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ORIGINAL ARTICLE

The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma

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Key words: **Asthma control – Health-related quality of life – Inhaled corticosteroids – Long-acting β_2-adrenergic agonists – Patient-reported outcomes – Patient satisfaction**

ABSTRACT

Objective: To determine the effects of budesonide and formoterol administered via one pressurized metered-dose inhaler (budesonide/formoterol pMDI) on patient-reported outcomes (PROs) and to determine the contributions of budesonide and formoterol to those effects in adults with asthma.

Research design and methods: A 12-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter study was conducted in 480 patients aged ≥12 years with mild-to-moderate persistent asthma. After a 2-week run-in period during which current asthma therapy was discontinued, patients were randomized to receive two inhalations twice daily of budesonide/formoterol pMDI 80/4.5 µg (160/9 µg), budesonide pMDI 80 µg (160 µg), formoterol via dry powder inhaler (DPI) 4.5 µg (9 µg), or placebo.

Main outcome measures: Analyses included a subpopulation of 405 patients aged ≥18 years. PROs included the standardized Asthma Quality of Life Questionnaire (AQLQ(S)), the Medical Outcomes Study (MOS) Sleep Scale, the Patient Satisfaction with Asthma Medication (PSAM) questionnaire, and asthma control variables (recorded via electronic diaries), such as asthma symptoms, rescue medication use, and nighttime awakenings due to asthma. Patient and physician global assessments were collected at the end of the study.

Results: Patients aged ≥18 years receiving budesonide/formoterol pMDI reported significantly greater improvements from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores, and asthma control variables than patients receiving placebo ($p \leq 0.033$). Improvements from baseline in AQLQ(S) overall and domain scores, daily asthma symptoms scores, percentage of symptom-free days, percentage of rescue medication-free days, and percentage of asthma control days were significantly greater in patients receiving budesonide/formoterol pMDI versus formoterol DPI ($p \leq 0.042$). Patients receiving budesonide/formoterol pMDI reported significantly greater PSAM scores than did patients in all other treatment arms ($p \leq 0.004$). Study limitations may include the fact that the formoterol-alone arm used a different device and formulation than the other active arms as well as the absence of a treatment arm with budesonide and formoterol administered concomitantly in separate inhalers. In addition, these results may not be generalized to all patients with asthma, as this analysis included only patients aged ≥18 years.

Conclusions: Patients receiving treatment with budesonide/formoterol pMDI experienced significantly greater improvements from baseline in asthma-related quality of life, quality of sleep, and asthma control and greater satisfaction with treatment than patients receiving placebo. The combination of budesonide and formoterol in one pMDI is beneficial in improving how a patient feels and functions as a result of treatment.

Introduction

Asthma is characterized by wheezing, chest tightness, breathlessness, and coughing – symptoms brought about by airflow obstruction caused by chronic inflammation of the airways[1]. Because asthma is a chronic disease, patients often require daily preventive medication for optimum asthma control[2]. Current guidelines for the pharmacological management of persistent asthma recommend inhaled corticosteroids (ICSs) as first-line therapy[1]. The addition of long-acting β_2-adrenergic agonists (LABAs) to ICS therapy is recommended for patients with moderate or severe persistent asthma[1]. There is a strong scientific rationale for treating asthma with a combination of an ICS and a LABA in that ICSs suppress chronic inflammation and LABAs act as bronchodilators[3]. For patients whose asthma is not adequately controlled by ICS therapy alone, the addition of a LABA to the treatment regimen results in greater improvements in lung function and control of asthma symptoms than does simply increasing the dose of ICS[4–6].

Currently, two fixed ICS/LABA combination therapies are available: fluticasone/salmeterol and budesonide/formoterol. Several clinical studies have demonstrated the superior efficacy of ICS/LABA combination therapy for the treatment of persistent asthma compared with treatment with equivalent or higher doses of ICS monotherapy, and have shown that combination therapy is as well tolerated as treatment with either agent alone[7–11]. A recent meta-analysis also concluded that ICS/LABA combination therapy is more effective than treatment with higher doses of ICS for improving lung function and asthma symptoms and reducing the use of rescue medication in adult patients with asthma[12]. Additionally, results from a second meta-analysis demonstrated that ICS/LABA combination therapy reduces the rate of moderate and severe exacerbations to a significantly greater extent than treatment with high-dose ICSs[13].

The goals of asthma management from the physician's standpoint are to relieve asthma symptoms, achieve normal airway function, and prevent asthma exacerbations while minimizing the impact of the disease on the patient's daily life[14]. However, as noted by Juniper *et al.*[15], the primary goal of asthma therapy from the patient's perspective is to improve health-related quality of life (HRQL). Instruments that measure patient-reported outcomes (PROs), such as HRQL, patient perception of asthma control, and patient satisfaction, provide a method for evaluating treatment benefits from the patient's perspective[16]. PRO instruments can supplement the knowledge acquired from physiologic measures, which is important because changes in clinical parameters may not necessarily correlate with changes in how patients function or feel. This is particularly true for the treatment of respiratory conditions such as asthma and chronic obstructive pulmonary disease, where clinically meaningful improvements in lung function correlate poorly with improvements in patients' HRQL[17,18].

This article reports the effects of budesonide and formoterol delivered via one pressurized metered-dose inhaler (budesonide/formoterol pMDI) on PROs (i.e., HRQL, quality of sleep, satisfaction with treatment, and asthma control) compared with placebo in adult patients previously treated with low-to-medium doses of ICSs and describes the relative contributions of budesonide and formoterol to budesonide/formoterol pMDI combination therapy. The data presented herein are from a larger study of patients aged ≥ 12 years with mild-to-moderate persistent asthma, for which the primary (i.e., pre-dose forced expiratory volume in 1 second (FEV_1) and 12-h post-dose FEV_1) and secondary (i.e., morning and evening peak expiratory flow and diary variables) efficacy and tolerability data were published previously and demonstrated significantly better pulmonary function with twice-daily treatment with budesonide/formoterol pMDI compared with its monocomponents[19]. The present article reports the results of PRO measures that were evaluated in the original study, along with the results from a secondary analysis of patient-reported diary data and patient- and physician-reported global assessments in a subset of patients aged ≥ 18 years, to provide important patient- and physician-reported information about treatment efficacy that supplements the more physiologic measures of clinical efficacy reported by Corren *et al.*[19].

Patients and methods

Patients

Males and females with a documented asthma diagnosis for ≥ 6 months, as defined by the American Thoracic Society[20], were eligible to participate in the study. Patients were required to have a prebronchodilator FEV_1 of 60–90% of predicted normal and to have used low-to-medium doses of ICSs consistently for ≥ 4 weeks before screening (doses based on specific product dose ranges[1]). Patients were required to demonstrate FEV_1 reversibility of ≥ 12% and ≥ 0.20 L within 15–30 min of inhalation of a standard dose of albuterol. Patients receiving ICS/LABA combination treatment (e.g., fluticasone/salmeterol) were to be switched to monotherapy with an equivalent dose of an ICS ≥ 24 h before spirometry testing at screening. Other inclusion and exclusion criteria for this study have been described previously[19].

Study design

This was a 12-week, multicenter (56 US centers), randomized, double-blind, double-dummy, placebo-controlled study (study code, SD-039-0716). Eligible patients discontinued their current asthma therapy and received single-blind placebo pMDI and rescue albuterol for use during the 2-week run-in period. The length of the run-in period ranged from 7 to 21 days to accommodate any possible symptom deterioration in patients with varying response to corticosteroid withdrawal. Patients were eligible for randomization if they reported daytime or nighttime asthma symptom scores of >0 (where 0 = no symptoms and 3 = severe symptoms) on ≥3 of 7 consecutive days during the run-in period, and had a pre-dose FEV_1 of ≥50% to ≤85% of predicted normal at randomization. After the run-in period, patients meeting these criteria were randomized (1:1:1:1) using a computer-generated allocation schedule to receive budesonide/formoterol pMDI 80/4.5 µg × 2 inhalations (160/9 µg) twice daily, budesonide pMDI 80 µg × 2 inhalations (160 µg) twice daily, formoterol via dry powder inhaler (DPI) 4.5 µg × 2 inhalations (9 µg) twice daily, or placebo twice daily (Figure 1). To maintain blinding, patients received both a pMDI and a DPI with active treatment and/or placebo, as appropriate. Placebo inhalers were identical in appearance to those containing active study drugs. Patients administered medication via the pMDI first, followed by the DPI. Patients were provided with albuterol pMDI as rescue medication and asked to return to the clinic for follow-up visits at weeks 2, 6, and 12.

The study protocol was approved by an institutional review board at each site, and the study adhered to the guidelines for good clinical practice and for the ethical treatment of human subjects and complied with all applicable local regulations. Written informed consent was acquired from all patients before inception of any study procedures. Complete details regarding permitted and prohibited concomitant medications have been published elsewhere[19].

Patient-reported outcomes

Asthma Quality of Life Questionnaire (Standardized) (AQLQ(S))

Patients' perceptions of the effects of asthma on their HRQL were assessed with the standardized Asthma Quality of Life Questionnaire (AQLQ(S)), a validated questionnaire that consists of 32 items in four domains: symptoms, activity limitations, emotional function, and exposure to environmental stimuli[21,22]. Patients completed the AQLQ(S) on the day of randomization (which served as the baseline) and during the double-blind treatment period at each clinic visit using a validated electronic version of the questionnaire (Assist Technologies, Scottsdale, Arizona, USA)[23]. AQLQ(S) overall and domain scores range from 1 (greatest possible impairment) to 7 (least possible impairment). A clinically meaningful change for the AQLQ(S) has been defined as the achievement of a minimal important difference from baseline of ≥0.5 points[24].

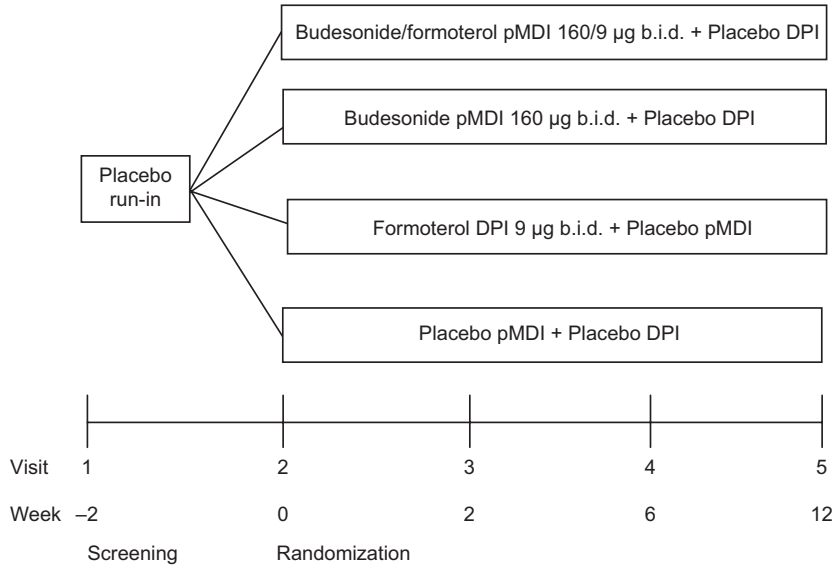

Figure 1. *Study design. Upon enrollment at visit 1, patients began a single-blind placebo run-in period, during which patients discontinued use of current asthma therapy and used a single-blind placebo pressurized metered-dose inhaler (pMDI) (two inhalations b.i.d.). Patients had access to a short-acting β_2-agonist as rescue treatment for acute relief of asthma symptoms during the run-in and treatment periods of the study. Treatments were administered in double-dummy fashion using a placebo pMDI or placebo dry powder inhaler (DPI) as appropriate to account for the different devices used in the study*

Medical Outcomes Study (MOS) Sleep Scale

Sleep quantity and quality were evaluated using the Medical Outcomes Study (MOS) Sleep Scale, which has been validated for use in a general population of patients aged ≥ 18 years in the United States[25]. Patients completed the 12-item MOS sleep questionnaire on the day of randomization (baseline) and at weeks 6 and 12 during the double-blind treatment period via electronic entry (Assist Technologies). Scores were transformed to a scale from 0 (best sleep) to 100 (worst sleep). Mean scores for the individual questions for 'awaken during sleep' and 'awaken short of breath or with a headache' and for the Long Index (nine of the 12 questions) were analyzed.

Patient Satisfaction with Asthma Medication (PSAM) questionnaire

Assessment of patient satisfaction with the study medications was evaluated using the validated Patient Satisfaction with Asthma Medication (PSAM) questionnaire[26]. The 23 asthma-specific questions of the PSAM use a variety of 5- or 6-point response options, which were transformed to a scale of 0–100 (where 0 represents the lowest level of satisfaction and 100 represents the highest level of satisfaction) for analysis[26]. Items in the PSAM map to four domains: the overall perception of medication index (four items), the control relief index (five items), the comparison with other medications index (four items), and the inhaler index (eight items). The inhaler index was not analyzed because all patients used both types of inhalers throughout the study. Patients completed the PSAM at each clinic visit during the double-blind treatment period via electronic entry (Assist Technologies). Domain scores were calculated as the mean score for items in each domain. In a post hoc data analysis, the percentages of patients with the two highest ratings and two lowest ratings (on the original response scale) were assessed.

Diary variables

Rescue medication use (number of inhalations) and asthma symptoms were assessed via electronic diary entry (LogPad, PHT Corporation, Charlestown, MA, USA) twice daily (morning and evening). Nighttime awakenings were recorded once daily in the morning. A rescue medication-free day was defined as a calendar day with no use of rescue medication during the daytime or the nighttime. Patients scored their asthma symptoms on a scale from 0 (none) to 3 (severe) for the period since their previous recording. The average daily symptom score was calculated as the mean of daytime and nighttime symptom scores. A symptom-free day was defined as a calendar day with no daytime or nighttime symptoms and no awakenings due to asthma. An asthma control day was defined as a rescue medication-free and symptom-free day. An awakening-free night was defined as a night with no awakenings due to asthma.

Global assessments

At end of treatment (final study visit), global asthma control was assessed by both the patients and physicians. Patients were asked the following questions: (1) Compared to the start of the study, how would you rate your health now? (5-point response scale: a great deal better, somewhat better, unchanged, somewhat worse, and a great deal worse); (2) Since the start of the study, how would you evaluate your ability to manage your asthma? (5-point response scale: a great deal easier, somewhat easier, unchanged, somewhat more difficult, and a great deal more difficult). Physicians were asked the following questions: (1) Since the start of the study, how would you evaluate the patient's asthma symptoms? (5-point response scale: a great deal better, somewhat better, unchanged, somewhat worse, and a great deal worse); (2) Since the start of the study, how would you evaluate your ability to manage the patient's asthma? (5-point response scale: a great deal easier, somewhat easier, unchanged, somewhat more difficult, and a great deal more difficult). Responses were analyzed by combining the top two responses (representing an improvement in asthma control/overall health compared with before the study) into one category and comparing the percentage of respondents across treatment groups.

Statistical analyses

The analyses for all variables presented herein include patients aged ≥ 18 years only, as the AQLQ(S) and PSAM questionnaire are validated for use in patients aged ≥ 18 years with asthma[22,26]. For consistency, the results for the diary variables and patient and physician global assessments from the original analyses that included the overall population (patients aged ≥ 12 years) were reanalyzed to exclude data from patients aged ≤ 17 years. The prespecified primary comparison for all assessments presented herein was between the budesonide/formoterol pMDI and the placebo groups. All statistical analyses were conducted as two-sided tests. A hierarchical approach[27] to control for multiplicity of statistical testing was applied to the data from this study,

involving the coprimary endpoints (pre-dose FEV_1 and post-dose FEV_1) and the percentage of patients who met predefined criteria for worsening asthma (all presented elsewhere[19]), as well as the AQLQ(S) overall score and the percentage of patients with symptom-free days (presented herein). All other variables were analyzed without adjustment for multiple comparisons, with $p \leq 0.05$ considered statistically significant.

For variables recorded at clinic visits, the mean change in score from baseline (with the exceptions of the PSAM indices and global assessments, for which no baseline values were measured) to the end of treatment was analyzed. Baseline for these variables was defined as the value recorded on the day of randomization, before receiving the first dose of randomized study medication, and end of treatment was defined as the last valid value recorded before the termination of double-blind treatment. Patient diary data were analyzed as the change from baseline (defined as the mean of all run-in data) to the mean over the double-blind treatment period in patients aged ≥ 18 years, whereas the previously published analysis of patients aged ≥ 12 years assessed the change from baseline to the end of treatment (defined as the mean of the last 7 days of treatment)[19].

Data for AQLQ(S), MOS Sleep Scale, and diary variables were compared between treatment groups using analysis of covariance models adjusting for center and baseline. Because there were no baseline values for PSAM scores, results were analyzed using an analysis of variance model adjusting for center. To analyze the proportion of patients who demonstrated a clinically meaningful improvement (≥ 0.5 points) from baseline in HRQL, a χ^2-test was performed on the AQLQ(S) overall and domain scores. A χ^2-test also was performed on response data from the patient and physician global assessments.

Results

A total of 405 patients aged ≥ 18 years were included in the primary and secondary analyses. Demographic and baseline characteristics were similar among the treatment groups (Table 1).

Table 1. *Patient demographics and baseline characteristics*

Characteristic	BUD/FM pMDI 160/9 µg b.i.d. (*n* = 105)	BUD pMDI 160 µg b.i.d. (*n* = 100)	FM DPI 9 µg b.i.d. (*n* = 93)	PBO (*n* = 107)
Sex, *n* (%)				
Male	39 (37.1)	33 (33.0)	29 (31.2)	37 (34.6)
Female	66 (62.9)	67 (67.0)	64 (68.8)	70 (65.4)
Race, *n* (%)				
White	91 (86.7)	85 (85.0)	82 (88.2)	98 (91.6)
Black	8 (7.6)	10 (10.0)	8 (8.6)	6 (5.6)
Other	6 (5.7)	5 (5.0)	3 (3.2)	3 (2.8)
Age in years				
Mean (SD)	41.1 (13.5)	41.8 (13.3)	40.0 (13.9)	39.1 (12.8)
Range	18–77	18–78	18–73	18–66
Duration of asthma in years				
Mean (SD)	22.0 (12.6)	21.5 (13.4)	21.8 (12.5)	22.3 (13.9)
Range	1.3–57.7	1.4–58.3	0.8–54.8	1.2–60.9
Total ICS dose at entry, µg/day				
Mean (SD)	357.9 (145.1)	355.3 (184.1)	328.9 (171.5)	352.0 (181.2)
Range	88.0–1000.0	88.0–1200.0	88.0–1200.0	80.0–1000.0
Mean rescue medication use at entry, total number of inhalations per day (SD)	2.84 (2.4)	3.12 (3.0)	2.92 (2.6)*	2.68 (2.8)†
FEV_1, mean (SD)				
Liters	2.4 (0.6)	2.3 (0.6)	2.3 (0.7)	2.4 (0.7)
% Predicted	69.9 (10.3)	69.4 (9.7)	70.1 (10.5)	69.0 (9.9)

*n = 90; †n = 102

BUD = budesonide; FM = formoterol; pMDI = pressurized metered-dose inhaler; b.i.d. = twice daily; SD = standard deviation; DPI = dry powder inhaler; PBO = placebo; FEV_1 = forced expiratory volume in 1 second

Patient-reported outcomes

AQLQ(S)

Figure 2A shows the adjusted mean change from baseline (from analysis of covariance) at the end of treatment for the overall and domain scores of the AQLQ(S). Mean improvements from baseline in overall score (Table 2) and individual domain scores on the AQLQ(S) were significantly greater for the patients who received budesonide/formoterol pMDI compared with those who received formoterol DPI or placebo ($p \leq 0.042$) and for patients receiving budesonide pMDI compared with those receiving placebo ($p \leq 0.007$). Patients receiving formoterol DPI demonstrated significantly greater mean improvements from baseline in the overall score and the symptoms and emotional function domain scores compared with patients receiving placebo ($p \leq 0.011$). Mean improvements from baseline in overall score and individual domain scores also were significantly greater for patients receiving budesonide/formoterol pMDI compared with those receiving formoterol DPI ($p \leq 0.042$). No significant differences were observed between patients who received budesonide/formoterol pMDI and those who received budesonide pMDI ($p = 0.064$ for the emotional function domain and ≥ 0.234 for the overall score and other domain scores).

A clinically meaningful improvement from baseline (≥ 0.5-point difference) was attained for the mean overall score and each domain score (except for the environmental exposure domain) for patients receiving budesonide/formoterol pMDI. In addition, the mean differences between the budesonide/formoterol pMDI group and the placebo group in changes from baseline indicated a clinically meaningful difference for the overall AQLQ(S) score as well as for three of the four domain scores. Figure 2B shows the percentage of patients in each treatment group who experienced a clinically meaningful improvement or deterioration from baseline to end of treatment in overall AQLQ(S) scores. A significantly greater percentage of patients who received budesonide/formoterol pMDI (62.7%) or budesonide pMDI (55.6%) experienced a clinically meaningful improvement in overall AQLQ(S) score at the end of treatment than did patients who received placebo (35.0%, $p \leq 0.006$). No significant differences in the percentage of patients with a clinically meaningful improvement in overall AQLQ(S) score were observed for formoterol DPI versus placebo ($p = 0.105$) or for budesonide/formoterol pMDI versus budesonide pMDI ($p = 0.372$) or formoterol DPI ($p = 0.053$).

MOS Sleep Scale

Patients receiving budesonide/formoterol pMDI reported a significant improvement in the overall quality of sleep they experienced during the double-blind treatment period, as assessed with the Long Index Score, compared with those receiving placebo ($p = 0.013$; Table 2). No significant differences in the changes from baseline to end of treatment in overall quality of sleep were observed for budesonide pMDI versus placebo ($p = 0.105$), formoterol DPI versus placebo ($p = 0.318$), or budesonide/formoterol pMDI versus budesonide pMDI ($p = 0.386$) or formoterol DPI ($p = 0.171$). Questions related to nighttime awakening and awakening short of breath or with a headache were analyzed individually and showed that patients receiving budesonide/formoterol pMDI were significantly less likely to awaken during the night or to awaken with shortness of breath or with a headache compared with patients receiving placebo ($p \leq 0.033$; Table 2). Patients receiving budesonide pMDI also were significantly less likely to awaken short of breath or with a headache compared with patients who received placebo ($p < 0.001$). No significant differences were observed for nighttime awakenings or awakening short of breath or with a headache for formoterol DPI versus placebo ($p \geq 0.093$) or for budesonide/formoterol pMDI versus budesonide pMDI ($p \geq 0.280$) or formoterol DPI ($p \geq 0.207$).

PSAM questionnaire

Patients receiving budesonide/formoterol pMDI had significantly greater mean PSAM scores at end of treatment for all three indices (control relief, perception of medication, and comparison with other medications) compared with patients receiving any other treatment ($p \leq 0.004$; Table 2). Mean PSAM scores at end of treatment for all three indices also were significantly better for patients receiving budesonide pMDI or formoterol DPI compared with those receiving placebo ($p < 0.001$). A greater percentage of patients receiving budesonide/formoterol pMDI reported higher satisfaction ratings for individual parameters measured within the three PSAM indices compared with patients receiving placebo, budesonide pMDI, or formoterol DPI (Figure 3A–C).

Diary variables

Changes from baseline to the mean over the double-blind treatment period for diary variables are shown in Table 2. Decreases from baseline to the mean over the double-blind treatment period in mean asthma symptom scores were significantly greater for patients who received budesonide/formoterol pMDI compared with patients who received placebo ($p < 0.001$) or formoterol DPI ($p = 0.008$; Table 2), but not compared with patients who received budesonide pMDI ($p =$

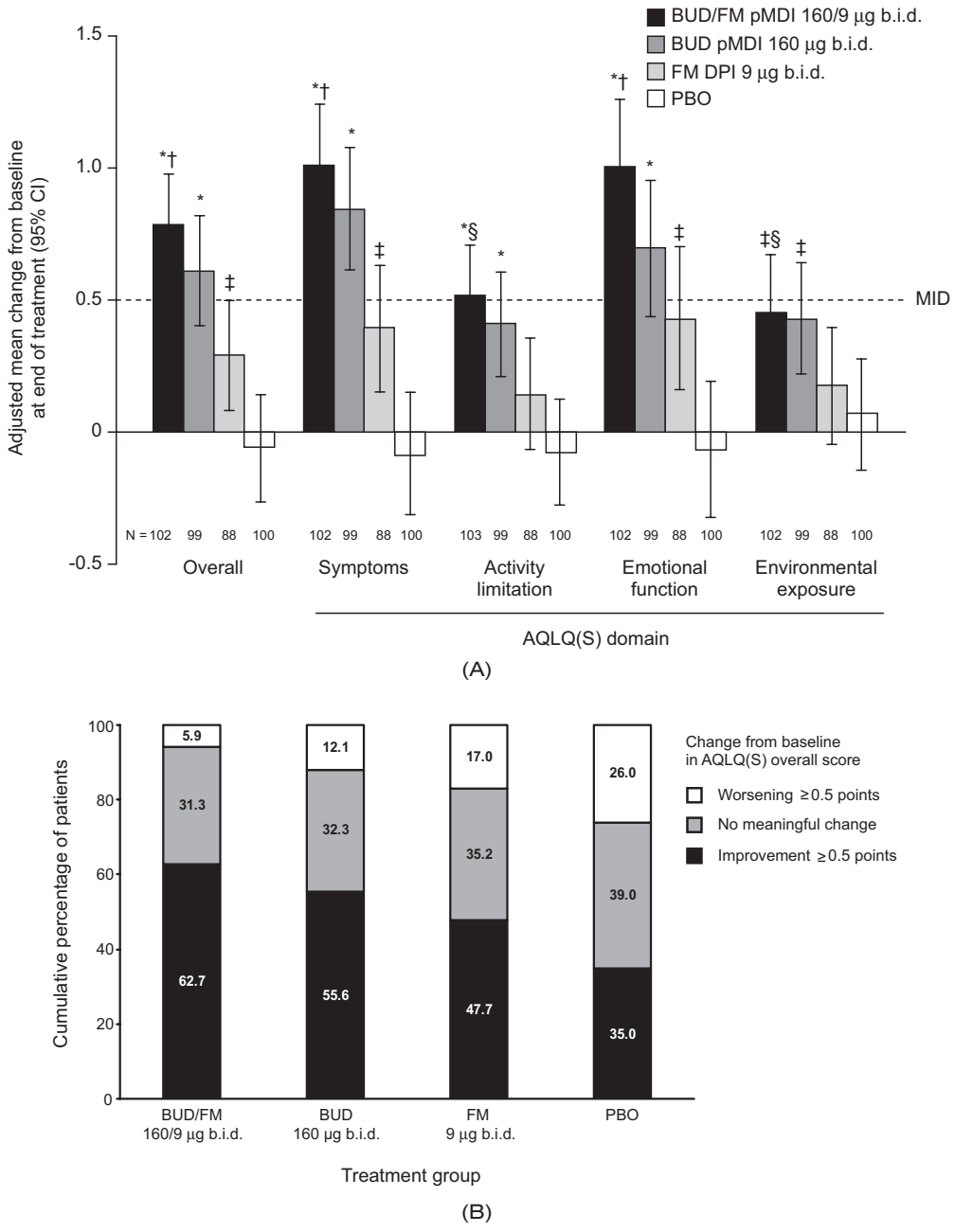

Figure 2. *(A) AQLQ(S) adjusted mean change from baseline at end of treatment for overall score and domain scores from analysis of covariance. *p < 0.001 vs. placebo; †p < 0.001 vs. FM; ‡p < 0.05 vs. placebo; §p < 0.05 vs. FM. MID, minimal important difference of ≥0.5 points in AQLQ(S) score. (B) Percentage of patients experiencing clinically meaningful changes in health-related quality of life throughout the treatment period for each treatment group. A clinically meaningful change for the AQLQ(S) has been defined as the achievement of a minimal important difference from baseline of ≥0.5 points[24]. Baseline defined as the pre-dose score at day of randomization. End of treatment defined as the last valid score recorded before the termination of the double-blind treatment or at the time of treatment failure. BUD, budesonide; FM, formoterol; pMDI, pressurized metered-dose inhaler; b.i.d., twice daily; DPI, dry powder inhaler; PBO, placebo; CI, confidence interval; AQLQ(S), standardized Asthma Quality of Life Questionnaire*

0.793). Treatment with budesonide/formoterol pMDI resulted in significantly greater increases in the mean percentage of symptom-free days from baseline to the mean over the double-blind treatment period compared with placebo ($p < 0.001$) or formoterol DPI ($p = 0.020$; Table 2), but not compared with patients who received budesonide pMDI ($p = 0.930$). Changes from baseline to the mean over the double-blind treatment period in mean asthma symptom scores and percentage of symptom-free days also were significantly greater for patients receiving budesonide pMDI or formoterol DPI compared with those receiving placebo ($p \leq 0.032$).

Patients who received budesonide/formoterol pMDI experienced a significantly greater decrease from

Table 2. *Results from patient-reported outcome variables*

	BUD/FM pMDI 160/9 µg b.i.d.	BUD pMDI 160 µg b.i.d.	FM DPI 9 µg b.i.d.	PBO	Adjusted mean differences between groups (95% CI)*		
					BUD/FM minus BUD	BUD/FM minus FM	BUD/FM minus PBO
HRQL variables							
AQLQ(S) overall score†							
No. of patients	102	99	88	100			
Baseline mean‡	5.24	5.09	5.08	5.10			
Mean change§	0.79	0.73‖	0.44¶	0.05	0.16 (–0.10, 0.41) $p = 0.234$	0.49 (0.22, 0.75) $p < 0.001$	0.84 (0.58, 1.09) $p < 0.001$
MOS Sleep Scale#							
No. of patients	101	97	81	92			
Long Index Score							
Baseline mean‡	33.79	34.74	33.93	32.88			
Mean change§	–7.10	–5.62	–4.71	–1.84	–1.73 (–5.64, 2.18) $p = 0.386$	–2.87 (–6.98, 1.24) $p = 0.171$	–5.01 (–8.97, –1.06) $p = 0.013$
Awaken during sleep score							
Baseline mean‡	23.37	28.25	25.19	22.17			
Mean change§	–5.74	–5.57	–5.43	1.09	–3.31 (–9.32, 2.70) $p = 0.280$	–1.89 (–8.19, 4.40) $p = 0.555$	–6.59 (–12.64, –0.54) $p = 0.033$
Awaken short of breath or with headache score							
Baseline mean‡	32.87	34.23	31.60	31.30			
Mean change§	–13.66	–16.08‖	–10.12	–2.61	0.94 (–5.36, 7.24) $p = 0.769$	–4.25 (–10.87, 2.37) $p = 0.207$	–10.09 (–16.47, –3.72) $p = 0.002$
PSAM end of treatment mean**							
No. of patients	102	100	88	100			
Control relief index††	74.27	59.24‖	62.62‖	38.28	15.03 (8.25, 21.81) $p < 0.001$	11.65 (4.65, 18.66) $p = 0.001$	35.99 (29.28, 42.71) $p < 0.001$
Perception of medication index††	74.87	60.66‖	64.91‖	40.45	14.22 (8.00, 20.44) $p < 0.001$	9.96 (3.54, 16.38) $p = 0.002$	34.42 (28.26, 40.58) $p < 0.001$

Table 2. *Contd.*

	BUD/FM pMDI 160/9 µg b.i.d.	BUD pMDI 160 µg b.i.d.	FM DPI 9 µg b.i.d.	PBO	Adjusted mean differences between groups (95% CI)*		
					BUD/FM minus BUD	BUD/FM minus FM	BUD/FM minus PBO
HRQL variables *(continued)*							
Comparison with other medications index††	66.51	47.01‖	55.37‖	25.25	19.50 (12.23, 26.77) $p < 0.001$	11.14 (3.63, 18.65) $p = 0.004$	41.27 (34.06, 48.47) $p < 0.001$
Asthma control variables							
Asthma daily symptom score							
No. of patients	105	100	90	102			
Baseline mean‡‡	1.13	1.11	1.09	1.12			
Mean change§§	–0.45	–0.43‖	–0.28‖	–0.08	–0.02 (–0.14, 0.10) $p = 0.793$`	–0.17 (–0.29, –0.05) $p = 0.008$	–0.38 (–0.50, –0.26) $p < 0.001$
Symptom-free days (%)							
No. of patients	105	100	90	101			
Baseline mean‡‡	6.32	7.66	8.55	7.02			
Mean change§§	24.71	24.64‖	15.99¶	6.01	0.37 (–7.90, 8.64) $p = 0.930$	10.14 (1.63, 18.64) $p = 0.020$	19.52 (11.35, 27.70) $p < 0.001$
Rescue medication use (inhalations/day)							
No. of patients	105	100	90	102			
Baseline mean‡‡	2.84	3.12	2.92	2.68			
Mean change§§	–1.91	–1.52‖	–1.55‖	0.15	–0.52 (–1.04, –0.01) $p = 0.044$	–0.47 (–1.00, 0.05) $p = 0.079$	–1.94 (–2.45, –1.44) $p < 0.001$
Rescue medication-free days (%)							
No. of patients	105	100	90	101			
Baseline mean‡‡	30.27	25.71	29.09	32.12			
Mean change§§	40.86	30.64‖	32.04‖	6.75	14.14 (5.91, 22.37) $p < 0.001$	10.85 (2.41, 19.30) $p = 0.012$	34.43 (26.30, 42.55) $p < 0.001$

Table 2. *Contd.*

	BUD/FM pMDI 160/9 µg b.i.d.	BUD pMDI 160 µg b.i.d.	FM DPI 9 µg b.i.d.	PBO	Adjusted mean differences between groups (95% CI)*		
					BUD/FM minus BUD	BUD/FM minus FM	BUD/FM minus PBO
Asthma control variables *(continued)*							
Asthma control days (%)							
No. of patients	105	100	90	102			
Baseline mean‡‡	4.87	6.26	7.40	4.58			
Mean change§§	23.84	22.98‖	14.19¶	5.39	0.95 (–6.66, 8.56) $p = 0.807$	11.03 (3.21, 18.86) $p = 0.006$	19.48 (11.98, 26.98) $p < 0.001$
Awakening-free nights (%)							
No. of patients	105	100	90	102			
Baseline mean‡‡	70.82	69.30	70.27	69.55			
Mean change§§	21.41	21.19‖	19.56‖	13.19	1.27 (–2.79, 5.34) $p = 0.538$	2.96 (–1.22, 7.13) $p = 0.165$	9.45 (5.44, 13.45) $p < 0.001$

BUD, budesonide; FM, formoterol; pMDI, pressurized metered-dose inhaler; b.i.d., twice daily; DPI, dry powder inhaler; PBO, placebo; HRQL, health-related quality of life; AQLQ(S), Asthma Quality of Life Questionnaire (standardized); SD, standard deviation; CI, confidence interval; MOS, Medical Outcomes Study; PSAM, Patient Satisfaction with Asthma Medication

*Adjusted mean differences between groups and 95% CIs from analysis of covariance using least squares mean data for all variables except PSAM, which was calculated from analysis of variance

†A clinically meaningful change for the AQLQ(S) has been defined as a change of ≥ 0.5 points[24]

‡Baseline defined as pre-dose value on the day of randomization

§Change from baseline defined as the last valid value during double-blind treatment minus the pre-dose value on the day of randomization

‖$p < 0.01$ vs. PBO

¶$p < 0.05$ vs. PBO

#MOS Sleep Scale scores range from 0 to 100, with lower scores representing better sleep

**PSAM scores range from 0 to 100, with higher scores representing greater satisfaction

††Last valid data during double-blind treatment calculated as least squares mean value

‡‡Baseline defined as the mean of all run-in data

§§Change from baseline defined as mean values over double-blind treatment minus the mean of all run-in data

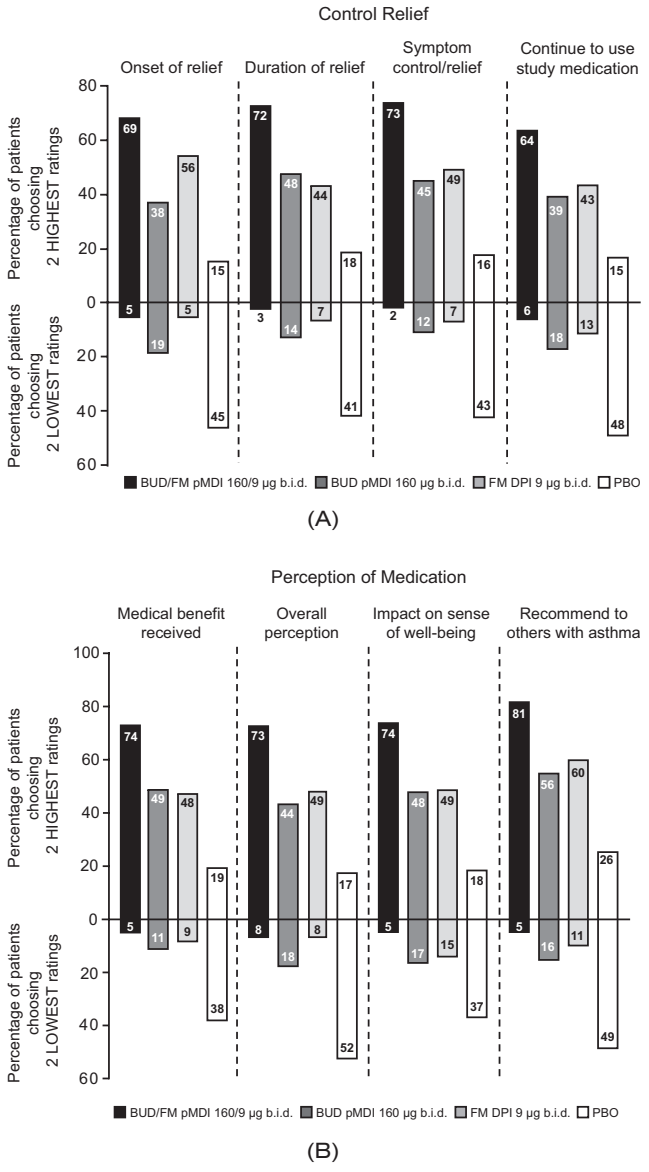

Figure 3. *Percentage of patients reporting the two highest and lowest possible responses for individual questions in the PSAM questionnaire indices of (A) control relief, (B) perception of medication and (C) comparison with other medications at the end of treatment (each question allowed for five or six possible responses). Highest ratings included responses such as 'extremely satisfied/pleased/happy' for the control relief and perception of medication indices and 'much better/faster/longer' for the comparison with other medications index. Lowest ratings included responses such as 'extremely dissatisfied/displeased/unhappy' for the control relief index, 'had a very negative impact' for the perception of medication index and 'much less/slower/shorter/poorer' for the comparison with other medications index. BUD, budesonide; FM, formoterol; b.i.d., twice daily; PBO, placebo*

baseline to the mean over the double-blind treatment period in daily rescue medication use compared with patients who received budesonide pMDI ($p = 0.044$) or placebo ($p < 0.001$) (Table 2), but not compared with patients who received formoterol DPI ($p = 0.079$). Decreases from baseline in daily rescue medication use in the budesonide pMDI and formoterol DPI groups also were significantly different from the increase from baseline observed in the placebo group ($p < 0.001$, both comparisons). Significantly greater increases from baseline to the mean over the double-blind treatment period in the percentage of rescue medication-free days were observed with budesonide/formoterol pMDI versus placebo ($p < 0.001$), budesonide pMDI ($p < 0.001$), and formoterol DPI ($p = 0.012$) and with budesonide pMDI and formoterol DPI versus placebo ($p < 0.001$, both comparisons) (Table 2). The increase in rescue medication-free days observed in the budesonide/formoterol pMDI group compared with the placebo group was observed within 1 day of the first dose of study medication and was maintained throughout the treatment period (Figure 4).

Patients receiving budesonide/formoterol pMDI experienced a significantly greater increase from baseline to the mean over the double-blind treatment period in the percentage of asthma control days compared with those receiving placebo ($p < 0.001$) or formoterol DPI ($p = 0.006$; Table 2), but not compared with those receiving budesonide pMDI ($p = 0.807$). The increase in the percentage of patients experiencing asthma control days observed in the budesonide/formoterol pMDI group compared with the placebo group was evident within 1 day of the first dose of study medication, and continued improvement was observed throughout the double-blind treatment period (data not shown). Increases from baseline to the mean over the double-blind treatment period in the percentage of asthma control days also were significantly greater for budesonide pMDI and formoterol DPI compared with placebo ($p \leq 0.036$). Increases from baseline to the mean over

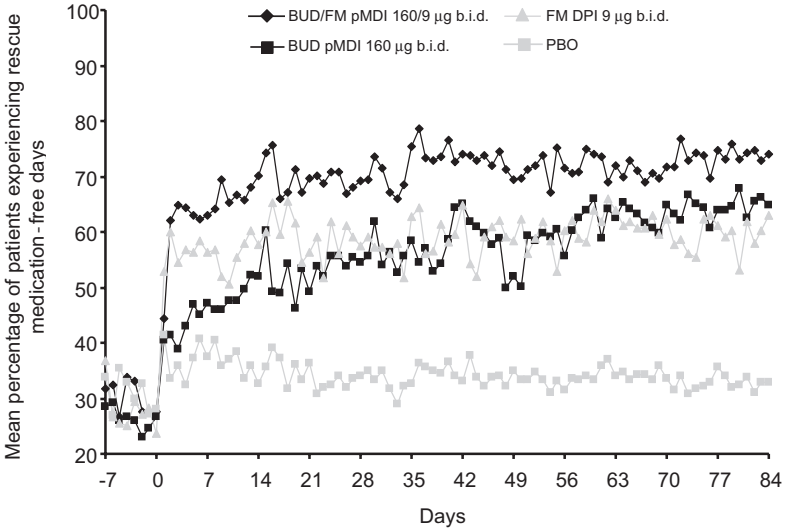

Figure 4. *Mean percentage of patients in each treatment group with rescue medication-free days throughout the study period. Missing data were imputed using the average of the three previous days carried forward (last observation carried forward). BUD, budesonide; FM, formoterol; b.i.d., twice daily; pMDI, pressurized metered-dose inhaler; PBO, placebo*

the double-blind treatment period in the percentage of awakening-free nights were significantly greater for all active treatments compared with placebo ($p \leq 0.003$; Table 2), with no significant differences observed for budesonide/formoterol pMDI versus budesonide pMDI ($p = 0.538$) or formoterol DPI ($p = 0.165$). A secondary assessment of diary data evaluating changes from baseline to the average over the randomized treatment period in the overall population (patients aged ≥12 years; data not shown) yielded results similar to those observed in patients aged ≥18 years.

Global assessments

At the final study visit, the percentage of patients reporting improvement in overall health was significantly higher in the budesonide/formoterol pMDI group (61.0%) than in the placebo group (19.5%, $p < 0.001$), while improvements in the budesonide pMDI group (50.5%) and in the formoterol DPI group (54.4%) were not significantly different from the budesonide/formoterol pMDI group ($p = 0.14$ and 0.38, respectively). The percentage of patients reporting improvement in overall health also was significantly higher in the budesonide pMDI (50.5%) and formoterol DPI (54.4%) groups compared with placebo ($p < 0.001$, both comparisons). The percentage of patients who reported that they were better able to manage their asthma during the course of treatment compared with before treatment was significantly greater in the budesonide/formoterol pMDI group (62.0%) compared with the placebo (20.5%, $p < 0.001$) and budesonide pMDI (45.5%, $p = 0.02$) groups, but not compared with the formoterol DPI group (55.7%, $p = 0.40$). The percentage of patients who reported that they were better able to manage their asthma during the course of treatment compared with before treatment also was significantly greater for budesonide pMDI and formoterol DPI compared with placebo ($p < 0.001$, both comparisons).

The percentage of physicians reporting that their patients experienced improvements in their asthma symptoms was significantly higher for those whose patients were receiving budesonide/formoterol pMDI (68.9%), budesonide pMDI (53.5%), or formoterol DPI (58.0%) than for those whose patients were receiving placebo (17.5%, $p < 0.001$, all comparisons). Significantly greater percentages of physicians reported improvements in their patients' asthma symptoms for those receiving budesonide/formoterol pMDI compared with those who received budesonide pMDI ($p = 0.03$), but not formoterol DPI ($p = 0.12$). The percentage of physicians reporting that they were better able to manage their patient's asthma was significantly higher for those whose patients were receiving budesonide/formoterol pMDI (63.1%) than for those whose patients were receiving placebo (15.5%, $p < 0.001$), budesonide pMDI (40.4%, $p = 0.001$), or formoterol DPI (47.7%, $p = 0.03$). The percentage of physicians who reported easier asthma management also was significantly higher for those whose patients received budesonide pMDI or formoterol DPI compared with those who received placebo ($p < 0.001$, both comparisons).

Discussion

Results from the present analyses of a subpopulation of patients aged ≥18 years demonstrate that treatment

with budesonide/formoterol pMDI led to significant improvements from baseline in HRQL and sleep quality and greater patient satisfaction with asthma medication at the end of treatment when compared with placebo. In addition, treatment with budesonide/formoterol pMDI led to significant improvements in diary variables from baseline to the mean over the double-blind treatment period compared with placebo. These PRO data complement the improvements in objective measures observed in this study[19] with respect to the efficacy of budesonide/formoterol pMDI therapy for improving asthma control.

In the previously published analysis of the overall study population (aged ≥ 12 years), diary variables were analyzed as the change from baseline to end of treatment (mean of values recorded on the last 7 days of the double-blind treatment period)[19]. In the present analysis, diary variables (symptom scores, symptom-free days, asthma control days, awakening-free nights, rescue medication use, and rescue medication-free days) were assessed as the change from baseline to the mean over all days in the double-blind treatment period in a subset of patients aged ≥ 18 years. Evaluation of variables over the entire treatment period (i.e., including data from up to 84 days of study treatment), as opposed to including data from only the final 7 days of study treatment, may lead to more efficient statistical analyses by reducing variability in the outcome variables[28]. However, the results of diary variables assessed as changes from baseline to the mean over the double-blind treatment period in patients aged ≥ 18 years in the present analysis were generally similar to the changes from baseline to end of treatment reported by Corren *et al.* in the overall population of patients aged ≥ 12 years[19].

Patients receiving budesonide/formoterol pMDI also experienced significantly better improvements from baseline in AQLQ(S) scores, mean asthma symptom scores, symptom-free days, asthma control days, and rescue medication-free days compared with patients receiving formoterol DPI. Although improvements in patients receiving budesonide/formoterol pMDI compared with those receiving budesonide pMDI were evident for most of the assessments, statistical differences were demonstrated in only the three PSAM indices, rescue medication use, and rescue medication-free days. The latter results are similar to those from two other studies that evaluated improvements in HRQL in patients with mild-to-moderate asthma treated with an ICS/LABA combination compared with patients treated with ICS monotherapy[29,30]. While greater improvements in AQLQ(S) scores were noted in these studies in patients treated with ICS in combination with a LABA versus comparable doses of ICS alone, differences between treatment groups were not statistically significant[29,30]. In contrast to the present study and the studies by Juniper *et al.*[29] and Bergmann *et al.*[30], a study comparing HRQL in patients treated with fluticasone/salmeterol 250/50 µg twice daily or budesonide 800 µg twice daily demonstrated significant differences in the AQLQ(S) scores for all domains between treatment groups, with patients receiving fluticasone/salmeterol experiencing significantly ($p \leq 0.032$) greater improvements compared with budesonide alone[15]. However, the difference in mean overall AQLQ(S) scores in the fluticasone/salmeterol versus budesonide groups was less than the minimally important difference of 0.5. These results differ from previously conducted studies in that they compare two different ICSs (one in combination with a LABA), thereby making comparisons to the current and previous studies difficult to interpret.

While the mean improvement from baseline exceeded the minimally important difference threshold in four of the five AQLQ(S) scores in the budesonide/formoterol group, mean differences between the combination group and the budesonide monotherapy group were not statistically significant. A possible explanation is that this study enrolled patients with mild-to-moderate persistent asthma. As a result, baseline values on most of the PRO variables were high, which contributed to a substantial 'ceiling effect' that left little room for improvement during the double-blind phase of the study. This effect was particularly noticeable with the mean AQLQ(S) overall scores at baseline, which ranged from 5.1 to 5.2 (out of 7) in the four treatment groups. Nevertheless, the mean AQLQ(S) overall scores at end of treatment were similar to end-of-treatment scores reported in two large-scale pivotal trials with fluticasone/salmeterol combination therapy[31], even though the mean baseline AQLQ(S) values reported for those trials (i.e., from 4.73 to 5.03 in one study and from 4.75 to 5.04 in the other) were markedly lower than those observed for the present study.

Treatment with budesonide/formoterol pMDI combination therapy led to significantly greater patient satisfaction with asthma medication (i.e., PSAM scores) and improved physician-reported management of patients' asthma compared with either budesonide pMDI or formoterol DPI alone at the end of the study. These results suggest a complementary effect on these outcomes in patients receiving combination therapy and demonstrate the contributions of both budesonide and formoterol.

Results from this study also suggest that in patients previously taking low-to-medium doses of ICSs, some PRO improvements are predominantly

attributable to the budesonide component, whereas other PRO outcomes are influenced more by the formoterol component of the combination product. Patients treated with budesonide/formoterol pMDI experienced significantly greater improvements in AQLQ(S) overall and domain scores compared with patients treated with formoterol DPI or placebo; improvements in these measures with the combination were similar to those with budesonide pMDI, suggesting that the budesonide component is primarily responsible for these improvements. These findings are similar to those observed in a previous study that demonstrated similar AQLQ(S) scores for patients treated with budesonide plus formoterol via separate inhalers compared with patients treated with budesonide alone in patients with mild-to-moderate asthma[32]. In the present study, budesonide also appeared to be the key component responsible for the improvements observed in symptom variables (i.e., asthma symptoms, symptom-free days, asthma control days, and awakening-free nights) because patients treated with either budesonide/formoterol pMDI or budesonide pMDI alone experienced similar improvements. Although patients treated with budesonide/formoterol pMDI experienced significantly better improvements in these symptom variables (except awakening-free nights) than patients treated with formoterol DPI, the improvements with formoterol DPI were still substantial.

In contrast, improvements in patient-reported asthma management and asthma symptom severity evaluated by the physician appeared to be related more to the formoterol component of the combination since treatment with budesonide/formoterol pMDI led to significant improvements in these measures compared with treatment with budesonide pMDI or placebo but not compared with formoterol. These improvements in PROs in patients with mild-to-moderate persistent asthma are similar to results of studies that evaluated the effect of budesonide/formoterol pMDI treatment on lung function, asthma symptoms, and exacerbations[5,6]. In the OPTIMA study[6], the addition of formoterol to budesonide improved lung function in patients with mild asthma not previously taking ICSs (baseline percentage predicted FEV_1 ranged from 89.1 to 90.1%), but the combination had no greater effect on symptoms or exacerbations than did budesonide alone. In patients with mild asthma previously receiving ICSs (baseline percentage predicted FEV_1 ranged from 86.3 to 87.0%), the addition of formoterol to budesonide improved lung function, had no greater effect on symptoms, and decreased the incidence of asthma exacerbations compared with budesonide alone[6]. In the FACET study, patients with more severe asthma (baseline percentage predicted FEV_1 ranged from 75.4 to 76.3%) treated with the combination of budesonide and formoterol experienced improved lung function, decreased asthma symptoms, and a decreased incidence of asthma exacerbations compared with patients treated with budesonide alone[5]. These data suggest that adding formoterol to budesonide may have a greater benefit as asthma severity increases.

Limitations of the present study may include the absence of a budesonide and formoterol comparator arm in which medication was administered concomitantly in separate inhalers as well as the use of a DPI in the formoterol-alone arm compared with a pMDI in all other treatment arms, as potential differences in formulations or devices may affect measures of efficacy. However, a similar study reported by Noonan *et al.* found no difference in the efficacy and safety of budesonide/formoterol pMDI compared with coadministration of budesonide pMDI and formoterol DPI in separate inhalers[33]. Furthermore, the results of a study reported by Miller *et al.* demonstrated similar bronchodilatory effects of formoterol when administered alone via DPI or in combination with budesonide in one pMDI at the same dose of formoterol[34]. Finally, the AQLQ(S) and PSAM questionnaires have been validated only in patients aged ≥ 18 years; therefore, the results from these questionnaires may be applicable only to adult patients with asthma.

Conclusion

In this study in patients with mild-to-moderate persistent asthma previously treated with low-to-medium doses of ICSs, treatment with budesonide/formoterol pMDI resulted in significant improvements in PROs, specifically HRQL, asthma control, rescue medication use, and sleep quality, and in significantly greater satisfaction with asthma medication compared with placebo. The reported findings suggest that both the budesonide and formoterol components of combination treatment contribute, perhaps in complementary ways, to improvements in PRO variables. Thus, the combination of budesonide and formoterol in one pMDI is beneficial in improving how a patient feels and functions as a result of treatment.

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