ORIGINAL RESEARCH ARTICLE

Efficacy and Tolerability of Budesonide/Formoterol in One Hydrofluoroalkane Pressurized Metered-Dose Inhaler in Patients with Chronic Obstructive Pulmonary Disease
Results from a 1-Year Randomized Controlled Clinical Trial

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Abstract

Background: Combination therapy with a long-acting bronchodilator and an inhaled corticosteroid (ICS) is recommended in patients with chronic obstructive pulmonary disease (COPD) who have frequent exacerbations. The efficacy and tolerability of the combination of budesonide/formoterol have been demonstrated in patients with COPD when administered via the dry powder inhaler (DPI) in a 1-year study and when administered via the hydrofluoroalkane (HFA) pressurized metered-dose inhaler (pMDI) in a 6-month study.

Objective: This study assessed the long-term efficacy and tolerability of budesonide/formoterol HFA pMDI in patients with moderate to very severe COPD.

Methods: This was a 12-month, randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled, multicentre study (NCT00206167) of 1964 patients aged ≥40 years with moderate to very severe COPD conducted from 2005 to 2007 at 237 sites in the US, Europe and Mexico. After 2 weeks of treatment based on previous therapy (ICSs, short-acting bronchodilators allowed), patients received one of the following treatments twice daily: budesonide/formoterol pMDI 160/4.5 μg × two inhalations (320/9 μg); budesonide/formoterol pMDI 80/4.5 μg × two inhalations (160/9 μg); formoterol DPI 4.5 μg × two inhalations (9 μg); or placebo.

Main outcome measures: The co-primary efficacy variables were pre-dose forced expiratory volume in 1 second (FEV_1) and 1-hour post-dose FEV_1.

Results: Budesonide/formoterol 320/9 μg demonstrated greater improvements in pre-dose FEV_1 versus formoterol (p = 0.008), and both budesonide/formoterol doses demonstrated greater improvements in 1-hour post-dose FEV_1 versus placebo (p < 0.001). The rate of COPD exacerbations was lower in both budesonide/formoterol groups compared with formoterol and placebo (p ≤ 0.004). Both budesonide/formoterol doses were more effective than placebo (p ≤ 0.006) for controlling dyspnoea and improving health status (St George's Respiratory Questionnaire). All treatments were generally well tolerated. The incidence of pneumonia was not different for active (3.4–4.0%) and placebo (5.0%) groups.

Conclusions: Budesonide/formoterol pMDI (320/9 μg and 160/9 μg) improved pulmonary function and reduced symptoms and exacerbations over 1 year in patients with moderate to very severe COPD. Only budesonide/formoterol pMDI 320/9 μg demonstrated greater efficacy for both co-primary variables compared with formoterol DPI 9 μg. Both budesonide/formoterol pMDI dosages were well tolerated relative to formoterol and placebo.

Background

In patients with chronic obstructive pulmonary disease (COPD) and frequent exacerbations, the combination of a long-acting bronchodilator and an inhaled corticosteroid (ICS) is recommended.[1] Budesonide and formoterol delivered via a single dry powder inhaler (DPI; Symbicort® Turbuhaler®; AstraZeneca, Lund, Sweden) have been shown to improve pulmonary function[2,3] and reduce COPD exacerbation rates.[2,3] Fixed-combination budesonide/formoterol is available in the US in a hydrofluoroalkane pressurized metered-dose inhaler (pMDI; Symbicort® Inhalation Aerosol; AstraZeneca LP, Wilmington, DE, USA). While most patients with COPD can benefit from either a pMDI or DPI, the pMDI formulation allows patients who may have inadequate peak inspiratory flow for optimal delivery from a DPI to use the pMDI effectively. A recent 6-month study demonstrated the efficacy and tolerability of budesonide/formoterol pMDI in patients with moderate to very severe COPD.[4] Treatment with budesonide/formoterol pMDI resulted in significant improvements in pulmonary function, dyspnoea and health-related quality of life; however, the duration of the study was limiting with respect to the analysis of low-frequency events, such as COPD exacerbations, and pre-cluded an assessment of safety outcomes with long-term exposure.[4] In this study, the long-term efficacy and tolerability of two dosage strengths of budesonide/formoterol pMDI were assessed over 12 months in patients with moderate to very severe COPD.

Patients and Methods

Patients

The inclusion criteria were designed to select a population with moderate to very severe COPD with previous exacerbations (i.e. appropriate candidates for combination ICS/long-acting β_2-adrenoceptor agonist [LABA] therapy): age ≥40 years, diagnosis of symptomatic COPD for >2 years, ≥10 pack-year smoking history, prebronchodilator forced expiratory volume in 1 second (FEV_1) of ≤50% of predicted normal and prebronchodilator FEV_1/forced vital capacity (FVC) of <70%. Patients were to have a Modified Medical Research Council dyspnoea scale score of ≥2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1–12 months before the first study visit. Additional enrolment criteria were the same as those in a similar 6-month study by Tashkin et al.[4]

Study Design

This was a randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled, multicentre trial (ClinicalTrials.gov identifier: NCT00206167) conducted from 2005 to 2007 at 237 sites in the US, Europe and Mexico. The study protocol was approved by a local institutional review board and ethics committee, and written informed consent was obtained from patients. The study was designed to conform with the Declaration of Helsinki, and was consistent with the International Conference on Harmonisation and Good Clinical Practice and applicable regulatory requirements.

After meeting eligibility criteria, patients entered a 2-week run-in period, during which they received ICS monotherapy if previously stable on ICS (alone or in combination) and ipratropium bromide at a fixed dose if previously receiving anticholinergics. Albuterol (salbutamol) was permitted for rescue use throughout the study. At randomization, all previous ICSs were discontinued and patients were randomized to one of four treatments (figure 1). Patients who were treated with ipratropium bromide during the run-in period were allowed to continue on it throughout the study period. Other allowed and dis-allowed concomitant medications were the same as those reported in the study by Tashkin et al.[4]

Efficacy Evaluations

The co-primary efficacy variables, measured at all clinic visits, were pre-dose FEV_1 and 1-hour post-dose FEV_1. Additional pulmonary function variables included pre-dose and 1-hour post-dose FVC measured at all clinic visits, and morning and evening peak expiratory flow (PEF) recorded daily in patient diaries. In a subset of patients (n = 491 of 1964; 25%) who agreed to undergo spirometry testing, 12-hour serial spirometry was performed and pre-dose and 1-hour post-dose inspiratory capacity (IC) were collected at randomization and months 6 and 12. FEV_1 was measured pre-dose and at 5, 15, 30, 60, 120, 180, 240, 360, 480, 600 and 720 minutes post-dose. Baseline-adjusted average 12-hour FEV_1 was calculated as the area between the 12-hour post-dose FEV_1-over-time curve and the baseline pre-dose FEV_1, divided by observation time. Spirometry was performed according to American Thoracic Society guidelines.[6] Crapo-predicted normals for FEV_1 were used.[7]

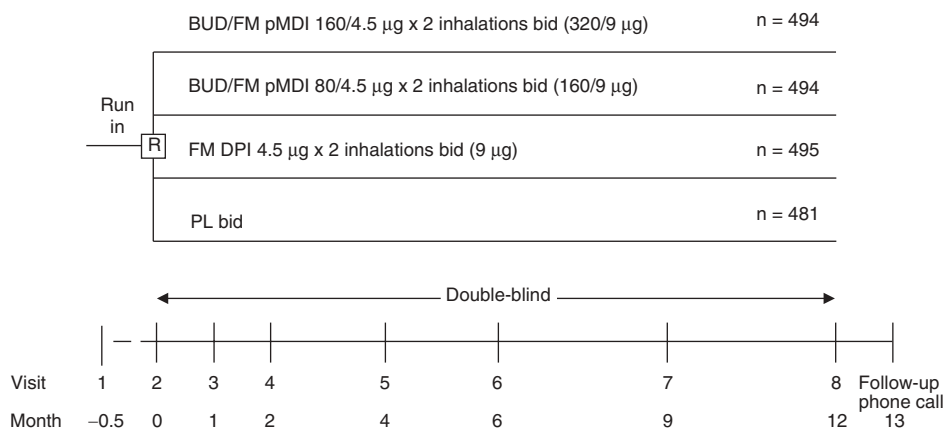Secondary efficacy endpoints included COPD exacerbations, dyspnoea (separate and composite

Fig. 1. Study design. To maintain blinding, patients received both a pressurized metered-dose inhaler (pMDI) and a dry powder inhaler (DPI) containing either active treatment or double-dummy placebo (PL) as appropriate. This study used formoterol (FM) DPI (Oxis® Turbuhaler®, AstraZeneca, Lund, Sweden) as the FM comparator because FM is not available as a hydrofluoroalkane pMDI in the US. A previous study in asthma patients reported equivalent FM-related bronchodilatory effects when FM was administered in combination with budesonide (BUD) via pMDI or alone via DPI.[5] Patients were asked to return to the clinic for follow-up visits 3–8 at the end of months 1, 2, 4, 6, 9 and 12, and received a telephone call 4 weeks after the last clinic visit. **bid** = twice daily; **R** = randomization.

scores) and health status, all assessed as previously described.[4] A COPD exacerbation was defined as worsening of COPD requiring an oral corticosteroid or hospitalization.[4] Dyspnoea was assessed daily before the evening dose of study medication using the Breathlessness Diary, a validated single-item component of the Breathlessness Cough and Sputum Scale (BCSS).[8] Health status was assessed at months 1, 2, 6 and 12 using the St George's Respiratory Questionnaire (SGRQ).[9,10] Sleep score, percentage of awakening-free nights (sleep score of 0) and study rescue medication use were assessed as previously described by Tashkin et al.[4]

Safety Evaluations

Safety was assessed by adverse event (AE) reporting. Pneumonia events were reported by physicians based on the Medical Dictionary for Regulatory Activities (version 10.0) pneumonia-related preferred terms (pneumonia, bronchopneumonia, lobar pneumonia or pneumonia staphylococcal). Vital signs and 12-lead ECGs were evaluated as previously described by Tashkin et al.[4] Subsets of patients were assessed for 24-hour urinary cortisol (n = 179), 24-hour Holter monitoring (n = 520), bone mineral density (BMD) at the hip and spine regions (n = 326), and ophthalmological assessments (n = 461), including intraocular pressure and progression of lenticular opacities. In all patients, blood and urine samples were collected, and comprehensive physical examinations were carried out at the time of screening and at the end of month 12. Blood and urine samples were analysed by a central laboratory (Quest Diagnostics Clinical Laboratories, Van Nuys, CA, USA). Vital signs, including heart rate and blood pressure, were measured at all study visits.

Samples to assess 24-hour urinary cortisol levels were collected in a subset of patients at or before randomization and within 1 week before the 6- and 12-month visits, and analysed by Quest Diagnostics. 24-Hour Holter monitoring was performed at screening and months 1 and 4, BMD assessments (two sets of dual energy x-ray absorptiometry scans in the hip and spine regions) were performed at

screening and the end of month 12, and ophthalmology assessments (intraocular pressure and lenticular opacities) were performed at screening and the end of months 6 and 12.

Statistical Analyses

The efficacy analysis set (i.e. intent-to-treat population) included all randomized patients who received at least one dose of randomized study medication and contributed sufficient data for at least one co-primary or secondary efficacy endpoint to be calculated during the randomized treatment period. The safety analysis population included all randomized patients who received at least one dose of randomized study medication and from whom any post-randomization data were available. For the subsets of patients who underwent serial spirometry, 24-hour urinary cortisol, BMD, 24-hour Holter monitoring and ophthalmological analyses, analysis sets were defined as those patients who received at least one dose of randomized study medication and had baseline and on-treatment values for the variable being assessed. Patients who discontinued prematurely completed final visit (month 12) assessments at the time of discontinuation, followed by the 4-week follow-up. A sample size of approximately 400 patients per treatment group was calculated to allow 90% power to detect a reduction in the number of COPD exacerbations of approximately 30%, adjusting for overdispersion of 2.3. This sample size ensured >95% power to detect a difference of 0.10L in FEV_1, given an estimated standard deviation of 0.3 L. All tests were two-sided, with $p \leq 0.05$ considered significant.

The prespecified primary comparators were formoterol DPI for pre-dose FEV_1 to demonstrate the contribution of budesonide and placebo for 1-hour post-dose FEV_1. To address issues of multiplicity relating to multiple-dose comparisons and multiple variables of interest, a fixed-sequence testing procedure was adopted. The primary comparisons were prespecified as budesonide/formoterol pMDI 320/9 µg compared with (i) placebo for pre-dose FEV_1 and 1-hour post-dose FEV_1; and (ii) formoterol DPI 9 µg for pre-dose FEV_1. If significant differ-

ences were obtained, comparisons continued with budesonide/formoterol pMDI 320/9 µg compared with placebo for (i) dyspnoea; (ii) SGRQ total score; and (iii) number of exacerbations. If significant differences were obtained for each of these key secondary variables, the lower dose of budesonide/formoterol pMDI was tested on the co-primary variables, as previously described, and, if significant differences were obtained, testing continued with number of exacerbations, dyspnoea and SGRQ total score compared with placebo. For all secondary efficacy variables, the primary comparison was budesonide/formoterol pMDI versus placebo.

Primary and secondary variables were assessed as the change from baseline to the average over the randomized treatment period except for average 12-hour FEV_1, mean FEV_1 at 12 hours and SGRQ at end of treatment. Changes from baseline in the co-primary efficacy variables were analysed via analysis of co-variance (ANCOVA), adjusting for treatment, country and baseline value. The following three key secondary efficacy variables were identified: (i) dyspnoea; (ii) SGRQ total score; and (iii) exacerbations. Secondary variables were analysed similar to the co-primary efficacy variables; however, exacerbation rate (number/patient-treatment year) was analysed using a Poisson regression model, adjusted for country and differential randomization time, and time to first COPD exacerbation was described via Kaplan-Meier plot and analysed using the log-rank test. The number and percentage of patients experiencing clinically meaningful changes (based on a prespecified minimal important difference) in dyspnoea were analysed using the Cochran-Mantel-Haenszel test, adjusting for country.

Geometric mean 24-hour urinary cortisol levels at end of treatment were compared between treatment groups using a multiplicative ANCOVA model. Mean changes from baseline to the average during the randomized treatment period in 12-lead ECG, and Holter variables and ophthalmology variables were analysed using a model similar to that used for the co-primary variables. BMD variables (natural logarithm of the analysis timepoint minus the natural logarithm of the respective baseline value for hip and spine) were analysed using an ANCOVA model adjusting for country, treatment and natural logarithm of the baseline value. Other safety data were summarized using descriptive statistics. No formal hypothesis testing of the safety data was performed.

Results

Patients

Of 1964 randomized patients, 1355 completed the study (figure 2). Discontinuation was greater with placebo versus budesonide/formoterol and formoterol driven by withdrawal of consent. Time to discontinuation was significantly ($p \leq 0.004$) prolonged in both budesonide/formoterol groups versus placebo. AE was the most common reason for study discontinuation, with a similar incidence across treatments (12.1–13.5%). Approximately 60% of patients had documented use of an ICS, either alone or in combination before entering the study. The percentage of patients who discontinued from the study in the formoterol and placebo groups was slightly higher in patients previously treated with ICS (34.9% and 38.0%, respectively) compared with those not previously receiving ICS before the study (26.8% and 33.9%, respectively). In contrast, patients in the budesonide/formoterol 320/9-µg group previously receiving ICS had a lower discontinuation rate compared with those not previously receiving ICS (23.1% vs 34.1%, respectively). In the budesonide/formoterol 160/9-µg group, the percentage of patients who discontinued the study was similar for those who were previously receiving an ICS (29.5%) and those who were not (28.2%).

Most demographic and disease characteristics at baseline were similar across treatments (table I). However, in the serial spirometry subset (n = 491), mean percentage reversibility was greater in the budesonide/formoterol 320/9 µg (19.9%), budesonide/formoterol 160/9 µg (20.7%) and placebo (19.5%) groups versus formoterol (16.9%). COPD severity[1] was moderate in 17.8%, severe in 60.4% and very severe in 21.5% of patients. Common co-
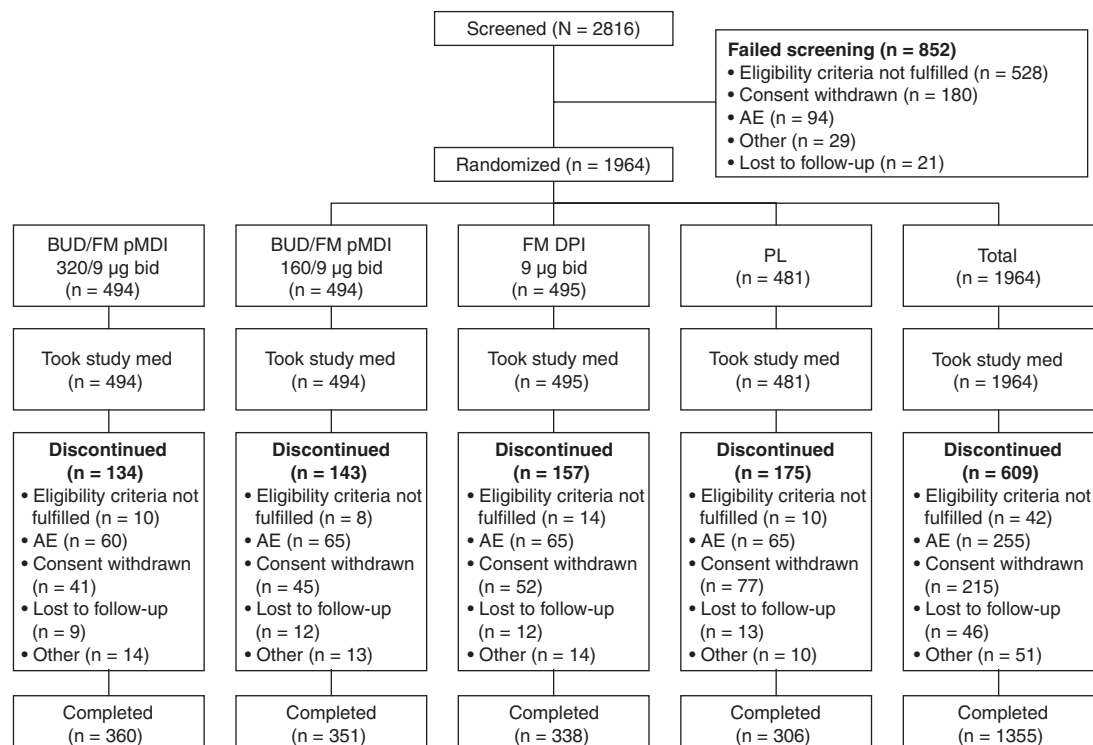
Fig. 2. Patient disposition. **AE** = adverse event; **bid** = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **med** = medication; **PL** = placebo; **pMDI** = pressurized metered-dose inhaler.

morbid conditions included hypertension (41.6%), lipid profile abnormalities (22.0%), cardiac disease (17.7%), diabetes mellitus (11.0%), osteoporosis (10.5%), cataracts (5.2%), atrial fibrillation/arrhythmia (4.3%) and congestive cardiac failure (2.9%).

Efficacy Evaluations

Pulmonary Function

Co-Primary Assessments

Improvements in pre-dose FEV_1 were significantly greater for budesonide/formoterol 320/9 μg compared with formoterol (primary comparison; p = 0.008) and for both budesonide/formoterol dosages compared with placebo (p < 0.001) [figure 3a]. Although improvements in 1-hour post-dose FEV_1 were significantly greater for both budesonide/formoterol dosages compared with placebo (primary comparison; p < 0.001), budesonide/formoterol 320/9 μg also resulted in significantly greater improve-

ments compared with formoterol (p = 0.023) [figure 3b]. Improvements from baseline were apparent at the first assessment (pre-dose FEV_1 at end of month 1; 1-hour post-dose FEV_1 at day of randomization) and overall maintained over the 12-month treatment period for both budesonide/formoterol dosages (figure 3a and b).

Secondary Assessments

Morning and evening PEF improved significantly for all active treatments compared with placebo (p ≤ 0.012) and for both budesonide/formoterol dosages compared with formoterol (p ≤ 0.017) [table II]. Results for pre-dose and 1-hour post-dose FVC are presented in the online supplement (see figures S1a and b in the supplementary material ['ArticlePlus'] at http://links.adisonline.com/DGZ/A5).

In the serial spirometry subset, a ≥15% improvement in FEV_1 was observed at 5 minutes after dose administration (first assessment) with all active

treatments on the day of randomization (budesonide/formoterol 320/9 µg, 17.7%; budesonide/formoterol 160/9 µg, 20.3%; formoterol 9 µg, 16.5%) and at end of treatment (budesonide/formoterol 320/9 µg, 21.8%; budesonide/formoterol 160/9 µg, 22.4%; formoterol 9 µg, 15.0%) [figures 4a, b and c]. There was no evidence of a diminished effect at end of treatment over the 12-hour period in the budesonide/formoterol groups. Mean FEV_1 at 12 hours and baseline-adjusted average 12-hour FEV_1 were significantly improved with both budesonide/formoterol dosages compared with placebo on the day of randomization and at end of treatment ($p \leq 0.002$) [table II]. Although both budesonide/formoterol dosages demonstrated significant improvements in mean FEV_1 at 12 hours and in baseline-adjusted average 12-hour FEV_1 compared with formoterol on the day of randomization ($p \leq 0.029$), only budesonide/formoterol 320/9 µg demonstrated this effect at the end of treatment ($p \leq 0.004$) [table II].

No significant differences in pre-dose IC were observed among the treatment groups (figure 5a). Improvements from baseline to the average over the randomized treatment period in 1-hour post-dose IC were significantly greater with both budesonide/formoterol dosages compared with placebo ($p < 0.001$) and formoterol ($p \leq 0.018$) [figure 5b].

Table I. Patient demographic and baseline clinical characteristics of randomized patients

Characteristic	BUD/FM pMDI		FM DPI	Placebo
	320/9 µg bid (n = 494)	160/9 µg bid (n = 494)	9 µg bid (n = 495)	(n = 481)
Male sex [n] (%)	308 (62.3)	310 (62.8)	323 (65.3)	314 (65.3)
Age [y]				
mean (SD)	63.2 (8.9)	63.6 (9.2)	62.9 (9.1)	62.9 (9.2)
range	40–83	42–89	41–88	40–84
Race [n] (%)				
White	457 (92.5)	460 (93.1)	457 (92.3)	441 (91.7)
Black	13 (2.6)	13 (2.6)	10 (2.0)	11 (2.3)
Asian	1 (0.2)	1 (0.2)	4 (0.8)	2 (0.4)
other	23 (4.7)	20 (4.0)	24 (4.8)	27 (5.6)
Smoking history				
ex-smoker [n] (%)	301 (60.9)	287 (58.1)	272 (54.9)	270 (56.1)
habitual smoker[a] [n] (%)	172 (34.8)	183 (37.0)	204 (41.2)	190 (39.5)
occasional smoker[b] [n] (%)	21 (4.3)	24 (4.9)	19 (3.8)	21 (4.4)
median pack-years	40	40	40	40
Months since first COPD symptoms [mean] (SD)	125 (80.6)	133 (92.1)	135 (87.2)	127 (84.5)
COPD severity [n] (%)				
mild	0	0	1 (0.2)	1 (0.2)
moderate	84 (17.0)	85 (17.2)	89 (18.0)	91 (18.9)
severe	290 (58.7)	314 (63.6)	285 (57.6)	298 (62.0)
very severe	120 (24.3)	94 (19.0)	119 (24.0)	90 (18.7)
Percentage predicted FEV_1 at screening (postbronchodilator) [mean] (SD)	38.6 (11.4)	39.6 (10.9)[c]	39.3 (11.9)[d]	40.8 (11.5)[e]
FEV_1 (L) at baseline[f] (prebronchodilator) [mean] (SD)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	1.1 (0.4)

a   Smokes at least one cigarette/day and has been smoking for ≥1 year before screening.

b   Smokes less than one cigarette/day or has been smoking for <1 year before screening or stopped smoking within 6 months before screening.

c   n = 493.

d   n = 494.

e   n = 480.

f   Baseline is defined as the last pre-dose FEV_1 value before the first dose of randomized treatment period.

bid = twice daily; **BUD** = budesonide; **COPD** = chronic obstructive pulmonary disease; **DPI** = dry powder inhaler; **FEV₁** = forced expiratory volume in 1 second; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler.

Both dosages of budesonide/formoterol resulted in a 350 mL (≈25%) improvement from baseline to the average over the randomized treatment period in 1-hour post-dose IC, and formoterol resulted in a 210 mL (17%) improvement in 1-hour post-dose IC.

Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

Time to first COPD exacerbation was significantly prolonged with both budesonide/formoterol dosages compared with placebo ($p \leq 0.004$) and with

budesonide/formoterol 320/9 µg compared with formoterol ($p = 0.026$) [figure 6]. In addition, significant reductions in the overall number of exacerbations per patient-treatment year were observed with budesonide/formoterol 320/9 µg and 160/9 µg versus placebo (37% and 41%, respectively; $p < 0.001$) and formoterol (25% and 29%, respectively; $p \leq 0.004$) [see figure S2 in the supplementary material]. These reductions were driven by exacerbations treated with oral corticosteroids, the rate of which was reduced with budesonide/formoterol 320/9 µg and 160/9 µg versus placebo (37.5% and 42.9%, respectively) and formoterol (24.1% and 30.6%, respectively) [$p \leq 0.006$]. In addition, the percentage of patients in the budesonide/formoterol 320/9 µg, budesonide/formoterol 160/9 µg, formoterol and placebo groups who experienced an exacerbation was greater in those receiving ICS therapy either alone or in combination before the study (33.7%, 38.2%, 39.9% and 40.1%, respectively) compared with those not previously receiving ICS (25.8%, 24.9%, 29.4% and 32.8%, respectively).
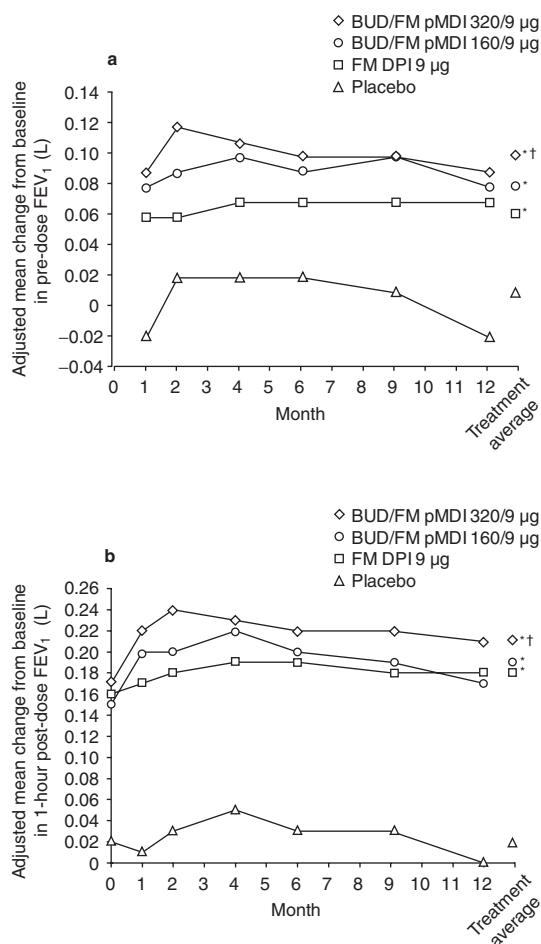
Health Status and COPD Symptoms

Improvements in SGRQ total score were significantly greater for both budesonide/formoterol dosages compared with placebo ($p \leq 0.006$) and for budesonide/formoterol 160/9 µg compared with formoterol ($p = 0.006$; table III). The improvements from baseline in SGRQ total score in the active treatment groups were not clinically meaningful versus placebo (i.e. decrease of ≥ 4 points). Significantly greater improvements in COPD symptom variables were observed for both budesonide/formoterol dosages versus placebo for all variables (BCSS, dyspnoea score, cough score, sputum score, sleep score, percentage of awakening-free nights and total daily rescue medication use) [$p \leq 0.003$]. Compared with formoterol, mean improvements were significantly greater with budesonide/formoterol 320/9 µg ($p \leq 0.038$) for all COPD symptom variables except sputum score and percentage of awakening-free nights, and with budesonide/formoterol 160/9 µg ($p \leq 0.047$) for all COPD symptom variables except BCSS, dyspnoea and sputum score (table IV).

Fig. 3. Co-primary efficacy endpoints. Least squares mean change from baseline by study visit over the randomized treatment period in (**a**) pre-dose forced expiratory volume in 1 second (FEV_1) and (**b**) 1-hour post-dose FEV_1. **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler. * $p < 0.001$ vs placebo; † $p \leq 0.023$ vs FM.

Table II. Mean (SD) changes from baseline in additional pulmonary function assessments

Variable	BUD/FM pMDI		FM DPI	Placebo
	320/9 µg bid	160/9 µg bid	9 µg bid	
Average 12-h FEV$_1$[a] [L]				
Day of randomization				
n	121	121	124	125
baseline[b]	1.02 (0.40)	0.97 (0.39)	1.00 (0.38)	1.02 (0.43)
mean change (baseline adjusted)	0.20 (0.21)[*†]	0.17 (0.21)[*†]	0.12 (0.15)[*]	0.03 (0.15)
End of treatment				
n	121	120	124	125
baseline[b]	1.02 (0.40)	0.97 (0.40)	1.00 (0.38)	1.02 (0.43)
mean change (baseline adjusted)	0.19 (0.32)[*†]	0.16 (0.27)[*]	0.10 (0.20)[*]	−0.00 (0.21)
FEV$_1$ at 12 h[a] [L]				
Day of randomization				
n	121	121	124	125
baseline[b]	1.02 (0.40)	0.97 (0.39)	1.00 (0.38)	1.02 (0.43)
mean change	0.14 (0.25)[*†]	0.10 (0.20)[*†]	0.04 (0.15)	0.02 (0.19)
End of treatment				
n	121	120	124	125
baseline[b]	1.02 (0.40)	0.97 (0.40)	1.00 (0.38)	1.02 (0.43)
mean change	0.12 (0.31)[*†]	0.09 (0.28)[*]	0.03 (0.21)	−0.02 (0.26)
Morning PEF [L/min]				
n	487	488	489	466
Baseline[c]	177 (66.6)	183 (62.0)	185 (72.7)	185 (71.8)
Mean change[d]	20.7 (39.5)[*†‡]	15.2 (33.4)[*†]	9.8 (35.9)[*]	1.9 (33.5)
Evening PEF [L/min]				
n	486	84	484	466
Baseline[c]	186 (67.8)	192 (64.1)	194 (74.7)	194 (72.7)
Mean change[d]	17.3 (39.7)[*†]	12.6 (32.5)[*†]	6.9 (35.9)[*]	1.2 (34.5)

a FEV$_1$ measurements were performed in the subset of patients undergoing serial spirometry testing (n = 491).

b Baseline is defined as the last pre-dose FEV$_1$ value before the first dose of the randomized treatment period.

c Baseline is defined as the mean of all values obtained during the last 10 days of the run-in period.

d Mean change from baseline to the average over the randomized treatment period.

bid = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler; **FEV$_1$** = forced expiratory volume in 1 second; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **PEF** = peak expiratory flow. * $p < 0.05$ vs placebo; † $p < 0.05$ vs FM DPI 9 µg bid; ‡ $p < 0.05$ vs BUD/FM 160/9 µg bid.

Improvements (i.e. reductions) in dyspnoea scores were significantly greater for all active treatments versus placebo ($p \le 0.003$) and for budesonide/formoterol 320/9 µg versus formoterol ($p = 0.032$; table IV). All active treatment arms demonstrated ≥ 0.2 points (minimal important difference) change from baseline, but only budesonide/formoterol 320/9 µg had an increase of ≥ 0.2 points over placebo. A significantly ($p < 0.001$) greater percentage of patients in both budesonide/formoterol groups and in the formoterol group experienced

clinically meaningful improvements in dyspnoea versus placebo (see figure S3 in the supplementary material).

Safety Evaluations

Mean treatment exposure was lowest for placebo (270 days) compared with budesonide/formoterol 320/9 µg (305 days), budesonide/formoterol 160/9 µg (299 days) and formoterol (289 days). The most commonly reported AE (irrespective of causality) was COPD, which had a lower incidence with

budesonide/formoterol 320/9 μg versus placebo and a slightly higher incidence with budesonide/formoterol 160/9 μg versus placebo (table V). AEs considered by the investigator to be related to study medication were generally similar among treatment groups with the most commonly reported being oral candidiasis, COPD and dysphonia (see table SI in the supplementary material).

The total incidence of pneumonia-related AEs (pneumonia, bronchopneumonia, lobar pneumonia and pneumonia staphylococcal) was similar for budesonide/formoterol 320/9 μg and 160/9 μg (4.0% and 3.4%, respectively) compared with formoterol (3.4%) and placebo (5.0%) [see table SII in the supplementary material]. For potential lung infections other than pneumonia, the incidence was slightly higher in the active treatment groups versus placebo, which was driven largely by bronchitis (see table SII in the supplementary material). AEs typically or potentially associated with local and systemic effects of inhaled corticosteroids (local effects: aphonia, dysphonia, oral candidiasis and candidiasis; systemic effects: weight gain, adrenal suppression, ocular effects, skin effects, psychiatric disorder, diabetes control, thirst, taste effects and bone effects) were more frequent with budesonide/formoterol 320/9 μg (10.3% and 4.0%, respectively) and budesonide/formoterol 160/9 μg (5.7% and 4.5%, respectively) than formoterol (0.6% and 2.6%, respectively) and placebo (2.5% and 2.7%, respectively). The overall incidence of LABA class effects (i.e. tremor, palpitation, tachycardia, potassium changes, glucose changes, headache, agitation, anxiety, sleep effects and muscle cramp) was low, but higher among active treatment groups (budesonide/formoterol 320/9 μg [9.5%], budesonide/formoterol 160/9 μg [8.9%] and formoterol [6.5%]) versus placebo (4.8%). The incidence of cardiac-related AEs was higher for all active treatments (10.5–11.3%) versus placebo (6.9%). The most common cardiac-related AEs were hypertension and angina pectoris (budesonide/formoterol 320/9 μg [2.4% and 1.2%, respectively], budesonide/formoterol 160/9 μg [1.6% and 0.8%, respectively], formoterol [2.6% and 1.8%, respectively] and placebo [2.1% and 1.0%, respectively]). Although the number of atrial fibrillation AEs was low, all cases occurred within the active treatment groups.
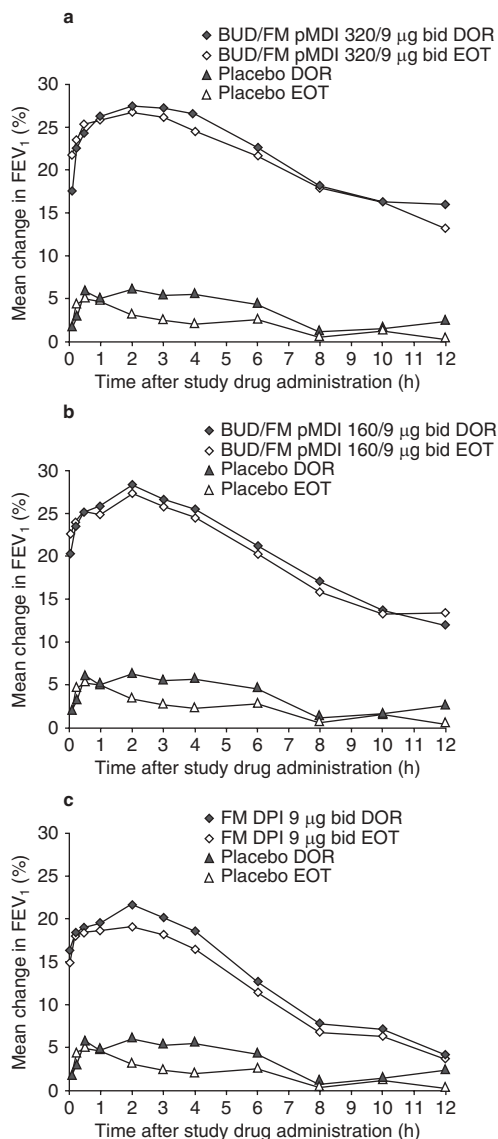

Fig. 4. Mean percentage change from baseline in forced expiratory volume in 1 second (FEV_1) over 12 hours at randomization and end of treatment (EOT) for (**a**) budesonide (BUD)/formoterol (FM) 320/9 μg twice daily (bid) vs placebo, (**b**) BUD/FM 160/9 μg bid vs placebo and (**c**) FM 9 μg bid vs placebo. **DOR** = day of randomization; **DPI** = dry powder inhaler; **pMDI** = pressurized metered-dose inhaler.

Discontinuations due to AEs (DAEs) occurred in 238 patients, with a similar incidence observed across treatment groups (range 11.3–12.5%) [see table SIII in the supplementary material]. The most common DAE was COPD, which was highest in the formoterol group (7.3%) and lowest in the budesonide/formoterol 320/9 μg group (4.0%); the incidence was similar in the budesonide/formoterol 160/9 μg (6.1%) and placebo (6.0%) groups (see table SIII in the supplementary material). The overall incidence of non-fatal serious adverse events (SAEs) was highest with formoterol (17.8%) compared with the other treatment groups and higher with budesonide/formoterol 320/9 μg (15.6%) and budesonide/formoterol 160/9 μg (13.6%) versus placebo (12.1%) [see table SIV in the supplementary material]. The most common non-fatal SAEs (occurring in five or more patients [all treatment groups combined]) were COPD (6.8%), pneumonia (1.5%), atrial fibrillation (0.5%), angina pectoris (0.3%), bronchitis (0.3%) and coronary artery disease (0.3%). These non-fatal SAEs occurred at a similar incidence in all treatment groups, except for COPD, which was slightly more common in the active treatment groups (budesonide/formoterol 320/9 μg [7.1%], budesonide/formoterol 160/9 μg [6.7%] and formoterol [7.9%]) versus placebo (5.6%). Fifteen patients died during the randomized treatment period with no imbalance across treatments: three in the budesonide/formoterol 320/9 μg group; six in the budesonide/formoterol 160/9 μg group; two in the formoterol group; and four in the placebo group. Fifteen patients died after the randomized treatment period (≥2 days after stopping study treatment) with no imbalance across treatments: five in the budesonide/formoterol 320/9 μg group; two in the budesonide/formoterol 160/9 μg group; four in the formoterol group; and four in the placebo group. None of the deaths were considered drug related by the investigator.

Clinically significant changes in vital signs, 24-hour urinary cortisol, and 12-lead ECGs, QT interval and Holter assessments were rare. The geometric mean values of 24-hour urinary cortisol at 6 months and end of treatment were lower in both budesonide/
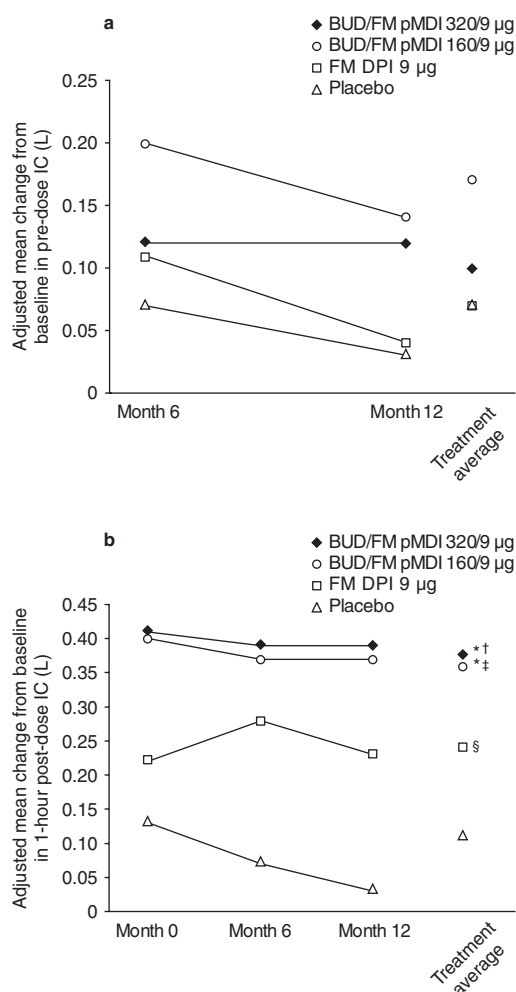

Fig. 5. Least squares mean change from baseline by study visit over the randomized treatment period in (**a**) pre-dose inspiratory capacity (IC) and (**b**) 1-hour post-dose IC. **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler. * $p < 0.001$ vs placebo; † $p = 0.01$ vs FM; ‡ $p < 0.05$ vs FM; § $p < 0.01$ vs placebo.

formoterol dosage groups compared with formoterol and placebo (see table SV in the supplementary material). Significant differences in 24-hour urinary cortisol were observed between the budesonide/formoterol 320/9 μg and placebo groups ($p = 0.035$) at month 6 and between the budesonide/formoterol 320/9 μg and formoterol groups ($p = 0.044$) at end of treatment.
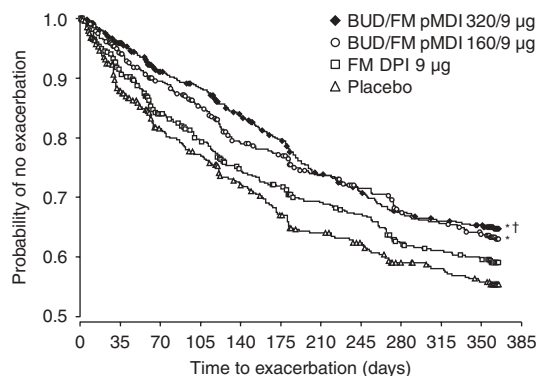
Fig. 6. Kaplan-Meier probability curve for the time to first chronic obstructive pulmonary disease exacerbation during randomized treatment. **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler. * p ≤ 0.004 vs placebo; † p = 0.026 vs FM.

Corrected QT (QTc) intervals ≥450 msec were experienced by similar percentages of patients across all treatment groups, whereas few patients experienced QTc intervals ≥500 msec or a QTc change ≥60 msec (see table SVI in the supplementary material). Data from ECG and Holter recordings

showed a similar incidence of new onset atrial fibrillation in the active and placebo groups.

BMD was stable over the 1-year study period in all treatment groups, with small but statistically significant differences in changes from baseline observed for budesonide/formoterol 320/9 μg compared with all other treatments for total lumbar spine BMD (p ≤ 0.037) and for budesonide/formoterol 320/9 μg versus formoterol for total hip BMD (p = 0.012) [see table SVII in the supplementary material]. The differences between the treatment groups in changes from baseline in BMD were of unclear clinical relevance, as the geometric least squares mean ratios for these treatment group comparisons were close to 1 (range 0.98–0.99).

Minor increases in lenticular opacities and intraocular pressure were noted across all treatment groups in the ophthalmological analysis subset; the magnitude of these changes was similar among the treatment groups (see table SVIII in the supplementary material). Small but significant differences were observed for the change from baseline in posterior subcapsular score between the budesonide/

Table III. Mean changes (SD) in SGRQ total and domain scores from baseline[a] to end of treatment[b]

Score	BUD/FM pMDI		FM DPI	Placebo
	320/9 μg bid	160/9 μg bid	9 μg bid	
Total score				
n	442	453	446	408
Baseline	54.6 (17.4)	55.7 (16.7)	55.1 (16.4)	54.7 (16.1)
Mean change	–3.9 (13.5)*	–5.3 (13.7)*†	–2.9 (13.3)	–1.5 (12.7)
Symptoms domain				
n	461	470	460	431
Baseline	66.8 (20.0)	67.2 (18.0)	65.6 (19.2)	66.3 (18.1)
Mean change	–7.9 (19.9)*†	–7.4 (19.4)*	–4.6 (19.9)	–2.8 (19.2)
Activity domain				
n	452	467	454	415
Baseline	68.6 (19.9)	70.8 (18.2)	70.1 (17.6)	69.5 (18.1)
Mean change	–2.3 (14.9)*	–3.9 (15.9)*	–2.1 (15.0)	–0.5 (15.5)
Impacts domain				
n	458	464	458	421
Baseline	42.9 (20.0)	43.4 (19.8)	43.3 (19.8)	42.5 (18.8)
Mean change	–3.6 (16.4)*	–5.3 (16.3)*†	–2.8 (15.8)	–1.4 (15.0)

a   Baseline defined as the last assessment before the first dose of randomized treatment.

b   End of treatment defined as the last assessment during randomized treatment.

bid = twice daily; **BUD** = budesonide; **DPI** = dry powder inhaler**; FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **SGRQ** = St George's Respiratory Questionnaire. * p < 0.05 vs placebo; † p < 0.05 vs FM DPI 9 μg bid.

Table IV. Mean (SD) changes in chronic obstructive pulmonary disease (COPD) symptom variables from baseline[a] to the average over the randomized treatment period

Variable	BUD/FM pMDI		FM DPI	Placebo
	320/9 μg bid	160/9 μg bid	9 μg bid	
BCSS [0–12]				
n	489	488	489	467
Baseline	5.4 (2.1)	5.5 (2.0)	5.4 (2.0)	5.3 (2.1)
Mean change	–0.8 (1.8)*†	–0.8 (1.7)*	–0.6 (1.6)*	–0.3 (1.7)
Dyspnoea score [0–4]				
n	489	488	489	467
Baseline	2.16 (0.67)	2.15 (0.71)	2.15 (0.68)	2.11 (0.71)
Mean change	–0.37 (0.66)*†	–0.32 (0.66)*	–0.29 (0.62)*	–0.16 (0.64)
Cough score [0–4]				
n	489	488	489	467
Baseline	1.80 (0.89)	1.91 (0.85)	1.83 (0.87)	1.82 (0.86)
Mean change	–0.29 (0.71)*†	–0.33 (0.66)*†	–0.23 (0.67)	–0.15 (0.68)
Sputum score [0–4]				
n	489	488	488	467
Baseline	1.41 (0.92)	1.49 (0.90)	1.44 (0.89)	1.43 (0.88)
Mean change	–0.15 (0.74)*	–0.18 (0.65)*	–0.10 (0.68)	–0.04 (0.66)
Sleep score [0–4]				
n	489	489	489	463
Baseline	1.0 (0.9)	1.0 (0.9)	1.0 (0.9)	1.0 (0.9)
Mean change	–0.3 (0.7)*†	–0.3 (0.6)*†	–0.2 (0.7)*	–0.1 (0.7)
Percentage awakening-free nights[b]				
n	489	489	489	463
Baseline	42.7 (42.9)	38.1 (42.2)	39.6 (42.4)	42.2 (43.0)
Mean change	11.8 (32.1)*	15.3 (35.6)*†	10.7 (33.9)*	4.6 (32.9)
Rescue medication use [inhalations/day]				
n	490	489	489	467
Baseline	3.8 (3.2)	4.2 (3.4)	3.9 (3.3)	3.7 (3.2)
Mean change	–1.1 (2.7)*†	–1.3 (3.0)*†	–0.8 (2.7)*	0.1 (2.6)

a   Baseline is defined as the mean of all values obtained during the last 10 days of the run-in period.

b   Night with a sleep score of 0.

bid = twice daily; **BCSS** = Breathlessness Cough and Sputum Scale; **BUD** = budesonide; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler. * p < 0.05 vs placebo; † p < 0.05 vs FM DPI 9 μg bid.

formoterol groups (p = 0.022). Clinically significant changes in ophthalmological assessment were infrequent.

Discussion

In this study, both budesonide/formoterol dosage strengths resulted in significant improvements from baseline over the randomized treatment period in pulmonary function, health status and COPD symptoms, as measured by dyspnoea, cough and sputum production, and a clinically significant reduction in COPD exacerbation rate compared with placebo. In addition, both budesonide/formoterol pMDI dosages were well tolerated relative to formoterol alone and placebo.

The results of this 12-month study confirm those from the earlier related 6-month study by Tashkin et al.[4] and are consistent with those from studies of budesonide/formoterol DPI.[2,3] Taken together, the results demonstrate that this ICS/LABA combination provides benefits beyond formoterol alone in the treatment of COPD. The contribution of budesonide to improvements from baseline in pulmonary function and COPD symptoms was demonstrated by the greater efficacy of budesonide/formoterol 320/9 μg compared with formoterol alone for the co-

Table V. Overall adverse events (AEs) [irrespective of relationship to study medication] reported by ≥3% of patients

Variable	BUD/FM pMDI		FM DPI	Placebo
	320/9 µg bid (n = 494)	160/9 µg bid (n = 494)	9 µg bid (n = 495)	(n = 481)
Mean exposure [days] (SD)	305 (115)	299 (118)	289 (127)	270 (139)
AE [n] (%)				
≥1 AE	322 (65.2)	323 (65.4)	299 (60.4)	268 (55.7)
COPD	66 (13.4)	93 (18.8)	83 (16.8)	77 (16.0)
Nasopharyngitis	35 (7.1)	44 (8.9)	30 (6.1)	22 (4.6)
Bronchitis	24 (4.9)	22 (4.5)	24 (4.8)	18 (3.7)
Viral URTI	21 (4.3)	22 (4.5)	22 (4.4)	17 (3.5)
Pneumonia	15 (3.0)	15 (3.0)	17 (3.4)	23 (4.8)
Oral candidiasis	36 (7.3)	21 (4.3)	2 (0.4)	8 (1.7)
Sinusitis	19 (3.8)	19 (3.8)	19 (3.8)	8 (1.7)
Back pain	18 (3.6)	5 (1.0)	14 (2.8)	11 (2.3)
URTI	14 (2.8)	16 (3.2)	10 (2.0)	5 (1.0)
Muscle spasms	16 (3.2)	16 (3.2)	4 (0.8)	6 (1.2)
Dysphonia	16 (3.2)	6 (1.2)	1 (0.2)	4 (0.8)

bid = twice daily; **BUD** = budesonide; **COPD** = chronic obstructive pulmonary disease; **DPI** = dry powder inhaler; **FM** = formoterol; **pMDI** = pressurized metered-dose inhaler; **URTI** = upper respiratory tract infection.

primary variables of pre-dose FEV_1 and 1-hour post-dose FEV_1, and for dyspnoea and total BCSS scores, supporting use of the higher-dose combination for COPD symptoms. Both budesonide/formoterol dosage strengths demonstrated greater improvements from baseline compared with formoterol alone in morning and evening PEF, 12-hour FEV_1, symptom scores and rescue medication use.

In addition, the 25–29% reduction in exacerbation rate observed with both budesonide/formoterol dosage strengths beyond the substantial reduction achieved with formoterol alone further demonstrates the important contribution of budesonide to the combination product. The magnitude of the reduction in exacerbation rates reported in this study is similar to that reported previously for fixed-dose regimens of budesonide/formoterol 320/9 µg twice daily[2-4] and fluticasone propionate/salmeterol[11-13] relative to LABA alone. A key difference between this 12-month study and the 6-month study of similar design reported by Tashkin et al.[4] is that this study was powered to show a difference in exacerbations, while the 6-month study was not. This study demonstrated a significant reduction in exacerbation rates in patients treated with budesonide/formoterol

320/9 µg and 160/9 µg compared with those receiving formoterol or placebo.

The fact that a greater percentage of patients in the formoterol and placebo groups who previously received ICS therapy, either alone or in combination, experienced exacerbations compared with those who did not previously receive ICS therapy may result in a skewing of the data; however, a similar response was observed in combination budesonide/formoterol patients with a greater percentage of patients who previously received ICS experiencing exacerbations compared with patients who were not previously treated with ICS therapy. Similarly, a greater percentage of patients who previously received ICS therapy discontinued in the formoterol and placebo groups than those who did not previously receive ICS therapy; however, this trend was reversed in the combination budesonide/formoterol groups.

The long-term nature of this study allowed for a more thorough assessment of tolerability compared with the 6-month study.[4] No differences in pneumonia incidence were observed among treatment groups in this study or in the 6-month study, despite a shorter exposure time in the placebo group.[4] These results contrast with previous COPD studies

that showed an increased incidence of pneumonia with fluticasone propionate/salmeterol treatment.[11-14] However, in this study and the 6-month study,[4] the incidence of potential lung infections other than pneumonia was slightly higher in all active treatments compared with placebo; these differences were largely driven by an increased incidence of bronchitis. The incidence of SAEs, including COPD SAEs, was slightly higher in both budesonide/formoterol groups compared with placebo. This finding may be attributed to the earlier discontinuation in the placebo group, which resulted in a shorter study drug exposure (35 and 29 fewer days vs budesonide/formoterol 320/9 μg and 160/9 μg, respectively). Although the overall incidence of atrial fibrillation, a known LABA class effect, was small (1.1%), an imbalance was noted between the formoterol-containing arms and placebo. However, no differences in new-onset atrial fibrillation were apparent among groups based on 24-hour Holter monitoring or ECG data collected at repeated visits during the randomized treatment period. Overall, the safety profile of budesonide/formoterol pMDI in this 12-month study was similar to that reported in the 6-month study by Tashkin et al.,[4] suggesting no increase in safety concerns with a longer duration of treatment.

Conclusions

Both dosage strengths of budesonide/formoterol pMDI (320/9 μg and 160/9 μg) were effective and well tolerated over 1 year of treatment in this population of patients with moderate to very severe COPD. In addition, budesonide/formoterol pMDI 320/9 μg demonstrated greater efficacy compared with formoterol for pre-dose FEV_1, suggesting that the higher dosage strength containing twice the daily dose of budesonide is appropriate in this patient population.

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