

Treatment with budesonide/formoterol pressurized metered-dose inhaler in patients with asthma: a focus on patient-reported outcomes

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Abstract: In the United States, budesonide/formoterol pressurized metered-dose inhaler (pMDI) is approved for treatment of asthma in patients aged ≥ 12 years whose asthma is not adequately controlled with an inhaled corticosteroid (ICS) or whose disease severity clearly warrants treatment with an ICS and a long-acting β_2 -adrenergic agonist. This article reviews studies of budesonide/formoterol pMDI in patients with persistent asthma, with a particular focus on patient-reported outcomes (eg, perceived onset of effect, patient satisfaction with treatment, health-related quality of life [HRQL], global assessments, sleep quality and quantity), as these measures reflect patient perceptions of asthma control and disease burden. A search of PubMed and respiratory meetings was performed to identify relevant studies. In two pivotal budesonide/formoterol pMDI studies in adolescents and adults, greater efficacy and similar tolerability were shown with budesonide/formoterol pMDI 160/9 μg and 320/9 μg twice daily versus its monocomponents or placebo. In those studies, improvements in HRQL, patient satisfaction, global assessments of asthma control, and quality of sleep also favored budesonide/formoterol pMDI compared with one or both of its monocomponents or placebo. Budesonide/formoterol pMDI has a rapid onset of effect (within 15 minutes) that patients can feel, an attribute that may have benefits for treatment adherence. In summary, budesonide/formoterol pMDI is effective and well tolerated and has additional therapeutic benefits that may be important from the patient's perspective.

Keywords: budesonide, formoterol, patient-reported outcomes, efficacy, tolerability, onset of effect

Introduction

Asthma is a chronic condition that affects approximately 23 million people in the United States alone and is associated with significant clinical morbidity and economic burden.¹ Poorly controlled asthma also imparts substantial burden to the patient, including decrements in health-related quality of life (HRQL) and interference with daily activities.² According to the National Asthma Education and Prevention Program (NAEPP) guidelines, the goal of treatment is to control asthma by reducing impairment (eg, preventing asthma symptoms, maintaining near normal pulmonary function and HRQL, achieving patient satisfaction with care) and risk (eg, preventing exacerbations, loss of pulmonary function, adverse events [AEs]).³ The 2009 joint statement of the American Thoracic Society and the European Respiratory Society recommends the use of composite measures comprising multiple end points, including those that are patient-reported, for a more complete assessment of asthma control.⁴ Thus, asthma control measures that provide objective clinical assessments of the disease, as well as

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those that measure the burden of disease from the patient's perspective, are important for assessing the benefits and risks of asthma medications.

The NAEPP guidelines recommend a stepwise approach to treatment, with inhaled corticosteroids (ICSs) recommended as first-line treatment for patients with persistent asthma because of their potent anti-inflammatory effects.³ Several long-term control medications are available for treating patients with persistent asthma, including ICS, long-acting β_2 -adrenergic agonists (LABAs), leukotriene modifiers, cromolyn and nedocromil, immunomodulators, and methylxanthines.³ The addition of a LABA to an ICS is recommended as one of the preferred treatment options in patients 5 years of age or older with persistent asthma that is not controlled with an ICS alone.³

In the United States, the combination of the ICS budesonide and the LABA formoterol administered via one pressurized metered-dose inhaler (pMDI; Symbicort® Inhalation Aerosol, AstraZeneca LP, Wilmington, DE) is indicated for the treatment of asthma in patients aged ≥ 12 years who are not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants treatment with ICS/LABA combination therapy.⁵ In countries outside of the United States, budesonide/formoterol administered via dry powder inhaler (DPI) (Symbicort® Turbuhaler®, AstraZeneca, Lund, Sweden) is indicated as maintenance therapy in patients aged ≥ 6 years with persistent asthma for whom combination therapy is appropriate or as maintenance and reliever therapy in patients aged ≥ 18 years with persistent asthma.⁶ Budesonide/formoterol administered via pMDI is not approved for use as maintenance and reliever therapy in any country.⁵ Budesonide/formoterol pMDI is approved for asthma in two dosage strengths (80/4.5 $\mu\text{g} \times 2$ inhalations [160/9 μg] twice daily and 160/4.5 $\mu\text{g} \times 2$ inhalations [320/9 μg] twice daily) in the United States.⁵ This review describes the clinical profile of budesonide/formoterol pMDI for asthma, with a particular focus on patient-reported outcomes.

Clinical pharmacology

Budesonide is a potent corticosteroid that exhibits anti-inflammatory properties by acting on several inflammatory mediators (eg, histamine, leukotrienes, eicosanoids, cytokines) and cell types (eg, mast cells, eosinophils, lymphocytes, macrophages).⁷ Budesonide acts locally and directly on the respiratory tract, reducing inflammation and decreasing airway hyperresponsiveness.^{7,8} Formoterol, a potent LABA and full agonist, has high affinity and selectivity for β_2 -adrenergic receptors of the pulmonary smooth muscle.⁹

These characteristics have translated to greater maximum relaxation of airway smooth muscle activity with formoterol compared with the partial agonist salmeterol *in vitro*.^{9,10} In humans, the magnitude of bronchodilation and duration of effect (~12 hours) were shown to be similar with formoterol and salmeterol, but the onset of bronchodilation was faster with formoterol compared with salmeterol.^{9,11}

Evidence suggests an additive effect of budesonide and formoterol when they are administered concomitantly.^{12,13} When coadministered, the bronchodilatory effects of a LABA complements the anti-inflammatory effects of an ICS, improving pulmonary function and reducing symptoms and exacerbations compared with increasing the ICS alone.¹⁴ In addition, there may be a synergistic interaction between an ICS and a LABA.^{13,15,16} Combination therapy with an ICS and a LABA has been shown to enhance nuclear translocation of the glucocorticoid receptor.¹³ Studies also suggest that a LABA may enhance the inhibitory effect of an ICS on allergen-induced activation of certain inflammatory cytokines (eg, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α , interleukin-1 β , interleukin-2).^{15,16} Specific details of the pharmacokinetic properties of budesonide and formoterol administered via pMDI have been described in detail previously.^{17,18}

Clinical efficacy of budesonide/formoterol pMDI

The efficacy of budesonide/formoterol pMDI has been evaluated in clinical studies in patients with asthma across a range of disease severities and ages (Table 1).^{19–28} Budesonide/formoterol pMDI also has been evaluated across a range of doses (up to 640/18 μg twice daily [twice the US-approved maximum daily dose]) and treatment regimens (fixed-dose once or twice daily, adjustable dose) and in comparison with active treatments (fluticasone propionate/salmeterol, budesonide alone [similar or higher dose], formoterol alone) and placebo (Table 1).^{19–28}

Budesonide/formoterol pMDI twice daily versus its monocomponents and placebo

Two pivotal 12-week US studies of similar design evaluated the efficacy of budesonide/formoterol pMDI (160/9 μg or 320/9 μg) twice daily in adolescents and adults with mild to moderate²⁰ or moderate to severe¹⁹ persistent asthma who were previously receiving ICS therapy (Table 1).^{19,20} In those studies, patients had to be symptomatic during a 1- to 3-week run-in period on placebo (mild to moderate) or budesonide

Table 1 Designs for studies of budesonide/formoterol pMDI

Reference	N	Age	Asthma severity	Design	Duration	Treatment groups
Adolescents and adults						
Noonan et al (NCT00652002) ¹⁹	596	≥ 12 years	Moderate to severe	R, DB, double-dummy, PBO-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 320/9 µg bid • BUD pMDI 320 µg bid + FM DPI 9 µg bid • BUD pMDI 320 µg • FM DPI 9 µg bid • PBO
Corren et al (NCT00651651) ²⁰	480	≥ 12 years	Mild to moderate	R, DB, double-dummy, PBO-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 160/9 µg bid • BUD pMDI 160 µg bid • FM DPI 9 µg bid • PBO
Peters et al (NCT00651768) ²¹	708	≥ 12 years	Moderate to severe	R, DB, parallel-group, single-dummy	52 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 640/18 µg bid • BUD/FM pMDI 320/9 µg bid • BUD pMDI 640 µg bid
Kerwin et al (NCT00646516) ²²	619	≥ 12 years	Mild to moderate	R, DB, parallel-group, single-dummy, active-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 160/9 µg bid • BUD/FM pMDI 320/9 µg qd • BUD/FM pMDI 160/9 µg qd • BUD pMDI 320 µg qd
Berger et al (NCT00652392) ²³	752	≥ 16 years	Mild to moderate	R, DB, double-dummy, PBO- and active-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 160/9 µg bid • BUD/FM pMDI 320/9 µg qd • BUD/FM pMDI 160/9 µg qd • BUD pMDI 320 µg qd • PBO
Busse et al (NCT00646594) ²⁴	1225	≥ 12 years	Moderate to severe	R, open-label	7 months	<ul style="list-style-type: none"> • BUD/FM pMDI 320/9 µg bid • FP/SM DPI 250/50 µg bid • Adjustable-dose BUD/FM pMDI
Children and adolescents						
Murphy et al (NCT00651547) ²⁵	411	6–15 years	Mild to moderate	R, DB, double-dummy, active-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 80/9 µg bid • BUD pMDI 80 µg bid • FM DPI 9 µg bid
Morice et al (SD-039-0682) ²⁶	622	6–11 years		R, DB, double-dummy, parallel-group	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 160/9 µg bid • BUD/FM DPI 160/9 µg bid • BUD pMDI 200 µg bid
Berger et al (NCT00646529) ²⁷	187	6–11 years		R, open-label	26 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 320/9 µg bid • BUD DPI 400 µg bid
Eid et al (NCT00646321) ²⁸	522	6–15 years		R, DB, parallel-group, active-controlled	12 weeks	<ul style="list-style-type: none"> • BUD/FM pMDI 80/9 µg bid • BUD/FM pMDI 160/9 qd • BUD pMDI 160 µg qd

Abbreviations: bid, twice daily; BUD, budesonide; DB, double-blind; DPI, dry powder inhaler; FM, formoterol; FP, fluticasone propionate; N, number of patients; PBO, placebo; pMDI, pressurized-metered dose inhaler; qd, once daily; R, randomized; SM, salmeterol.

160 µg twice daily (moderate to severe) to qualify for randomization.^{19,20} In both studies, the anti-inflammatory effect of budesonide and the bronchodilatory effect of formoterol each contributed to the efficacy of budesonide/formoterol pMDI, as shown by the significant improvements in predose forced expiratory volume in 1 second (FEV₁) compared with formoterol DPI and in 12-hour postdose FEV₁ compared with budesonide, respectively (Table 2).^{19,20} Treatment with budesonide/formoterol pMDI also resulted in significant ($P \leq 0.05$) benefits in symptom-related variables compared with its monocomponents or placebo,^{19,20} with significant differences from budesonide observed only in patients with moderate to severe persistent asthma (Table 2).¹⁹ The risk

of asthma worsening also was assessed based on predefined criteria, including a decrease in morning predose FEV₁ of $\geq 20\%$ or $< 40\%$ of predicted normal; use of ≥ 12 inhalations per day of albuterol or 20% decrease in morning peak expiratory flow [PEF] on ≥ 3 days within any consecutive 7-day period; ≥ 2 night-time awakenings requiring rescue medication use within any consecutive 7-day period; or a clinical exacerbation requiring emergency treatment, hospitalization, or nonprotocol treatment.^{19,20} The risk of having a predefined event of asthma worsening was significantly ($P \leq 0.05$) reduced with budesonide/formoterol pMDI compared with its monocomponents and placebo in patients with moderate to severe persistent asthma¹⁹ and compared with formoterol and

Table 2 Efficacy of budesonide/formoterol pMDI in patients with asthma

	Predose FEV ₁ (L) ^a	12-Hour mean FEV ₁	Morning PEF (L/min)	Evening PEF (L/min)	Symptom- free days (%)	Awakening- free nights (%)	Rescue medication use (inh/day) ^b
Adolescents and adults							
Mean change from baseline to end of treatment							
Noonan et al ¹⁹							
BUD/FM pMDI 320/9 µg bid	0.19 ^{c,d,e}	0.37 ^{c,d,e}	35 ^{c,d,e}	34 ^{c,d,e}	23.1 ^{c,d,e}	12.7 ^e	-1.0 ^{d,e}
BUD pMDI 320 µg bid + FM DPI 9 µg bid	0.14	0.35	28	26	21.8	13.4	-1.5
BUD pMDI 320 µg	0.10	0.15	9	7	9.5	15.1	-0.8
FM DPI 9 µg bid	-0.12	0.17	-9	-7	2.9	9.4	-0.3
PBO	-0.17	-0.03	-18	-18	2.4	8.6	0.8
Corren et al ²⁰							
BUD/FM pMDI 160/9 µg bid	0.37 ^{c,d,e}	0.50 ^{c,d,e}	54 ^{c,d,e}	40 ^{c,d,e}	26.5 ^{d,e}	21.6 ^e	-2.0 ^{d,e}
BUD pMDI 160 µg bid	0.23	0.32	24	17	29.8	22.2	-1.9
FM DPI 9 µg bid	0.17	0.41	21	16	18.1	18.5	-1.3
PBO	0.03	0.12	-4	0	7.5	12.8	0.2
Mean change from baseline to the average over the treatment period							
Peters et al ²¹							
BUD/FM pMDI 640/18 µg bid	0.18 ^c	NA	40 ^c	NA	19.0 ^c	NA	-0.8 ^c
BUD/FM pMDI 320/9 µg bid	0.16 ^c	NA	34 ^c	NA	23.5 ^c	NA	-0.7 ^c
BUD pMDI 640 µg bid	0.08	NA	6	NA	5.9	NA	-0.2
Kerwin et al ²²							
BUD/FM pMDI 160/9 µg bid	0.01 ^{c,f,g}	NA	-1 ^c	0.3 ^{c,f,g}	1.8 ^{c,f,g}	-3.0 ^c	0.02 ^{c,f,g}
BUD/FM pMDI 320/9 µg qd	-0.08 ^{c,f}	NA	-3 ^c	-12 ^c	-4.5 ^c	-2.7	0.16
BUD/FM pMDI 160/9 µg qd	-0.12 ^c	NA	-6 ^c	-16	-6.4	-1.9 ^c	0.18
BUD pMDI 320 µg qd	-0.18	NA	-22	-22	-11.0	-4.4	0.29
Berger et al ²³							
BUD/FM pMDI 160/9 µg bid	-0.04 ^{c,e}	NA	1 ^{c,e,f}	1 ^{c,e,f,g}	4.1 ^{c,e,f}	-2.3 ^{c,e}	-0.04 ^{c,e,f,g}
BUD/FM pMDI 320/9 µg qd	-0.07 ^{c,e}	NA	-4 ^{c,e}	-14 ^{c,e}	-6.0 ^{c,e,f}	-2.3 ^{c,e}	0.21 ^{c,e}
BUD/FM pMDI 160/9 µg qd	-0.06 ^{c,e}	NA	-6 ^{c,e}	-14 ^{c,e}	-11.0 ^e	-2.6 ^{c,e}	0.26 ^e
BUD pMDI 320 µg qd	-0.20 ^e	NA	-30 ^e	-32 ^e	-16.2 ^e	-4.8 ^e	0.41 ^e
PBO	-0.31	NA	-43	-39	-27.5	-10.7	0.88
Busse et al ²⁴							
BUD/FM pMDI 320/9 µg bid	0.15	NA	31	NA	25.8	10.0	-1.32
FP/SM DPI 250/50 µg bid	0.16	NA	34	NA	25.4	7.7	-1.30
Children and adolescents							
Murphy et al ²⁵							
BUD/FM pMDI 80/9 µg bid	0.07 ^c	NA	24 ^{c,d}	20 ^{c,d}	NA	NA	NA
BUD pMDI 80 µg bid	0.01	NA	8	6	NA	NA	NA
FM DPI 9 µg bid	0.03	NA	9	7	NA	NA	NA
Morice et al ²⁶							
BUD/FM pMDI 160/9 µg bid	0.15	NA	30 ^c	24 ^c	34.9	NA	-0.50
BUD/FM DPI 160/9 µg bid	0.18	NA	30 ^c	26 ^c	37.4	NA	-0.54
BUD pMDI 200 µg bid	0.08	NA	20	18	35.2	NA	-0.42
Berger et al ²⁷							
BUD/FM pMDI 320/9 µg bid	0.15 ^c	NA	NA	NA	NA	NA	NA
BUD DPI 400 µg bid	0.07	NA	NA	NA	NA	NA	NA
Eid et al ²⁸							
BUD/FM pMDI 80/9 µg bid	-0.04 ^c	NA	8 ^c	7 ^c	-0.9	-1.8	0 ^{c,f}
BUD/FM pMDI 160/9 qd	-0.03 ^c	NA	4 ^c	0.5 ^c	-0.2	-2.4	0.08
BUD pMDI 160 µg qd	-0.11	NA	-5	-6	-3.7	-2.7	0.10

Notes: ^aPredose FEV₁ was assessed in the evening for the Kerwin et al study; for all other studies, predose FEV₁ was assessed in the morning;^{19–23,27,28} ^bRescue medication use was presented as total inhalations (day and night) for all studies except the studies assessing once- versus twice-daily budesonide/formoterol pMDI, for which data are presented for the number of inhalations during the day (assessing the second half of the once-daily 24-hour dosing interval);^{22,23,28} ^c*P* ≤ 0.05 vs BUD; ^d*P* ≤ 0.05 vs FM DPI; ^e*P* ≤ 0.05 vs PBO; ^f*P* ≤ 0.05 vs BUD/FM pMDI 160/9 µg qd; ^g*P* ≤ 0.05 vs BUD/FM pMDI 320/9 µg qd; ^hAll data from the study by Morice et al are presented as adjusted mean change from baseline values.

Abbreviations: bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; FM, formoterol; FP, fluticasone propionate; NA, not assessed; PBO, placebo; PEF, peak expiratory flow; pMDI, pressurized-metered dose inhaler; qd, once daily; SM, salmeterol.

placebo in patients with mild to moderate persistent asthma.²⁰ The percentage of patients with moderate to severe persistent asthma who experienced ≥ 1 predefined asthma worsening event was 29.8% in those treated with budesonide/formoterol pMDI compared with 44.0%, 55.3%, and 67.2% in patients taking budesonide, formoterol, and placebo, respectively.¹⁹ In patients with mild to moderate persistent asthma, the proportion of patients who experienced ≥ 1 predefined asthma worsening event was 18.7% with budesonide/formoterol pMDI compared with 21.5%, 42.1%, and 56.6% with budesonide, formoterol, and placebo, respectively.²⁰

Consistent with the study reported by Noonan et al¹⁹ the results from a 1-year safety and efficacy study reported by Peters and colleagues, which also was conducted in patients with moderate to severe persistent asthma (Table 1), showed significant ($P < 0.01$) improvements in pulmonary function and symptom-related variables with budesonide/formoterol pMDI (320/9 μg or 640/18 μg twice daily) compared with budesonide pMDI (640 μg twice daily) (Table 2).²¹ In that study, the proportion of patients with at least 1 asthma exacerbation also was significantly ($P = 0.006$) lower with budesonide/formoterol pMDI 640/18 μg twice daily (12.2%) and numerically lower with budesonide/formoterol pMDI 320/9 μg twice daily (14.4%) compared with budesonide 640 μg twice daily alone (21.8%).²¹

Budesonide/formoterol pMDI is indicated in patients with persistent asthma aged ≥ 12 years; however, clinical studies of this combination product also have been conducted in children aged 6 to 15 years²⁵ and 6 to 11 years^{26,27} (Table 1). Results from these studies generally showed significant ($P < 0.05$) benefits to pulmonary function of treatment with budesonide/formoterol pMDI twice daily compared with budesonide twice daily alone.^{25–27} In the efficacy and safety study reported by Murphy et al treatment with budesonide/formoterol pMDI also significantly ($P < 0.05$) improved morning and evening PEF, decreased nighttime asthma symptoms and nighttime rescue medication use, and increased the percentage of rescue medication-free days compared with formoterol alone.²⁵

Twice-daily versus once-daily dosing

Two studies evaluated the efficacy of once-daily budesonide/formoterol pMDI, administered at half the daily formoterol dose (320/9 μg) or half the daily budesonide and formoterol doses (160/9 μg) compared with twice-daily budesonide/formoterol pMDI (320/18 μg daily), versus once-daily budesonide pMDI (320 μg) alone in adolescents and adults

with mild to moderate persistent asthma previously stabilized during a 4- to 5-week run-in on twice-daily budesonide/formoterol pMDI (320/18 μg daily) (Table 1).^{22,23} Both studies showed that treatment with once- or twice-daily budesonide/formoterol pMDI generally was more effective on pulmonary function and symptom-related variables than treatment with budesonide pMDI alone (Table 2).^{22,23} However, twice-daily budesonide/formoterol pMDI maintained pulmonary function and asthma control more effectively than once-daily budesonide/formoterol pMDI in both studies (Table 2).^{22,23} Similar results were reported by Eid et al in a study including children and adolescents (6–15 years) (Table 2).²⁸

Budesonide/formoterol pMDI versus fluticasone propionate/salmeterol

In a 7-month open-label study, Busse et al compared the efficacy of fixed-dose budesonide/formoterol pMDI 320/9 μg twice daily with that of fixed-dose fluticasone propionate/salmeterol DPI 250/50 μg twice daily in adolescents and adults with moderate to severe persistent asthma.²⁴ Findings showed similar efficacy for all pulmonary function and symptom-related variables between the two treatments (Table 2).²⁴ In addition, the proportion of patients who experienced at least 1 exacerbation (primary variable) was not significantly different between the fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI groups (8.8% and 9.2%, respectively).²⁴

Patient-focused perspectives

In addition to objective measures of asthma control, outcomes reflecting the patient's perception of disease burden and the effects of treatment are critical to effective asthma management. The poor correlation between clinical asthma status parameters and patient-reported outcomes, such as HRQL, suggest that such measures offer a unique assessment of the effects of the disease and of treatment from the perspective of the patient.^{3,4} Patient-reported outcomes have been assessed in several studies of budesonide/formoterol pMDI, including measures of the patient's perception of onset of effect,^{29,30} patient satisfaction with treatment,^{30–32} and HRQL.^{30–32}

Onset of effect

Onset of effect is an important concept in asthma management, as evidence suggests that asthma controller medications that have a rapid onset of effect may contribute to improved patient adherence.³³ In addition, study findings indicate that

the majority of patients prefer a reliever medication with a fast onset and a long duration of effect.³⁴ Measured onset of effect of budesonide/formoterol pMDI has been compared with that of its monocomponents and placebo in the two pivotal studies of budesonide/formoterol pMDI in patients aged ≥ 12 years^{19,20,29} and with that of fluticasone propionate/salmeterol DPI in two crossover studies in patients aged ≥ 18 years³⁵ based on serial spirometry. Patient perception of the onset of effect of budesonide/formoterol pMDI was evaluated based on the Onset of Effect Questionnaire (OEQ) in the two pivotal budesonide/formoterol pMDI studies in patients aged ≥ 18 years with mild to moderate or moderate to severe persistent asthma²⁹ and in the study comparing fixed-dose budesonide/formoterol pMDI with fluticasone propionate/salmeterol DPI.³⁰ The 5-item OEQ has been validated in patients with asthma aged ≥ 18 years and provides an assessment of patients' ability to perceive an asthma therapy working right away (item 2) and satisfaction with how quickly they feel their medication begins to work (item 5) based on a 1-week recall, with responses scored on a 5-point Likert-type scale.³⁶ These items were identified previously as being important to patients³⁷ and as the items that best capture patients' perceptions of onset of effect.³⁶

In the two pivotal trials of budesonide/formoterol pMDI, the percentage of patients who experienced clinically significant bronchodilation (eg, $\geq 15\%$ FEV₁ improvement) within 15 minutes of administering study medication on the day of randomization was significantly ($P < 0.05$) higher in patients treated with budesonide/formoterol pMDI (49%–57%) compared with budesonide pMDI (6% for both studies) or placebo (6%–8%) on the day of randomization.²⁹ Combining data from both studies, the median time to onset of clinically significant bronchodilation (achievement of $\geq 15\%$ FEV₁ improvement in 50% of patients) after administration of study medication was 13 minutes for budesonide/formoterol pMDI.²⁹

Patient-perceived onset of effect, assessed based on the OEQ in patients aged ≥ 18 years in the two pivotal studies, was consistent with the findings for measured onset of effect in those studies.²⁹ In both studies, a significantly greater percentage of patients in the budesonide/formoterol pMDI groups indicated that they could feel their study medication begin to work right away and that they were satisfied with how quickly they felt their medication begin to work compared with the budesonide pMDI ($P \leq 0.04$) or placebo groups ($P < 0.001$) at the end of the first treatment week and at the end of treatment (Figure 1).²⁹ In a separate study, a consensus panel of 12 community-based health care professionals blinded to the study drug names agreed that

the observed differences between the treatment groups for patient perceptions of onset of effect and satisfaction in the two pivotal studies were clinically important.³⁸ Moreover, all of the panelists agreed that if a patient is able to perceive onset of effect, it would improve adherence to maintenance asthma treatment.³⁸ The findings from this study further suggest that improved adherence to treatment may be facilitated by a medication with a rapid onset of effect.

In two single-dose, randomized, active- and placebo-controlled crossover studies (NCT00646620 and NCT00646009) of identical design, Hampel et al evaluated the onset of effect of budesonide/formoterol pMDI 160/9 μg compared with that of fluticasone propionate/salmeterol DPI 250/50 μg , albuterol pMDI 180 μg , or placebo in patients aged ≥ 18 years with persistent asthma.³⁵ In a combined analysis of both studies, a significantly ($P \leq 0.001$) greater percentage of patients in the budesonide/formoterol pMDI group (40%) achieved a $\geq 15\%$ improvement in FEV₁ within 15 minutes compared with fluticasone propionate/salmeterol DPI (19%) or placebo (2%).³⁵ Budesonide/formoterol pMDI treatment also resulted in significantly ($P < 0.001$) greater mean adjusted FEV₁ values at 3 minutes postdose compared with fluticasone propionate/salmeterol DPI and placebo (2.71 L vs 2.52 L and 2.45 L, respectively), and similar improvement compared with albuterol pMDI (2.69 L).³⁵

OEQ findings from the open-label study comparing fixed-dose budesonide/formoterol pMDI with fixed-dose fluticasone propionate/salmeterol DPI^{24,30} were consistent with the results of measured onset of effect reported in the crossover studies by Hampel et al.³⁵ Compared with fixed-dose fluticasone propionate/salmeterol DPI, a significantly higher ($P \leq 0.025$) percentage of patients in the fixed-dose budesonide/formoterol pMDI group indicated that they could feel their study medication begin to work right away (71% vs 59%, respectively) and that they were satisfied with how quickly they felt their medication begin to work (80% vs 73%, respectively) at the end of treatment.³⁰ These findings show that budesonide/formoterol pMDI has a more rapid onset of bronchodilatory effect compared with fluticasone propionate/salmeterol DPI that patients can perceive.

Satisfaction

One of the goals of asthma therapy according to the NAEPP asthma management guidelines is to maintain patient satisfaction with asthma care, as improvements in patient satisfaction have been associated with improved treatment adherence.³ Satisfaction with budesonide/formoterol pMDI treatment was assessed in a subset of patients aged ≥ 18 years in the two previously described pivotal

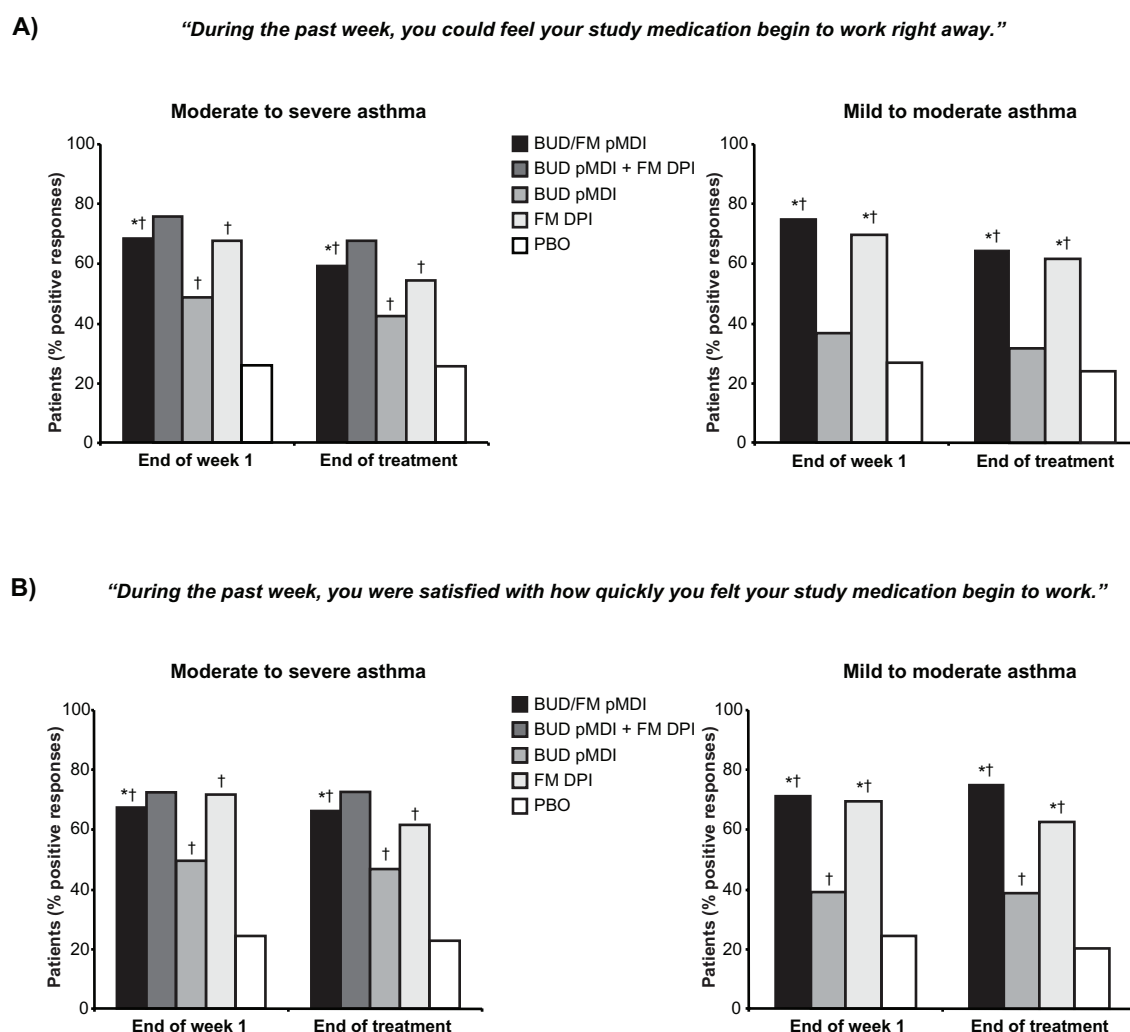


Figure 1 Onset of Effect Questionnaire: Percentage of patients who indicated that they could feel their study medication begin to work right away (**A**) and that they were satisfied with how quickly they felt their study medication begin to work (**B**).²⁹ Statistical analyses comparing FM DPI vs BUD pMDI and BUD pMDI + FM DPI vs BUD pMDI and PBO not performed in study I.

Notes: * $P < 0.05$ vs BUD pMDI; † $P < 0.05$ vs PBO. Copyright © 2008. Elsevier. Reprinted with permission from Kaiser H, Parasuraman B, Boggs R, Miller CJ, Leidy NK, O'Dowd L. Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2008;101(3):295–303.²⁹

Abbreviations: BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; PBO, placebo; pMDI, pressurized metered-dose inhaler.

studies (553 patients with moderate to severe asthma;³¹ 405 patients with mild to moderate asthma³²) using three domains of the Patient Satisfaction with Asthma Medication (PSAM) questionnaire (Control Relief, Perception of Medication, and Comparison With Other Medications).^{31,32} The 23-item PSAM questionnaire has demonstrated reliability and validity in patients aged ≥ 18 years with asthma,^{31,32,39} and is scored on a scale from 0–100, with 0 representing the lowest level of satisfaction and 100 representing the highest level of satisfaction.^{31,32,39} In both pivotal studies, mean PSAM scores at the end of treatment were significantly ($P \leq 0.004$) higher with budesonide/formoterol pMDI compared with its monocomponents or placebo (Figure 2).^{31,32,40}

Patient satisfaction with fixed-dose budesonide/formoterol pMDI also has been evaluated in comparison

with fixed-dose fluticasone propionate/salmeterol DPI using the Asthma Treatment Satisfaction Measure (ATSM) in patients aged ≥ 18 years.³⁰ The ATSM assessment has been validated in patients aged ≥ 18 years and contains four parts: expectations for treatment, importance rating of treatment attributes, outcomes of treatment, and satisfaction with asthma treatment.⁴¹ It evaluates 11 predefined medication attributes: timely relief of symptoms, level of symptom relief, rescue medication use, asthma attack frequency, medication worked, feel medication working, daily activity, leisure activity, dosing management, medication convenience, and side effects.^{30,41} ATSM responses are scored on a scale ranging from 0–100, with 0 representing the lowest level of satisfaction and 100 representing the highest level of satisfaction.^{30,41} In the study reported by O'Connor et al there

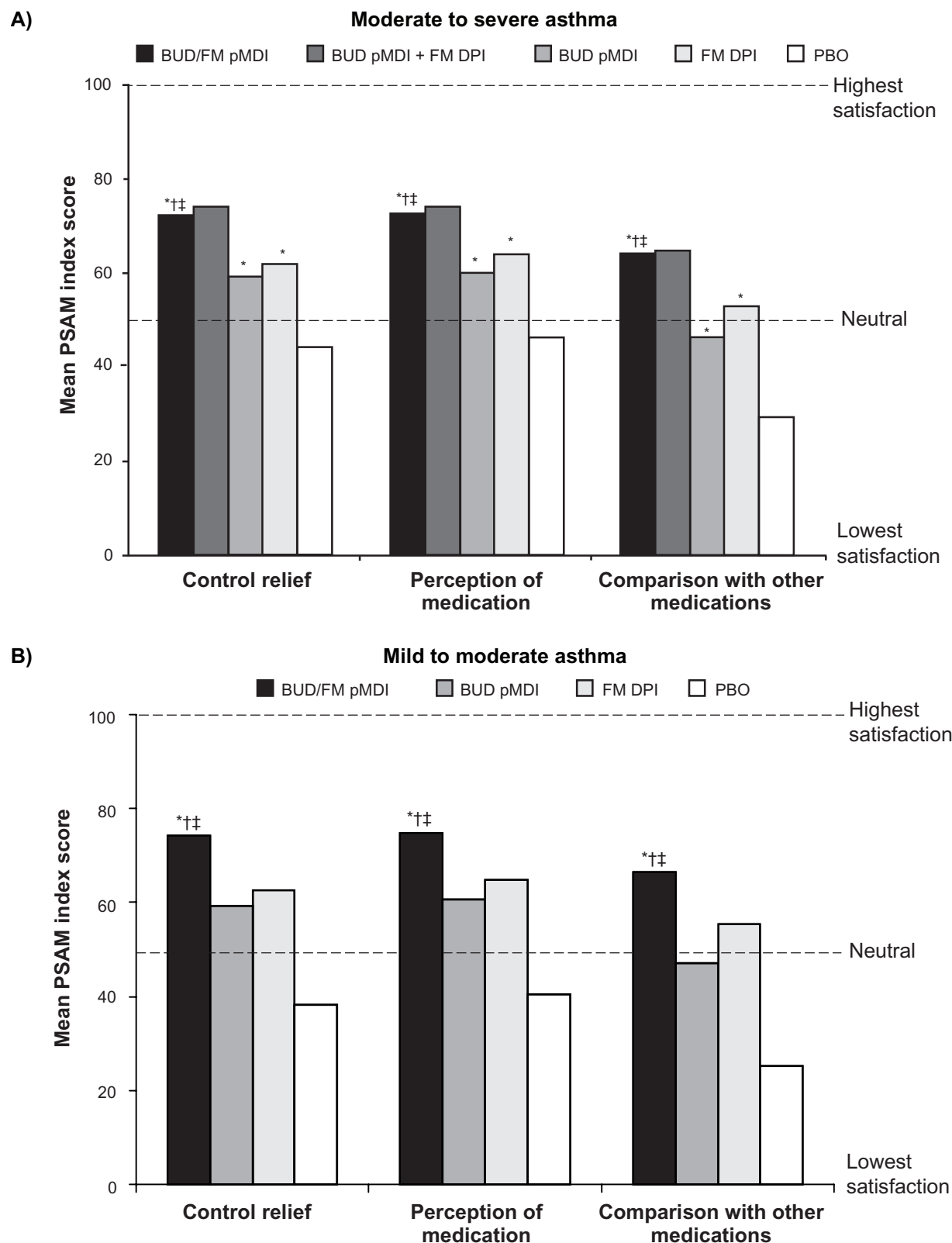


Figure 2 Mean PSAM scores at the end of treatment in patients with (A) moderate to severe³¹ or (B) mild or moderate³² persistent asthma.

Notes: * $P < 0.001$ vs PBO; † $P < 0.001$ vs BUD; ‡ $P < 0.005$ vs FM. Copyright © 2008. Elsevier. Reprinted with permission from Chervinsky P, Baker J, Bensch G, et al. Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via a pressurized metered-dose inhaler. *Ann Allergy Asthma Immunol.* 2008;101(5):463–473.³¹ Copyright © 2010. Oceanside Publications Inc. Korenblat PE, Rosenwasser LJ. Budesonide/formoterol pressurized metered-dose inhaler for patients with persistent asthma. *Allergy Asthma Proc.* 2010;31(3):190–202.⁴⁰

Abbreviations: BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; PBO, placebo; pMDI, pressurized metered-dose inhaler; PSAM, Patient Satisfaction with Asthma Medication.

was no significant difference between fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI in mean overall ATSM score at the end of treatment (47.7 and 46.7, respectively).³⁰ However, treatment with fixed-dose budesonide/formoterol pMDI resulted in significantly ($P < 0.05$) greater treatment satisfaction scores compared with fixed-dose fluticasone propionate/salmeterol DPI for the attributes of timely relief of symptoms (52.9 vs 47.7, respectively) and feel medication working (36.6 vs 32.8, respectively) at the end of treatment.³⁰

Health-related quality of life

Clinical asthma parameters provide important information about disease status and the effects of treatment, but the information derived from each measure may be applicable only to specific domains of the disease.^{3,4} Assessment of HRQL from the patient's perspective provides a more global view of treatment effectiveness, as well as potentially unique information about the effects of treatment that may be identified only by the patient.⁴ The effect of budesonide/formoterol pMDI on HRQL has been evaluated in several clinical studies^{22,23,27,28,30–32} using validated instruments that are asthma-specific and recommended by the NAEPP guidelines.³

The validated, standardized Asthma Quality of Life Questionnaire (AQLQ[S])⁴² was included in several clinical studies of budesonide/formoterol pMDI in subsets of patients aged ≥ 18 years.^{22,23,30–32} The 32-item AQLQ(S) comprises four domains: symptoms, emotional function, activity limitation, and exposure to environmental stimuli.^{30–32,43} Overall and domain scores range from 1 (greatest impairment) to 7 (least impairment).^{30–32,43} A change of ≥ 0.5 points in overall or domain scores has been defined as a clinically meaningful change for the AQLQ(S).⁴⁴

Results from the two pivotal studies showed mean improvements in AQLQ(S) overall and domain scores from baseline to the end of treatment that were significantly ($P \leq 0.042$) greater with budesonide/formoterol pMDI compared with formoterol DPI or placebo in patients with mild to moderate³² or moderate to severe³¹ persistent asthma (Figure 3). In addition, in patients with moderate to severe persistent asthma, treatment with budesonide/formoterol pMDI resulted in significantly ($P \leq 0.047$) greater improvements in the AQLQ(S) overall score and all domain scores except emotional function compared with budesonide pMDI alone.³¹ A significantly ($P \leq 0.006$) higher percentage of patients achieved clinically meaningful improvements from baseline in AQLQ(S) overall score with budesonide/

formoterol pMDI compared with placebo in patients with mild to moderate (63% vs 35%)³² or moderate to severe (44% vs 23%)³¹ persistent asthma at the end of treatment.

Quality of life based on the AQLQ(S) also was assessed in the studies evaluating budesonide/formoterol pMDI once or twice daily compared with budesonide pMDI once daily in patients with mild to moderate persistent asthma who were previously stabilized on twice-daily budesonide/formoterol pMDI (Table 1).^{22,23} In the study by Kerwin et al quality of life was better maintained with twice-daily budesonide/formoterol pMDI (320/18- μ g total daily dose) compared with once-daily budesonide pMDI (320- μ g daily dose) based on AQLQ(S) overall and all domain scores ($P < 0.05$); however benefits of once-daily budesonide/formoterol pMDI (320/9- μ g or 160/9- μ g daily dose) relative to once-daily budesonide pMDI were less apparent and significantly better only on the AQLQ(S) environmental exposure domain score ($P < 0.05$).²² In the study by Berger et al quality of life was significantly better maintained with budesonide/formoterol pMDI twice daily (320/18- μ g daily dose) and once daily (320/9- μ g daily dose) compared with once-daily budesonide pMDI ($P < 0.05$), except for the environmental exposure domain, for which differences were significant only for twice-daily budesonide/formoterol pMDI.²³ These results were consistent with the overall efficacy results from those studies showing generally more favorable results with twice-daily budesonide/formoterol pMDI relative to once-daily budesonide/formoterol pMDI and once-daily budesonide pMDI.^{22,23}

In a study directly comparing fixed-dose budesonide/formoterol pMDI twice daily with fluticasone propionate/salmeterol DPI twice daily, mean improvements from baseline to end of treatment in AQLQ(S) overall and domain scores were not significantly different.³⁰ Similarly, the percentages of patients who achieved a clinically meaningful change from baseline to the end of treatment in AQLQ(S) overall score were similar in the fixed-dose budesonide/formoterol pMDI (63%) and fixed-dose fluticasone propionate/salmeterol DPI (62%) groups.³⁰

In pediatric studies of budesonide/formoterol pMDI,^{27,28} HRQL was evaluated in children with asthma using the standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S])⁴⁵ and in their caregivers using the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).⁴⁵ The 23-item PAQLQ(S) has been validated in children aged 7 to 17 years⁴⁶ and the 13-item PACQLQ has been validated in caregivers of children aged 7 to 17 years.⁴⁶ Scores for both questionnaires are based on a 7-point scale

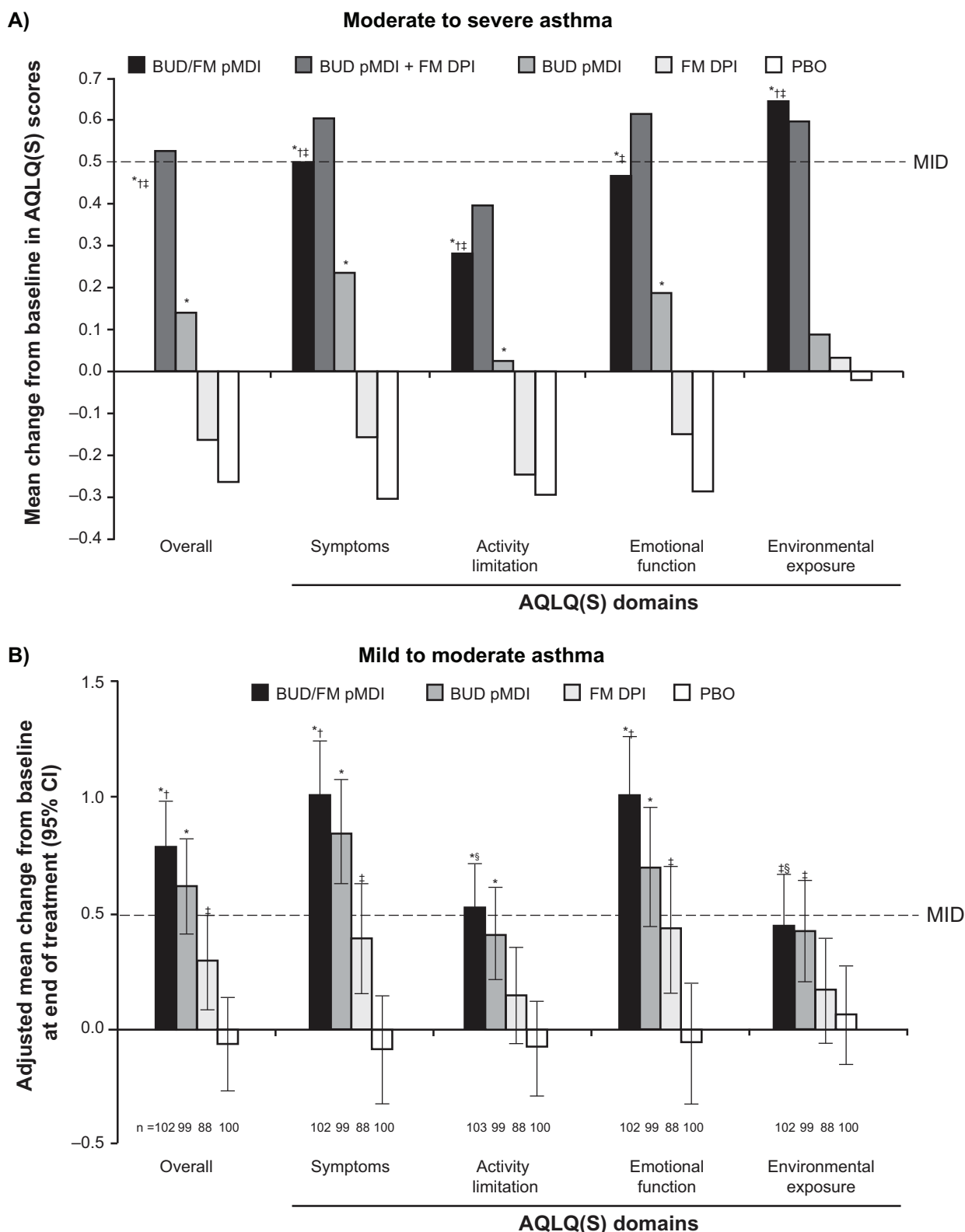


Figure 3 Adjusted mean change from baseline to end of treatment in AQLQ(S) overall and domain scores in patients with (A) moderate to severe³¹ or (B) mild to moderate³² persistent asthma.

Notes: A: * $P < 0.01$ vs PBO; † $P < 0.05$ vs BUD; ‡ $P < 0.001$ vs FM. B: * $P < 0.001$ vs PBO; † $P < 0.001$ vs FM; ‡ $P < 0.05$ vs PBO; § $P < 0.05$ vs FM. Copyright © 2008. Elsevier. Reprinted with permission from Chervinsky P, Baker J, Bensch G, et al. Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via a pressurized metered-dose inhaler. *Ann Allergy Asthma Immunol.* 2008;101(5):463–473.³¹ Copyright © 2008. Informa Healthcare. Murphy K, Nelson H, Parasuraman B, Boggs R, Miller C, O'Dowd L. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. *Curr Med Res Opin.* 2008;24(3): 879–894.³²

Abbreviations: AQLQ(S), Asthma Quality of Life Questionnaire (Standardized); BUD, budesonide; CI, confidence interval; DPI, dry powder inhaler; FM, formoterol; PBO, placebo; pMDI, pressurized metered-dose inhaler.

ranging from 1 (greatest possible impairment) to 7 (least impairment).^{45,46} A mean change from baseline of ≥ 0.5 points in overall PAQLQ(S) and PACQLQ scores has been defined as a clinically meaningful change.^{27,28,46}

In the 26-week study by Berger et al budesonide/formoterol pMDI resulted in significantly greater ($P \leq 0.006$) mean improvements from baseline to end of treatment in the overall PAQLQ(S) and PACQLQ scores compared with budesonide DPI.²⁷ Improvements from baseline in the PAQLQ(S) score were clinically meaningful (eg, >0.5) for patients in the budesonide/formoterol pMDI group; however, the differences between the two treatment groups did not reach the minimally important difference for the PAQLQ(S) or the PACQLQ.²⁷ In that study, clinically meaningful differences might have been difficult to achieve because baseline scores for both the PAQLQ(S) and the PACQLQ were high (5.84–6.21 out of 7 points).²⁷ In the 12-week study by Eid et al the PAQLQ(S) and PACQLQ overall scores were stable at baseline and maintained throughout the randomized study period in all treatment groups, with no significant or clinically meaningful differences observed.²⁸ Similar to the 26-week study reported by Berger et al baseline overall PAQLQ(S) and PACQLQ scores were high (6.34–6.62 out of 7 points) and clinically meaningful changes difficult to show.²⁸

Patient perspectives of asthma control

The NAEPP recommends using patients' self-assessments and caregivers' assessments as one of the principal methods to monitor asthma control.³ The effects of budesonide/formoterol pMDI on patient global assessments^{22,31,32} and caregiver global assessments^{27,28} have been assessed in clinical studies. In studies evaluating budesonide/formoterol pMDI in adult patients, a 5-point scale was used by patients to rate their overall health (a great deal better, somewhat better, unchanged, somewhat worse, and a great deal worse) and ability to manage their asthma (a great deal easier, somewhat easier, unchanged, somewhat more difficult, and a great deal more difficult) at the end of the study compared with the start of the study.^{22,31,32} Similarly, in pediatric studies of budesonide/formoterol pMDI, caregivers rated their child's health and their own ability to manage the child's asthma at the end of treatment on a 5-point scale.^{27,28}

Findings in patients aged ≥ 18 years from the two pivotal trials showed significantly ($P \leq 0.01$) higher percentages of patients reporting improvement in overall health with budesonide/formoterol pMDI (61%) compared with placebo (20%) in patients with mild to moderate asthma³² and with budesonide/formoterol pMDI (59%) compared with formoterol DPI (40%) or placebo (13%) in patients with moderate

to severe asthma (59% vs 40%).³¹ A significantly ($P \leq 0.03$) higher percentage of patients reported easier management of their asthma with budesonide/formoterol pMDI compared with budesonide pMDI or placebo in patients with mild to moderate (62% vs 46% and 21%, respectively)³² or moderate to severe (62% vs 46% and 19%, respectively)³¹ persistent asthma.

Kerwin et al reported a significantly ($P \leq 0.033$) higher percentage of patients reporting overall health improvements with budesonide/formoterol pMDI twice daily (320/18- μ g daily dose) (63%) and budesonide/formoterol pMDI once daily (160/9- μ g daily dose) (60%) compared with budesonide pMDI once daily (320 μ g) (48%) and a significantly ($P = 0.008$) higher percentage of patients reporting easier management of their asthma with budesonide/formoterol pMDI twice daily (66%) compared with budesonide pMDI once daily (51%).²² In the pediatric study by Eid et al the percentages of caregivers who reported improvements in their child's health or ease of asthma management were similar across all treatment groups (57%–60%).²⁷ However, Berger et al reported a significantly ($P \leq 0.048$) higher percentage of caregivers indicating improvements in their child's health and easier management of their child's asthma with budesonide/formoterol pMDI (69% and 70%, respectively) compared with budesonide DPI (52% for each question).²⁷

Patient perspectives of sleep quantity and quality

Impaired quality and quantity of sleep, including difficulty in falling asleep, difficulty in maintaining sleep, and increased daytime sleepiness, is common in patients with asthma.⁴⁷ The NAEPP recommends the periodic assessment of patients for key areas of quality of life, including sleep disturbances due to asthma.³ Sleep quality and quantity with budesonide/formoterol pMDI treatment was assessed in the two pivotal studies using the Medical Outcomes Study (MOS) Sleep Scale, including the Long Index and the "awaken during sleep" and "awaken short of breath or with a headache" questions (scored on a scale from 0 [best sleep] to 100 [worst sleep]).^{31,32} The 12-item MOS Sleep Scale has been validated in a general population of adults aged ≥ 18 years in the United States.⁴⁸

In patients with moderate to severe asthma, there were no significant differences across treatment groups in mean changes from baseline in the Long Index or "awaken during sleep" question scores.³¹ However, patients reported awakening short of breath or with a headache significantly ($P < 0.01$) less frequently with budesonide/formoterol pMDI (–8.87) compared with formoterol (–1.49) or placebo (4.00).³¹ Patients with mild to moderate asthma experienced significant improvements in overall quality of sleep, as assessed by the

Long Index, and a lower likelihood of awakening during sleep and awakening short of breath or with a headache with budesonide/formoterol pMDI (mean change from baseline in Long Index score, -7.1 , -5.7 , -13.7 , respectively) compared with placebo (-1.8 , 1.1 , -2.6 , respectively) ($P \leq 0.033$).³²

Safety and tolerability

The benefits of ICSs and LABAs are well established in patients with asthma;³ however, each class of medication is associated with potential risks.³ Common local drug-related AEs for ICSs may include oral candidiasis and hoarseness, and in very rare cases, systemic effects (eg, reduction in growth velocity in children, reduced bone mineral density, increased risk of cataracts or glaucoma) may occur.³ Common drug-related AEs for LABAs are similar to those observed with short-acting β_2 -adrenergic agonists (SABAs) (eg, cardiovascular AEs, tremor).^{3,9}

The tolerability of budesonide/formoterol pMDI has been evaluated in 10 active- and placebo-controlled studies with 3393 patients aged ≥ 12 years with varying severities of asthma⁵ and in three studies in children and adolescents.^{26–28} Findings from the two 12-week pivotal studies reported by Noonan et al and Corren et al and from a 1-year safety study reported by Peters et al show that budesonide/formoterol pMDI is well tolerated at doses of 160/9 μg , 320/9 μg , and 640/18 μg twice daily in adolescents and adults with persistent asthma, with safety findings consistent with the known safety profiles of ICS and LABA medications.^{19–21} In the long-term safety study, which evaluated two doses of budesonide/formoterol pMDI (320/9 μg twice daily and 640/18 μg twice daily – twice the highest Food and Drug Administration [FDA]-approved dose) compared with budesonide pMDI 640 μg twice daily, dose-related AEs were few, and the authors reported no unexpected patterns of abnormalities for safety findings.²¹ In the 6-month study in children (aged 6–11 years) reported by Berger et al the safety profile of budesonide/formoterol pMDI 320/9 μg twice daily was similar to that of budesonide administered at the same dose, with no new safety concerns identified.²⁷ Fixed-dose budesonide/formoterol pMDI 320/9 μg twice daily also has shown a safety profile similar to that of fixed-dose fluticasone propionate/salmeterol DPI 250/50 μg twice daily in the 7-month study reported by Busse et al.²⁴

Recently, the FDA issued new requirements for LABA-containing product labeling^{49,50} based on a meta-analysis conducted by the US FDA Office of Safety and Epidemiology⁵¹ and two previous studies of salmeterol showing an increased risk of asthma-related death or life-threatening experience

compared with placebo in one study⁵² and an increased number of respiratory and asthma-related deaths compared with albuterol in another study.⁵³ The new labeling states that combination ICS/LABA therapy should be used only in patients whose asthma is not adequately controlled with a long-term asthma control medication (eg, an ICS) and that the LABA should be discontinued if possible once asthma control is achieved.⁵⁰ In addition, the new FDA guidance states that data are inadequate to determine whether concomitant administration with an ICS mitigates these safety risks.⁵⁰ Because of differences in methodologies used, conflicting results have been reported in different analyses and meta-analyses.^{54–63} In addition, because of the rarity of serious asthma-related events in clinical trials, results of meta-analyses assessing the risk of such events with LABAs, alone or with an ICS, have been inconclusive.^{54–62} To more clearly determine the safety of ICS/LABA combination therapies, the FDA is requiring LABA manufacturers to conduct additional large clinical trials.⁶⁴ Until more definitive findings on the safety of LABA-containing products are available, budesonide/formoterol pMDI should be used in accordance with the product label and current asthma guidelines.

Place in therapy

The 2009 Global Initiative for Asthma (GINA) guidelines recommend adjustment of asthma therapy in a continuous cycle, driven by the asthma control status of each patient.⁶⁵ In treatment-naïve patients with persistent asthma, GINA guidelines recommend initiating therapy with low-dose ICS (eg, 200 to 500 μg beclomethasone dipropionate [BDP] or equivalent) as the preferred therapy, unless patients have very symptomatic (uncontrolled) asthma, for whom the recommended initial treatment consists of the combination of low-dose ICS plus LABA (eg, budesonide/formoterol pMDI 160/9 μg twice daily) as the preferred therapy.⁶⁵ The 2007 NAEPP guidelines recommend initiating treatment based on the patient's asthma severity, which is assessed using measures of impairment (eg, asthma symptoms, pulmonary function, HRQL) and risk (eg, exacerbations).³ The 2007 NAEPP guidelines recommend that adolescents and adults with mild asthma initiate step 2 treatment (low-dose ICS as preferred treatment), while patients with asthma of moderate severity should initiate step 3 treatment (low-dose ICS plus LABA or medium-dose ICS as equally preferred treatment options).³

Subsequently, asthma therapy should be adjusted using a stepwise approach according to the patient's level of asthma control.^{3,65} According to the 2007 NAEPP guidelines, patients

whose asthma is not well controlled on low-dose ICS therapy (step 2) should be stepped up to low-dose ICS plus LABA or medium-dose ICS therapy (step 3).³ The 2009 GINA guidelines show a preference for stepping up to low-dose ICS plus LABA therapy in patients whose asthma is not controlled on a low-dose ICS, with step-up to a medium- or high-dose ICS listed as alternative step-up treatments.⁶⁵ Stepping down therapy also is recommended once asthma control is achieved and maintained for approximately 3 months.^{3,65} Thus, according to the 2007 NAEPP guidelines,³ if a patient has been well controlled on step 4 therapy (medium-dose ICS/LABA [eg, budesonide/formoterol pMDI 320/9 µg twice daily]) for at least 3 months, stepping down to step-3 therapy (either medium-dose ICS or low-dose ICS/LABA [budesonide/formoterol pMDI 160/9 µg twice daily]) may be appropriate. According to the updated recommendations from the FDA in February 2010, LABA should be discontinued, if possible, once asthma control is achieved, and patients should be maintained on an asthma control medication, such as an ICS.⁶⁴ As noted in the NAEPP guidelines, physicians also must base treatment decisions on the individual patient's needs and circumstances and on his or her response to treatment.³

Conclusions

The efficacy and tolerability of budesonide/formoterol pMDI have been shown in several clinical studies of children, adolescents, and adults with mild to moderate and moderate to severe persistent asthma.^{19–28} Greater efficacy for pulmonary function and asthma control measures was shown with budesonide/formoterol pMDI compared with its monocomponents or placebo.^{19–23,25–28} Findings from patient-reported outcomes further support the benefits of budesonide/formoterol pMDI in patients with asthma.^{29–32} In adults with asthma, treatment with budesonide/formoterol pMDI was associated with patient satisfaction and HRQL benefits that were greater than that of its monocomponents or placebo^{31,32} and similar to that of fluticasone propionate/salmeterol.³⁰ In addition, global assessments of asthma control suggested significant benefits of budesonide/formoterol pMDI relative to one or both monocomponents and placebo for overall health and the ability to manage asthma.^{22,27,31,32} Measures of sleep quality and quantity also suggested benefits of budesonide/formoterol pMDI relative to placebo in adults with mild to moderate³² or moderate to severe³¹ persistent asthma.

In addition, more patients receiving budesonide/formoterol pMDI perceived their medication working right away and were satisfied with how quickly they felt their

medication begin to work compared with patients receiving budesonide pMDI or placebo.²⁹ In addition, patient perception of onset of effect and satisfaction with timely relief of symptoms with treatment favored budesonide/formoterol pMDI compared with fluticasone propionate/salmeterol DPI.³⁰ The findings for patient perception of onset of effect were consistent with those observed for measured onset of effect.^{29,35} Evidence from studies that have not directly evaluated the effects of budesonide/formoterol pMDI suggest that patients prefer and are more satisfied with medications with a rapid onset of effect^{33,37} and that the ability of patients to perceive their medication working right away may contribute to improved patient adherence.³³

Studies also have shown that budesonide/formoterol pMDI is well tolerated, with a safety profile similar to that of its monocomponents^{19–21,23,28} and fluticasone propionate/salmeterol.²⁴ Across studies, budesonide/formoterol pMDI showed an acceptable safety profile across a range of assessments.^{19–21,23,28} Even in patients receiving twice the maximum daily recommended dose (640/18 µg twice daily) of budesonide/formoterol pMDI for up to 1 year of treatment, there were no unexpected abnormalities in safety assessments.²¹

In summary, budesonide/formoterol pMDI is an effective and well tolerated maintenance therapy that provides benefits of treatment from the patient's perspective, including improved treatment satisfaction, HRQL, asthma control, and sleep quality and quantity. Compared with its monocomponents and placebo, budesonide/formoterol pMDI has been shown to be more effective in achieving the established goals of therapy (eg, preventing asthma symptoms, maintaining pulmonary function, HRQL, satisfaction with care), particularly in patients with moderate to severe persistent asthma. In addition, its rapid onset of effect (within 15 minutes), combined with the ability of patients to perceive their medication working right away, may have benefits for treatment adherence. Overall, the findings from studies of budesonide/formoterol pMDI support its use in patients with persistent asthma that is not adequately controlled with an ICS alone, or whose disease severity warrants initiation of treatment with both an ICS and a LABA.

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Disclosure

Dr. O'Connor has served on advisory boards for GlaxoSmithKline and Sepracor.

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