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Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study

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Summary
Background: Treatment with an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations. This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.
Methods: Following a 2-week run-in during which COPD patients aged ≥40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 μg, budesonide/formoterol pMDI 160/9 μg, or formoterol dry powder inhaler 9 μg. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.
Results: Budesonide/formoterol 320/9 and 160/9 reduced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol ($p \leq 0.002$).

Budesonide/formoterol 320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ratio (0.788 [95% CI: 0.639, 0.972]; $p = 0.026$). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol ($p \leq 0.023$). Both budesonide/formoterol doses were well tolerated with safety profiles similar to formoterol. Pneumonia adverse events occurred in 6.4%, 4.7%, and 2.7% of patients in the budesonide/formoterol 320/9, 160/9, and formoterol groups.

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Conclusions: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NCT00419744).
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Introduction

Although a standard definition has not been established,[1] the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define an exacerbation of chronic obstructive pulmonary disease (COPD) as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.[2] Increasing frequency of COPD exacerbations are an indication of increased disease severity[2] and have been associated with pulmonary function decline,[3,4] reduced quality of life,[5] and increased mortality.[6] Moreover, severe exacerbations of COPD are associated with increased health care utilization[7] and costs compared with mild or moderate exacerbations.[7,8]

Preventing and treating exacerbations of COPD is an important goal of disease management.[2] In patients with severe or very severe COPD who have repeated exacerbations, adding an inhaled corticosteroid (ICS) to a long-acting bronchodilator treatment is recommended.[2] Studies have shown benefits of regular ICS therapy relative to placebo in improving COPD symptoms,[9] reducing exacerbation frequency,[10,11] and improving quality of life.[10]

Treatment with budesonide/formoterol administered via a pressurized metered-dose inhaler (pMDI) has shown greater clinical benefits with regard to reducing COPD symptoms and improving pulmonary function and quality of life versus each monocomponent in a 6-month study[12] and versus formoterol in a 12-month study[13] in patients with moderate to very severe COPD. The effect of budesonide/formoterol pMDI treatment on COPD exacerbations, defined as a worsening of COPD requiring oral corticosteroid treatment, hospitalization, or both, also was assessed in these studies.[12,13] In the 12-month study, a significant prolongation of the time to first COPD exacerbation and reduction in exacerbation rate were observed with budesonide/formoterol pMDI compared with formoterol treatment. Exacerbations were assessed as a prespecified secondary end point controlling for multiplicity of testing in that study.[13] In the 6-month study, a numerical reduction in exacerbation rate was shown for treatment with budesonide/formoterol pMDI compared with formoterol.[12] However, the 6-month study was not powered a priori for evaluating exacerbations.[12]

The present randomized, double-blind, double-dummy, 12-month clinical study was specifically designed to compare the efficacy of 2 dosages of budesonide/formoterol pMDI (320/9 μg twice daily and 160/9 μg twice daily) with formoterol DPI 9 μg twice daily in preventing exacerbations in patients with COPD. Secondary efficacy, safety, and health economic outcomes also were assessed.

Methods

Patients

The inclusion and exclusion criteria were designed to enroll patients with COPD who were appropriate candidates for ICS/long-acting β_2-adrenergic agonist (LABA) combination therapy. Patients were current smokers or ex-smokers with a smoking history of $\geq$10 pack-years, aged $\geq$40 years, with a clinical diagnosis of COPD with symptoms for $>$2 years. Patients were required to have a history of $\geq$1 COPD exacerbation requiring treatment with a course of systemic corticosteroids, antibiotics, or both, within 1–12 months before screening (visit 1) and documented use of an inhaled short-acting bronchodilator as rescue medication. At screening, a prebronchodilator forced expiratory volume in 1 s (FEV_1) of $\leq$50% of predicted normal and a prebronchodilator FEV_1/forced vital capacity (FVC) of $<$70% also were required. Exclusion criteria included current, previous (within past 60 days), or planned enrollment in a COPD pulmonary rehabilitation program, treatment with oral corticosteroids, and incidence of a COPD exacerbation or any other significant medical diagnosis between the screening and randomization visits (visit 1–3). Additional inclusion and exclusion criteria are the same as those described in a previous study by Tashkin et al.[12]

Study design and treatments

This was a randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study (NCT00419744; AstraZeneca LP D589CC00003) conducted between January 2007 and August 2009 at 180 study sites in the United States (106 sites), Central and South America (53 sites), and South Africa (21 sites). The study consisted of an initial screening visit (visit 1), a 2-week run-in period (beginning at visit 2), a 12-month randomized treatment period (visits 3–9), and telephone follow-up 2 weeks after study treatment cessation.

Before the run-in period, current COPD medications except ICSs, including LABAs, short-acting β_2-adrenergic agonists (SABAs), short- or long-acting anticholinergics, short-acting and slow-release oral β_2-agonists, xanthine derivatives (eg, theophylline), leukotriene antagonists or synthase inhibitors, and ephedrine-containing medications, were discontinued. Patients previously receiving ICS/LABA combination treatment were switched to a comparable dose of an ICS alone. Rescue medication (albuterol pMDI 90 μg $\times$ 2 inhalations) was provided for as-needed use during screening and run-in, and throughout the study. After the run-in period (at visit 3), ICS therapies were discontinued and eligible patients who met inclusion, exclusion, and randomization criteria were randomly assigned

(1:1:1) to 1 of 3 treatments: budesonide/formoterol pMDI 160/4.5 μg × 2 inhalations (320/9 μg) twice daily, budesonide/formoterol pMDI 80/4.5 μg × 2 inhalations (160/9 μg) twice daily, or formoterol DPI 4.5 μg × 2 inhalations (9 μg) twice daily. Assignments were made sequentially by interactive voice response system following a computer-generated allocation schedule produced in advance. To maintain patient and investigator blinding, all active treatments were provided in blinded treatment kits. Patients in the budesonide/formoterol pMDI groups received a placebo DPI and those in the formoterol DPI group received a placebo pMDI. Additional details are included in the Supplementary Material.

The study protocol was approved by an institutional review board for each of the clinical sites and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable local regulations. Written informed consent was obtained from patients or guardians before any study procedures were initiated.

Efficacy evaluations

The primary variable was the number of COPD exacerbations during the randomized treatment period. Exacerbations were defined per protocol as worsening of COPD that required treatment with a course of oral corticosteroids, hospitalization, or both. The time to first COPD exacerbation, defined as the difference between the date of randomization and the date of the first exacerbation, also was assessed. Antibiotic use for COPD or potentially related conditions (eg, respiratory infection) was not prespecified as part of the protocol-defined COPD exacerbation. However, a post hoc analysis of the number of COPD exacerbations based on antibiotic use alone and a composite definition (requiring antibiotics and/or oral corticosteroids and/or hospitalizations) during the randomized treatment period was performed. Subcategories of COPD exacerbations were not mutually exclusive.

Secondary pulmonary efficacy variables included predose forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and morning and evening peak expiratory flow (PEF). Spirometry measurements were conducted according to guidelines by the American Thoracic Society (ATS); the highest of 3 values from technically satisfactory maneuvers was recorded.[14] Secondary symptoms variables, recorded by patients in an electronic diary, included dyspnea, cough, and sputum scores; nighttime awakenings caused by COPD symptoms; and rescue medication use. Dyspnea was assessed with the validated Breathlessness Diary.[15] This single-item is derived from the Breathlessness, Cough, and Sputum Scale and rated on a 5-point Likert-type scale ranging from 0 to 4, with higher scores indicating more severe symptoms.[15] The percentages of awakening-free nights and rescue medication−free days also were calculated. Additional details of secondary pulmonary function and symptoms variables are included in the Supplementary Material.

Additional secondary variables included the BODE index, which is a composite of body mass index, airflow obstruction (percentage of predicted FEV_1), dyspnea (Modified Medical Research Council scale[16]), and exercise capacity (6-min walk test).[17] Health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ).[18]

Health care resource utilization

Details of assessment of COPD-related health care use by patients are available in the Supplementary Material.

Safety evaluations

Safety evaluations included adverse events (AEs), discontinuations due to AEs (DAEs), serious adverse events (SAEs), vital signs, physical examinations, laboratory data (hematology and chemistry), and 12-lead electrocardiograms (ECGs). Serious AEs were defined as those that were immediately life-threatening or resulted in death, hospitalization, or significantly disability. COPD signs or symptoms were recorded as AEs if they were serious, and/or if they resulted in patient discontinuation from the study, and/or if they were new to the patient or inconsistent with the patient's previous COPD history. Investigators assessed the causal relationship of AEs to study medication. Clinical laboratory data were collected at visit 2 (run-in) and visit 9 (month 12), vital signs and physical examinations were assessed at visit 2 and each clinic visit during the randomized treatment period, and 12-lead ECGs were assessed at visits 2 (run-in), 7 (month 6), and 9 (month 12).

Statistical analysis

The efficacy analysis set included all randomized patients who received $\geq$1 dose of study medication and contributed sufficient data for $\geq$1 efficacy end point. A sample size of 400 patients per treatment group was estimated to provide $\geq$90% power to detect a reduction from 1.07 to 0.74 in the number of exacerbations, adjusting for a deviance of 2.3.

A closed-testing procedure was used to control for multiplicity. If the difference between budesonide/formoterol pMDI 320/9 μg and formoterol for the primary variable was statistically significant ($p < 0.05$), secondary variables were tested in the following predefined order until the first comparison did not achieve statistical significance at the 0.05 level: 1) morning PEF, 2) evening PEF, 3) predose FEV_1, 4) dyspnea, 5) rescue medication use, and 6) SGRQ. If each of these comparisons were significant, then budesonide/formoterol pMDI 160/9 μg versus formoterol was tested in the same sequence for the primary then secondary variables.

The mean number of exacerbations per patient-treatment year was compared between treatment groups using a Poisson regression model, adjusting for differential treatment exposure, country, and over dispersion. The COPD exacerbation rates were evaluated using the per-protocol definition in the primary analysis and using the composite definition, including antibiotic treatment, in the post hoc analysis. Analysis of rates of subcategories of COPD exacerbations (those requiring oral corticosteroids, hospitalization, or antibiotic treatment) were not prespecified in the statistical analysis plan; thus, p values associated with these variables are considered descriptive in nature. The time to first COPD exacerbation was

described using a Kaplan–Meier plot and analyzed using a log-rank test to compare the survival curves between treatment groups. A Cox proportional hazards model was used to estimate hazard ratios.

Predose pulmonary function and diary variables were analyzed as the mean change from baseline to the mean during the randomized treatment period (with no imputation of missing data) using an analysis of covariance (ANCOVA) model and adjusting for treatment, country, and baseline. The data for other time points were analyzed similarly. Baseline was defined as the last predose value before the first dose of randomized study treatment for FEV_1 and FVC and as the mean of the last 10 days of run-in for diary variables.

Changes in BODE index score and SGRQ total score from baseline (randomization) to the end of treatment were assessed using an ANCOVA model, adjusting for treatment, country, and baseline score. The minimal clinically important difference (MCID) was defined as a change in SGRQ total score of $\geq$4 units.[19] Health care resource utilization variables were analyzed as the mean number of events per patient-treatment year for each variable, using methods similar to those used to analyze exacerbation rates.

The safety analysis included all randomized patients who received $\geq$1 dose of study medication and contributed data after randomization. AEs and physical examination results were summarized descriptively. Changes from baseline in laboratory data, ECGs, and vital signs were analyzed using ANCOVA, adjusting for treatment, country, and baseline.

Results

Patients

Patient disposition is shown in Fig. 1. The discontinuation rate during the randomized treatment period was lower in the budesonide/formoterol groups (320/9 μg: 28.7%, 160/9 μg: 28.9%) than in the formoterol group (32.9%). Demographic and baseline characteristics generally were similar across treatment groups (Table 1). Most patients had 1 (59.2%) or 2 (23.6%) exacerbations in the previous 12 months; the remaining 17.2% of patients had $\geq$3 exacerbations.

COPD exacerbations

For the primary variable, the number of overall protocol-defined exacerbations per patient-treatment year was lower with both budesonide/formoterol doses compared with formoterol ($p \leq 0.002$) (Table 2), with a 34.6% reduction observed with budesonide/formoterol 320/9 μg and a 25.9% reduction observed with budesonide/formoterol 160/9 μg compared with formoterol. Compared with formoterol, treatment with budesonide/formoterol 320/9 μg and 160/9 μg resulted in reductions in the COPD exacerbation rate of 34.8% and 25.9%, respectively, for those requiring oral corticosteroids and of 26.8% and 12.2%, respectively, for those requiring hospitalization.

Budesonide/formoterol 320/9 μg prolonged the mean time to first protocol-defined exacerbation compared with formoterol (277.9 days versus 249.8 days; $p = 0.029$); there was a 21.2% risk reduction observed (hazard ratio: 0.788 [95% confidence interval (CI): 0.639, 0.972]; $p = 0.026$; Fig. 2). Treatment with budesonide/formoterol 160/9 μg resulted in numerical reductions in the mean time to first protocol-defined exacerbation compared with formoterol (263.7 days vs 249.8 days) and a 15.3% risk reduction (hazard ratio: 0.847 [95% CI: 0.688, 1.043]; Fig. 2); however, this difference was not statistically significant.

In a post hoc analysis evaluating exacerbations based on the composite definition (antibiotics and/or oral corticosteroids and/or hospitalizations), the overall number of COPD exacerbations per patient-treatment year was reduced by 25.9% and 18.7% with budesonide/formoterol

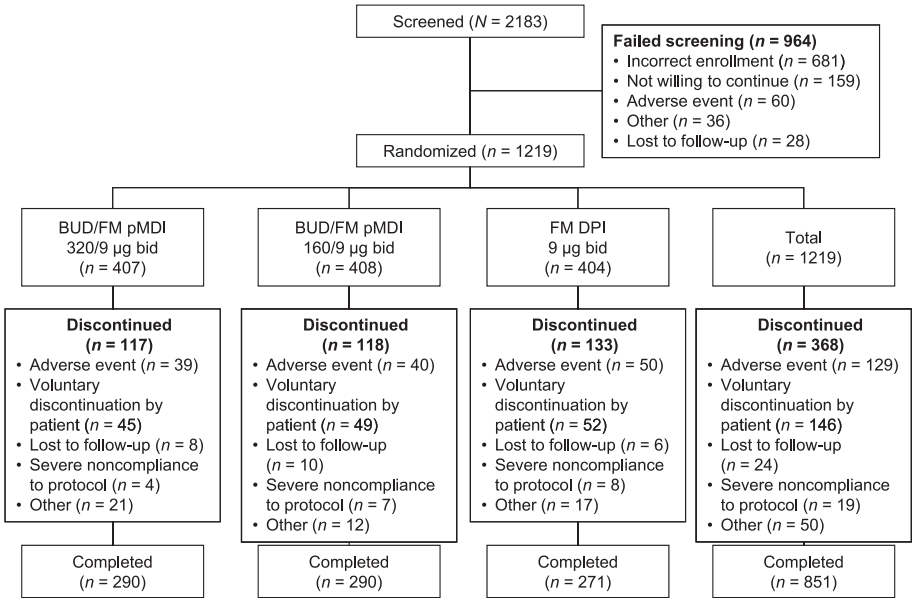

Figure 1 Patient disposition. bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler.

Table 1 Patient demographic and baseline clinical characteristics.

Characteristic	BUD/FM pMDI		FM DPI
	320/9 μg bid (n = 407)	160/9 μg bid (n = 408)	9 μg bid (n = 403)
Men, n (%)	262 (64.4)	264 (64.7)	229 (56.8)
Age, years			
Mean (SD)	63.8 (9.4)	62.8 (9.2)	62.5 (9.4)
Range	40–86	40–84	40–87
Race, *n* (%)			
White	338 (83.0)	332 (81.4)	332 (82.4)
Black	14 (3.4)	15 (3.7)	19 (4.7)
Asian	7 (1.7)	4 (1.0)	3 (0.7)
Other	48 (11.8)	57 (14.0)	49 (12.2)
Smoking history			
Ex-smoker, *n* (%)	269 (66.1)	265 (65.0)	249 (61.8)
Habitual smoker,[a] *n* (%)	130 (31.9)	135 (33.1)	138 (34.2)
Occasional smoker,[b] *n* (%)	8 (2.0)	8 (2.0)	16 (4.0)
Median pack-years	46	44	43
MMRC dyspnea scale, mean (SD)	2.9 (0.9)	3.0 (0.9)	3.1 (0.9)
Months since first COPD symptoms, mean (SD)	126 (86.7)	122 (81.8)	120 (86.5)
≥2 Exacerbations in past 1–12 months, *n* (%)	163 (40.0)	165 (40.4)	169 (41.9)
Most common COPD medications before run-in, *n* (%)			
Selective β_2-adrenergic agonists (includes long- and short-acting single agents)	320 (78.6)	324 (79.4)	321 (79.7)
Adrenergics/other drugs for obstructive airway diseases[c]	198 (48.6)	200 (49.0)	196 (48.6)
Anticholinergics	123 (30.2)	121 (29.7)	109 (27.0)
Inhaled corticosteroids	108 (26.5)	113 (27.7)	117 (29.0)
Treated with statins (HMG-CoA reductase inhibitors) during run-in,[d] *n* (%)	71 (17.4)	76 (18.6)	58 (14.4)
% Predicted FEV_1 at screening (postbronchodilator)	n = 402	n = 398	n = 395
Mean (SD)	37.9 (11.8)	37.6 (11.6)	37.5 (12.4)
FEV_1 (L) at baseline (prebronchodilator)	n = 404	n = 404	n = 400
Mean (SD)	1.01 (0.43)	1.02 (0.38)	0.97 (0.40)

bid, twice daily; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; MMRC, Modified Medical Research Council; pMDI, pressurized metered-dose inhaler; SD, standard deviation.

[a] Smokes ≥1 cigarette/day and has been smoking for ≥1 year before screening.

[b] Smokes <1 cigarette/day or has been smoking for <1 year before screening, or stopped smoking within 6 months before screening.

[c] Most commonly fluticasone + salmeterol (n = 328), ipratropium bromide + albuterol (n = 218), and budesonide + formoterol (n = 138) (categories not mutually exclusive).

[d] Included simvastatin (n = 79), atorvastatin (n = 71), lovastatin (n = 30), rosuvastatin (n = 17), pravastatin (n = 7), and fluvastatin (n = 4).

320/9 μg (0.867; $p = 0.001$) and 160/9 μg (0.952; $p = 0.023$), respectively, compared with formoterol (1.171). However, the number of COPD exacerbations requiring antibiotics per patient-treatment year was higher for budesonide/formoterol 320/9 μg (0.229; $p = 0.031$) and 160/9 μg (0.223; $p = 0.052$) compared with formoterol (0.167).

Pulmonary function

Improvements from baseline to the mean during the randomized treatment period in morning and evening PEF were numerically greater with both budesonide/formoterol doses compared with formoterol, but these differences were not statistically significant (Table 3). Compared with formoterol, improvements from baseline to the mean during the randomized treatment period were larger with both budesonide/formoterol doses for predose FEV_1 ($p \leq 0.032$). Improvements from baseline in predose FEV_1 also were larger with both budesonide/formoterol doses compared with formoterol at months 1 and 2 ($p \leq 0.013$) and with budesonide/formoterol 160/9 μg compared with formoterol at month 4 ($p = 0.040$) (Fig. 3). Improvements were numerically greatest with budesonide/formoterol 320/9 μg at end of treatment ($p = 0.091$). For predose FVC, improvements were similar for budesonide/formoterol 320/9 μg and formoterol, but greater for budesonide/formoterol 160/9 μg compared with formoterol ($p = 0.025$) (Table 3).

COPD symptoms

Improvements from baseline to the mean during the randomized treatment period for COPD symptom variables (Table 4) were shown in all 3 treatment groups. Improvements (ie, reductions) in sleep score and rescue medication use were greater with both budesonide/formoterol

Table 2 COPD exacerbations.

	BUD/FM pMDI		FM DPI
	320/9 μg bid (n = 404)	160/9 μg bid (n = 403)	9 μg bid (n = 403)
Patients with ≥1 exacerbation, n (%)	169 (41.8)	173 (42.9)	182 (45.2)
Estimated total number of overall exacerbations per patient-treatment year (SE)[a]	0.700 (0.084)	0.794 (0.092)	1.072 (0.119)
Treatment ratio (95% CI) vs FM DPI 9 μg	0.654 (0.535, 0.798)	0.741 (0.610, 0.899)	
p Value	<0.001	0.002	
Estimated total number of OCS-related exacerbations per patient-treatment year (SE)[a]	0.680 (0.082)	0.772 (0.090)	1.043 (0.116)
Treatment ratio (95% CI) vs FM DPI 9 μg	0.652 (0.533, 0.797)	0.741 (0.609, 0.900)	
p Value[b]	<0.001	0.003	
Estimated total number of hospitalization-related exacerbations per patient-treatment year (SE)[a]	0.106 (0.014)	0.127 (0.015)	0.144 (0.016)
Treatment ratio (95% CI) vs FM DPI 9 μg	0.732 (0.522, 1.026)	0.878 (0.635, 1.215)	
p Value[b]	0.070	0.433	

bid, twice daily; BUD, budesonide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FM, formoterol; OCS, oral corticosteroid; pMDI, pressurized metered-dose inhaler; SE, standard error.

[a] Number of exacerbations per patient-treatment year was estimated using a Poisson Regression model adjusted for differential treatment exposure with person years as an offset variable and country.

[b] Analyses of subcategories of COPD exacerbations were not prespecified in the statistical analysis plan; thus, these unadjusted p values are considered descriptive in nature.

doses compared with formoterol (unadjusted $p \leq 0.044$; Table 4). Compared with formoterol, treatment with budesonide/formoterol 320/9 μg resulted in greater reductions in dyspnea score and improvements in rescue medication−free days (unadjusted $p \leq 0.026$), whereas treatment with budesonide/formoterol 160/9 μg resulted in greater improvements from baseline in awakening-free nights (unadjusted $p = 0.024$; Table 4).

BODE index and quality of life

Improvements (ie, decreases) from baseline to the end of treatment in the adjusted mean BODE index score were small and similar in all 3 treatment groups (budesonide/formoterol pMDI 320/9 μg, −0.38; budesonide/formoterol 160/9 μg, −0.46; formoterol, −0.34), with no significant differences between the budesonide/formoterol groups and the formoterol group. Mean changes from baseline to the end of treatment in the SGRQ total score met the MCID for a clinically meaningful improvement with all 3 treatments; however, differences between treatment groups were not statistically significant (Table 5).

Health care resource utilization

Patients treated with either budesonide/formoterol dose had lower rates of emergency department (ED) visits, specialist visits, primary care provider visits, other health

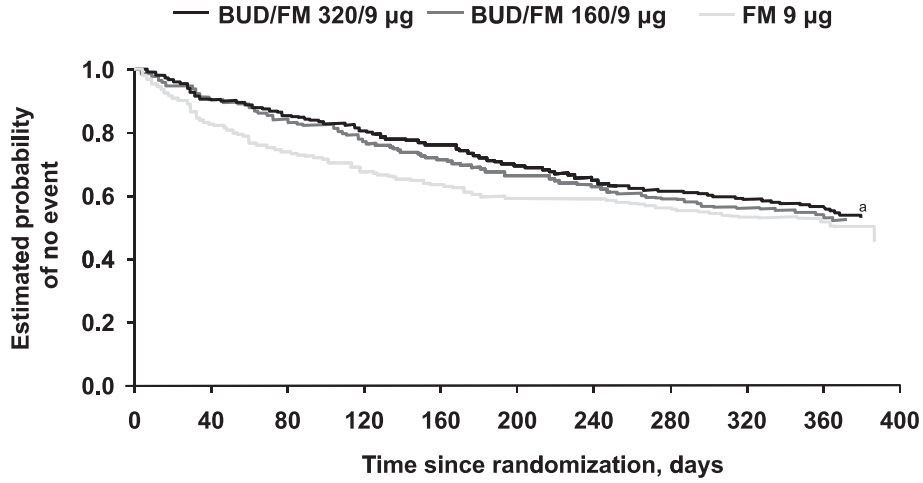

Figure 2 Kaplan−Meier probability curve for the time to first COPD exacerbation during randomized treatment. bid, twice daily; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler. [a]$p < 0.05$ BUD/FM 320/9 μg vs FM.

Table 3 Least squares mean changes in pulmonary function assessments from baseline to the mean during the randomized treatment period.

Variable	BUD/FM pMDI		FM DPI
	320/9 μg bid	160/9 μg bid	9 μg bid
Morning PEF, L/minute	$n = 399$	$n = 397$	$n = 389$
Baseline mean (SD)	186.0 (70.3)	183.0 (67.8)	173.4 (65.3)
Adjusted mean change (SD)	21.2 (3.11)	20.8 (3.08)	16.7 (3.09)
Evening PEF, L/minute	$n = 400$	$n = 397$	$n = 393$
Baseline mean (SD)	194.7 (71.4)	191.6 (70.2)	183.5 (69.4)
Adjusted mean change (SD)	18.6 (3.06)	18.5 (3.03)	14.6 (3.03)
Predose FEV_1, L	$n = 399$	$n = 399$	$n = 399$
Baseline mean (SD)	1.00 (0.43)	1.01 (0.37)	0.97 (0.40)
Adjusted mean change (SD)	0.07 (0.01)[a]	0.07 (0.01)[a]	0.04 (0.01)
Predose FVC, L	$n = 399$	$n = 399$	$n = 399$
Baseline mean (SD)	2.20 (0.78)	2.16 (0.69)	2.12 (0.76)
Adjusted mean change (SD)	0.08 (0.02)	0.10 (0.02)[a]	0.06 (0.02)

bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; PEF, peak expiratory flow; pMDI, pressurized metered-dose inhaler; SD, standard deviation.
[a] $p < 0.05$ vs FM DPI 9 μg bid.

care provider home visits, and oral corticosteroid use per patient-treatment year compared with formoterol (unadjusted $p < 0.05$; Fig. 4). In addition, treatment with budesonide/formoterol 320/9 μg resulted in reduced rates of urgent care visits and other health care visits per patient-treatment year compared with formoterol (unadjusted $p \leq 0.020$).

Safety

The mean overall treatment exposure was similar in all treatment groups (Table 6). Both budesonide/formoterol doses were well tolerated relative to formoterol. The percentage of patients with ≥1 AE during the randomized treatment period was similar in all treatment groups (Table 6), and most AEs were of mild or moderate intensity. The most commonly reported AE was COPD, which occurred less frequently with both budesonide/formoterol doses compared with formoterol (Table 6). The overall incidence of AEs judged by the study investigator to be treatment-related was higher in both budesonide/formoterol groups (320/9 μg: 9.8%, 160/9 μg: 8.3%) than in the formoterol group (4.7%). The incidence of individual treatment-related AEs generally was low. Oral candidiasis was the only treatment-related AE that occurred in ≥2% of patients in any treatment group (budesonide/formoterol 320/9 μg: 9/407 [2.2%], budesonide/formoterol 160/9 μg: 7/408 [1.7%], formoterol: 4/403 [1.0%]).

The formoterol group had a higher incidence of DAEs (11.7%) compared with the budesonide/formoterol 320/9-μg (8.6%) and budesonide/formoterol 160/9-μg (8.8%) groups. The most commonly observed DAE was COPD, occurring in 13 patients (3.2%) in the budesonide/formoterol 320/9-μg group, 15 (3.7%) in the budesonide/formoterol 160/9-μg group, and 21 (5.2%) in the formoterol group. Two of these COPD events were considered to be treatment-related by the study investigator (1 in the budesonide/formoterol 320/9-μg group and 1 in the formoterol group).

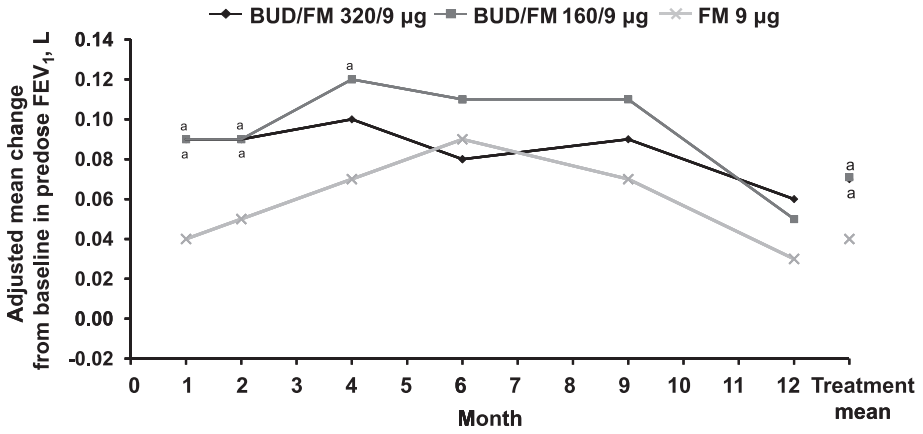

Figure 3 Adjusted mean changes in predose FEV_1 during the 12-month randomized treatment period. [a]$p < 0.05$ vs FM. BUD, budesonide; FEV_1, forced expiratory volume in 1 s; FM, formoterol.

Table 4 Least squares mean changes in COPD symptom variables from baseline to the mean during the randomized treatment period.

Variable	BUD/FM pMDI		FM DPI
	320/9 μg bid	160/9 μg bid	9 μg bid
Total symptom score	$n = 401$	$n = 400$	$n = 398$
Baseline mean (SD)	4.99 (2.22)	5.12 (2.11)	5.22 (2.14)
Adjusted mean change (SD)	−1.06 (0.12)	−1.08 (0.12)	−0.96 (0.12)
Dyspnea score	$n = 401$	$n = 400$	$n = 398$
Baseline mean (SD)	1.81 (0.81)	1.84 (0.77)	1.91 (0.73)
Adjusted mean change (SD)	−0.39 (0.05)[a]	−0.36 (0.05)	−0.29 (0.05)
Cough score	$n = 401$	$n = 400$	$n = 398$
Baseline mean (SD)	1.74 (0.83)	1.82 (0.78)	1.81 (0.81)
Adjusted mean change (SD)	−0.42 (0.05)	−0.45 (0.04)	−0.41 (0.05)
Sputum score	$n = 401$	$n = 400$	$n = 398$
Baseline mean (SD)	1.45 (0.86)	1.46 (0.83)	1.50 (0.87)
Adjusted mean change (SD)	−0.25 (0.04)	−0.26 (0.04)	−0.27 (0.04)
Sleep score	$n = 400$	$n = 398$	$n = 395$
Baseline mean (SD)	1.12 (0.88)	1.19 (0.85)	1.24 (0.88)
Adjusted mean change (SD)	−0.32 (0.04)[a]	−0.32 (0.04)[a]	−0.24 (0.04)
% Awakening-free nights	$n = 401$	$n = 401$	$n = 399$
Baseline mean (SD)	39.4 (38.8)	35.0 (37.8)	33.8 (37.0)
Adjusted mean change (SD)	10.1 (2.26)	11.3 (2.23)[a]	6.7 (2.23)
Rescue medication use, inhalations/day	$n = 401$	$n = 401$	$n = 399$
Baseline mean (SD)	5.8 (4.6)	6.1 (5.1)	6.0 (4.5)
Adjusted mean change (SD)	−1.5 (0.26)[b]	−1.2 (0.26)[b]	−0.5 (0.26)
% Rescue medication−free days	$n = 401$	$n = 401$	$n = 399$
Baseline mean (SD)	12.9 (28.9)	10.8 (27.3)	11.4 (27.2)
Adjusted mean change (SD)	13.1 (2.25)[b]	11.4 (2.23)	7.5 (2.23)

bid, twice daily; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler; SD, standard deviation.

[a] $p < 0.05$ vs FM DPI 9 μg bid.

[b] $p < 0.01$ vs FM DPI 9 μg bid.

A total of 198 patients experienced nonfatal SAEs during the randomized treatment period: 76/407 (18.7%) in the budesonide/formoterol 320/9-μg group, 54/408 (13.2%) in the budesonide/formoterol 160/9-μg group, and 68/403 (16.9%) in the formoterol group. Three of these nonfatal SAEs were considered by the study investigator to be treatment-related: 2 SAEs of atrial fibrillation (1 in each of the budesonide/formoterol groups) and 1 SAE of COPD in

Table 5 Least squares mean changes in SGRQ total and domain scores from baseline to end of treatment.

Score	BUD/FM pMDI		FM DPI
	320/9 μg bid	160/9 μg bid	9 μg bid
Total	$n = 375$	$n = 366$	$n = 357$
Baseline mean (SD)	55.9 (17.6)	57.8 (16.7)	58.6 (16.9)
Adjusted mean change (SD)	−7.2 (1.18)	−5.5 (1.17)	−5.9 (1.17)
Symptoms	$n = 375$	$n = 370$	$n = 360$
Baseline mean (SD)	64.6 (20.5)	65.1 (18.0)	66.4 (19.1)
Adjusted mean change (SD)	−14.5 (1.58)	−11.3 (1.56)	−11.8 (1.56)
Activity	$n = 376$	$n = 366$	$n = 358$
Baseline mean (SD)	71.7 (18.0)	73.6 (18.0)	74.3 (18.9)
Adjusted mean change (SD)	−6.8 (1.30)	−5.3 (1.29)	−5.6 (1.29)
Impacts	$n = 376$	$n = 368$	$n = 360$
Baseline mean (SD)	44.0 (20.8)	46.3 (20.2)	47.2 (20.0)
Adjusted mean change (SD)	−5.6 (1.37)	−4.0 (1.36)	−4.5 (1.36)

bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

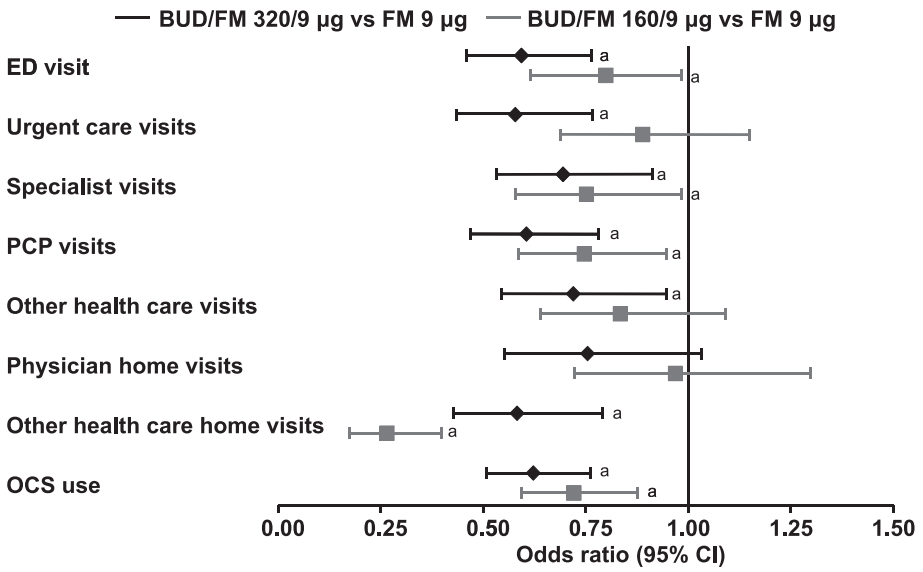

Figure 4 Treatment ratios for events of resource utilization per patient-treatment year. [a]$p < .05$ vs FM. BUD, budesonide; CI, confidence interval; ED, emergency department; FM, formoterol; OCS, oral corticosteroid; PCP, primary care provider.

the formoterol group. Twenty-six patients experienced SAEs leading to death during the randomized treatment period: 7 in the budesonide/formoterol 320/9-µg group; 9 in the budesonide/formoterol 160/9-µg group; and 10 in the formoterol group. None of the deaths were considered to be treatment-related by the investigator.

Pneumonia-related AEs occurred in 6.4% (26/407), 4.7% (19/408), and 2.7% (11/403) of patients in the budesonide/formoterol 320/9, 160/9, and formoterol groups, respectively; the overall incidence of pneumonia-related AEs was low (4.6%). The most commonly reported pneumonia-related AE was bacterial pneumonia (Table 7). SAEs of pneumonia occurred in 3.2% (13/407), 1.0% (4/408), and 1.7% (7/403) of patients in the budesonide/formoterol 320/9, 160/9, and formoterol groups, respectively. One patient in the budesonide/formoterol 160/9 group experienced an SAE of pneumonia leading to death during the randomized treatment period. None of the SAEs of pneumonia were considered treatment-related by the investigator.

Cardiac-related AEs occurred more frequently in the budesonide/formoterol groups (320/9 µg: 12.3%, 160/9 µg: 9.6%) than in the formoterol group (6.9%). Hypertension was the most common cardiac-related AE: budesonide/formoterol 320/9 µg: 21/407 (5.2%), budesonide/formoterol 160/9 µg: 15/408 (3.7%), formoterol: 8/403 (2.0%). All other individual cardiac-related AEs occurred at an incidence of <2.0%.

No clinically meaningful or statistically significant differences were observed between the treatment groups for mean changes from baseline to the end of month 12 in systolic or diastolic blood pressure (Supplemental Table E1). There were

Table 6 Overall adverse events reported by ≥5% of patients in any treatment group.

Variable	BUD/FM pMDI		FM DPI
	320/9 µg bid (n = 407)	160/9 µg bid (n = 408)	9 µg bid (n = 403)
Mean exposure (SD), wk	42.4 (16.8)	41.4 (17.6)	40.2 (18.3)
Adverse event, *n* (%)			
Any adverse event	308 (75.7)	295 (72.3)	304 (75.4)
COPD	85 (20.9)	76 (18.6)	95 (23.6)
Headache	56 (13.8)	46 (11.3)	43 (10.7)
Nasopharyngitis	31 (7.6)	35 (8.6)	41 (10.2)
Bronchitis	37 (9.1)	32 (7.8)	28 (6.9)
Influenza	29 (7.1)	26 (6.4)	25 (6.2)
Back pain	21 (5.2)	18 (4.4)	21 (5.2)
Bacterial upper respiratory tract infection	18 (4.4)	24 (5.9)	17 (4.2)
Sinusitis	18 (4.4)	19 (4.7)	20 (5.0)
Viral upper respiratory tract infection	21 (5.2)	14 (3.4)	14 (3.5)
Hypertension	21 (5.2)	16 (3.9)	9 (2.2)

bid, twice daily; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler; SD, standard deviation.

Table 7 Number (%) of patients with pneumonia adverse events.

Adverse event	BUD/FM pMDI		FM DPI
	320/9 μg bid (n = 407)	160/9 μg bid (n = 408)	9 μg bid (n = 403)
Patients with any pneumonia adverse event	26 (6.4)	19 (4.7)	11 (2.7)
Bacterial pneumonia	18 (4.4)	14 (3.4)	9 (2.2)
Pneumonia	5 (1.2)	2 (0.5)	0
Lobar pneumonia	2 (0.5)	2 (0.5)	2 (0.5)
Bronchopneumonia	1 (0.2)	0	0
Staphylococcal pneumonia	0	1 (0.2)	0
Pneumonitis	0	0	1 (0.2)

bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler.

no clinically meaningful differences between the treatment groups for mean changes from baseline to the end of month 12 in pulse rate; however, the difference between the budesonide/formoterol 160/9-μg group and the formoterol group was statistically significant ($p = 0.012$; Supplemental Table E1). The percentages of patients with clinically important abnormalities in blood pressure and pulse are shown in Supplemental Table E2. No clinically meaningful or statistically significant differences were observed among the treatment groups for mean changes from baseline to the end of treatment in heart rate, QT interval, QTc (Bazett's) interval, or QTc (Fredericia's) interval (Supplemental Table E3). Additionally, no clinically meaningful differences in clinical laboratory data or physical examination findings were noted among the treatment groups.

Discussion

This study is the first designed specifically to evaluate the long-term effect of budesonide/formoterol pMDI on COPD exacerbations relative to formoterol alone. In this study, the percentage of patients experiencing a COPD exacerbation, defined as a worsening of COPD requiring the use of oral corticosteroids, hospitalization, or both, and the total number of overall exacerbations per patient-treatment year, were lower in both budesonide/formoterol pMDI groups compared with the formoterol group. These findings were largely driven by the number of COPD exacerbations requiring treatment with oral corticosteroids, which were lower for both budesonide/formoterol pMDI doses compared with formoterol. Moreover, budesonide/formoterol pMDI 320/9 μg significantly prolonged the time to first exacerbation compared with formoterol.

The reduction in the number of exacerbations per patient-treatment year for budesonide/formoterol pMDI versus formoterol from the present study were consistent with those from studies of budesonide/formoterol DPI versus formoterol[20,21] and confirmed the results of previous studies evaluating the effect of budesonide/formoterol pMDI on COPD exacerbations as a secondary outcome.[12,13] The 26%–35% reduction in overall exacerbations per patient-treatment year (primary end point) observed with both budesonide/formoterol pMDI doses relative to formoterol were similar to those reported previously for budesonide/formoterol pMDI relative to formoterol (20%–29%)[12,13] and for fluticasone propionate/salmeterol relative to salmeterol (12%–31%).[22–24] Additionally, budesonide/formoterol pMDI 320/9 μg significantly prolonged the time to first exacerbation (secondary end point) relative to formoterol by 21%, which also was similar to the 25%–27% reduction in risk associated with fluticasone propionate/salmeterol compared with salmeterol.[22,23] In this study, a third of patients were receiving ICS before study enrollment, and it is unclear whether discontinuation of ICS in those patients who were randomized to receive formoterol alone could have contributed to worse exacerbation outcomes in the formoterol group compared with the budesonide/formoterol group. Because such qualitative data were not collected before study entry, it is impossible to determine the effect of prestudy ICS discontinuation on COPD exacerbations in patients randomized to the formoterol group. Overall, these results demonstrated that ICS/LABA combination treatment provides clinical benefits beyond a LABA alone in the management of COPD exacerbations, supporting the use of ICS/LABA combination treatments in patients with COPD and a history of previous exacerbations.

Comparison of the exacerbation findings from the present study with previous studies is limited because different COPD exacerbation definitions may have been used. A standardized definition has not been established but definitions can be symptom-based or event-based.[1] Symptom-based definitions typically describe COPD exacerbations as worsening of dyspnea and increased sputum production or purulence.[1] Event-based definitions, such as the one used in the present study, rely on hospitalization or changes in COPD treatment, particularly use of antibiotics or oral corticosteroids.[1] However, patients' assessments of symptoms generally are considered by physicians when making decisions about changes in treatment regimens or whether hospitalization is required. In the present study, patients' perception of COPD deterioration prompted a call to the study investigator. Although event-based definitions may fail to capture some symptom-related exacerbations, and therefore may result in under-reporting of exacerbations, they are a practical method of identifying COPD exacerbations in the clinical setting.[25] In addition, an event-based method of capturing exacerbations is less ambiguous than symptom-based methods, which commonly are based on patient diaries and subjective assessments of symptoms.[1,25]

The present study also evaluated other secondary variables such as pulmonary function, COPD symptoms, the BODE, index, quality of life, and health care resource utilization. Both budesonide/formoterol pMDI doses resulted in nonsignificant improvements in morning PEF compared with formoterol. According to the prespecified multiplicity rule, *p* values for the remaining secondary efficacy variables, evening PEF, predose FEV_1, dyspnea, rescue medication use, and SGRQ, were unadjusted and to be interpreted as descriptive in nature. Previous studies have shown that both doses of budesonide/formoterol pMDI significantly improved morning and evening PEF compared with formoterol.[12,13] In the present study, both budesonide/formoterol pMDI doses demonstrated improvements in morning and evening PEF similar to previous studies, but the magnitude of improvement observed for formoterol was approximately 1.5 times greater for morning PEF and 2 times greater for evening PEF in the present study compared with previously conducted studies.[12,13] A potential reason for this difference is that the baseline morning and evening PEF values were lower in the formoterol groups in the present study (173 L/min and 184 L/min, respectively) than in the previously reported COPD studies (183—185 L/min and 192—194 L/min, respectively).[12,13] The large formoterol effect in the present study may explain why improvements with the combination product were not significant compared with the formoterol group.

The incidence of pneumonia-related AEs was higher in both budesonide/formoterol pMDI groups compared with the formoterol group, and in the budesonide/formoterol pMDI 320/9-μg group compared with the budesonide/formoterol pMDI 160/9-μg group. These findings are inconsistent with previous COPD studies of budesonide/formoterol pMDI[12,13] and budesonide/formoterol DPI[21] that showed no differences in the incidence of pneumonia between the budesonide/formoterol groups and the formoterol group, but are similar to findings from fluticasone propionate/salmeterol studies, which have consistently shown an increased incidence of pneumonia when compared with salmeterol treatment.[23,24,27] A meta-analysis of data from 7 COPD studies of ≥6 months ($N = 7042$) showed no increase in the risk of pneumonia reported as an AE for budesonide treatment given with or without a LABA.[26] The percentage of patients with pneumonia-related AEs in the meta-analysis (3.0%)[26] is similar to that in the formoterol treatment group (2.7%) in the present study.

A limitation of the pneumonia findings from both the present and previous studies is that a diagnosis of pneumonia typically was based on clinical judgment and not radiological or microbiological assessments. Reported SAEs of pneumonia, which were associated with hospitalization, were more likely to have been confirmed by chest radiograph than AEs of pneumonia, which were likely managed in an outpatient setting. In this study, no differences in the incidence of SAEs of pneumonia or deaths due to pneumonia were shown between the budesonide/formoterol pMDI groups and the formoterol group. These findings are consistent with previous COPD studies of budesonide/formoterol pMDI.[12,13]

Other tolerability results in the present study generally were consistent with those from previously conducted budesonide/formoterol pMDI studies.[12,13] The incidence of AEs was generally similar across the 3 treatment groups, and treatment-related AEs occurred at a low frequency. Although the incidence of individual cardiac-related AEs was low, the percentage of patients with any cardiac-related AE was slightly higher for both budesonide/formoterol doses than for formoterol. Fewer patients discontinued the study because of AEs in the budesonide/formoterol pMDI treatment groups than in the formoterol group. There also were lower rates of COPD-related AEs leading to discontinuation with budesonide/formoterol pMDI.

Conclusions

In summary, both budesonide/formoterol pMDI doses significantly reduced the number of overall exacerbations per patient-treatment year compared with formoterol. In addition, both doses of budesonide/formoterol pMDI were well tolerated during 1 year of treatment. Apart from the somewhat elevated incidence of pneumonia in the budesonide/formoterol pMDI groups compared with the formoterol group, overall safety profiles were similar to that of formoterol and commensurate with previously reported data for ICS/LABA therapy.

Conflict of interest

Amir Sharafkhaneh, MD, PhD, is on the speakers bureaus of AstraZeneca LP, GlaxoSmithKline, Pfizer, and DEY Pharmaceuticals. John G. Southard, MD, PhD, is on the speaker bureaus for AstraZeneca LP and GlaxoSmithKline. T Uryniak, MS, M Goldman, MD, PhD, and UJ Martin, MD, are employees of the sponsor and authors who participated in the conception and design of the study and analysis or interpretation of the data, revised the article for important intellectual content, and provided final approval of the version to be submitted.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.07.020.

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