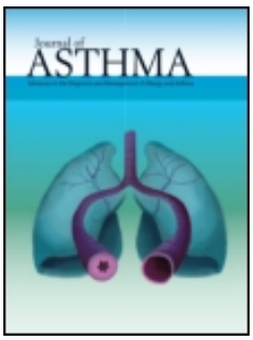

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Comparison of Patient-Reported Outcomes During Treatment With Adjustable- and Fixed-Dose Budesonide/Formoterol Pressurized Metered-Dose Inhaler Versus Fixed-Dose Fluticasone Propionate/Salmeterol Dry Powder Inhaler in Patients With Asthma

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Objective. Assessment of patient-reported outcomes is important in evaluating the impact of asthma treatment. This study was conducted to compare effects of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler with fixed-dose fluticasone propionate/salmeterol dry powder inhaler regimens on patient-reported outcomes in patients aged ≥18 years with moderate to severe asthma. *Methods*. In this phase III, randomized, open-label study, 1225 patients were randomized 2:1 to fixed-dose budesonide/formoterol 160/4.5 μg × 2 inhalations (320/9 μg) twice daily or fixed-dose fluticasone propionate/salmeterol 250/50 μg twice daily for 1 month. In the subsequent 6 months, patients receiving fixed-dose fluticasone propionate/salmeterol continued therapy, whereas those receiving fixed-dose budesonide/formoterol were randomized 1:1 to fixed-dose or adjustable-dose budesonide/formoterol (adjustable from 320/9 μg twice daily to 320/9 μg once daily or 640/18 μg twice daily). *Results*. Mean improvements from baseline to end of treatment in the Asthma Quality of Life Questionnaire (standardized) overall and individual domain scores and the Asthma Control Questionnaire score were clinically important (≥0.5 points) for all treatments. Patients in both budesonide/formoterol groups reported greater treatment satisfaction on the Asthma Treatment Satisfaction Measure questionnaire than patients in the fluticasone propionate/salmeterol dry powder inhaler group for the attributes of timely relief of symptoms ($p \leq .037$) and feel medication working ($p \leq .020$). Onset of Effect Questionnaire scores showed a greater percentage of patients perceiving onset of effect with budesonide/formoterol regimens versus fixed-dose fluticasone propionate/salmeterol ($p \leq .002$). *Conclusions*. Treatment regimens did not differ regarding improvements in asthma-specific quality of life and asthma control. Questions related to perceived rate of onset and feeling medication working in the Asthma Treatment Satisfaction Measure and Onset of Effect Questionnaire generally elicited somewhat more favorable responses with budesonide/formoterol pressurized metered-dose inhaler regimens versus fixed-dose fluticasone propionate/salmeterol dry powder inhaler.

Keywords budesonide; formoterol; fluticasone; patient-reported outcomes; salmeterol

Introduction

Both US and international treatment guidelines recommend the use of an inhaled corticosteroid (ICS) in combination with a long-acting β_2-adrenergic agonist (LABA) for patients aged ≥12 years with asthma not adequately controlled with low- to medium-dose ICS monotherapy (1, 2). Currently available fixed-dose ICS/LABA combination treatments include budesonide/formoterol and fluticasone propionate/salmeterol. The combination of budesonide/formoterol administered via one pressurized metered-dose inhaler (pMDI) at a fixed dose of 160/4.5 μg × 2 inhalations twice daily has shown no difference in clinical efficacy and tolerability from fixed-dose fluticasone propionate/salmeterol administered via one dry powder inhaler (DPI) at a dose of 250/50 μg × 1 inhalation twice daily for patients with moderate to severe persistent asthma (3).

The ultimate goal of asthma treatment is to minimize the effects of asthma on patients' daily lives, including reducing the symptoms, functional limitations, quality-of-life impairments, and risk of adverse events associated with this disease (2). Because of the often poor correlation between clinical asthma parameters and quality-of-life assessments, the National Heart, Lung, and Blood Institute treatment guidelines place a renewed emphasis on assessing both clinical status and the effect of asthma on patient-reported outcomes (PROs), such as quality of life, as necessary measures of disease impairment (2). Patient questionnaires are important instruments for measuring the impact of asthma and its treatment on quality of life and other PROs, such as asthma control and satisfaction with treatment (2). Assessment of patient satisfaction with asthma care is important because greater satisfaction can improve treatment adherence (4, 5), whereas a dislike of treatment can negatively affect medication adherence (6) and has been associated with an increased risk of exacerbation requiring an emergency department visit or hospitalization (7).

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Randomized studies have shown that treatment with budesonide/formoterol pMDI results in improved health-related quality of life (HRQL) compared with budesonide monotherapy (8, 9) or placebo (9, 10). A recent phase III, randomized, open-label study compared the efficacy and tolerability of adjustable-dose budesonide/formoterol pMDI with fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI in patients with moderate to severe asthma (3). The effects of these treatments on PROs in the same study, including asthma-related HRQL, asthma control, treatment satisfaction, and perception of onset of effect, are presented herein.

Methods

Patients and Study Design

Full details of the study design, treatment schedule, and inclusion and exclusion criteria of this study (NCT00646594; D5896C00005) have been previously described (3). Briefly, this was a phase III, randomized, open-label, 7-month study enrolling patients aged ≥12 years with moderate to severe asthma. After 10 to 14 days of usual therapy, patients were randomized 2:1 to receive fixed-dose budesonide/formoterol 160/4.5 μg × 2 inhalations (320/9 μg) via pMDI twice daily or fixed-dose fluticasone propionate/salmeterol 250/50 μg × 1 inhalation via DPI twice daily. After 1 month, patients receiving fixed-dose fluticasone propionate/salmeterol continued therapy, whereas those who received fixed-dose budesonide/formoterol were randomized 1:1 to continue fixed-dose budesonide/formoterol or to receive adjustable-dose budesonide/formoterol (adjustable from 2 inhalations [320/9 μg] twice daily to 2 inhalations [320/9 μg] once daily or to 4 inhalations [640/18 μg] twice daily) for 6 months.

The final study protocol was approved by the institutional review board at each study site before enrollment of any patient into the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, good clinical practice guidelines, and applicable local regulations. Adult patients or caregivers/guardians provided written informed consent, with minor patients providing written assent.

Patient-Reported Outcomes

Asthma Quality of Life Questionnaire. The standardized Asthma Quality of Life Questionnaire (AQLQ[S]) is validated for patients aged ≥18 years and is an instrument that measures asthma HRQL. It consists of 32 equally weighted questions in four domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), and environmental exposure (4 items) (11). Individual domain and overall scores are reported on a scale from 1 (greatest impairment) to 7 (least impairment). Assessments of HRQL using the AQLQ(S) were made at prescreening and at all postscreening visits (i.e., 1, 4, and 7 months).

Asthma Control Questionnaire. The Asthma Control Questionnaire (ACQ) is validated for patients aged ≥17 years and is an instrument that measures asthma control (12). This 7-item questionnaire assesses symptoms, impact of asthma on sleep and activities, bronchodilator use, and percentage predicted forced expiratory volume in 1 s (FEV_1). An abbreviated version was used in this study, consisting of the first 6 items but not the FEV_1 item; removal of that item does not result in loss of validity or a requirement to alter interpretation of the results (13). Scores are reported on a scale ranging from 0 (well-controlled asthma) to 6 (extremely poor asthma control). The ACQ was administered at all postscreening visits.

Asthma Treatment Satisfaction Measure. The Asthma Treatment Satisfaction Measure (ATSM) is a newly developed and validated instrument for patients aged ≥18 years that assesses satisfaction with treatment based on baseline expectations, rating of treatment attributes, and outcomes of treatment (14). The conceptual model of the ATSM was built on a validated migraine treatment satisfaction questionnaire (15, 16). ATSM scores are derived from 11 predefined attributes of asthma treatment (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). An overall satisfaction score is also derived based on the average of the 11 individual attribute scores. ATSM scores are reported (there is a transformation to the 0–100 scale) on a scale of 0 to 100, with higher scores indicating greater satisfaction with treatment. Assessments using the ATSM were conducted to evaluate patients' satisfaction with current medication at study entry in addition to the end of treatment (i.e., 7 months).

Onset of Effect Questionnaire. The Onset of Effect Questionnaire (OEQ) is a newly developed and validated 5-item instrument for patients aged ≥18 years designed to assess patient perception of and satisfaction with time to onset of treatment effect (17). Primary OEQ endpoints are item 2 ("During the past week, you could feel your study medication begin to work right away") and item 5 ("During the past week, you were satisfied with how quickly you felt your study medication begin to work") (17). Responses are scored using a 5-point Likert scale (strongly agree to strongly disagree). The OEQ was completed at 7, 14, 21, 28, 35, 42, 49, and 56 days after visit 2 (at 0 month), and also at visit 4 (at 4 months) and visit 5 (at 7 months).

Statistical Analyses

For the AQLQ(S), response was assessed as mean change in overall score and each domain score from baseline at prescreening and at end of treatment, with higher scores indicating greater improvement in quality of life. The overall score was calculated as a weighted average of the domain scores. Statistical significance was assessed using analysis of covariance (ANCOVA) models and adjusting for the fixed factors of treatment and site and for the covariate of baseline. A change in score of at least 0.5 points was considered a clinically meaningful difference (i.e., minimum important difference [MID]) (18).

For the ACQ, change from baseline to end of treatment for each treatment period was calculated for the overall score (defined as the mean of the 6 items weighted equally), with higher scores indicating poorer asthma control. Statistical significance was assessed using ANCOVA models and adjusting for the fixed factors of treatment and site and for the covariate of baseline. A 0.5 change in score was considered the MID (13).

For the ATSM, individual attribute domain scores and the overall score (defined as the mean of the 11 derived attribute scores) were calculated. Statistical significance was assessed using an analysis of variance model and adjusting for the fixed factors of treatment and site (15, 16).

The 5-point Likert scale was transformed to a binary scale on which "yes" indicated a response of strongly agree or somewhat agree and "no" indicated a response of neither agree nor disagree, somewhat disagree, or strongly disagree. Yes/no responses were analyzed at end of treatment and assessed for statistical significance using a chi-square test.

Results

Patients

As presented in detail elsewhere (3), 2080 patients were screened and 1225 were randomized 2:1 to receive fixed-dose budesonide/formoterol pMDI ($n = 817$) or fixed-dose fluticasone propionate/salmeterol DPI ($n = 408$) for an initial 1-month treatment period. The 778 patients remaining in the fixed-dose budesonide/formoterol pMDI group after this time were subsequently randomized to continue fixed-dose budesonide/formoterol pMDI ($n = 389$) or to switch to adjustable-dose budesonide/formoterol pMDI ($n = 389$) for 6 months. The 391 patients remaining in the fixed-dose fluticasone propionate/salmeterol DPI group after the initial 1-month treatment period continued with this same treatment for the remainder of the study. Patients aged ≥18 years were included in all PRO assessments; patients aged 17 years were also included in ACQ assessments. Demographics and baseline characteristics for patients aged ≥18 years were generally similar among treatment groups (Table 1). Demographics and baseline characteristics that included patients aged 17 years were similar to those for patients aged ≥18 years (data not shown).

Patient-Reported Outcomes

Asthma Quality of Life Questionnaire. No differences were observed between treatment groups in the percentages of patients with clinically meaningful improvements (≥0.5) in overall score from baseline to end of treatment (adjustable-dose budesonide/formoterol pMDI [$n = 217$, 66.7%], fixed-dose budesonide/formoterol pMDI [$n = 212$, 63.0%], fixed-dose fluticasone propionate/salmeterol DPI [$n = 207$, 61.9%]; Figure 1). Mean improvements from baseline to end of treatment in AQLQ(S) overall and individual domain scores were greater than or equal to the MID (0.5) for clinical significance for all treatment groups. Although improvements were statistically significantly greater ($p \leq .04$) in the majority of domains for adjustable dosing versus either fixed-dose regimen, no clinically meaningful between-group differences were observed. There were no statistically significant differences between fixed-dose regimens in mean improvement from baseline for overall or individual domain scores at the end of treatment.

Asthma Control Questionnaire. At the end of treatment, the mean change from baseline for all treatment groups exceeded the MID (0.5) for this instrument (Table 2). There were no statistically significant or clinically meaningful between-group changes in overall ACQ score from baseline to end of treatment (Table 2).

Asthma Treatment Satisfaction Measure. As indicated by the ATSM overall score at the end of treatment, patients reported significantly greater treatment satisfaction with adjustable-dose budesonide/formoterol pMDI compared with fixed-dose fluticasone propionate/salmeterol DPI ($p = .020$); there was no significant between-group difference for the fixed-dose budesonide/formoterol pMDI and fluticasone propionate/salmeterol DPI groups (Table 3). Patients in both budesonide/formoterol pMDI groups reported significantly greater treatment satisfaction than those in the fluticasone propionate/salmeterol DPI group for the attributes of timely relief of symptoms ($p \leq .037$) and feel medication working ($p \leq .020$; Table 3). Patients in the adjustable-dose budesonide/formoterol pMDI group reported significantly greater treatment satisfaction for the attribute of dosing management than patients in the fixed-dose fluticasone propionate/salmeterol DPI group ($p < .001$) and reported significantly greater treatment satisfaction for the attributes of daily activity, leisure activity, and dosing management than patients in the fixed-dose budesonide/formoterol pMDI group ($p \leq .048$).

Table 1.—Demographics and baseline characteristics for patients aged ≥18 years.

	Adjustable-dose budesonide/formoterol pMDI ($n = 330$)	Fixed-dose budesonide/formoterol pMDI ($n = 368$)	Fixed-dose fluticasone propionate/salmeterol DPI ($n = 350$)
Sex, *n* (%)			
Men	133 (40.3)	106 (28.8)	137 (39.1)
Women	197 (59.7)	262 (71.2)	213 (60.9)
Mean (*SD*) age, years	42.7 (13.0)	43.5 (13.3)	42.6 (13.5)
Age groups, *n* (%)			
≥18–<65 years	314 (95.2)	340 (92.4)	326 (93.1)
≥65 years	16 (4.8)	28 (7.6)	24 (6.9)
Race, *n* (%)			
White	274 (83.0)	311 (84.5)	299 (85.4)
Black	39 (11.8)	45 (12.2)	39 (11.1)
Asian	3 (0.9)	1 (0.3)	3 (0.9)
Other	14 (4.2)	11 (3.0)	9 (2.6)
Years since asthma diagnosis			
Mean (*SD*)	20.4 (15.2)	21.4 (15.9)	20.6 (14.9)
Daily ICS dose at entry, μg			
Mean (*SD*)	550.1 (211.7)	555.6 (209.6)	544.0 (171.5)

DPI = dry powder inhaler; ICS = inhaled corticosteroid; pMDI = pressurized metered-dose inhaler.

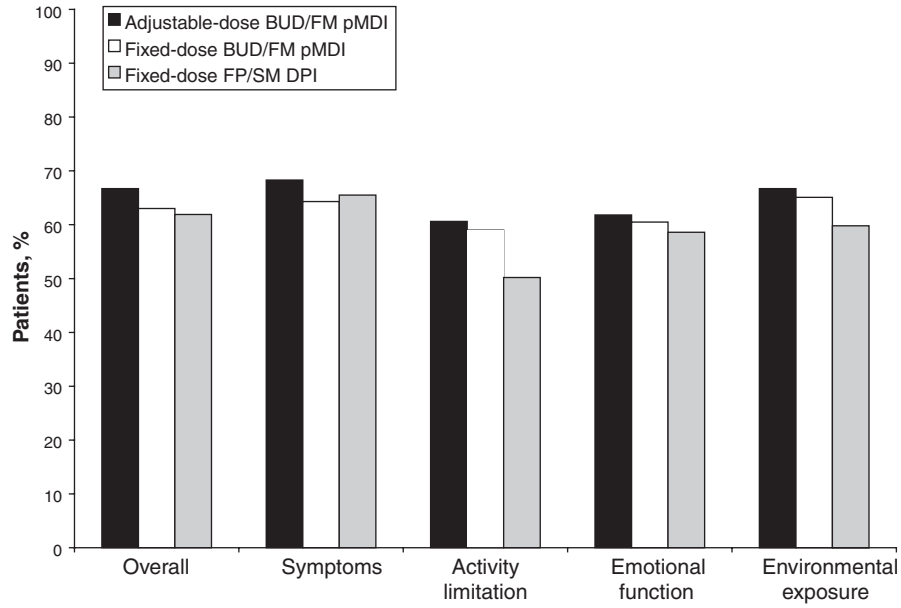

FIGURE 1.—Percentage of patients with clinically meaningful improvements (≥0.5) from baseline to end of treatment for the overall and domain scores of the standardized Asthma Quality of Life Questionnaire among patients receiving adjustable-dose budesonide/formoterol (BUD/FM) in a pressurized metered-dose inhaler (pMDI), fixed-dose BUD/FM pMDI, or fixed-dose fluticasone propionate/salmeterol (FP/SM) in a dry powder inhaler (DPI).

Onset of Effect Questionnaire. For the predefined item, "During the past week, you could feel your study medication begin to work right away," 71% of patients in the adjustable-dose budesonide/formoterol pMDI group, 71% in the fixed-dose budesonide/formoterol pMDI group, and 59% in the fixed-dose fluticasone propionate/salmeterol DPI group responded positively at the end of treatment. The differences observed between the budesonide/formoterol pMDI groups and the fixed-dose fluticasone propionate/salmeterol DPI group were statistically significant ($p \leq .002$; Figure 2A). For the predefined item, "During the past week, you were satisfied with how quickly you felt your study medication begin to work," 78% of patients in the adjustable-dose budesonide/formoterol pMDI group, 80% in the fixed-dose budesonide/formoterol pMDI group, and 73% in the fixed-dose fluticasone propionate/salmeterol DPI group responded positively at the end of treatment. The difference between the fixed-dose budesonide/formoterol pMDI and fixed-dose fluticasone propionate/salmeterol DPI groups was small but statistically significant ($p = 0.025$; Figure 2B).

DISCUSSION

Previously reported efficacy data from this randomized open-label study of patients aged ≥12 years with moderate to severe asthma demonstrated no significant differences across the three treatment groups for the primary endpoint, which was asthma exacerbation (assessed as time to first exacerbation after initiation of randomized treatment, number of exacerbations per patient–treatment year, and number of patients with ≥1 exacerbation), and secondary endpoints of predose FEV_1 and measures of asthma control (i.e., symptom scores, symptom-free days, asthma control days, daily rescue medication use, and rescue medication–free days) (3). On average, patients in the adjustable-dose budesonide/formoterol pMDI group used significantly fewer daily inhalations of medication compared with those in the fixed-dose group (3 versus 4 inhalations/day; $p < .001$) (3).

In the present analysis of patients aged ≥18 years (≥17 years for the ACQ assessment), AQLQ(S) results demonstrated a number of statistically significant differences generally favoring adjustable dosing with budesonide/formoterol

TABLE 2.—Mean change from baseline in Asthma Control Questionnaire overall score at end of treatment.

Treatment	n^*	Baseline value, mean (*SD*)	Final value, mean (*SD*)	Change, mean (*SD*)	From ANCOVA	
					LS mean change from baseline, mean (*SEM*)	95% CI
Adjustable-dose budesonide/formoterol pMDI	331	1.78 (0.89)	0.89 (0.76)	−0.89 (0.92)	−0.85 (0.05)	−0.93 to −0.76
Fixed-dose budesonide/formoterol pMDI	342	1.74 (0.88)	0.97 (0.79)	−0.77 (0.91)	−0.73 (0.05)	−0.82 to −0.64
Fixed-dose fluticasone propionate/salmeterol DPI	341	1.75 (0.82)	0.97 (0.83)	−0.79 (0.88)	−0.77 (0.05)	−0.86 to −0.68

ANCOVA = analysis of covariance; DPI = dry powder inhaler; LS = least squares; pMDI = pressurized metered-dose inhaler.
*Asthma Control Questionnaire was administered to patients aged ≥17 years.

TABLE 3.—Mean Asthma Treatment Satisfaction Measure scores at end of treatment.

Attribute	*n*	From ANCOVA	
		LS mean (*SEM*)	95% CI
Overall score			
Adjustable-dose BUD/FM pMDI	265	49.3 (0.9)*	47.6–51.0
Fixed-dose BUD/FM pMDI	297	47.7 (0.8)	46.1–49.4
Fixed-dose FP/SM DPI	270	46.7 (0.9)	45.0–48.4
Timely relief of symptoms			
Adjustable-dose BUD/FM pMDI	262	51.3 (1.3)*	48.7–54.0
Fixed-dose BUD/FM pMDI	297	52.9 (1.3)†	50.4–55.4
Fixed-dose FP/SM DPI	265	47.7 (1.3)	45.0–50.3
Level of symptom relief			
Adjustable-dose BUD/FM pMDI	265	56.7 (1.2)	54.3–59.0
Fixed-dose BUD/FM pMDI	294	56.6 (1.2)	54.3–58.9
Fixed-dose FP/SM DPI	269	55.5 (1.2)	53.1–57.8
Rescue medication use			
Adjustable-dose BUD/FM pMDI	265	50.6 (1.3)	48.1–53.2
Fixed-dose BUD/FM pMDI	297	49.2 (1.3)	46.7–51.7
Fixed-dose FP/SM DPI	269	50.3 (1.3)	47.7–52.9
Asthma attack frequency			
Adjustable-dose BUD/FM pMDI	264	58.1 (1.4)	55.4–60.8
Fixed-dose BUD/FM pMDI	297	57.4 (1.3)	54.8–60.0
Fixed-dose FP/SM DPI	267	56.6 (1.4)	53.9–59.3
Medication worked			
Adjustable-dose BUD/FM pMDI	264	49.5 (1.0)	47.5–51.6
Fixed-dose BUD/FM pMDI	297	48.7 (1.0)	46.7–50.6
Fixed-dose FP/SM DPI	270	49.1 (1.0)	47.1–51.2
Feel medication working			
Adjustable-dose BUD/FM pMDI	264	40.1 (1.3)†‡	37.6–42.7
Fixed-dose BUD/FM pMDI	296	36.6 (1.2)*	34.2–39.1
Fixed-dose FP/SM DPI	268	32.8 (1.3)	30.2–35.3
Daily activity			
Adjustable-dose BUD/FM pMDI	265	51.1 (0.9)‡	49.3–53.0
Fixed-dose BUD/FM pMDI	296	48.7 (0.9)	46.9–50.4
Fixed-dose FP/SM DPI	270	48.8 (0.9)	47.0–50.7
Leisure activity			
Adjustable-dose BUD/FM pMDI	264	49.4 (0.9)‡	47.6–51.3
Fixed-dose BUD/FM pMDI	295	47.0 (0.9)	45.2–48.8
Fixed-dose FP/SM DPI	268	47.2 (1.0)	45.3–49.0
Dosing management			
Adjustable-dose BUD/FM pMDI	263	41.6 (1.4)†‡	39.0–44.3
Fixed-dose BUD/FM pMDI	294	37.1 (1.3)	34.6–39.6
Fixed-dose FP/SM DPI	267	34.8 (1.4)	32.2–37.5
Medication convenience			
Adjustable-dose BUD/FM pMDI	263	48.5 (1.0)	46.5–50.6
Fixed-dose BUD/FM pMDI	296	46.4 (1.0)	44.5–48.4
Fixed-dose FP/SM DPI	268	47.8 (1.0)	45.8–49.9
Side effects			
Adjustable-dose BUD/FM pMDI	264	47.5 (1.1)	45.4–49.5
Fixed-dose BUD/FM pMDI	296	46.0 (1.0)	44.0–47.9
Fixed-dose FP/SM DPI	266	47.1 (1.1)	45.1–49.2

ANCOVA = analysis of covariance; BUD = budesonide; DPI = dry powder inhaler; FM = formoterol; FP = fluticasone propionate; LS = least squares; pMDI = pressurized metered-dose inhaler; SM = salmeterol.

*$p < .05$ versus fixed-dose FP/SM DPI.

†$p < .01$ versus fixed-dose FP/SM DPI.

‡$p < .05$ versus fixed-dose BUD/FM pMDI.

pMDI over either fixed-dose regimen for asthma-related HRQL. Regarding patients' perception of onset of treatment effect, patient responses to the ATSM questionnaire for the attribute of timely relief of symptoms and for items 2 and 5 of the OEQ questionnaire indicated that one or, in most cases, both budesonide/formoterol pMDI treatment regimens were slightly favored over fixed-dose fluticasone/salmeterol DPI. Asthma-specific HRQL is an essential component of assessing asthma control and treatment response (2). Both fixed-dose budesonide/formoterol pMDI and fluticasone propionate/salmeterol DPI treatments provided similar patterns of improvement in HRQL, as assessed by the AQLQ(S). Although adjustable-dose budesonide/formoterol pMDI treatment demonstrated statistically greater improvements in AQLQ(S) overall and for individual domain scores compared with one or both fixed-dose treatments, none of these differences were considered clinically meaningful. Comparable effects of adjustable- and fixed-dose budesonide/formoterol DPI treatments on HRQL were previously demonstrated in a randomized open-label study of adult patients with mild to moderate asthma (19).

Clinically meaningful decreases from baseline were reported in the present study for ACQ scores at end of treatment for all treatment groups, consistent with an increase in asthma control with all treatments. However, no significant or clinically meaningful differences were observed between treatment groups. Although most treatment attributes evaluated with the ATSM showed no difference between groups, the attributes of timely relief of symptoms and feel medication working received slightly but significantly better ratings by patients in both budesonide/formoterol pMDI groups compared with those receiving fixed-dose fluticasone propionate/salmeterol DPI. Assessment of patient satisfaction is important, and satisfaction with treatment as well as certain aspects of medical care received (e.g., waiting time, length of consultation, friendliness of physician, physician's understanding of patient concerns, physician communication skills) have been shown to be closely related to compliance (4, 5), which in turn may be associated with improved disease control (20).

Based on OEQ assessments, significantly more patients receiving budesonide/formoterol pMDI treatment felt their study medication begin to work right away compared with those receiving fixed-dose fluticasone propionate/salmeterol DPI. OEQ-based assessments further showed that a small but significantly greater percentage of patients receiving fixed-dose budesonide/formoterol pMDI reported satisfaction with the speed of onset of their medication compared with those receiving fixed-dose fluticasone propionate/salmeterol DPI. These findings support those reported in other studies comparing budesonide/formoterol and fluticasone propionate/salmeterol treatments, in which budesonide/formoterol treatment elicited a more rapid onset of bronchodilatory effects compared with fluticasone propionate/salmeterol treatment (21–23). These results also are consistent with data demonstrating faster onset of effect with formoterol versus salmeterol (24). A rapid onset of effect may result in improved treatment compliance; a recent survey of 200 adult patients with asthma showed that patients felt that their compliance with controller medication could be improved "if [they] could feel it helping [their] asthma soon after taking it" (25). Also, a majority of patients preferred a maintenance medication for which they are satisfied with how quickly they feel it begin to work (80%), and which they feel begin to work right away (62%) (26).

Although similar to a real clinical setting, the open-label design of this study may be considered a study limitation because knowledge of treatment assignment may have affected the subjective outcomes reported by patients. The lack of a placebo arm may also have limited a complete assessment of the effect of these treatments on PROs. Furthermore, the addition of a once-daily fluticasone propionate/salmeterol DPI arm would have been useful in allowing for more informative comparisons between the fixed-dose fluticasone

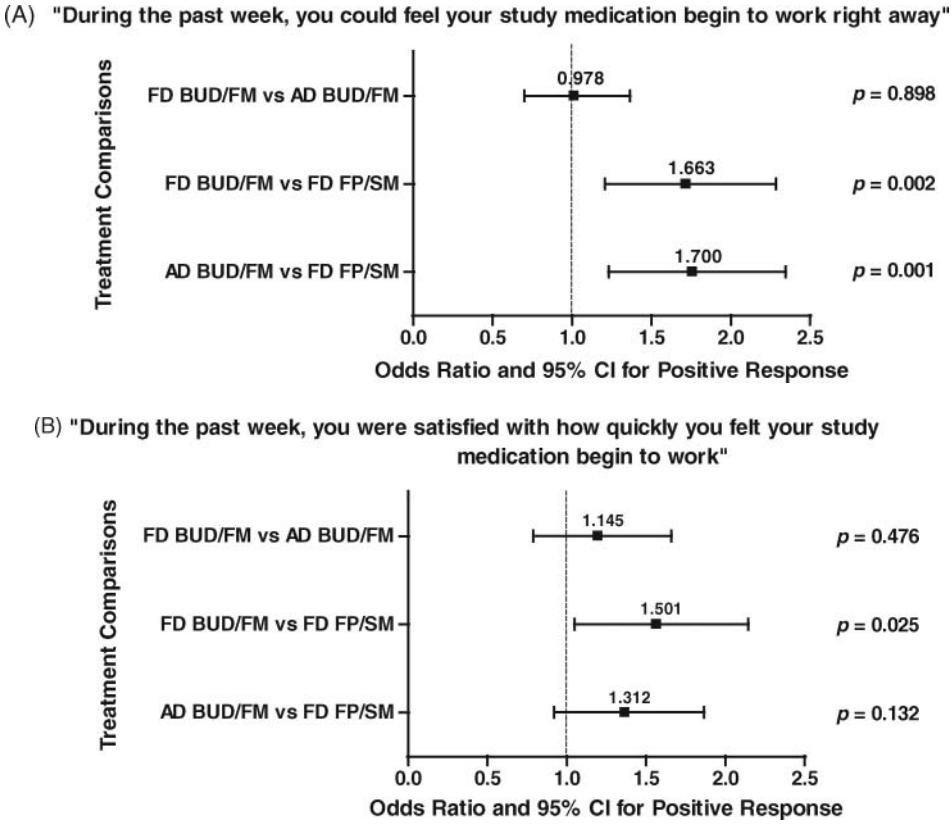

Figure 2.—Odds ratios and 95% CIs for a positive response ("strongly agree" or "somewhat agree") on the Onset of Effect Questionnaire for (A) item 2 and (B) item 5 at end of treatment. AD = adjustable dose; BUD/FM = budesonide/formoterol; FD = fixed dose; FP/SM = fluticasone propionate/salmeterol.

propionate/salmeterol DPI and the adjustable-dose budesonide/formoterol pMDI treatment arms. In this study, 2 inhalations were required to deliver a full dose of budesonide/formoterol pMDI, whereas only 1 inhalation of fluticasone propionate/salmeterol DPI was required to deliver a full dose (3).

In conclusion, there were few statistically significant differences between treatment groups regarding improvements observed in asthma-specific HRQL, asthma control, and satisfaction with asthma treatment. However, small but significant differences between treatment groups in favor of both budesonide/formoterol pMDI regimens were observed with regard to the attributes timely relief of symptoms and feel medication working in the ATSM questionnaire and feeling the medication work right away in the OEQ.

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Declaration of Interest

R. O'Connor has been on a speakers bureau for AstraZeneca and Glaxo SmithKline. He has also served as a member of the Asthma Leadership Council for AstraZeneca. D. Patrick has received consulting fees from AstraZeneca for participation in this project. B. Parasuraman is employed by AstraZeneca. P. Martin and M. Goldman are employed by and own stock in AstraZeneca.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda, MD: National Heart, Lung, and Blood Institute; 2006. NIH Publication No. 02-3659.
2. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH Publication No. 07-4051.
3. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immunol 2008; 121:1407–1414, e1401–1406.
4. Marquis P, Trudeau E. Quality of life and patient satisfaction: Two important aspects in asthma therapy. Curr Opin Pulm Med 2001; 7(suppl 1):S18–S20.
5. Smith NA, Ley P, Seale JP, Shaw J. Health beliefs, satisfaction and compliance. Patient Educ Couns 1987; 10:279–286.
6. Osman LM. How do patients' views about medication affect their self-management in asthma? Patient Educ Couns 1997; 32:S43–S49.
7. Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. Thorax 2000; 55:566–573.
8. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and

budesonide/formoterol DPI in asthma. Int J Clin Pract 2007; 61:1874–1883.
9. Chervinsky P, Baker J, Bensch G, Parasuraman B, Boggs R, Martin P, O'Dowd L. Patient-reported outcomes in adults with moderate to severe asthma after use of budesonide and formoterol administered via 1 pressurized metered-dose inhaler. Ann Allergy Asthma Immunol 2008; 101:463–473.
10. 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; 24:879–894.
11. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999; 115:1265–1270.
12. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14:902–907.
13. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99:553–558.
14. Martin ML, Patrick DL, Bushnell DM, Meltzer EO, Gutierrez B, Parasuraman B. The Asthma Treatment Satisfaction Measure (ATSM) for patients with asthma. Curr Med Res Opin 2009; 25:2495–2506.
15. Patrick DL, Martin ML, Bushnell DM, Pesa J. Measuring satisfaction with migraine treatment: Expectations, importance, outcomes, and global ratings. Clin Ther 2003; 25:2920–2935.
16. Martin ML, Patrick DL, Bushnell DM, Gandra SR, Gilchrist K. Further validation of an individualized migraine treatment satisfaction measure. Value Health 2008; 11:904–912.
17. Leidy NK, Mathias SD, Parasuraman BM, Patrick DL, Pathak D. Development and validation of an onset of effect questionnaire for patients with asthma. Allergy Asthma Proc 2008; 29:590–599.
18. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol 1994; 47:81–87.
19. Buhl R, Kardos P, Richter K, Meyer-Sabellek W, Bruggenjurgen B, Willich SN, Vogelmeier C. The effect of adjustable dosing with budesonide/formoterol on health-related quality of life and asthma control compared with fixed dosing. Curr Med Res Opin 2004; 20:1209–1220.
20. Smith JR, Mildenhall S, Noble M, Mugford M, Shepstone L, Harrison BD. Clinician-assessed poor compliance identifies adults with severe asthma who are at risk of adverse outcomes. J Asthma 2005; 42:437–445.
21. Hampel FC, Martin P, Mezzanotte WS. Early bronchodilatory effects of budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI and albuterol pMDI: 2 randomized controlled trials in adults with persistent asthma previously treated with inhaled corticosteroids. J Asthma 2008; 45:265–272.
22. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lotvall J. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther 2001; 14:29–34.
23. Van Der Woude HJ, Boorsma M, Bergqvist PB, Winter TH, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. Pulm Pharmacol Ther 2004; 17:89–95.
24. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: Onset of action, duration of effect and potency. Eur Respir J 1997; 10:2484–2489.
25. Bender BG, Long A, Parasuraman B, Tran ZV. Factors influencing patient decisions about the use of asthma controller medication. Ann Allergy Asthma Immunol 2007; 98:322–328.
26. Hauber AB, Mohamed AF, Johnson FR, Meddis D, Wagner S, O'Dowd L. Quantifying asthma patient preferences for onset of effect of combination inhaled corticosteroids and long-acting beta2-agonist maintenance medications. Allergy Asthma Proc 2009; 30:139–147.