

# Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma

## The OPTIMA Randomized Trial

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The optimal treatment for mild asthma is uncertain. We assessed the effects of adding a long-acting inhaled beta-agonist, formoterol, to low doses of an inhaled corticosteroid, budesonide, for 1 yr in subjects with mild asthma, receiving no or only a small dose of inhaled corticosteroid. The 698 corticosteroid free patients (Group A) were assigned to twice daily treatment with 100  $\mu$ g budesonide, 100  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol, or placebo. The 1,272 corticosteroid-treated patients (Group B) were assigned to twice daily treatment with 100  $\mu$ g budesonide, 100  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol, 200  $\mu$ g budesonide, or 200  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol. The main outcome variables were time to the first severe asthma exacerbation and poorly controlled asthma days. In Group A, budesonide alone reduced the risk for severe exacerbations by 60% and poorly controlled days by 48%; adding formoterol increased lung function with no change in other end points. By contrast, in Group B, adding formoterol reduced the risk for the first severe exacerbation and for poorly controlled days by 43 and 30%, respectively. Thus, in corticosteroid-free patients, low dose inhaled budesonide alone reduced severe exacerbations and improved asthma control, and in patients already receiving inhaled corticosteroid, adding formoterol was more effective than doubling the corticosteroid dose.

**Keywords:** mild asthma; inhaled corticosteroids; budesonide; long acting beta-agonists; formoterol; management

Asthma management has undergone a number of important changes over the past 10 yr. Clinical studies have shown that the regular use of short-acting inhaled beta-agonists does not improve asthma control (1–3). Also, in patients with more severe asthma, the benefit from a 2- or 2.5-fold increase in the dose of an inhaled corticosteroid is limited, when compared with that achieved by adding a long-acting inhaled beta-agonist (4, 5). In addition, for patients with moderately severe asthma, the addition of formoterol, a fast onset, long-acting inhaled beta-agonist, reduced asthma exacerbations and improved symptoms and lung function when added to low or moderate doses of inhaled budesonide (the FACET study) (6).

The effect of combining a low dose of inhaled corticosteroids with low doses of an inhaled long-acting beta-agonist is attractive since the benefits are at least additive, as in the FACET study (6), and the long-term risks from adverse effects of higher doses of inhaled corticosteroids may be reduced. However, the effect of combined treatment has never

been evaluated in patients with mild asthma, although they account for the majority of patients in primary care. In this randomized controlled trial, we studied patients with mild asthma, who experienced symptoms but were either taking no inhaled corticosteroid or taking low dose inhaled corticosteroids ( $\leq 400$   $\mu$ g budesonide/d or its equivalent). The aim was to determine whether regular treatment with low doses of inhaled budesonide, with or without low doses of inhaled formoterol, would reduce severe asthma exacerbations and improve asthma control compared with placebo.

## METHODS

### Patients

Patients were  $\geq 12$  yr of age with mild asthma. Group A patients (corticosteroid-free) had used no inhaled corticosteroid for  $\geq 3$  mo, had a FEV<sub>1</sub>  $\geq 80\%$  predicted normal (7) after inhaling 1 mg terbutaline (Bricanyl Turbuhaler; AstraZeneca, Lund, Sweden). Group B patients were taking  $\leq 400$   $\mu$ g/d of inhaled budesonide or its equivalent for  $\geq 3$  mo, with a FEV<sub>1</sub>  $\geq 70\%$  predicted normal after terbutaline. Randomized patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 wk of run-in, a  $\geq 15\%$  variability in peak expiratory flows (PEF), or a  $\geq 12\%$  increase in FEV<sub>1</sub> after terbutaline.

### Study Design

The study was double-blind, randomized, and parallel-group, carried out in 198 centers in 17 countries and conducted in accordance with the principles of good clinical practice. Approval from regulatory agencies and ethics committees was obtained in all countries and centers. All patients gave written, informed consent.

The study had a 4-wk run-in, when Group A patients took placebo and Group B patients took budesonide 100  $\mu$ g twice daily. Eligible patients were randomly assigned to treatment twice daily for 1 yr: in Group A with 100  $\mu$ g budesonide, 100  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol, or placebo; in Group B with 100  $\mu$ g budesonide, 100  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol, 200  $\mu$ g budesonide, or 200  $\mu$ g budesonide plus 4.5  $\mu$ g formoterol, all delivered by Turbuhaler (AstraZeneca). The stated doses are metered doses for budesonide and delivered doses for formoterol. Patients attended the clinic on nine occasions, at the same time of day, over the year. No additional treatments were allowed unless the patient had a severe exacerbation, after which medications could be added at the physician's discretion.

### Outcome Measures

The primary outcomes were (*I*) time to the first severe asthma exacerbation, defined as need for treatment with oral corticosteroids, as judged by the investigator, or hospital admission or emergency treatment for worsening asthma, or a decrease in morning PEF  $> 25\%$  from baseline (the mean values during the last 14 d of the run-in) on two consecutive days. This was chosen because it would not be influenced by a change in the patient's asthma treatment initiated by the occurrence of the initial exacerbation, which was allowed in the protocol. Patients were not excluded from the study unless they experienced three severe exacerbations during the initial 6 mo or five exac-

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TABLE 1. SUBJECT CHARACTERISTICS FOR RANDOMIZED PATIENTS\*

Variable	Group A			Group B			
	Placebo (n = 239)	BUD200 (n = 228)	BUD200+F (n = 231)	BUD200 (n = 322)	BUD200+F (n = 323)	BUD400 (n = 312)	BUD400+F (n = 315)
Age, yr	30.6	30.6	31.2	38.1	36.5	37.5	36.8
Female sex, n %	138 (57.7)	135 (59.2)	146 (63.2)	181 (56.2)	179 (55.4)	179 (57.4)	186 (59.1)
Prebronchodilator FEV <sub>1</sub> , % pred	89.9 (0.96)	90.1 (0.94)	89.1 (0.97)	86.3 (0.94)	86.4 (0.91)	87.0 (0.93)	86.5 (0.92)
PEF morning, L/min	416 (7.1)	421 (7.4)	416 (7.5)	419 (7.1)	429 (7.1)	416 (6.5)	412 (6.5)
Days with symptoms, %	41.8 (2.4)	37.8 (2.3)	39.8 (2.3)	37.4 (2.1)	37.5 (2.0)	36.0 (2.0)	40.2 (2.1)
Rescue inhalations, n	0.95 (0.1)	0.82 (0.08)	0.92 (0.08)	0.98 (0.08)	0.96 (0.08)	0.92 (0.07)	0.82 (0.06)
Nights with awakenings, %	12.2 (1.4)	11.9 (1.5)	8.9 (1.1)	7.7 (1.0)	5.1 (0.7)	8.2 (1.0)	5.8 (0.8)

\* Values are means with SEM shown in parentheses, unless otherwise stated.

eruations in total; (2) poorly controlled asthma days, defined as days with morning PEF values  $\geq 20\%$  below baseline, or the use of rescue medication was  $\geq 2$  above baseline, or with asthma awakening.

The secondary outcomes were changes in morning PEF, FEV<sub>1</sub> % predicted, percentage of days with symptoms, percentage of asthma awakenings, number of rescue inhalations, and rate per patient per year of severe asthma exacerbations. Patients completed a daily diary card during the run-in and for the first 7 d after each visit. They recorded morning PEF from a peak flow meter (Vitalograph, Buckingham, UK) before medication, number of rescue inhalations, symptoms, and asthma awakenings. Patients also kept a notebook to record health contacts, changes in medications, asthma-related events, and morning PEF.

### Analysis

The study was analyzed using intention-to-treat principles. For Group A, pairwise comparisons were made. For Group B, the data were analyzed using a factorial design by appropriate contrasts. Time to the first severe exacerbation was analyzed using a Cox model for proportional hazards. Poorly controlled asthma days and the rate of severe exacerbations were analyzed using a Poisson regression model. The results are reported as risk ratios (RR) with 95% CI. Other variables were analyzed using analysis of covariance, with baseline values as covariates.

### RESULTS

A total of 900 patients were enrolled in Group A and 1,625 patients into Group B, of whom 698 and 1,272, respectively, were subsequently randomized to treatment (Table 1). A total of 23 patients were excluded from the efficacy evaluation: eight from Group A, 15 from Group B. There were no significant differences in baseline demographic or spirometric characteristics between the treatment arms in either group (Table 1). The year-long study was completed by 81% in Group A (n = 554) and by 87% in Group B (n = 1,092). Efficacy data were available for 1,947 patients. Of the 301 (15%) patients who did not complete the study, 51 (3%) discontinued because of adverse events, including 14 because of deteriorating asthma, and 250 (13%) were either ineligible for the study or left for personal reasons.

#### Group A (Corticosteroid-free Patients)

In the placebo group, 79 of 237 patients had a severe asthma exacerbation, and asthma was poorly controlled in 14.4% of days. Patients receiving budesonide alone showed a 60% reduction in the risk for the first severe asthma exacerbation (RR = 0.40, 95% CI = 0.27 to 0.59) and a 48% reduction in

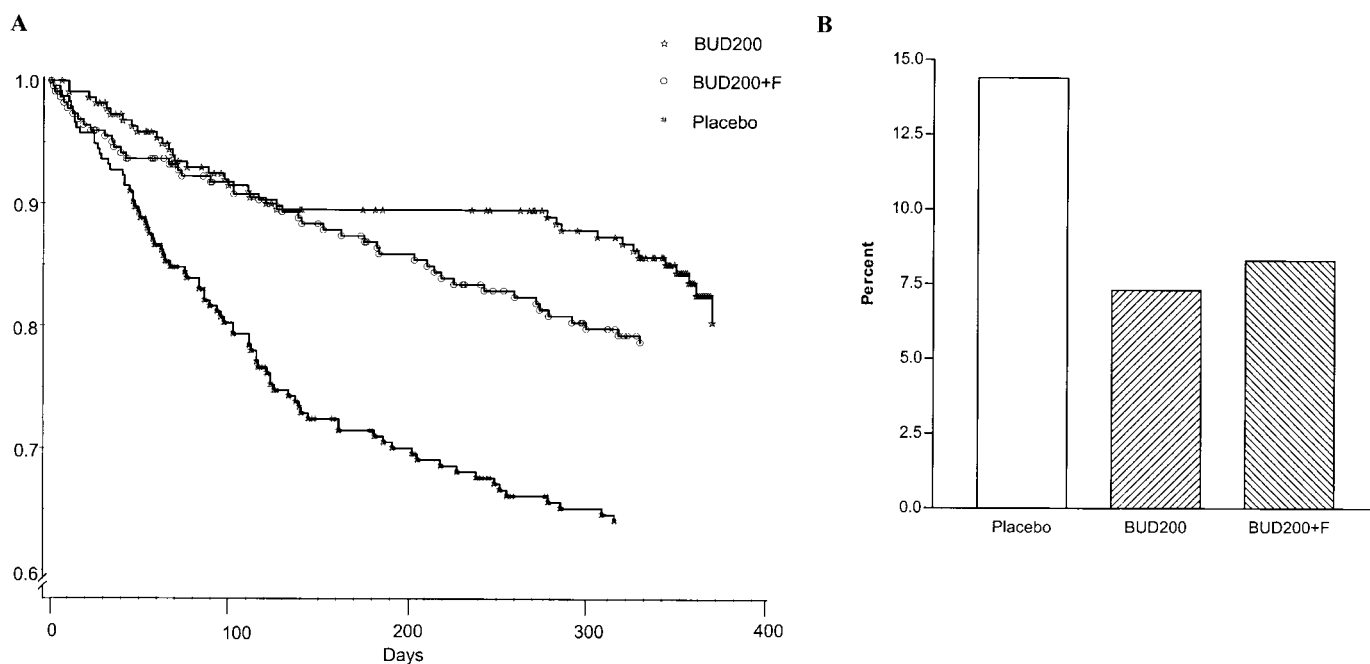


Figure 1. (A) Kaplan-Meier survival curve for the time to the first severe asthma exacerbation. (B) Proportion (%) of poorly controlled asthma days in Group A (corticosteroid-free patients). BUD 200 = budesonide 100  $\mu\text{g}$  twice daily; F = formoterol 4.5  $\mu\text{g}$  twice daily.

TABLE 2. RESULTS GROUP A: END VALUES (ADJUSTED MEANS)

Variable	Placebo	BUD200	BUD200+F	p Values Comparing:		
				BUD200 vs Placebo	BUD200+F vs BUD200	BUD200+F vs Placebo
Change in FEV <sub>1</sub> , % pred	1.79	4.04	5.87	0.0045	0.023	0.0001
Change in PEF Morning, L/min	8.66	15.12	31.81	0.12	0.0001	0.0001
Days with symptoms, %	29.4	23.1	21.5	0.0074	0.48	0.0007
Number of rescue inhalations per day	0.75	0.51	0.51	0.0008	0.97	0.0008
Nights with awakenings, %	7.0	2.5	3.1	0.0001	0.52	0.0001
Rate per year of severe exacerbations	0.77	0.29	0.34	0.0001	0.50	0.0001

the rate of poorly controlled asthma days (RR = 0.52, 95% CI = 0.40 to 0.67) when compared with patients given placebo (Figure 1A and 1B). There was also a reduction in the rate of exacerbations (RR = 0.38, 95% CI = 0.25 to 0.57), asthma symptoms, nocturnal awakening, and number of rescue inhalations of short-acting inhaled beta agonists in the budesonide group and an increase in FEV<sub>1</sub> (Table 2). The addition of formoterol to budesonide provided further benefit over that seen for budesonide alone for FEV<sub>1</sub> and morning PEF (Figure 2A), but not for other outcome variables (Table 2).

#### Group B (Patients Taking Inhaled Corticosteroids)

In the budesonide 100 µg group, 107 of 317 patients had a severe asthma exacerbation and asthma was poorly controlled on 13% of days. When the groups taking budesonide 100 µg

and 200 µg twice daily were compared, the higher dose of budesonide was associated with a 19% reduction in the risk of a first severe exacerbation (RR = 0.81, 95% CI = 0.65 to 1.01) (Figures 3A) and a 13% reduction in the rate of poorly controlled asthma days (RR = 0.87, 95% CI = 0.75 to 1.01) (Figure 3B). There was also a trend towards a reduction in the rate of severe exacerbations (RR = 0.82, 95% CI = 0.67 to 1.01) and small, but significant, improvements in the percentage of days with asthma symptom, FEV<sub>1</sub>, and morning PEF with the higher dose of budesonide (p < 0.05) (Figure 2B and Table 3).

Adding formoterol to either the lower or higher dose of budesonide reduced the risk of the first asthma exacerbation by 43% (RR = 0.57, 95% CI = 0.46 to 0.72) (Figure 3A) and the rate of poorly controlled asthma days by 30% (RR = 0.70, 95% CI = 0.60 to 0.82) (Figure 3B). There was also a significant 52% reduction in the rate of severe exacerbations (RR = 0.48, 95% CI = 0.39 to 0.59) on adding formoterol to either the lower or the higher dose of budesonide. Formoterol also increased FEV<sub>1</sub> and morning PEF and reduced the percentage of asthma symptom days and the number of rescue inhalations of short-acting inhaled beta-agonists (Table 3). Adding formoterol to the lower dose of budesonide was more effective than doubling the dose of budesonide, in terms of reducing the risk of a severe exacerbation day (RR = 0.71, 95% CI = 0.52 to 0.96) or a poorly controlled asthma day (RR = 0.81, 95% CI = 0.66 to 0.99). In addition, significant improvements were observed for the rate of severe exacerbations (RR = 0.58, 95% CI = 0.44 to 0.76), FEV<sub>1</sub>, and morning PEF (p = 0.001, p < 0.05, and p < 0.005, respectively).

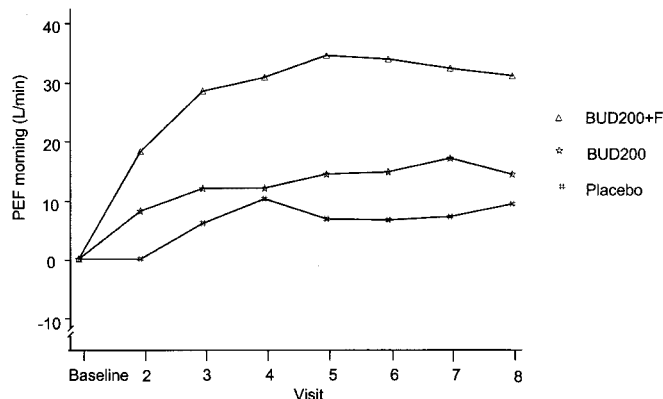
#### Adverse Events

All treatments were well tolerated throughout the study. The frequency of reported adverse events, including those described as serious or causing patients to discontinue, was similar in Groups A and B and between the different treatments. Class-specific adverse effects of beta-agonist and inhaled corticosteroid occurred in less than 2% of patients in all treatment arms.

#### DISCUSSION

We examined the role of regular treatment with low dose budesonide and low doses of formoterol for patients with mild, but symptomatic, asthma. Our primary end points were the time to the first severe asthma exacerbation and the percentage of poorly controlled asthma days. In patients who were not currently taking an inhaled corticosteroid (corticosteroid-free), a low dose of inhaled budesonide reduced the rate of severe exacerbations and poorly controlled asthma days by more than half. Adding formoterol resulted in improved lung function, but no further clinical benefit. In patients taking a low dose of inhaled corticosteroid (≤ 400 µg/d budesonide), the addition of formoterol improved all outcome variables, including reducing severe exacerbations, and this benefit was significantly superior to that seen with doubling the dose of budesonide.

#### GROUP A



#### GROUP B

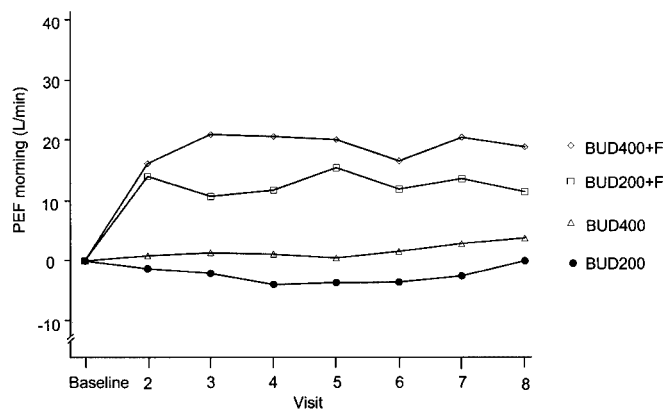
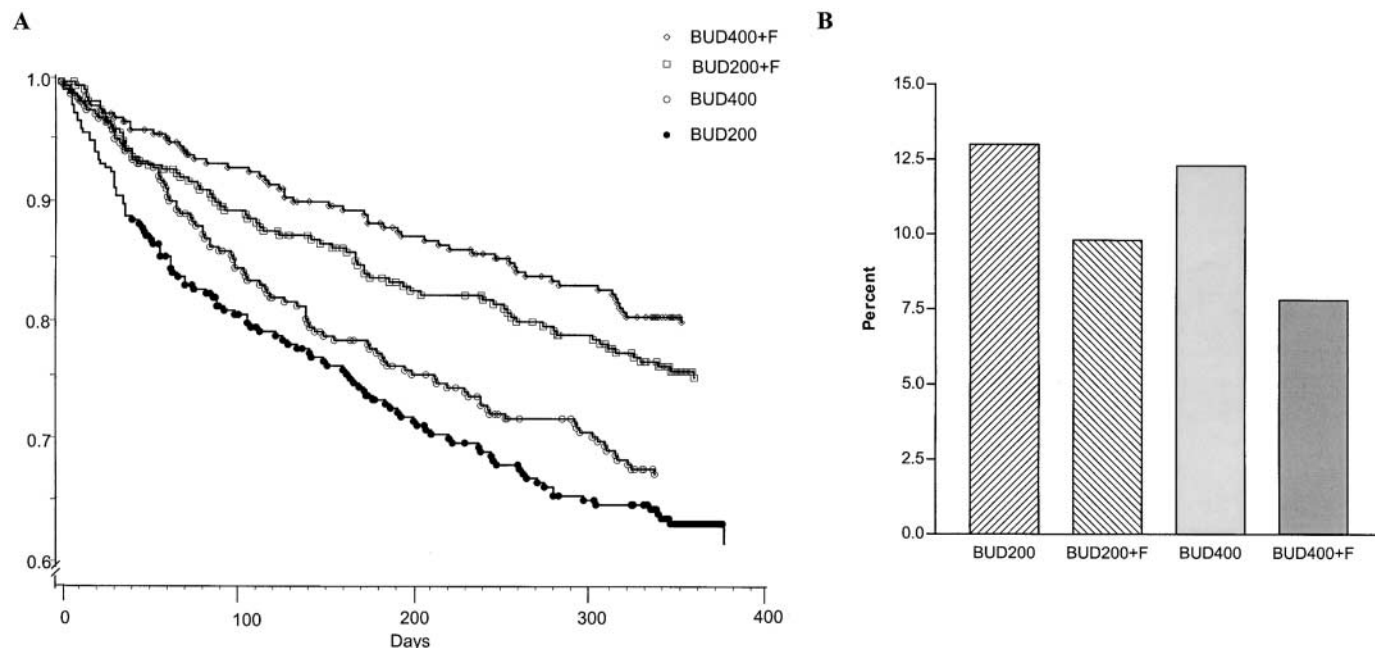


Figure 2. Adjusted mean change from baseline in morning peak expiratory flow in Group A (upper panel) and Group B (lower panel). BUD 200 = budesonide 100 µg twice daily; BUD 400 = budesonide 200 µg twice daily; F = formoterol 4.5 µg twice daily.



**Figure 3.** (A) Kaplan-Meier survival curve for the time to the first severe asthma exacerbation. (B) Proportion (%) of poorly controlled asthma days in Group B (corticosteroid-treated patients). BUD 200 and 400 = budesonide 100  $\mu$ g and 200  $\mu$ g twice daily; F = formoterol 4.5  $\mu$ g twice daily.

This is the largest study yet reported to assess management of patients with mild asthma, and it covered a wide age range from 12 yr upwards. The corticosteroid-free asthmatic patients (Group A) had close to normal lung function (mean prebronchodilator FEV<sub>1</sub> = 89.5%) and infrequent use of short-acting inhaled beta-agonists. Such patients are treated mainly in the primary care setting, often without inhaled corticosteroids (8, 9). Although such patients are considered to have mild asthma (10), one third of those taking placebo experienced a severe asthma exacerbation during the year of the study and asthma was poorly controlled on 14% of the days, confirming that appreciable morbidity is associated with the label of mild asthma (9). The most common cause of these poorly controlled days was asthma-related nocturnal awakenings (46.5%). In addition, the frequency of severe exacerbations was higher than expected, when planning the study, in this mild population. This reinforces the point that even patients thought to have mild asthma are at risk of severe, and even fatal, asthma exacerbations (11).

Patients in Group B were already taking low doses of inhaled corticosteroids on entry to the study, yet they were still mildly symptomatic and had lower lung function than in Group A. Doubling the budesonide dose produced little clinical benefit, whereas the addition of formoterol was associated with greater efficacy regarding the time to the first severe

asthma exacerbation, the rate of asthma exacerbations, and the number of poorly controlled asthma days. The fact that giving a low dose of budesonide to the steroid-free group had a marked effect on asthma exacerbations and poorly controlled days, whereas doubling the dose of budesonide in Group B had a marginal benefit, is of interest. It supports other studies suggesting much of the benefit achieved with inhaled corticosteroids occurs with lower doses and that the dose-response curves are relatively flat thereafter (12).

The doses of inhaled budesonide used in the study are small and long-term adverse effects should be minimal. The two main adverse effects of concern with long-term use of inhaled corticosteroids, growth in children, and bone mineral density in adults, do not appear to be relevant when low doses of inhaled corticosteroids are used for asthma management (13, 14). However, there may be concern, regarding bone mineral density, when higher doses of inhaled corticosteroids are used (15). In addition, the need for oral corticosteroids and other antiasthma drugs was reduced by treatment with budesonide alone in Group A and by the addition of formoterol, but not the increased dose of budesonide, in Group B. Taken together, these results suggest that many patients considered to have mild asthma would benefit from low doses of budesonide and that if asthma control is not achieved, inhaled formoterol would provide further benefit.

**TABLE 3. RESULTS GROUP B: END VALUES (ADJUSTED MEANS)**

Variable	BUD200	BUD200+F	BUD400	BUD400+F	p Values Comparing:		
					BUD 400 vs BUD 200	F vs Placebo	BUD 200+F vs BUD 400
Change in FEV <sub>1</sub> , % pred	0.27	2.55	0.90	4.13	0.022	0.0001	0.015
Change in PEF morning, L/min	2.78	12.89	1.73	18.50	0.042	0.0001	0.0015
Days with symptoms, %	32.8	27.4	29.7	25.1	0.017	0.0001	0.25
Number of Rescue inhalations, n	0.89	0.66	0.75	0.63	0.052	0.0001	0.17
Nights with awakenings, %	6.0	5.4	6.0	4.5	0.45	0.061	0.43
Rate per patient per year of severe exacerbations	0.92	0.56	0.96	0.36	0.069	0.0001	0.0001

TABLE 4. NUMBER OF PATIENTS RECEIVING EXTRA MEDICATION IN EACH STUDY GROUP

Added Medications	Group A			Group B			
	Placebo	BUD200	BUD200+F	BUD200	BUD200+F	BUD400	BUD400+F
Inhaled corticosteroids	15	1	8	9	9	14	9
Systemic corticosteroids	56	27	34	81	58	61	39
Long-acting $\beta_2$ -agonists	11	9	11	18	9	11	9
Xanthines	8	4	7	13	6	13	3
Leukotriene receptor antagonists	1	0	0	1	0	1	1
Antibiotics	3	2	5	7	9	6	6
Others	10	6	8	11	4	10	4
Total	104	49	73	140	95	116	71

A reduction in severe asthma exacerbations has also been demonstrated when formoterol is used as needed, at a similar dose, when compared with the short-acting inhaled beta-agonist, terbutaline (16). Neither the magnitude of this effect on severe asthma exacerbations nor of the effect on exacerbations described in the present study has yet been demonstrated with other long-acting inhaled beta-agonists, or other therapies, added to inhaled corticosteroids. The mechanism by which low-dose inhaled formoterol reduces severe asthma exacerbations in persons with mild asthma, as well as that seen with a double dose of formoterol in the FACET study, in those with more severe asthma (6), is uncertain. Possibilities include a reduction in airway eosinophils (17), or an inhibitory effect on mast cell activation (18).

A strength of this study is its size and general applicability to a large proportion of asthmatic patients and the fact that more than 84% of patients completed the year-long study. Patients' diaries were completed for 1 wk only after each study visit to improve compliance with their completion, although PEF was measured every day. We did not include a formoterol-only treatment arm for Group A since the role for regular bronchodilator therapy as monotherapy in asthma has been questioned (19), and long-acting inhaled beta-agonists used alone are not currently recommended for regular use in this patient group (10).

Additional asthma medications could be added, at the managing physician's discretion, once patients had recovered from their first severe asthma exacerbation during the study. This pragmatic approach mimics what happens in everyday management of asthma. The number of patients receiving additional treatment was highest in the placebo group in Group A and in those patients receiving budesonide 100  $\mu$ g twice daily with placebo in Group B (Table 4). Despite this, outcomes, such as poorly controlled asthma days, which were measured over the year of the study, were greater in these groups when compared with the other treatment arms.

Our results suggest that mild asthma may often be undertreated. The corticosteroid-free population had a frequency of severe asthma exacerbations that was approaching that previously reported for moderate to severe asthma (6), as well as symptoms, which were markedly improved by a low dose of inhaled budesonide. The definition of a severe asthma exacerbation in this study was slightly different (a 25% reduction in PEF for 2 consecutive d) from that in the FACET trial (a 30% reduction in PEF for 2 consecutive d) (6). This change from the FACET definition was decided on to increase the sensitivity of the definition because severe exacerbations were believed to be less likely in this milder patient population. In fact, the prevalence of severe exacerbations in the study was much greater than expected. In Group A, in the placebo-treated patients, 56 of the 79 identified as having a severe asthma exacerbation (71%) were identified by the managing

physician as needing systemic corticosteroids. In Group B, in the patients receiving budesonide 100  $\mu$ g twice daily with placebo with 81 of 107 (76%) with a severe exacerbation needed systemic corticosteroids (Table 4).

It is generally recommended that long-acting inhaled beta-agonists be added to moderate doses of inhaled corticosteroids (generally  $\geq$  500 to 800  $\mu$ g/d) (20). However, the current study suggests that better asthma control can be achieved with the addition of formoterol to lower doses of inhaled corticosteroids than currently recommended. This may be different for patients with moderate to severe disease, where fourfold higher doses of budesonide taken for 1 yr did reduce asthma exacerbations, as demonstrated in the FACET study (6). In addition, the study indicates that for patients with mild persistent asthma, not using inhaled corticosteroids, the introduction of a low dose of budesonide alone was sufficient to achieve close to optimal asthma control and only if optimal control is not achieved should additional therapy with formoterol be considered.

In summary, in corticosteroid-free patients, severe asthma exacerbations and asthma control benefit from a low dose of inhaled budesonide, with no further benefit from adding formoterol, except for lung function. By contrast, in patients already taking a low dose of inhaled corticosteroids, the addition of inhaled formoterol reduced asthma exacerbations and improved asthma control more effectively than doubling the dose of budesonide.

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