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ORIGINAL ARTICLE

Efficacy and safety of high-dose budesonide/formoterol (Symbicort®) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma

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Efficacy and safety of high-dose budesonide/formoterol (Symbicort®) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma

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Objective and background: Budesonide/formoterol 160/4.5 μg, two inhalations bd, is an effective and well-tolerated maintenance therapy for patients not controlled on inhaled corticosteroids alone. The authors assessed the efficacy and safety of a higher dose of budesonide/formoterol in patients with persistent symptomatic asthma.

Methods: This was a 24-week, double-blind, double-dummy randomized study. Budesonide/formoterol 320/9 μg, two inhalations bd (1280/36 μg/day), was compared with corresponding doses of budesonide during weeks 1–12 and budesonide plus formoterol via separate inhalers during weeks 1–24. Efficacy was assessed during weeks 1–12; the primary variable was morning PEF. Safety was assessed over weeks 1–24.

Results: Patients ($n = 456$; aged 12–79 years) had a mean reversibility in FEV_1 of 28% and mean pre-study inhaled corticosteroid dose of 1038 μg/day. Mean morning PEF increased by 37 L/min and 36 L/min with budesonide/formoterol and budesonide plus formoterol, respectively, versus an increase of 5 L/min with budesonide ($P < 0.001$ for both vs. budesonide). Budesonide/formoterol increased time to first mild exacerbation ($P < 0.005$) versus budesonide. Budesonide/formoterol and budesonide plus formoterol had similar efficacy. All treatments were well tolerated and the incidence of class-related adverse events was similarly low in all groups. Changes in serum potassium and plasma cortisol were comparable across treatments.

Conclusions: High-dose budesonide/formoterol (320/9 μg, two inhalations bd) is effective and well tolerated in patients with persistent symptomatic asthma. The findings also support the safety of regular high-dose formoterol (36 μg/day).

Key words: asthma, budesonide, formoterol, high dose, inhaled corticosteroid, Symbicort®.

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Conflict of interest statement: C.J. was principal investigator for this multicentre international study, which was designed and funded by AstraZeneca P/L. Statistical analysis was undertaken by AstraZeneca, but the author had access to the data and requested several additional analyses. The manuscript was prepared with the assistance of a medical writer, but drafts were reviewed and modified by C.J. who takes full responsibility for the content of the final paper. The Woolcock Institute of Medical Research receives funding for clinical research and consultancy advice from AstraZeneca.

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INTRODUCTION

It is well established that the addition of a long-acting β_2-agonist (LABA) to low doses of inhaled corticosteroids (ICS) provides more effective asthma control than higher doses of ICS alone.[1–3] The introduction of ICS/LABA combination products represents an advance in asthma management and their use is endorsed by international[4] and national[5] treatment guidelines. The formulation of budesonide and formoterol in one inhaler allows the simultaneous delivery of both an anti-inflammatory medication and an effective and fast-acting bronchodilator.[6,7]

Budesonide/formoterol 160/4.5 μg, two inhalations bd, has been shown to improve lung function and reduce symptoms to a greater extent than a corresponding dose of budesonide alone in patients with asthma not controlled on a mean ICS dose of 960 μg/day.[8] Furthermore, budesonide/formoterol is at least as effective as the monocomponents administered via separate inhalers in patients with moderate asthma not previously controlled by ICS alone.[8] Studies have shown that budesonide/formoterol is more effective and equally well tolerated as doubling the dose of ICS in adults with mild-to-moderate asthma[9] and is effective as a once-daily dosing regimen.[10]

A double-blind tolerability study has shown that temporary high doses of budesonide/formoterol (a maintenance dose of 160/4.5 μg, two inhalations bd, plus 10 additional inhalations on three separate study days (total daily dose: 2240/63 μg)) are well tolerated in patients with stable asthma.[11] Additionally, recent studies assessing adjustable maintenance dosing with budesonide/formoterol demonstrated that temporary high-dose budesonide/formoterol (total daily dose: 1280/36 μg for ≤2 weeks) is well tolerated and provides effective asthma control.[12–14] There remains a need, however, to establish the efficacy and safety of high doses of budesonide/formoterol when used regularly over longer periods in patients with more severe asthma.

This study is the first to examine the efficacy and safety of maintenance treatment with high-dose budesonide/formoterol (320/9 μg, two inhalations bd) in adult and adolescent patients with persistent symptomatic asthma.

METHODS

Patients

Outpatients aged ≥12 years, with a diagnosis of asthma (minimum duration 6 months), FEV_1 40–85% of predicted with ≥15% reversibility in increase from baseline FEV_1 after inhalation of a bronchodilator, were enrolled. Additionally, for patients aged ≥18 years, an increase in baseline FEV_1 of ≥200 mL 15–30 min post bronchodilator was required at study entry (visit 1). All patients had used ICS for ≥4 months at a constant daily dose of ≥750 μg for at least 4 weeks before study entry. Patients were excluded if their asthma deteriorated, resulting in a change of asthma therapy. Patients were only eligible for randomization if their total asthma symptom score was ≥1 on a scale of 0–6 for at least 4 of the last 7 days of run-in. The total asthma symptom score was the sum of daytime and night-time asthma symptom scores, each measured on a scale of 0–3 (where 0 = no symptoms and 3 = unable to perform usual activities (or to sleep) because of asthma).

The study (SD-039-0689) was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from regulatory agencies and ethics committees was obtained at each study centre. All patients and parents/guardians of patients aged <18 years gave written informed consent.

Study design

This was a 24-week, randomized, double-blind, double-dummy study conducted at 54 centres in six countries. After a 2-week run-in, during which patients continued to use their regular ICS therapy, patients were randomized to the 12-week treatment (two inhalations bd) with one of the following: budesonide/formoterol 320/9 μg (Symbicort® Turbuhaler®; AstraZeneca, Lund, Sweden); corresponding doses of budesonide 400 μg plus formoterol 9 μg via separate inhalers; or a corresponding dose of budesonide 400 μg (Fig. 1). The doses of budesonide in each treatment group were comparable; differences are explained by labelling changes for new inhaled drugs, which require the delivered dose rather than metered dose to be reported. At week 13, patients in the budesonide/formoterol and budesonide plus formoterol groups continued their treatment for the remaining 12 weeks of the study; patients receiving budesonide alone were switched to receive one of the other two treatments for the remaining 12 weeks of the study. The treatment switch for patients in the budesonide group was included in the original randomization. Terbutaline (0.5 mg) was used throughout the study for as-needed relief.

Individual treatment codes were computer-generated in balanced blocks of 8 at AstraZeneca R&D, Lund, Sweden; codes were then assigned to patients and kept in sealed envelopes until data analysis.

Efficacy assessments

Following instruction, patients measured their own morning and evening PEF using a Mini-Wright® peak flow meter (Clement Clarke, Harlow, UK). PEF readings were taken before inhalation of study medication and patients were asked not to take reliever medication for 6 h beforehand. The highest of three measurements was recorded on diary cards. The total number of inhalations of reliever medication (daytime and night-time inhalations) was recorded on diary cards. Daytime and night-time asthma symptom scores were recorded by patients. These scores were summed to obtain the total daily asthma symptom score (scale 0–6). Adherence to therapy was assessed by reviewing patient diary cards.

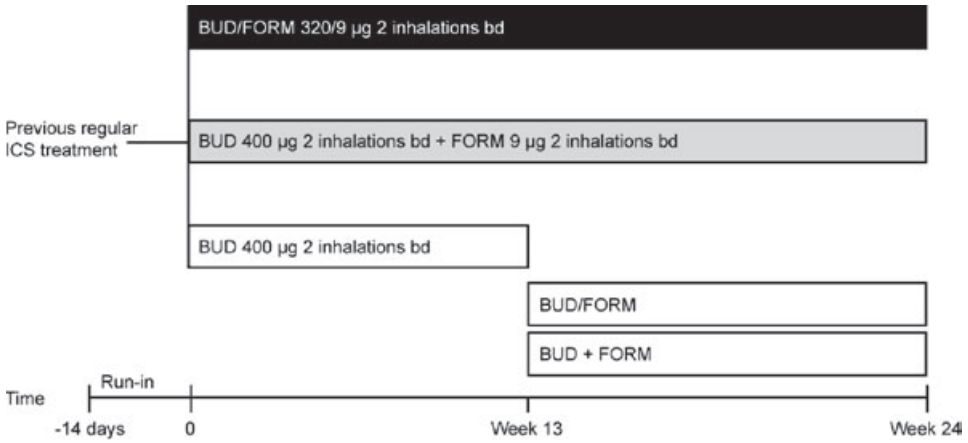

Figure 1 Study design. During weeks 1–12, patients received either budesonide/formoterol 320/9 µg two inhalations bd or corresponding doses of budesonide plus formoterol via separate inhalers or budesonide alone. At week 13, patients in the budesonide group were switched to either budesonide/formoterol (budesonide/budesonide/formoterol group) or budesonide plus formoterol (budesonide/budesonide + formoterol). BUD, budesonide; FORM, formoterol; ICS, inhaled corticosteroids.

Spirometry was performed at all clinic visits at approximately the same time of day, in accordance with the European Respiratory Society recommendations.[15] The highest value of three satisfactory FEV_1 readings was recorded as a percentage of the predicted normal value.[15,16]

Symptom-free days (a day and night with no asthma symptoms and no night-time awakenings due to asthma) and reliever-free days (a day and night with no use of reliever medication) were calculated from diary-card data. These end-points were combined to determine the percentage of asthma-control days (a day and night with no asthma symptoms, no intake of reliever medication and a night with no awakenings due to asthma symptoms).

A mild exacerbation day was defined as a day with one of the following: ≥20% decrease in morning PEF from baseline; night-time awakening(s) due to asthma; or an increase of ≥4 inhalations of reliever medication over a 24-h period compared with baseline. A mild exacerbation was defined as two consecutive mild exacerbation days of the same type.

Clinical safety assessments

The safety of all treatments was assessed over the 24-week study. Additional analysis to investigate the safety of regular high-dose formoterol (36 µg) during weeks 1–12 was performed by comparing budesonide/formoterol and budesonide plus formoterol with budesonide alone.

Adverse events, both spontaneously reported and in reported response to a standard question asked by the investigator, were recorded. A serious adverse event was one that resulted in death, was life-threatening, required new or prolongation of existing hospitalization, resulted in persistent or significant disability or resulted in a birth defect.

Vital signs and electrocardiogram (ECG) measurements were taken at study entry/baseline and at weeks 12 and 24. Serum (s)-potassium, s-glucose and morning plasma (p)-cortisol were obtained between 08:00 and 09:00 hours at baseline and at weeks 12 and 24.

An adrenocorticotropic hormone (ACTH) stimulation test was performed at baseline and at weeks 12 and 24 in a subgroup of patients. Blood samples were collected from subgroup patients immediately before (basal p-cortisol) and 30 and 60 min after i.v. administration of tetracosactrin (Synacthen®, Novartis, Switzerland) 0.25 mg. Concentrations of p-cortisol were analyzed using the method of Hsu and coworkers;[17] the lower limit of detection was 20 nmol/L.

Reference limits were predefined as follows: morning p-cortisol ≥150 nmol/L; ACTH-stimulated p-cortisol ≥400 nmol/L; s-potassium >3–<5.5 mmol/L; s-glucose >2.5–<9 mmol/L.

Statistical analysis

Efficacy analysis was performed on all randomized patients (intention to treat population) over 12 weeks. A total of 200, 100 and 100 patients were required in the budesonide/formoterol, budesonide plus formoterol and budesonide groups, respectively, to have a 90% chance of detecting an 18 L/min change from baseline in morning PEF (at the two-sided 5% level, with an assumed SD of 45 L/min). The primary efficacy variable (morning PEF) and all other patient diary variables were analyzed as change from baseline (average value over the last 10 days of run-in). The treatment mean was the average value calculated over weeks 1–12. For FEV_1, baseline was the value measured at randomization, and treatment was the mean of the available data from weeks 1–12. Analyses were performed using analysis of variance (ANOVA),

with treatment and country as fixed factors and the baseline value as a covariate. The primary comparison of efficacy variables was between budesonide/formoterol and budesonide alone. A secondary comparison was made between budesonide/formoterol and budesonide plus formoterol via separate inhalers. The time to first mild exacerbation was assessed using a log-rank test.

The safety of budesonide/formoterol versus budesonide plus formoterol was assessed over 24 weeks; the safety of formoterol was considered by comparing the safety of budesonide/formoterol and budesonide plus formoterol versus budesonide alone over weeks 1–12. Morning p-cortisol and ACTH-stimulated p-cortisol concentrations were log-transformed and an ANOVA similar to that used for diary-card variables was performed. The results were transformed back and expressed as adjusted ratios. All other safety variables, including adverse events and ECGs, were analysed using descriptive statistics and qualitative measures.

RESULTS

Patient flow

From a total of 489 patients enrolled in the study, 456 patients (177 men) aged 12–79 years (mean age 46 years) were randomized to treatment with budesonide/formoterol ($n = 226$); budesonide plus formoterol in separate inhalers ($n = 115$); or budesonide alone ($n = 115$, of whom 54 patients were switched to budesonide/formoterol and 61 patients were switched to budesonide plus formoterol at week 13). Patient flow is shown in Figure 2.

The treatment groups were comparable with regard to demographics and clinical baseline characteristics (Table 1). Self-reported adherence to study medication was high (mean > 98%) in the three treatment groups.

Efficacy

In the 12-week efficacy study, patients receiving budesonide/formoterol showed significantly greater increases from baseline in morning PEF compared with those receiving a corresponding dose of budesonide alone (37.4 vs. 4.5 L/min, respectively; $P < 0.001$) (Table 2). Budesonide/formoterol resulted in a similar increase in morning PEF compared with budesonide plus formoterol (Table 2). Improvements in evening PEF across the three groups were similar to those for morning PEF (Table 2). The large increases in morning PEF (Fig. 3) and evening PEF observed in patients treated with either budesonide/formoterol

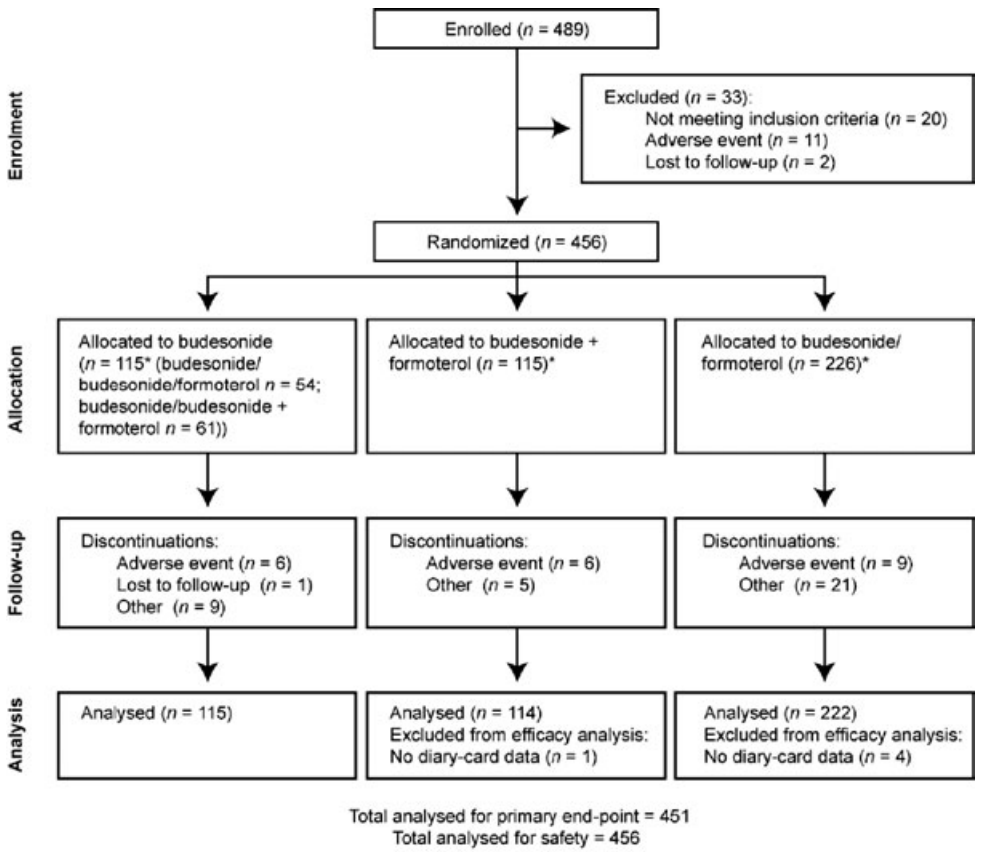

Figure 2 Flow diagram of patients' progress during the study. Patients were randomized to either budesonide/formoterol 320/9 μg two inhalations bd or corresponding doses of budesonide plus formoterol or budesonide alone. At week 13, patients in the budesonide group were switched to either budesonide/formoterol (budesonide/budesonide/formoterol group) or budesonide plus formoterol (budesonide/budesonide + formoterol). *All patients received allocate treatment.

Table 1 Baseline patient demographics and clinical characteristics

	BUD ($n = 115$)	BUD + FORM ($n = 115$)	BUD/FORM ($n = 226$)
Male/female (*n*)	49/66	46/69	82/144
Mean age (years (range))	46 (13–74)	47 (12–79)	46 (13–79)
Median duration of asthma (years (range))	8 (1–61)	10 (1–66)	8 (1–56)
Mean ICS dose at entry, (μg/day (range))	1052	1036	1033
Inhaled LABA use at study entry (*n* (%))	53 (46)	57 (50)	112 (50)
Reliever-free days[†] (%)	25	28	30
Asthma-control days[‡] (%)	7	9	10
Mean FEV_1 (L (range))	2.01 (0.80–3.73)	1.97 (0.63–3.88)	2.07 (0.74–3.92)
Mean FEV_1 (% predicted normal)	65	65	67
Mean reversibility (% (range))	28 (15–76)	29 (15–88)	27 (14–113)

[†]A night and day with no use of reliever medication.

[‡]A night and day with no symptoms (symptom score = 0), no use of reliever medication and no asthma-related night-time awakenings.

BUD, budesonide; FORM, formoterol; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist.

Table 2 Mean change from baseline in patient efficacy variables after the 12-week treatment with either BUD/FORM, BUD alone or BUD + FORM

				Between-group difference (95% CI)		
Efficacy variable	BUD	BUD + FORM	BUD/FORM	BUD/FORM versus BUD	BUD + FORM versus BUD	BUD/FORM versus BUD + FORM
Morning PEF (L/min)	4.5	36.2	37.4	32.9** (23.5, 42.3)	31.6** (20.9, 42.4)	1.3 (–8.2, 10.7)
Evening PEF (L/min)	–0.1	31.3	30.7	30.9** (22.1, 39.7)	31.5** (21.3, 41.6)	–0.6 (–9.5, 8.2)
Total asthma symptom score (0–6)[†]	–0.36	–0.66	–0.62	–0.26* (–0.44, –0.08)	–0.30* (–0.51, –0.09)	0.04 (–0.14, 0.22)
Symptom-free days[‡] (%)	15.6	32.2	31.2	15.6** (8.4, 22.8)	16.6** (8.4, 24.9)	–1.0 (–8.2, 6.2)
Reliever-free days[§] (%)	17.2	38.6	36.1	18.9** (11.8, 26.0)	21.4** (13.2, 29.6)	–2.5 (–9.6, 4.7)
Asthma-control days[¶] (%)	16.3	32.2	32.4	16.1** (8.8, 23.4)	15.8** (7.4, 24.2)	0.3 (–7.0, 7.6)

*$P < 0.01$; **$P < 0.001$.

[†]Sum of the mean daytime and night-time scores.

[‡]A night and day with no symptoms (symptom score = 0) and no asthma-related night-time awakenings.

[§]A night and day with no use of reliever medication.

[¶]A night and day with no symptoms (symptom score = 0), no use of reliever medication and no asthma-related night-time awakenings.

BUD, budesonide; CI, confidence interval; FORM, formoterol.

or budesonide plus formoterol were apparent from the start of treatment and were maintained throughout the 12-week period.

FEV_1 increased over time in all three treatment groups; the improvements were significantly greater for those receiving budesonide/formoterol versus budesonide alone (0.30 L vs. 0.14 L, respectively; $P < 0.001$).

Budesonide/formoterol significantly reduced total asthma symptom scores to a greater extent than budesonide alone ($P = 0.0051$) (Table 2). Patients receiving budesonide/formoterol had 16% more symptom-free days compared with patients receiving budesonide ($P < 0.001$) (Table 2). Patients receiving budesonide/formoterol had similar improvements in asthma symptom scores and symptom-free days as those receiving budesonide plus formoterol in separate inhalers (Table 2).

Reliever medication use was significantly lower in patients receiving budesonide/formoterol compared with those receiving budesonide alone (0.97 vs. 1.61 inhalations/day, respectively; $P < 0.001$). Patients in the budesonide/formoterol group had 19% more reliever-free days than those in the budesonide group ($P < 0.001$) (Table 2). These data suggest that patients treated with budesonide/formoterol would achieve an additional 69 reliever-free days per year compared with those receiving budesonide alone. Reliever medication use was similar in the budesonide/formoterol and budesonide plus formoterol groups (Table 2).

Budesonide/formoterol resulted in 16% more asthma-control days compared with budesonide

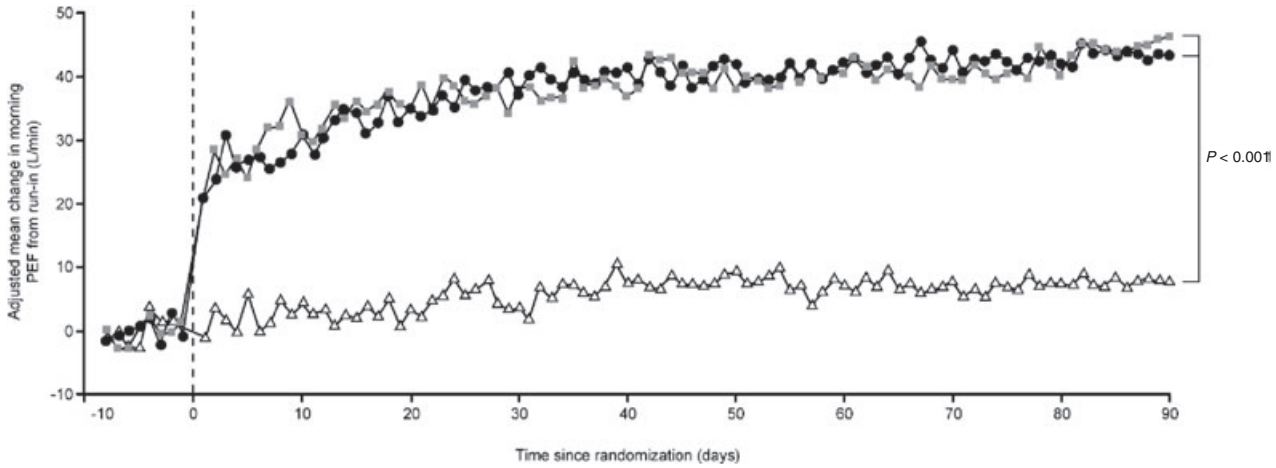

Figure 3 Change in morning PEF over the first 12 weeks of the study. Patients were randomized to either budesonide/formoterol 320/9 μg two inhalations bd, or corresponding doses of budesonide plus formoterol or budesonide alone. Terbutaline was used as needed in all treatment groups. During the 2-week run-in period, patients continued to use their regular inhaled corticosteroid medication at the same dose and frequency as prior to study enrolment and received terbutaline as needed. Budesonide/formoterol $n = 222$; budesonide + formoterol $n = 114$; budesonide $n = 115$. (–●–) Budesonide/formoterol; (–■–) budesonide + formoterol; (–△–) budesonide.

($P < 0.001$) (Table 2), corresponding to an additional 58 days per year of asthma control. The budesonide/formoterol group experienced a similar number of asthma control days as the budesonide plus formoterol group (Table 2).

Figure 4 shows Kaplan–Meier plots describing the distribution of time to first mild exacerbation for the three treatment groups. The time to first mild exacerbation was significantly longer in patients receiving budesonide/formoterol compared with those in the budesonide group. The instantaneous risk of a mild exacerbation was estimated to be 36% lower for patients receiving budesonide/formoterol than for patients in the budesonide group ($P = 0.0032$). Budesonide/formoterol also reduced the risk of a mild exacerbation compared with budesonide plus formoterol (instantaneous risk reduction 17%; $P = 0.13$).

Clinical safety assessments

All treatments were well tolerated and adverse events were mostly mild or moderate in intensity. The frequency and profile of adverse events were similar across treatment groups, both during weeks 1–12 and weeks 13–24 (Table 3). Serious adverse events were rare and none was considered causally related to the study medication (Table 3). One death occurred in the budesonide/formoterol group as a result of pulmonary embolism; this was not judged to be causally related to treatment.

Importantly, the incidence of adverse events related to LABA class effects in the budesonide/formoterol and budesonide plus formoterol groups was comparable with that in the budesonide group during weeks 1–12 (Table 3).

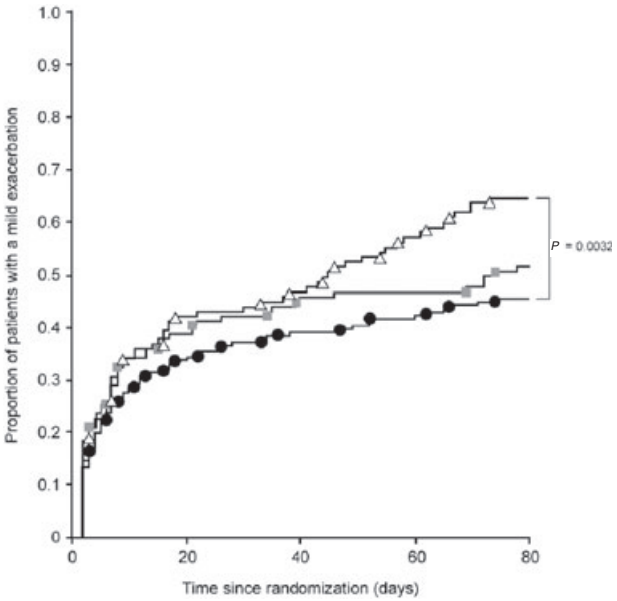

Figure 4 Kaplan–Meier curves of time to first mild exacerbation (defined as a ≥20% decrease in morning PEF from baseline; night-time awakening(s) due to asthma; or an increase of ≥4 inhalations of reliever medication over a 24-h period compared with baseline on two consecutive days) during the 12-week treatment with either budesonide/formoterol 320/9 μg two inhalations bd, or corresponding doses of budesonide plus formoterol or budesonide alone. Budesonide/formoterol $n = 222$; budesonide + formoterol $n = 114$; budesonide $n = 115$. (–●–) Budesonide/formoterol; (–■–) budesonide + formoterol; (–△–) budesonide.

Table 3 Most common adverse events by type (>5% incidence in BUD/FORM group at week 24) and pharmacologically predictable events related to ICS or LABA class effects

	Weeks 1–12, *n* (%)			Weeks 1–24, *n* (%)			
	BUD (*n* = 115)	BUD + FORM (*n* = 115)	BUD/FORM (*n* = 226)	BUD/BUD + FORM[†] (*n* = 61)	BUD/BUD/FORM[†] (*n* = 54)	BUD + FORM (*n* = 115)	BUD/FORM (*n* = 226)
Patients with adverse events	27 (23)	31 (27)	68 (30)	32 (52)	27 (50)	63 (55)	116 (51)
Patients with serious adverse events	2 (2)	0	5 (2)	1 (2)	4 (7)	3 (3)	8 (4)
Respiratory infection	6 (5)	11 (10)	16 (7)	10 (16)	9 (17)	17 (15)	30 (13)
Bronchitis	1 (1)	2 (2)	5 (2)	2 (3)	2 (4)	5 (4)	12 (5)
Rhinitis	1 (1)	2 (2)	6 (3)	3 (5)	2 (4)	4 (3)	12 (5)
Pharyngitis	3 (3)	0	7 (3)	3 (5)	2 (4)	3 (3)	12 (5)
Pharmacologically predictable events							
Headache[‡]	5 (4)	1 (1)	2 (1)	1 (2)	4 (7)	5 (4)	6 (3)
Tremor[‡]	3 (3)	1 (1)	1 (<0.5)	1 (2)	3 (6)	9 (8)	10 (4)
Dysphonia[§]	0	1 (1)	6 (3)	0	2 (4)	3 (3)	7 (3)

[†]Patients treated with budesonide from randomization to week 12 received either budesonide/formoterol or budesonide plus formoterol from weeks 13 to 24.

[‡]Adverse event related to treatment with LABA.

[§]Adverse event related to treatment with ICS.

BUD, budesonide; FORM, formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.

No clinically significant differences were observed between treatments for ECG, vital signs or laboratory variables during either weeks 1–12 or weeks 13–24. A high proportion of patients (≥98%) receiving budesonide alone had s-potassium and s-glucose concentrations within the predefined reference limits at baseline and after 12 weeks of treatment. A similar proportion of patients (≥97%) receiving high-dose formoterol (budesonide/formoterol and budesonide plus formoterol groups) also had s-potassium and s-glucose concentrations within the predefined reference limits at baseline and after 12 weeks of treatment. Overall, ≥98% and ≥94% of patients in all treatment groups had s-potassium and s-glucose concentrations within the predefined reference limits, respectively, at week 24.

Mean levels of morning p-cortisol declined over the duration of the study to a similar extent in all treatment groups; changes from baseline to weeks 12 and 24 were not statistically significant for any of the treatment groups (Fig. 5). Table 4 shows the change (expressed as adjusted ratio) in morning p-cortisol concentrations from baseline to after 12 and 24 weeks of treatment. Morning p-cortisol shifted from concentrations within the defined reference limit at baseline to concentrations below the limit at week 24 in 19–24% of patients in all treatment groups. However, no significant between-group differences occurred and no new safety concerns were identified.

The ACTH stimulation test was performed in a subgroup of patients from the budesonide/formoterol (*n* = 75), budesonide plus formoterol (*n* = 38) and budesonide (*n* = 38 (*n* = 20 in the budesonide/budesonide plus formoterol group; *n* = 18 in the budes-

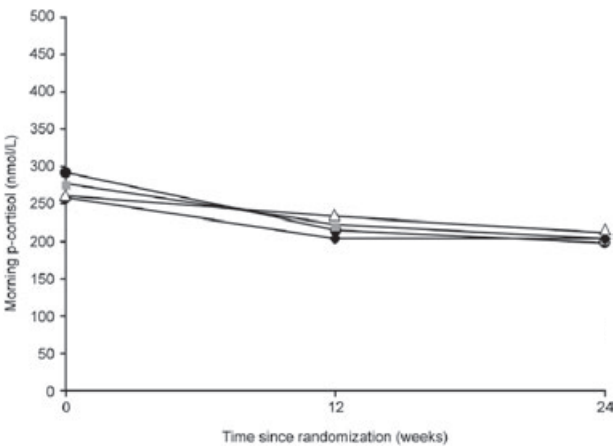

Figure 5 Mean morning plasma (p)-cortisol concentration during the entire 24-week study. Patients were randomized to either budesonide/formoterol 320/9 μg two inhalations bd, or corresponding doses of budesonide plus formoterol or budesonide alone. At week 13, patients in the budesonide group were switched to either budesonide/formoterol (budesonide/budesonide/formoterol group) or budesonide plus formoterol (budesonide/budesonide + formoterol). Budesonide/formoterol *n* = 193; budesonide + formoterol *n* = 106; budesonide/budesonide + formoterol *n* = 50; budesonide/budesonide/formoterol *n* = 52. (–●–) Budesonide/formoterol; (–■–) budesonide + formoterol; (–△–) budesonide/budesonide + formoterol; (–◆–) budesonide/budesonide/formoterol.

onide/budesonide/formoterol group)) groups. Over the treatment period, small reductions in ACTH-stimulated p-cortisol levels occurred from baseline; these were comparable across treatments after both 12 and 24 weeks of treatment (Fig. 6). However, a high proportion of patients (≥85%) had p-cortisol levels within the predefined limit (≥400 nmol/L) following ACTH stimulation at baseline and after 12 and 24 weeks of treatment (Table 5).

Table 4 Change in morning p-cortisol levels (nmol/L) from baseline (visit 2) to after 12 and 24 weeks of treatment[†]

	Week 12 Adjusted change from baseline[‡] (nmol/L)	Week 24 Adjusted change from baseline[‡] (nmol/L)
BUD[§]	0.75	NA
BUD/BUD + FORM[§]	NA	0.81
BUD/BUD/FORM[§]	NA	0.77
BUD + FORM	0.76	0.71
BUD/FORM	0.74	0.71

[†]No statistically significant differences were observed between treatment groups.

[‡]Expressed as adjusted ratio.

[§]Patients treated with budesonide from randomization to week 12 received either budesonide/formoterol or budesonide plus formoterol from weeks 13 to 24.

BUD, budesonide; FORM, formoterol; NA, not applicable.

DISCUSSION

This study is the first to demonstrate that a high regular maintenance dose of budesonide/formoterol 320/9 μg two inhalations bd provides effective asthma control and is well tolerated in patients with asthma not controlled by high-dose ICS. Budesonide/formoterol was more effective than a corresponding dose of budesonide and had comparable efficacy to budesonide and formoterol via separate inhalers. In addition, the findings from the safety analysis showed that the safety profiles of budesonide/formoterol and budesonide plus formoterol were similar to that of budesonide alone, indicating that long-term treatment with high-dose formoterol is well tolerated. These findings demonstrate that budesonide/formoterol 320/9 μg two inhalations bd is a safe and effective treatment regimen for patients with severe asthma.

Budesonide/formoterol improved lung function, reduced the incidence of mild exacerbations and reduced the need for reliever medication to a significantly greater extent than a corresponding dose of budesonide alone in patients with persistent symptomatic asthma. These findings are in agreement with studies both in patients with mild asthma[18] and in patients with moderate asthma not controlled on a mean ICS dose of 960 μg/day,[8] providing further evidence that the addition of formoterol to budesonide is more effective than a comparable dose of budesonide alone.

Importantly, budesonide/formoterol increased the percentage of reliever-free days and asthma-control

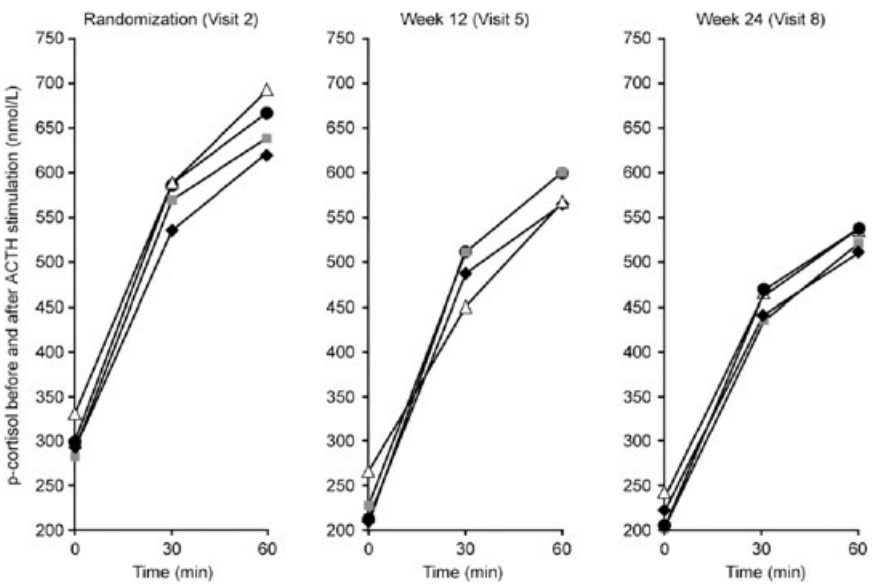

Figure 6 Mean plasma (p)-cortisol concentration before and after adrenocorticotropic hormone (ACTH) stimulation. Patients were randomized to either budesonide/formoterol 320/9 μg two inhalations bd, or corresponding doses of budesonide plus formoterol or budesonide alone. At week 13, patients in the budesonide group were switched to either budesonide/formoterol (budesonide/budesonide/formoterol group) or budesonide plus formoterol (budesonide/budesonide + formoterol). Budesonide/formoterol $n = 75$; budesonide + formoterol $n = 38$; budesonide/budesonide + formoterol $n = 20$; budesonide/budesonide/formoterol $n = 18$. (–●–) Budesonide/formoterol; (–■–) budesonide + formoterol; (–△–) budesonide/budesonide + formoterol; (–◆–) budesonide/budesonide/formoterol.

Table 5 Proportion of patients (*n* (%)) with shifts in ACTH-stimulated p-cortisol levels from baseline concentrations (visit 2) following 12 and 24 weeks of treatment

	Low† at baseline Week 12		Within reference limit‡ at baseline Week 12		Low† at baseline Week 24		Within reference limit‡ at baseline Week 24	
	Low†	Within reference limit‡	Low†	Within reference limit‡	Low†	Within reference limit‡	Low†	Within reference limit‡
BUD§ (*n* = 37)¶	1 (3)	0	2 (5)	34 (92)	NA	NA	NA	NA
BUD/BUD + FORM†† (*n* = 20)	NA	NA	NA	NA	0	0	3 (15)	17 (85)
BUD/BUD/FORM†† (*n* = 18)	NA	NA	NA	NA	0	1 (6)	1 (6)	16 (89)
BUD + FORM (*n* = 38)	0	1 (3)	3 (8)	34 (89)	1 (3)	0	3 (8)	34 (89)
BUD/FORM (*n* = 75)	0	0	5 (7)	70 (93)	0	0	5 (7)	70 (93)

†ACTH concentration <400 nmol/L.

‡ACTH concentration ≥400 nmol/L.

§Patients in the budesonide group from randomization to week 12 received either budesonide/formoterol (BUD/BUD/FORM) or budesonide plus formoterol (BUD/BUD + FORM) from weeks 12 to 24.

¶No data were available for one patient at week 12.

††Both BUD/BUD/FORM and BUD/BUD + FORM groups were receiving budesonide alone at baseline and week 12.

ACTH, adrenocorticotropic hormone; BUD, budesonide; FORM, formoterol; NA, not applicable; p-cortisol, plasma cortisol.

days by ~19% and 16%, respectively, compared with budesonide alone. This corresponds to approximately 70 additional reliever-free days and two additional months of asthma control per year with budesonide/formoterol compared with budesonide. Similarly, a previous study showed that budesonide/formoterol 160/4.5 μg two inhalations bd increased the percentage of asthma-control days by ~15% compared with a corresponding dose of budesonide alone.[8] Success in gaining control of asthma symptoms is highly desirable, especially in patients with more severe asthma who have a greater need for oral steroids and hospitalizations as a result of asthma exacerbations.

During the present study, the efficacy of budesonide/formoterol 320/9 μg two inhalations bd and budesonide plus formoterol via separate inhalers was comparable and no significant between-group differences were reported. This finding supports those of Zetterström and coworkers, who showed that budesonide/formoterol 160/4.5 μg two inhalations bd is at least as effective as the monocomponents administered via separate inhalers.[8]

Formoterol is a unique LABA, having an onset of effect as fast as the short-acting β_2-agonist salbutamol—1–3 min after inhalation.[19] In addition, although formoterol produces sustained bronchodilation in the airways for at least 12 h[20] (and possibly up to 24 h[21]), the duration of its systemic effects is approximately equal to that of short-acting bronchodilators.[22,23] Therefore, formoterol is able to provide prolonged bronchodilation with minimal systemic side-effects.

There has been some concern, however, that the regular use of LABAs may be associated with an increased risk of worsening asthma.[24,25] A study by Mann and coworkers suggested that regular high-dose formoterol (24 μg bd) may be associated with an increased risk of exacerbations compared with placebo, although this analysis failed to report the use of concomitant anti-inflammatory medication.[26] However, a large amount of clinical evidence supports the safety of LABAs, especially when combined with an ICS.[3,27,28] In particular, the addition of high-dose formoterol (24 μg bd) to ICS has been shown to be well tolerated, improving symptoms and lung function compared with placebo in patients with persistent asthma.[29]

A key aim of the present study was to investigate the tolerability of regular high-dose formoterol further by comparing the safety profile of budesonide/formoterol and budesonide plus formoterol with that of budesonide alone during weeks 1–12 of this study. High doses of β_2-agonists are associated with systemic adverse events, including muscle tremor and headache, in a small proportion of patients.[30] The incidence of β_2-agonist class effects was low in both groups receiving formoterol in the current study, however, and was comparable with that observed in the budesonide-alone group. The overall adverse-event profile was also similar across treatment groups. It has also been suggested that β_2-agonists cause reductions in s-potassium owing to the activation of β_2-receptors in skeletal muscle.[31] In the current study, ≥98% of patients receiving high-dose formoterol in the budesonide/formoterol or budesonide plus formoterol regimens had concentrations of s-potassium within the reference limits at week 24. These findings support the safety of regular high-dose formoterol administered as maintenance therapy with ICS.

It has been shown previously that occasional high doses of budesonide/formoterol up to 2240/63 μg are well tolerated, with no clinically relevant changes in s-potassium, blood glucose, pulse rate or other vital signs compared with similar doses of formoterol.[11] In addition, the efficacy and safety of short-term (1–

2 weeks) high doses of budesonide/formoterol 160/4.5 μg four inhalations bd (total daily dose: 1280/36 μg (as used in the current study)) have been demonstrated in studies using budesonide/formoterol with an adjustable maintenance dosing regimen.[12–14]

A large study evaluating a new treatment concept, whereby patients use budesonide/formoterol for maintenance therapy and take additional inhalations as needed for symptom relief, has recently been published.[32] In this study, a small proportion of patients were reported to use a high number of as-needed inhalations (>8 inhalations/day).[32] However, there were fewer such episodes in patients receiving budesonide/formoterol for both maintenance and reliever therapy, compared with those receiving fixed-dose budesonide/formoterol plus as-needed terbutaline or high-dose budesonide plus terbutaline as needed. Budesonide/formoterol for both maintenance and reliever therapy was well tolerated in that study.[32] In the present study, no clinically significant differences were observed in any laboratory safety variables for regular high-dose budesonide/formoterol 320/9 μg two inhalations bd and the other treatment groups, demonstrating that all treatments were similarly well tolerated over 24 weeks.

This is the first study to assess the efficacy and safety of a regular high dose of budesonide/formoterol in patients with moderate-to-severe asthma. The present results show that budesonide/formoterol provides superior asthma control compared with a corresponding dose of budesonide alone and has comparable efficacy and tolerability to budesonide and formoterol administered via separate inhalers. Furthermore, the findings of the present study support the safety of regular high-dose formoterol in combination with ICS. The present findings suggest that budesonide/formoterol 320/9 μg two inhalations bd is a well-tolerated treatment for adult and adolescent patients with asthma not controlled by high-dose ICS.

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