in significant disability or incapacity. Asthma symptoms or signs were to be recorded as AEs if they were serious, were judged by the investigator to be new to the patient or not consistent with the patient's preexisting asthma history (defined as within 1 year of screening), or caused the patient to discontinue the study.

Statistical analysis

The number of patients with 1 or more events for each direct resource use variable was analyzed in the efficacy analysis population by using a Cochran-Mantel-Haenszel test with modified ridit scores, with treatment and site as factors. When appropriate, the number of days or events per patient-treatment year of each variable was analyzed by using a Poisson regression model.

RESULTS

Patients

Compliance with fixed-dose regimens of the budesonide/formoterol pMDI and fluticasone propionate/salmeterol DPI

was 80% or greater for 92.8% and 93.8% of patients, respectively, during treatment period 1 and 90.7% and 91.6% of patients, respectively, during treatment period 2.

Health care resource use

During the overall randomized treatment period (including treatment periods 1 and 2), there were no significant differences between the treatment groups in the number of hospitalizations, emergency department or urgent care clinic visits, unscheduled health care provider visits, and days of use of oral or parenteral corticosteroids or other concomitant asthma-related medications per patient-treatment year (Table E2). However, events in resource use categories other than medication use were few, making it difficult to determine significant differences between treatment groups for these variables. Direct resource use results during treatment periods 1 and 2 were similar to the results from the overall randomized treatment period, with the exception of concomitant asthma-related medications other than oral or parenteral corticosteroids per patient-treatment year. The fixed-dose budesonide/formoterol pMDI group had significantly fewer days of concomitant asthma-related medication use than the fixed-dose fluticasone propionate/salmeterol DPI group for treatment periods 1 and 2 ($P < .001$), and both the fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI groups had significantly fewer days of concomitant asthma-related medication use ($P \leq .011$) than the adjustable-dose budesonide/formoterol pMDI group during treatment period 2.

Of the 389 patients receiving budesonide/formoterol pMDI (320/9 μg twice daily) in treatment period 1 and adjustable-dose budesonide/formoterol pMDI in treatment period 2, 77% were able to step down from 2 inhalations twice daily to 2 inhalations once daily, whereas 22% needed to step up from 2 inhalations once or twice daily to 4 inhalations twice daily. Approximately one fourth of the patients in the adjustable-dose arm continued budesonide/formoterol pMDI (320/9 μg daily) throughout treatment period 2, and only 8% received budesonide/formoterol pMDI (160/4.5 $\mu\text{g} \times 4$ inhalations [640/18 μg] twice daily) for 2 or more weeks. The numbers and percentages of patients able to step down therapy or who needed to step up therapy are summarized in Table E1. Overall, 110 episodes involved a step up in therapy: 79 involved stepping up from 2 inhalations twice daily, 28 from 2 inhalations once daily, and 3 from 4 inhalations twice daily. Of the 389 patients receiving the adjustable-dose budesonide/formoterol pMDI in treatment period 2, 321 (82.5%) did not require a step up in therapy; however, 43 (11.1%) patients had 1 step-up episode, 16 (4.1%) had 2 step-up episodes, 5 (1.3%) had 3 step-up episodes, 2 (0.5%) had 4 step-up episodes, and 2 (0.5%) had 6 step-up episodes.

Safety

All treatments were well tolerated. AEs were mostly mild (56.1%) or moderate (38.4%) in intensity, with a similar distribution in each treatment group. The most common AEs (occurring in $>0.5\%$ of all patients) judged by the investigators to be related to study medication during the overall randomized treatment period are presented in Table E3. During the overall randomized treatment period, the percentage of patients who experienced 1 or more AEs was 57.8% in the adjustable-dose budesonide/formoterol pMDI group, 61.6% in the fixed-dose budesonide/formoterol pMDI group, and 58.6% in the fixed-

dose fluticasone propionate/salmeterol DPI group. During treatment period 2, the percentage of patients experiencing 1 or more AEs was lowest in the adjustable-dose budesonide/formoterol pMDI group (46.3%) compared with the fixed-dose budesonide/formoterol pMDI group (55.8%) and the fixed-dose fluticasone propionate/salmeterol DPI group (50.4%).

No study medication-related AEs were considered serious. The number (percentages) of patients with any AE considered serious was low and similar across treatment groups: treatment period 1, 2 (0.2%) in the fixed-dose budesonide/formoterol pMDI group and 1 (0.2%) in the fixed-dose fluticasone propionate/salmeterol DPI group; treatment period 2, 6 (1.5%) in the adjustable-dose budesonide/formoterol pMDI group, 8 (2.1%) in the fixed-dose budesonide/formoterol pMDI group, and 8 (2.0%) in the fixed-dose fluticasone propionate/salmeterol DPI group. A total of 17 patients discontinued treatment because of drug-related AEs: 2 (0.5%) in the adjustable-dose budesonide/formoterol pMDI group, 12 (2.8%) in the fixed-dose budesonide/formoterol pMDI group, and 3 (0.7%) in the fixed-dose fluticasone propionate/salmeterol DPI group.

The incidence of asthma symptoms considered AEs during the overall randomized treatment period was, regardless of relationship to study medication, low and similar across the 3 treatment groups: 19 (4.9%) in the adjustable-dose budesonide/formoterol pMDI group, 18 (4.2%) in the fixed-dose budesonide/formoterol pMDI group, and 23 (5.7%) in the fixed-dose fluticasone propionate/salmeterol DPI group. There were 4 cases of asthma exacerbation resulting in hospitalization, 1 in the adjustable-dose budesonide/formoterol pMDI group and 3 in the fixed-dose fluticasone propionate/salmeterol DPI group.

No clinically important changes or treatment group differences were observed for vital signs (systolic and diastolic blood pressure, pulse rate, and height and weight) or physical examinations.

APPENDIX E1

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TABLE E1. Number (percentage) of patients in the budesonide/formoterol adjustable-dose group (n = 389) who stepped up or stepped down therapy during treatment period 2

Duration	Stepped down (BUD/FM 320/9 µg qd)	Stepped up (BUD/FM 640/18 µg bid)
Any duration	298 (77)	86 (22)
≥2 d	263 (68)	68 (18)
≥2 wk	254 (65)	31 (8)
≥12 wk	212 (54)	2 (1)
≥24 wk	102 (26)	0

BUD, Budesonide; *FM*, formoterol; *qd*, once daily; *bid*, twice daily.

TABLE E2. Direct resource use during the overall randomized treatment period*

Direct resource use variable†	Adjustable-dose BUD/FM (n = 389)	Fixed-dose BUD/FM (n = 422)	Fixed-dose FP/SM (n = 404)	Rate ratio (95% CI)‡§		
				Adjustable-dose BUD/FM minus fixed-dose FP/SM	Fixed-dose BUD/FM minus fixed-dose FP/SM	Fixed-dose BUD/FM minus adjustable-dose BUD/FM
Hospitalization due to asthma exacerbation						
Patients with ≥1 hospitalization, no. (%)	1 (0.3)	1 (0.2)	2 (0.5)			
Total no. of hospitalizations	1	1	3			
Total no. of hospitalizations per patient-treatment year	0.01	0.01	0.01	0.34 (0.04-3.25)	0.33 (0.04-3.20)	0.98 (0.06-15.71)
ED visit due to asthma exacerbation¶						
Patients with ≥1 visit, no. (%)	3 (0.8)	4 (0.9)	2 (0.5)			
Total no. of visits	3	4	3			
Total no. of visits per patient-treatment year	0.01	0.02	0.01	1.02 (0.21-5.03)	1.33 (0.30-5.94)	1.31 (0.29-5.85)
Urgent care clinic visits due to asthma exacerbation¶						
Patients with ≥1 visit, no. (%)	5 (1.3)	8 (1.9)	3 (0.7)			
Total no. of visits	5	8	3			
Total no. of visits per patient-treatment year	0.02	0.04	0.01	1.69 (0.40-7.08)	2.66 (0.71-10.03)	1.57 (0.51-4.81)
Unscheduled health care provider visits						
Patients with ≥1 visit, no. (%)	25 (6.4)	32 (7.6)	21 (5.2)			
Total no. of visits	44	43	34			
Total no. of visits per patient-treatment year	0.21	0.20	0.16	1.31 (0.84-2.06)	1.26 (0.81-1.98)	0.96 (0.63-1.46)
Oral and parenteral corticosteroids						
Patients with ≥1 use, no (%)	44 (11.3)	49 (11.6)	50 (12.4)			
Total no. of days of use	559	484	515			
Total no. of days of use per patient-treatment year	2.68	2.28	2.43	1.10 (0.81-1.50)	0.94 (0.68-1.29)	0.85 (0.62-1.17)
All other asthma-related medications						
Patients with ≥1 use, n (%)	16 (4.1)	26 (6.2)	24 (5.9)			
Total no. of days of use	449	312	438			
Total no. of days of use per patient-treatment year	2.15	1.47	2.07	1.04 (0.71-1.53)	0.71 (0.46-1.09)	0.68 (0.45-1.05)

BUD, Budesonide; FM, formoterol; FP, fluticasone propionate; SM, salmeterol; ED, emergency department.

*The overall randomized treatment period includes both treatment period 1 and treatment period 2.

†Patients might have been counted in 1 or more direct resource use subcategories.

‡P values were nonsignificant for all comparisons.

§Adjusted mean differences between groups and 95% CIs from analysis of covariance.

||The incidence of hospitalization caused by asthma exacerbation is based on data reported in patient diaries and differs from that reported by investigators as part of safety evaluations.

¶Results for emergency department visits and urgent care visits were mutually exclusive from results for unscheduled health care provider visit.

TABLE E3. Treatment-related AEs reported by more than 0.5% of all patients during treatment periods 1 and 2 and overall

AE	No. (%) of patients							
	Treatment period 1		Treatment period 2			Overall (treatment periods 1 and 2)		
	FD BUD/FM	FD FP/SM DPI	AD BUD/FM	FD BUD/FM	FD FP/SM DPI	AD BUD/FM	FD BUD/FM	FD FP/SM DPI
	pMDI (n = 816)	(n = 406)	pMDI (n = 389)	pMDI (n = 389)	(n = 391)	pMDI (n = 389)	pMDI (n = 427)	(n = 406)
Dysphonia	6 (0.7)	3 (0.7)	3 (0.8)	4 (1.0)	0	6 (1.5)	7 (1.6)	3 (0.7)
Headache	8 (1.0)	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.8)	6 (1.4)	3 (0.7)
Tremor	8 (1.0)	1 (0.2)	1 (0.3)	1 (0.3)	0	2 (0.5)	8 (1.9)	1 (0.2)
Oral candidiasis*	1 (0.1)	0	0	4 (1.0)	6 (1.5)	0	4 (0.9)	6 (1.5)
Pharyngolaryngeal pain	3 (0.4)	1 (0.2)	0	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.7)	4 (1.0)
Dysgeusia	5 (0.6)	0	2 (0.5)	0	0	3 (0.8)	3 (0.7)	0

FD, Fixed dose; BUD, budesonide; FM, formoterol; FP, fluticasone propionate; SM, salmeterol; AD, adjustable dose.

*Assessed on the basis of history and physical examination; culture confirmation was not required for reporting as an AE.