Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma

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Asthma control is improved by combining inhaled corticosteroids with long-acting β_2-agonists. However, fluctuating asthma control still occurs. We hypothesized that in patients receiving low maintenance dose budesonide/formoterol (bud/form), replacing short-acting β_2-agonist (SABA) reliever with as-needed bud/form would provide rapid symptom relief and simultaneous adjustment in antiinflammatory therapy, thereby reducing exacerbations. In this double-blind, randomized, parallel-group study, 2,760 patients with asthma aged 4–80 years (FEV_1 60–100% predicted) received either terbutaline 0.4 mg as SABA with bud/form 80/4.5 μg twice a day (bud/form + SABA) or bud 320 μg twice a day (bud + SABA) or bud/form 80/4.5 μg twice a day with 80/4.5 μg as-needed (bud/form maintenance + relief). Children used a once-nocte maintenance dose. Bud/form maintenance + relief prolonged time to first severe exacerbation ($p < 0.001$; primary endpoint), resulting in a 45–47% lower exacerbation risk versus bud/form + SABA (hazard ratio, 0.55; 95% confidence interval, 0.44, 0.67) or bud + SABA (hazard ratio, 0.53; 95% confidence interval 0.43, 0.65). Bud/form maintenance + relief also prolonged the time to the first, second, and third exacerbation requiring medical intervention ($p < 0.001$), reduced severe exacerbation rate, and improved symptoms, awakenings, and lung function compared with both fixed dosing regimens.

Keywords: inhaled corticosteroids; long-acting β_2-agonists; management; single inhaler

The combination of low or moderate doses of inhaled corticosteroids (ICS) with long-acting β_2-agonists (LABA) improves asthma control in adults and reduces exacerbations (OPTIMA study [1]; FACET study [2]); however, the evidence in pediatric patients is less compelling (3). The combination of ICS plus LABA for maintenance therapy is endorsed in asthma treatment guidelines for the treatment of moderate to severe asthma (4). Studies such as OPTIMA and FACET have led to marked improvements in asthma control using lower doses of ICS. Optimal asthma control was not achieved, however, as patients in these studies still had a notable requirement for short-acting reliever therapy or experienced exacerbations.

Periodic fluctuations in symptoms and airway inflammation are characteristics of asthma, which means that treatment requirements, especially reliever use, can vary over time. Moreover, reliever medication that provides rapid bronchodilation and symptom relief but that does not treat the underlying inflammatory process can be overrelied on (5). One possible solution could be to use a combination inhaler containing both an ICS and an LABA for both regular maintenance therapy and as needed. This strategy provides additional antiinflammatory therapy and rapid symptom relief if symptoms appear. Such an approach is possible with the combination inhaler containing budesonide and formoterol, as this combination has an onset of bronchodilator action within the first minute (6), with a similar efficacy and safety to salbutamol in patients with acute severe asthma (7).

We hypothesized that in patients already receiving a low daily maintenance dose of budesonide/formoterol (bud/form), replacing short-acting β_2-agonist (SABA) reliever therapy with the as-needed bud/form combination would enable patients to adjust more rapidly their antiinflammatory therapy at times of greatest need while simultaneously obtaining effective and rapid relief from symptoms. This approach should, therefore, further reduce asthma exacerbations and improve asthma control compared with the improvements seen with traditional fixed-dose combination therapy. Thus, this randomized, double-blind, 1-year study compared bud/form both for maintenance and symptom relief with fixed dosing using either bud/form or a fourfold higher dose of budesonide, both with SABA as reliever therapy. Previously, in the FACET study (2), which demonstrated that both budesonide and formoterol had complementary effects on reducing exacerbations in adults, a fourfold higher budesonide dose was more effective at reducing severe asthma exacerbations when compared with a low-dose bud/form combination, despite the combination providing greater improvements in symptoms (2). In this study, severe asthma exacerbations were selected as the primary outcome variable, as these are a sensitive clinical measure of control, responding to higher maintenance doses of budesonide, and thus are less likely to respond to low-dose combination therapy (2). Some of the results from this study have previously been presented in abstract form (8, 9).

METHODS

Patients

Outpatients aged 4 to 80 years with asthma treated with 400 to 1,000 μg/day of ICS for adults and 200 to 500 μg/day for children (4–11 years) with a history of one or more asthma exacerbation in the last year were enrolled. All patients had been using a constant dose of ICS for 3 or more months. Patients had an FEV_1 60–100% of predicted with 12% or more reversibility. To be eligible for randomization, patients had to have used 12 or more inhalations (or eight or more in children) of as-needed medication during the last 10 days of run-in. Patients using 10 or more inhalations of reliever on any 1 day (or seven or more for children) or with an asthma exacerbation during run-in were not randomized.

(*Received in original form July 8, 2004; accepted in final form October 18, 2004*)

Supported by AstraZeneca R&D, Lund, Sweden.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171. pp 129–136, 2005
Originally Published in Press as DOI: 10.1164/rccm.200407-884OC on October 22, 2004
Internet address: www.atsjournals.org

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from regulatory agencies and ethics committees was obtained at all centers. All patients gave written informed consent.

Study Design

This was a double-blind, randomized, parallel-group study conducted at 246 centers in 22 countries. Patients attended the clinic at the beginning and end of run-in and after 1, 3, 6, 9, and 12 months of treatment.

Patients were randomized to one of three treatment groups: bud/form 80/4.5 μg twice a day plus 80/4.5 μg as needed (bud/form maintenance + relief), bud/form 80/4.5 μg twice a day plus terbutaline 0.4 mg as needed (bud/form + SABA), and budesonide 320 μg twice a day plus terbutaline 0.4 mg as needed (bud + SABA). Children were given half the maintenance dose once daily at night. Treatment was stratified by age group in an 8:1 ratio (adults:children), with all medication delivered by Turbuhaler (AstraZeneca, Lund, Sweden).

Adults could use a maximum of 10 and children 7 as-needed inhalations per day before contacting the investigator. Severe exacerbations were treated with a 10-day course of oral prednisone (30 mg/day); for children aged 4 to 11 years, the option to add extra maintenance medication during exacerbations was also available.

Measurements

Severe asthma exacerbations were defined as a deterioration in asthma resulting in hospitalization/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning peak expiratory flow (PEF) of 70% or less of baseline on 2 consecutive days. Severe exacerbations confined to those requiring medical intervention were also analyzed separately. Mild exacerbations were defined as 2 consecutive days with either a morning PEF of 80% or less of baseline, as-needed use two or more inhalation per day above baseline, or awakenings caused by asthma.

Daily pretreatment PEF was assessed using a Mini-Wright PEF meter (Clement Clark, Harlow, UK); daily symptoms, awakenings, reliever medication use, and study drug use were recorded on diary cards. FEV_1 was assessed by spirometry (10) at clinic visits. Safety was assessed by adverse events, electrocardiogram, morning plasma cortisol, and vital signs. Height for children aged 4 to 11 years was measured using local procedures before run-in and after 6 and 12 months of treatment.

Statistical Analysis

Data were analyzed on an intention-to-treat basis for patients who received one dose or more of study drug. All hypothesis testing was two sided; p values of less than 5% were considered statistically significant. The primary efficacy outcome was the time to first severe asthma exacerbation, described using Kaplan-Meier plots and a log-rank test, with analysis of instantaneous risk described using a Cox proportional hazards model. Total numbers of severe exacerbations were compared using a Poisson regression model. Confidence limits and p values were adjusted for overdispersion. The sample size was based on the true incidence of asthma exacerbations in one group being 25%. Therefore, a sample size of 800 randomized patients per group (i.e., 200 exacerbations) would provide an 80% probability of detecting a reduction of more than 23% in another group.

Other daily diary card variables were analyzed as change from baseline using analysis of variance, with the baseline value (last 10 days of run-in) as covariate. Individual growth was calculated as change in height between enrollment and after 12 months' treatment. Growth was compared between treatments using analysis of variance, with height at enrollment as a covariate. Further information on the study design and data analysis is provided in the online supplement.

RESULTS

Patients

In total, 3,251 patients were enrolled. After run-in, 2,760 patients were randomized to study treatment: 925, 909, and 926 patients to bud/form maintenance + relief, bud/form + SABA, and bud + SABA, respectively (Figure E1 in the online supplement). There were 437 patients (16%) with one or more protocol deviation, with no differences between groups. The most common deviation was randomization in error (9%), with the majority of these patients failing to meet the criterion for as-needed medication use during the run-in. None of the deviations justified exclusion of data from the analysis and all data were included where available. Of the 2,760 patients randomized, 341 (12%) were children aged 4 to 11 years. Characteristics of the treatment groups were comparable at baseline (Table 1).

Self-reported compliance with maintenance therapy was similar in all groups, with incomplete records on 12 to 13% of days/year, self-reported compliance on 84 to 85% of days/year, and noncompliance reported on 3% of days.

Severe Exacerbations

Bud/form maintenance + relief significantly prolonged the time to first severe exacerbation when compared with bud/form + SABA and bud + SABA (both $p < 0.001$) (Figure 1A). The risk of experiencing a severe asthma exacerbation was 45% lower when bud/form was used for maintenance and relief versus bud/form + SABA (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.44, 0.67) and 47% lower than a fourfold higher maintenance dose of bud + SABA (HR, 0.53; 95% CI, 0.43, 0.65). Some of the asthma exacerbations in all groups were a result of a fall in PEF (Figure 1B). These were mainly discovered on retrospective analysis of diary card data and did not result in medical intervention in 87% of cases. When these PEF falls were removed and only severe exacerbations requiring medical intervention were assessed, there was still a 50% reduction in the risk of experiencing a severe asthma exacerbation requiring medical intervention with bud/form maintenance + relief compared with bud/form + SABA (HR, 0.50; 95% CI, 0.40, 0.64) and a 45% reduction compared with bud + SABA (HR, 0.55; 95% CI, 0.43, 0.70). Bud/form maintenance + relief was also shown to prolong significantly the time to all exacerbations, including repeats ($p < 0.001$ compared with both alternative regimens) (Figure 2). This highly significant reduction in severe exacerbations was consistent in children, adolescents, and adults.

The relative rate of all types of severe exacerbations/patient was lowered by 47% in patients using bud/form for maintenance and relief compared with patients using either bud/form for maintenance only (HR, 0.53; 95% CI, 0.44, 0.65) or higher dose budesonide for maintenance (HR, 0.53; 95% CI, 0.44, 0.64). The rate of severe exacerbations requiring medical intervention was also reduced by 53% for bud/form for maintenance + relief compared with bud/form for maintenance only (HR, 0.47; 95% CI, 0.39, 0.57) and by 46% compared with higher-dose maintenance therapy with budesonide (HR, 0.54; 95% CI, 0.44, 0.66). The effect of using bud/form for maintenance and relief on exacerbation risk remained constant over time (Figure 2). In addition, bud/form maintenance + relief reduced the overall burden of severe exacerbations requiring medical intervention, decreasing first and repeated events by 134 and 170 events compared with bud + SABA and bud/form +SABA, respectively (Figure E2).

Mild Exacerbations

Patients in the bud/form maintenance + relief group had a significantly longer time to first mild exacerbation compared with those in the bud/form + SABA and bud + SABA groups (both $p < 0.001$). In addition, the rate (exacerbation days/subject) was 30% lower for bud/form maintenance + relief compared with bud/form + SABA (HR, 0.70; 95% CI, 0.62, 0.80) and 36% lower compared with bud + SABA (HR, 0.64; 95% CI, 0.57, 0.73).

TABLE 1. PATIENTS' BASELINE CHARACTERISTICS

Characteristic	Bud + SABA (*n = 926*)	Bud/form + SABA (*n = 909*)	Bud/form Maintenance + Relief (*n = 925*)
Male/female, n	416/510	394/515	421/504
Age, yr	36 (4–79)	36 (4–79)	35 (4–77)
4–11 years, n (%)	106 (11)	117 (13)	118 (13)
Asthma duration, yr	9 (0–69)	9 (0–65)	9 (0–63)
FEV_1, L	2.14 (0.64–4.02)	2.10 (0.62–4.50)	2.13 (0.65–4.28)
FEV_1, % predicted normal	73 (49–100)	73 (46–108)	73 (43–108)
FEV_1 reversibility, %	21 (3–77)	21 (12–75)	21 (2–89)
ICS dose at entry,* μg/day	620 (100–1000)	598 (200–1,000)	619 (200–1,200)
Inhaled LABA use at study entry†	256 (28)	258 (29)	250 (27)
Reliever use, number of inhalations/day	1.69 (0.0–7.0)	1.69 (0.0–9.4)	1.74 (0.0–8.0)
Reliever use, number of inhalations/night	0.72 (0.0–3.7)	0.73 (0.0–6.6)	0.72 (0.0–5.7)
Asthma symptom score (scale 0–6)	1.5 (0.0–5.6)	1.4 (0.0–5.2)	1.5 (0.0–6.0)
Symptom-free days, %	23.5 (0–100)	24.0 (0–100)	23.1 (0–100)
Reliever-free days, %	8.8 (0–100)	8.3 (0–100)	8.2 (0–100)
Asthma control days, %	5.6 (0–90)	5.9 (0–80)	5.4 (0–90)
Awakenings, % of nights	20.6 (0–100)	20.2 (0–100)	21.8 (0–100)

Definition of abbreviations: Bud = budesonide; form = formoterol; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist.

All values are presented as absolute numbers or as mean (range), except asthma duration (median).

*Values are a combination of metered and delivered doses.

† Includes combinations of ICS/LABA and LABA.

Study Drug Use

The mean number of daytime or nighttime inhalations of reliever medication was significantly lower for patients using bud/form maintenance + relief than for either comparator using SABA for relief (all $p < 0.001$; Table 2 and Figure 3A). On the majority of days ($\geq 54\%$) patients remained reliever free in both the bud/form maintenance + relief group and in the bud/form + SABA group (Table 2). The mean daily budesonide dose used by adults and children is shown in Figure 4.

There were 495 episodes with an increase in as-needed medication to more than four inhalations per day over the baseline value in the bud/form maintenance + relief group, of which 37 were associated with an exacerbation; 1,347 episodes in the bud/form + SABA group, with 120 associated with an exacerbation; and 1,196 episodes in the bud + SABA group, with 96 associated with an exacerbation.

There were 26, 142, and 161 episodes of increased as-needed use of more than eight inhalations per day above baseline in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively; of these, only 2 preceded an exacerbation in the bud/form maintenance + relief group compared with 17 and 23 in the bud/form + SABA and bud + SABA groups, respectively. The distribution of average daily as-needed medication use is shown in Figure E3. Patients using bud/form for maintenance and relief also had fewer courses of oral steroids, 0.19 courses per year for patients aged 12 to 80 years and 0.05 courses/year for children 4 to 11 years compared with patients receiving bud/form + SABA (0.42 and 0.30 courses per year for patients aged 12–80 and 4–11 years, respectively) and bud + SABA (0.38 and 0.25 courses per year for patients aged 12–80 and 4–11 years, respectively) (descriptive statistics only).

Symptoms

All treatments improved both asthma symptoms, as seen by a reduced requirement for reliever treatment, and awakenings from run-in (Figure 3B). Nighttime symptoms and awakenings were significantly improved in patients using bud/form for maintenance + relief compared with those using bud/form + SABA or a fourfold higher maintenance dose of bud + SABA (all $p <$ 0.05; Table 2). Based on adjusted means, the improved symptom control with bud/form for maintenance + relief resulted in an extra 14 nights per year free from awakenings compared with both alternative regimens. Bud/form + SABA significantly improved daytime and nighttime symptoms ($p < 0.05$) and asthma control days ($p < 0.001$) compared with a fourfold higher maintenance dose of bud + SABA; however, awakenings were similar for both groups. In contrast, all symptoms were improved with bud/form for maintenance + relief compared with a fourfold higher maintenance dose of bud + SABA (Table 2).

Lung Function

Morning PEF was improved from baseline in all treatment groups (Figure 3C). Bud/form for maintenance + relief significantly improved morning and evening PEF and FEV_1 compared with bud/form + SABA and bud + SABA (all $p < 0.001$; Table 2). In addition, bud/form + SABA significantly improved both morning and evening PEF compared with bud + SABA.

Safety

All treatments were well tolerated, and adverse events were generally mild to moderate in intensity. There were no notable differences between the three groups for adverse events or adverse events related to treatment with β_2-agonists or ICS (Table 3). The total number of patients with one or more adverse event was 528 (57%) with bud + SABA, 475 (52%) with bud/form + SABA, and 496 (54%) with bud/form for maintenance + relief. The number of patients with one or more serious adverse event was similar in each of the treatment groups: 5% (48/925) for bud + SABA, 7% (62/906) for bud/form + SABA, and 5% (46/922) for bud/form maintenance + relief. There were 7, 15, and 14 discontinuations because of respiratory events in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively. Of these, aggravated asthma (worsening asthma) occurred in 2 patients in the bud/form maintenance + relief group compared with 13 and 8 patients in the bud/form + SABA and bud + SABA groups, respectively. There were one, two, and three cardiovascular events leading to discontinuation (general cardiovascular disorders, heart rate, and rhythm disorders, and myocardial, endocardial, and pericardial

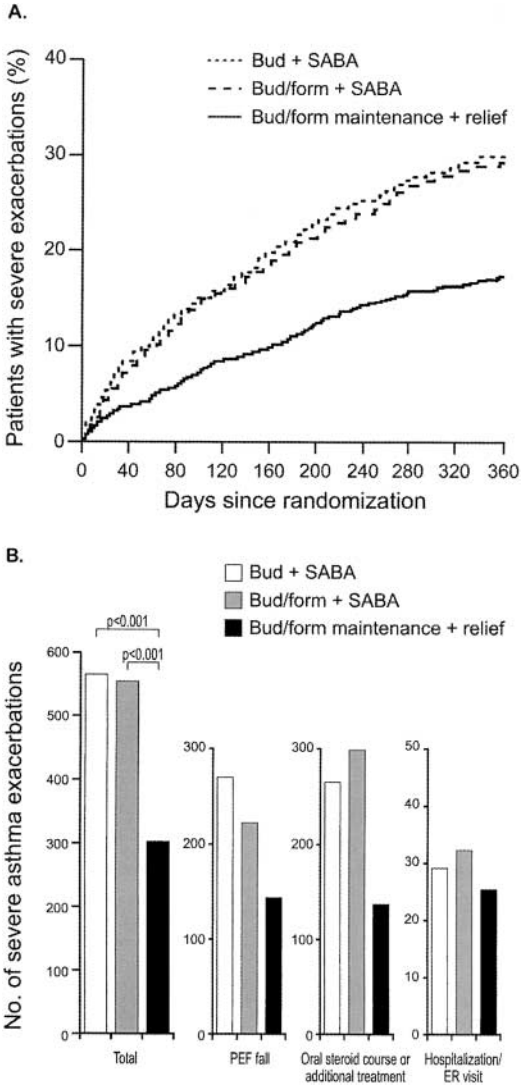

Figure 1. (*A*) Time to first severe exacerbation (deterioration in asthma resulting in morning peak expiratory flow [PEF] of 70% or less of baseline on 2 consecutive days; hospitalization/emergency room [ER] visit; treatment with oral steroids; or an increase in inhaled corticosteroids [ICS; via a separate inhaler] and/or other additional treatment as an additional criterion for patients aged 4–11 years). Bud/form maintenance + relief significantly prolonged the time to first severe exacerbation ($p < 0.001$ compared with both alternative regimens; Cox proportional hazards model). (*B*) Total number of severe asthma exacerbations and exacerbation subtypes (PEF fall, oral steroid course or additional treatment, hospitalization/ER visit). The p values are based on relative rate analysis (Poisson regression). Patients received 12 months of treatment with budesonide/formoterol (bud/form) 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + short-acting β_2-agonist [SABA]), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All maintenance treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years.

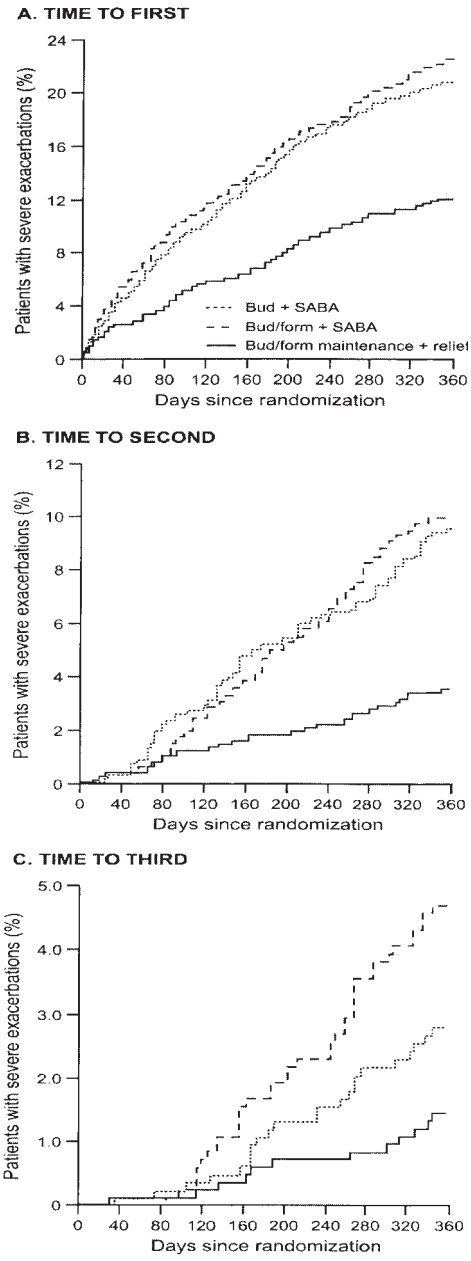

Figure 2. Kaplan-Meier plot of time to severe asthma exacerbation (defined as a deterioration in asthma resulting in hospitalization/ER visit; treatment with oral steroids and/or an increase in ICS [via a separate inhaler] and/or other additional treatment as an additional criterion for patients aged 4–11 years). (*A*) Time to first exacerbation. (*B*) Time to second. (*C*) Time to third. Patients received 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All maintenance treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years. Bud/form maintenance + relief significantly prolonged the time to all exacerbations, including repeats ($p < 0.001$ compared with both alternative regimens; Cox proportional hazards model).

disorders and valve disorders) in the bud/form maintenance + relief, bud/form + SABA, and bud + SABA groups, respectively. Other events led to 11, 23, and 13 discontinuations, respectively.

No clinically important differences in electrocardiogram, hematology, clinical chemistry, or urinalysis were observed between treatment groups or over time. In subgroups of patients aged 12–80 and 4–11 years in whom plasma cortisol was assessed, there were no significant findings (*see* Table E1).

Children (4–11 years) in both bud/form groups grew significantly more than those in the bud + SABA group. There was an

TABLE 2. CLINICAL OUTCOMES

Variable	Bud + SABA	Bud/form + SABA	Bud/form Maintenance + Relief	p Values: Bud/form + SABA vs. Bud + SABA	p Values: Bud/form Maintenance + Relief vs. Bud + SABA	p Values: Bud/form Maintenance + Relief vs. Bud/form + SABA
Severe exacerbations including PEF falls						
Patients with event, %*	28	27	16	0.74	< 0.001	< 0.001
Events/patient/year†	0.68	0.68	0.36	0.98	< 0.001	< 0.001
Severe exacerbations resulting in medical intervention						
Patients with event, %*	19	21	11	0.37	< 0.001	< 0.001
Events/patient/year†	0.35	0.40	0.19	0.11	< 0.001	< 0.001
Daily control measures						
Daytime symptom score‡	0.59	0.50	0.48	< 0.001	< 0.001	0.12
Night-time symptom score‡	0.42	0.36	0.31	0.01	< 0.001	< 0.001
Reliever use, inhs/day	1.03	0.84	0.73	< 0.001	< 0.001	< 0.001
Reliever use, inhs/night	0.43	0.37	0.28	0.003	< 0.001	< 0.001
Symptom-free days, %	46	53	54	< 0.001	< 0.001	0.52
Reliever-free days, %	45	54	55	< 0.001	< 0.001	0.60
Asthma control days, %§	37	44	45	< 0.001	< 0.001	0.64
Awakenings, % of nights	12	12	9	0.60	< 0.001	< 0.001
Mild exacerbation days, %¶	20	23	17	0.06	0.03	< 0.001
Morning PEF, L/min	339	346	355	< 0.001	< 0.001	< 0.001
Evening PEF, L/min	345	349	360	< 0.001	< 0.001	< 0.001
FEV_1, L	2.41	2.43	2.51	0.09	< 0.001	< 0.001

Definition of abbreviations: Bud = budesonide; form = formoterol; inhs = inhalations; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Daily control measures are mean values over 12 months of treatment.

* p Values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazard model).

† p Values based on relative rate analysis (Poisson regression).

‡ Symptoms were scored from 0 (no asthma symptoms) to 3 (unable to undertake normal activities [or to sleep] because of symptoms).

§ Asthma control days were defined as a day with no symptoms (day or night), no awakenings caused by asthma, and no as-needed medication use.

¶ Mild exacerbation days (periods with worsenings) were defined as any day with an awakening caused by asthma, or with as-needed medication use of two or more inhalations above the baseline mean value or with morning PEF of 80% or less of baseline mean value.

adjusted mean difference in growth of 1.0 cm between children treated with bud/form for maintenance + relief versus bud + SABA (95% CI, 0.3, 1.7; p = 0.0054) and a difference of 0.9 cm between bud/form + SABA versus bud + SABA (95% CI, 0.2, 1.6; p = 0.0099).

DISCUSSION

This study examined the hypothesis that bud/form used for regular maintenance therapy and symptom relief would further reduce exacerbations and improve overall asthma control compared with traditional ICS/LABA therapy. ICS plus LABA has demonstrated efficacy in adults with asthma (1, 2) and is recommended by guidelines as the optimal therapy for patients with moderate to severe asthma (4). The study demonstrated that bud/form for maintenance and relief significantly reduced total severe exacerbations, severe exacerbations requiring medication intervention, and exposure to oral steroids, as well as reducing reliever medication use, night-time symptoms including awakenings, and mild exacerbation days and improving lung function when compared with either bud/form or a fourfold higher dose of budesonide for maintenance therapy, both with SABA for relief.

The asthma management approach used in this study is an evolution of the ICS plus LABA approach demonstrated to be effective in the OPTIMA (1) and FACET (2) studies. These studies showed that exacerbations were less common in the majority of patients treated with the addition of LABA to ICS compared with those receiving a twofold or fourfold higher dose of ICS. The only notable benefit of the fourfold higher dose of budesonide in the FACET study was to prevent repeated severe exacerbations. This study is the first to show that a high-maintenance dose of budesonide is not necessary to reduce the incidence of first and repeated severe exacerbations requiring medical intervention. The risk of a severe exacerbation requiring medical intervention was reduced by 45% with bud/form for maintenance and relief compared with patients using a fourfold higher maintenance dose of budesonide with SABA for relief. Moreover, the time to second and third exacerbations was significantly prolonged with bud/form for maintenance and relief compared with the fourfold higher maintenance dose of budesonide with SABA. This suggests that bud/form for maintenance and relief is also effective in patients with more severe asthma who experience repeat exacerbations.

The magnitude of the benefits achieved in this study with bud/form for maintenance and relief (with a mean daily dose of budesonide of 240 μg/day in adults and 126 μg in children) when compared with a fourfold higher maintenance dose of budesonide (with a mean daily dose of 640 μg/day in adults and 320 μg/day in children) was surprising and suggests that it is the timing of the increase in ICS dose—resulting from as-needed use of bud/form in response to symptoms—rather than the total inhaled dose of ICS that improves efficacy. Studies that simply doubled the maintenance dose of ICS well into the course of an exacerbation have generally failed to show added benefits (11, 12). The evaluation by Tattersfield and colleagues (13) of all severe exacerbations that occurred in the FACET study suggests that there is a period of 5 to 7 days before a severe exacerbation is recognized and needs to be treated with oral corticosteroids, during which patients experience deteriorating symptoms and lung function. This represents an opportunity to intervene early with an increase in ICS. There is also evidence that as-needed use of formoterol has benefits for asthma control. Patients using as-needed formoterol in addition to regular maintenance therapy with an ICS or an ICS/LABA combination have fewer severe exacerbations than patients using terbutaline (14) or salbutamol

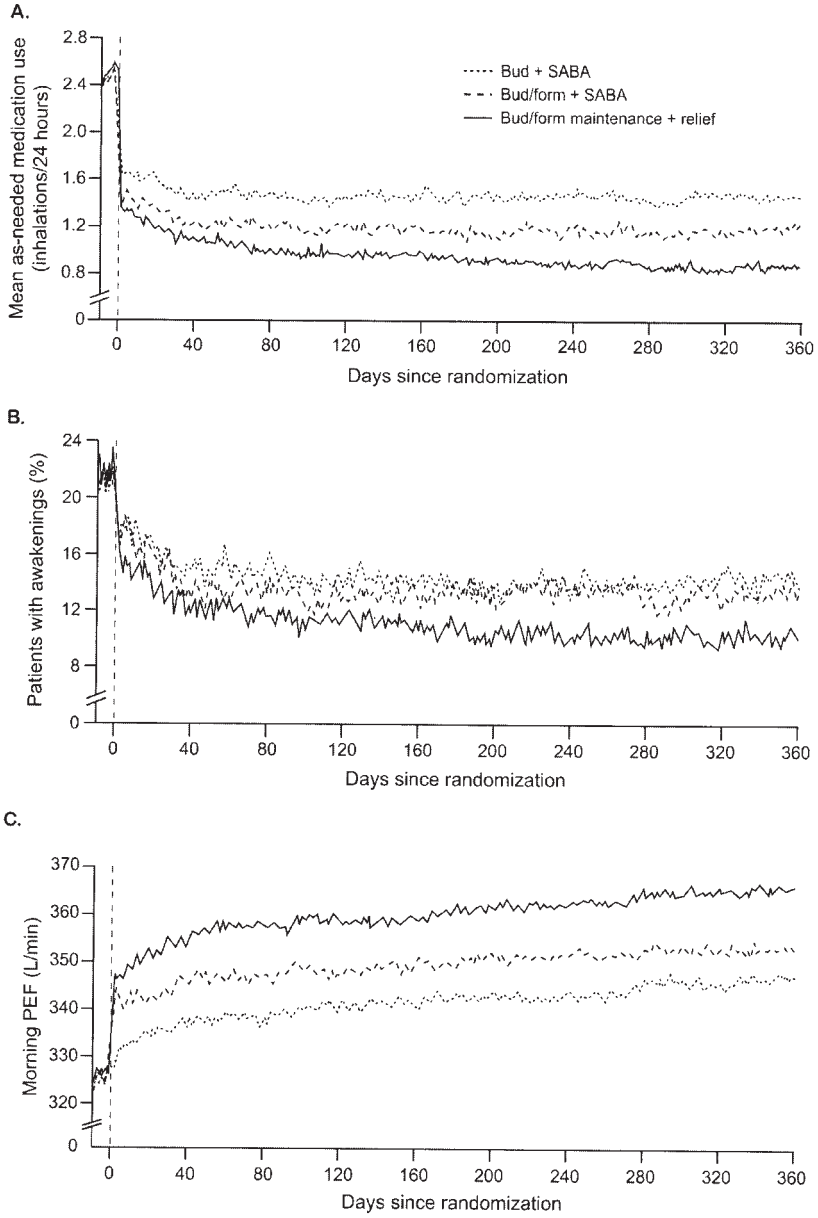

Figure 3. Diary card data showing change from run-in over the entire 12-month treatment period. (*A*) Mean reliever inhalations per 24 hours. (*B*) nights with awakenings because of asthma. (*C*) Morning PEF. Patients were randomized to 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years; $p < 0.001$ for bud/form maintenance + relief versus bud/form + SABA and bud + SABA for daily reliever use, nights with awakenings, and morning PEF (analysis of variance).

as needed (15). Furthermore, increasing both budesonide and formoterol provides greater protection from inflammatory challenges than increasing either agent alone (16).

Patients who do not adhere fully to ICS and instead overrely on SABAs as reliever medication are at increased risk of experiencing asthma exacerbations (17, 18). Bud/form for maintenance and relief reduces the potential for patients to overrely on their reliever medication (which, in the case of SABAs, do not treat underlying inflammation) and instead responds to symptoms with a combination of bud/form. This ensures that patients receive an immediate increase in antiinflammatory medication plus rapid and sustained symptom relief. Also, concerns that the use of the LABA alone may mask subclinical airway inflammation (19) are not an issue with bud/form for maintenance and relief, as ICSs are always delivered with reliever medication to control underlying inflammation. Importantly, there was no evidence of tolerance to medication in patients using bud/form for maintenance and relief, as improvements in exacerbation control, lung function, awakenings, and reliever-free days were maintained over the 12-month study period.

The fourfold higher maintenance dose of budesonide plus SABA may have been superior to the fixed-dose bud/form plus SABA treatment in controlling asthma exacerbations in the most severe patients, despite fixed-dose bud/form plus SABA providing superior improvements in lung function, reliever-free days, and asthma control days. Patients in the fourfold higher budesonide plus SABA group had fewer exacerbations requiring medical intervention, although this difference did not reach statistical significance. Although time to first exacerbation was similar in these two groups, time to a third exacerbation was prolonged to a greater extent by high-dose budesonide plus SABA treatment. This result is similar to the outcome of the FACET study (2), where patients with more severe asthma prone to frequent exacerbations benefited from a higher dose of ICS.

There was no evidence for overuse of reliever bud/form. On average, 55% of days were reliever use free in the bud/form maintenance plus relief group and the mean number of as-needed doses of bud/form was one additional dose per day. This amount of as-needed reliever use with fixed combination therapy

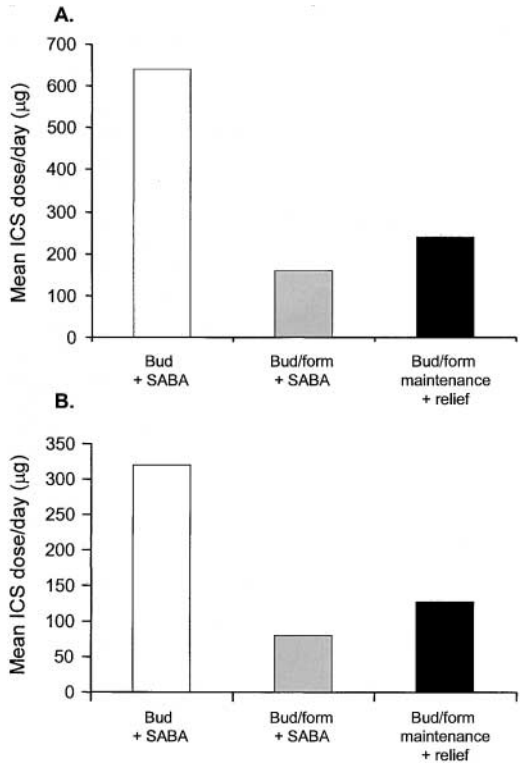

Figure 4. Mean daily ICS doses. (*A*) Patients aged 12–80 years. (*B*) patients aged 4–11 years. Patients were randomized to 12 months of treatment with bud/form 80/4.5 μg plus additional inhalations as needed (bud/form maintenance + relief), bud/form 80/4.5 μg plus terbutaline 0.4 mg (bud/form + SABA), or budesonide 320 μg plus terbutaline 0.4 mg (bud + SABA). All treatments were twice daily for patients aged 12–80 years and once daily for children aged 4–11 years.

(i.e., 50% of days with use or an average of one inhalation per day) has been a common finding in several studies of patients with moderate to severe asthma using salmeterol/fluticasone (20–22) and bud/form (22, 23). In addition, there were notably fewer episodes of high as-needed medication use, that is, at least eight inhalations above baseline, in the bud/form maintenance + relief group compared with the fixed dosing groups. Bud/form maintenance + relief was also associated with only 2 severe exacerbations in the high-user subgroup compared with 17–23 severe exacerbations in patients using terbutaline for reliever medication. The average daily dose of budesonide resulting from maintenance and relief use of bud/form was 80 μg higher than for patients who used bud/form for fixed maintenance only (bud/form + SABA group). Importantly, no additional drug-related adverse events were identified with the use of extra bud/form for relief in addition to maintenance.

Asthma treatment guidelines (4) advocate a stepwise approach to asthma management. bud/form for maintenance and relief mirrors this recommendation. Patients step up their controller medication by using bud/form for relief of breakthrough symptoms. Adjustments in medication occur from the first onset of symptoms, however, rather than after a medication review. Once control is regained, patients step down treatment by using bud/form for daily maintenance treatment only, without additional as-needed inhalations.

In conclusion, using bud/form for both maintenance and relief reduces the risk and rate of severe asthma exacerbations and the need for systemic steroids and improves asthma symptoms, nocturnal awakenings, and lung function compared with traditional fixed dosing regimens, therefore reducing the morbidity and potentially the mortality of asthma.

Conflict of Interest Statement: P.M.O. is a consultant and sits on advisory boards for AstraZeneca, Altan, GlaxoSmithKline (GSK), Topigen, Bristol-Myers Squibb (BMS) Roche, and Merck and has also been a paid lecturer for these companies and holds sponsored grants from Altana, AstraZeneca, Dynavax, GSK, Ono, and Merck and does not hold stock or options in any pharmaceutical company; H.B. has within the last 3 years received honoraria for lectures and attendance at pediatric Advisory Boards for Aerocrine, AstraZeneca, GSK, Hoffman La Roche, Merck, Novartis, and Yamanouchi and holds no stock options in pharmaceutical industry in the respiratory field and owns a world patent for an inhaler device but receives no royalty, and the COPSAC clinical research unit has in the last 3 years received research grants from the following industry partners in increasing order: Aerocrine, Merck, GSK, and AstraZeneca; P.P.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M. Pistolesi received a grant from AstraZeneca £51,000 to perform the STAY study; M. Palmqvist does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Y.Z. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.E. is an employee of AstraZeneca Sweden since 1997 with special reference to the clinical development of the fixed combination of bud/form and has stock options in the company and a pending patent on the as needed use of bud/form in asthma and also chairs yearly national advisory boards in respiratory medicine; E.D.B. has received honoraria for speaking at scientific meetings and courses organized and financed by AstraZeneca, Boehringer Ingelheim, and GSK and has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Hoffman le Roche, and GSK.

TABLE 3. COMMON ADVERSE EVENTS BY TYPE (≥ 5% INCIDENCE) AND ANY PHARMACOLOGICALLY PREDICTABLE ADVERSE EVENTS

	Number of Patients (%)		
	Bud + SABA (*n* = 925)	Bud/form + SABA (*n* = 906)	Bud/form Maintenance + Relief (*n* = 922)
Respiratory infection	182 (20)	144 (16)	158 (17)
Pharyngitis	86 (9)	88 (10)	88 (10)
Rhinitis	76 (8)	72 (8)	80 (9)
Bronchitis	76 (8)	61 (7)	51 (6)
Sinusitis	33 (4)	39 (4)	43 (5)
Headache	42 (5)	35 (4)	31 (3)
Pharmacologically predictable events			
Tremor	19 (2)	18 (2)	20 (2)
Palpitation	3 (< 0.5)	11 (1)	10 (1)
Tachycardia	3 (< 0.5)	4 (< 0.5)	5 (0.5)
Candidiasis	10 (1)	6 (1)	9 (1)
Dysphonia	12 (1)	13 (1)	11 (1)

Definition of abbreviations: Bud = budesonide; form = formoterol; SABA = short-acting β_2-agonist.

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