



Budesonide/formoterol maintenance and reliever therapy versus conventional best practice

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Summary

Budesonide/formoterol maintenance and reliever therapy (Symbicort SMART[®]) reduces asthma exacerbations and symptoms versus fixed-dose regimens plus short-acting β_2 -agonists (SABA) in double-blind trials. Information is lacking regarding its effectiveness versus conventional best practice (CBP).

This pooled analysis of six 6-month, randomized, open-label studies examined asthma control and exacerbation risk in asthmatics (aged ≥ 12 years). Patients ($N = 7855$) symptomatic on inhaled corticosteroids (ICS) or stable/symptomatic on ICS/long-acting β_2 -agonists (LABA) received budesonide/formoterol maintenance and reliever therapy (160/4.5 μg bid and as needed) or CBP (ICS or ICS/LABA \pm other agents at an approved dose plus as-needed SABA). Overall asthma control was assessed comparing the incidence of exacerbations and levels of asthma control using the asthma control questionnaire (ACQ).

Budesonide/formoterol maintenance and reliever therapy did not significantly reduce time to first severe exacerbation (primary variable) versus CBP ($P = 0.062$). However, patients in this group experienced 15% fewer exacerbations (0.20 versus 0.24/patient/year; $P = 0.021$) and used 27% less ICS ($P < 0.0001$). Odds of remaining well controlled (ACQ ≤ 0.75) over 6 months were higher with budesonide/formoterol maintenance and reliever therapy versus CBP (45% versus

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41%, odds ratio [OR] 1.29; $P < 0.01$) while risk of remaining uncontrolled decreased (25% versus 29%, OR 0.81; $P < 0.01$).

Budesonide/formoterol maintenance and reliever therapy improves key aspects of asthma control versus physicians' choice of CBP.

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Introduction

International and national guidelines for asthma management recommend assessment and review of asthma patients and a stepwise increase in therapy to achieve overall asthma control, i.e. clinical control of symptoms and prevention of exacerbations.^{1,2} Guidelines also aim to reduce the future risk of disease progression due to structural changes that may occur if chronic or heightened acute inflammation associated with exacerbations is not prevented.³

Treatment recommendations are based on a five-step approach, dependent on the current level of asthma control, ranging from Step 1, which reflects occasional reliever use, to Step 5, which includes regular use of oral corticosteroids.^{1,2} In patients whose asthma is uncontrolled (defined by the Global Initiative for Asthma [GINA] guidelines¹ as having an exacerbation or at least three of the following in a given week: daytime symptoms >2 times/week, any limitation of activities, any nocturnal symptoms/awakenings, need for reliever treatment >2 times/week or lung function $<80\%$ predicted normal) each progressive treatment step provides therapeutic options for increasing maintenance medication to achieve control. If control has been established and maintained for at least 3 months, treatment can be gradually reduced to the lowest dose of maintenance medication necessary to maintain control. For adults whose asthma is uncontrolled on low-dose inhaled corticosteroid (ICS) (Step 2), the addition of a long-acting β_2 -agonist (LABA) is the preferred step-up (Step 3), although alternative treatment options such as higher doses of ICS or adding leukotriene receptor antagonists (LTRAs) are also acceptable¹ – this can be defined as conventional best practice (CBP). Budesonide/formoterol maintenance and reliever therapy is endorsed by the GINA guidelines for asthma patients at Steps 3–5.¹ This management approach relies on the need for reliever therapy to guide patients to adjust the level of anti-inflammatory therapy in a timely fashion without the need to alter maintenance doses.⁴ Budesonide/formoterol maintenance and reliever therapy also eliminates the need for a separate short-acting β_2 -agonist (SABA), as budesonide/formoterol provides rapid symptom relief with one inhaler.⁵

Large-scale, randomized, double-blind clinical studies have shown that budesonide/formoterol maintenance and reliever therapy can improve symptom control and reduce exacerbations compared with higher fixed doses of ICS delivered with alternative ICS/LABA therapies plus SABA.^{6,7} However, observations from such randomized clinical trials cannot always be extrapolated into clinical settings where physicians have a free choice of treatment. Consequently, more recent studies have compared budesonide/formoterol maintenance and reliever therapy with physicians' free choice. One such study, conducted in Canada, confirmed

that similar control of eosinophilic airway inflammation was provided by budesonide/formoterol maintenance and reliever therapy compared with CBP, at a significantly lower ICS dose and without the use of LTRAs as concomitant anti-inflammatory therapy.⁸

This present analysis pooled the clinical data from the Canadian study with data from all other (five) 6-month open-label trials^{9,10} of similar size and duration that compared budesonide/formoterol maintenance and reliever therapy (160/4.5 μg /inhalation twice daily plus as needed) with CBP to assess clinical control based on current and emerging concepts of asthma control. Clinical control was assessed in the overall population from the incidence of exacerbations and as measured by the five-item asthma control questionnaire (ACQ-5), which assesses mean symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath and wheeze).^{11,12} In the pooled dataset, an additional *post hoc* analysis was also included using ACQ-5 cut-points to define control in individual patients; patients with a score of ≤ 0.75 are considered to have an 85% chance of being well controlled and those with a score ≥ 1.5 are considered to have an 88% chance of having uncontrolled asthma. By means of these efficacy assessments, this analysis aimed to investigate the clinical effectiveness of budesonide/formoterol maintenance and reliever therapy without adjustments in maintenance treatment compared with physicians' choice of CBP.

Methods

Study patients

Outpatients aged ≥ 12 years with asthma were recruited from Canada, France and Germany in three separate national trials (study codes D5890L00004, D5890L00005 and D5890L00011, respectively), Denmark, Finland and Norway in a fourth trial (D5890L00008), Belgium and Luxembourg in a further trial (D5890L00009) and Portugal, Iceland, Greece, Croatia, Czech Republic, Latvia, Lithuania, Slovakia, Slovenia and Chile in the final trial (D5890L00014).

Inclusion criteria in all trials comprised (a) asthma diagnosis for a minimum of 3 months (according to the American Thoracic Society definition),¹³ (b) use of ICS ≥ 320 μg daily of budesonide or equivalent (400 μg /day metered dose) during the last 3 months and (c) either daily maintenance treatment with both ICS and LABA or daily treatment with ICS alone and a history of suboptimal asthma control in the month prior to enrolment (as judged by the investigator). Patients not on combination therapy were required to have taken ≥ 3 inhalations of as-needed medication for symptom relief during the last 7 days before enrolment to establish a need for additional therapy.

Exclusion criteria included previous treatment with budesonide/formoterol for both maintenance and reliever therapy, use of any beta-blocking agents, use of oral corticosteroids as maintenance treatment, a smoking history exceeding 10 pack-years and, to ensure patients were stable at study entry, no asthma exacerbations requiring change in asthma treatment during the previous 14 days.

The six studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by independent ethics committees. Written informed consent was obtained from each adult patient; for underage patients, informed consent from both the patient and his/her legal guardian was obtained.

Study design

For each of the six randomized, 6-month, open-label, parallel-group studies, carried out in accordance with a core protocol, randomization was performed locally. All eligible patients were allocated a randomization code assigned from a computer-generated randomization schedule. Patients were randomized strictly sequentially, equally balanced to treatment with either budesonide/formoterol maintenance and reliever therapy or CBP using coded envelopes. When a patient had been randomized, the envelope was opened and the treatment code was revealed.

Following an optional 2-week run-in period, eligible patients were randomized to receive budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca, Lund, Sweden) 160/4.5 µg/inhalation twice daily for maintenance plus additional inhalations as needed (Symbicort SMART®) or active stepwise management with CBP, according to physicians' free choice and local treatment guidelines.

Patients randomized to the CBP arm were permitted to change their maintenance therapy up or down at study entry following an initial assessment or at any time during the course of the study at the discretion of the treating physician. Medications could include any ICS, ICS/LABA, LTRA, xanthine or other asthma medication within approved dosing limits. In the CBP arm, it was permitted for budesonide/formoterol to be used as maintenance therapy but not as reliever therapy, and traditional reliever therapy (including salbutamol, terbutaline or formoterol as needed) was used in all CBP patients. Patients in the budesonide/formoterol maintenance and reliever therapy arm were not permitted to add additional maintenance treatment or reliever therapy, or change the maintenance dose of budesonide/formoterol from 160/4.5 µg twice daily at any time during the study.

All patients were instructed to contact the investigator for reassessment if they used more than 10 inhalations of reliever medication on any single day, or if asthma symptoms were not relieved with the treatment provided or the patient noticed sudden worsening of his/her shortness of breath. Patients received training in the use of inhaler devices. Patients randomized to the budesonide/formoterol maintenance and reliever therapy group were further instructed to use their reliever medication for relief of symptoms and not for prophylaxis.

Patients had scheduled clinic visits at inclusion and at 4, 13 (optional) and 26 weeks after randomization. Additional

unscheduled visits, at the initiative of the physician and/or patient, were allowed.

Assessing overall asthma control

Exacerbations

The primary efficacy variable in all six studies was time to first severe exacerbation, defined as hospitalization/emergency room (ER) treatment and/or oral corticosteroid treatment for ≥ 3 days, due to asthma. In addition, the rate of severe asthma exacerbations (total number and by subtype) was assessed, as were the number of courses of oral corticosteroids and days with active exacerbation treatment.

Start and end dates for exacerbations were defined as the first and last day of any clinical intervention. If an exacerbation included both hospitalization/ER treatment and oral corticosteroid treatment, the start and end dates were the first and last day, respectively, that either of the criteria was fulfilled.

Asthma control using the ACQ-5

In individual patients, levels of asthma control were assessed by ACQ-5.¹⁴ The ACQ-5 was self-administered at clinic visits before any other related procedures took place. This shortened version of the ACQ assessed activity limitation plus daily and nocturnal asthma symptoms and provides very similar estimates of asthma control to the larger ACQ-7, which also includes clinic forced expiratory volume in 1 second and reliever use.^{11,12}

All five questions were assessed on a seven-point scale from 0 to 6, where 0 represents good control and 6 poor control. The overall score was a mean of the five responses. At least four out of the five questions had to be answered to provide a value. Cut-points were used to define the number of patients with well-controlled asthma (≤ 0.75), asthma with intermediate control (0.76–1.49), i.e. a less certain status, and uncontrolled asthma (≥ 1.5).¹¹ The mean change in overall score from baseline to the average value during treatment (visits 2–4) was also assessed.

Overall asthma control assessed by baseline treatment strata

The GINA recommendations for controller medications were used to classify individual patients by severity based on the asthma maintenance therapy they were taking when they entered the study.¹ In patients who entered at GINA Step 2 (low-dose ICS alone), Step 3 (medium- or high-dose ICS alone or low-dose ICS plus LABA or leukotriene modifier) or Step 4 (medium- or high-dose ICS plus LABA and/or ≥ 3 maintenance drugs [e.g. ICS, LABA and leukotriene modifiers]), clinical control and exacerbation rates were compared between the treatment groups to assess if treatment response was influenced by treatment level as an indicator of patients' asthma severity.

Other efficacy measures

Reliever use, excluded from the ACQ-5 test of control, was recorded at each clinic visit using a notebook completed by the patient every morning in the 2 weeks prior to each visit.

Individual patients using <4 inhalations/week were deemed likely to be well controlled.^{15,16} The highest of three measurements of pre- and post-bronchodilator peak expiratory flow (PEF) was also recorded at the clinic at baseline and at 6 months.

Safety and medication use

Adverse events, serious adverse events and discontinuations due to adverse events were recorded at each study visit. Any changes in prescribed asthma medications during the study period were also recorded. Use of medication was self-reported in a patient notebook.

Statistical analysis

The original studies were powered individually to detect a difference in the primary endpoint (time to first severe exacerbation). With a total of 500 patients/group, a log-rank test (at the two-sided 5% significance level) had an 80% chance of detecting a 5% between-group difference, assuming rates of 11% and 6% in the proportion of patients who experienced an exacerbation.¹⁷ This level of efficacy was apparent in studies where budesonide/formoterol maintenance and reliever therapy was compared with an increase in ICS alone.^{18–20} However, in other studies where the control group was a higher ICS/LABA dose,^{6,7,16} the significant difference seen in favour of budesonide/formoterol maintenance and reliever therapy, expressed as a percentage of patients experiencing an exacerbation, was, in absolute terms, in the range of 2–3%. As the CBP arm was allowed to use higher ICS/LABA ± any other controller therapy, the pooled analysis was deemed appropriate to provide greater power to detect any significant treatment difference.

All patients with data after randomization were included in the full analysis set for efficacy. Safety data were based on patients who received ≥1 dose of study drug and were analysed using descriptive statistics.

Time to first severe exacerbation was determined using Kaplan–Meier curves and treatment groups were compared using a Cox proportional hazards model stratified by country and with treatment as a factor. The mean number of exacerbations per patient and the number of exacerbation days were compared between groups using a Poisson regression model with treatment and country as factors and time in study as an offset. The confidence limits and *P*-values were adjusted for overdispersion. The mean number of exacerbation days was compared using a bootstrap method where individual patient's exposure time and number of days with severe exacerbations were sampled with replacement.²¹

In the overall population, ACQ-5 scores based on individual patient means from all post-randomization visits were used to assess the probability of patients being either well controlled (≤0.75) or uncontrolled (≥1.5). The proportion of well-controlled patients was compared between treatments using a logistic regression model with treatment, country and asthma control (well controlled or not) at baseline as factors.

The proportion of patients using <4 inhalations/week of reliever was compared between treatments using a logistic

regression model with treatment, country and level of reliever use at baseline as factors.

The between-treatment group changes in mean ACQ-5 scores, as-needed medication use and PEF from baseline to the average on treatment were compared using analysis of variance with treatment and country as factors and baseline as a covariate.

Results

Study patients

Enrolment began in May 2004 and the last patient completed in December 2006. Patient flow is summarized in Fig. 1. Of 7994 patients enrolled for screening, 7855 (98%) were randomized and 7149 (89%) completed the study; 7747 of the patients had data reported after randomization and were included in the full analysis set.

Subjects were randomized from national sites in the six studies: Belgium and Luxembourg (study code D5890L00009, *n* = 914), Canada (study code D5890L00004, *n* = 1538), France (study code D5890L00005, *n* = 1013), Germany (study code D5890L00011, *n* = 1528), three countries in a Nordic study (study code D5890L00008, Denmark *n* = 806, Finland *n* = 427, Norway *n* = 621 [total *n* = 1854]) and 10

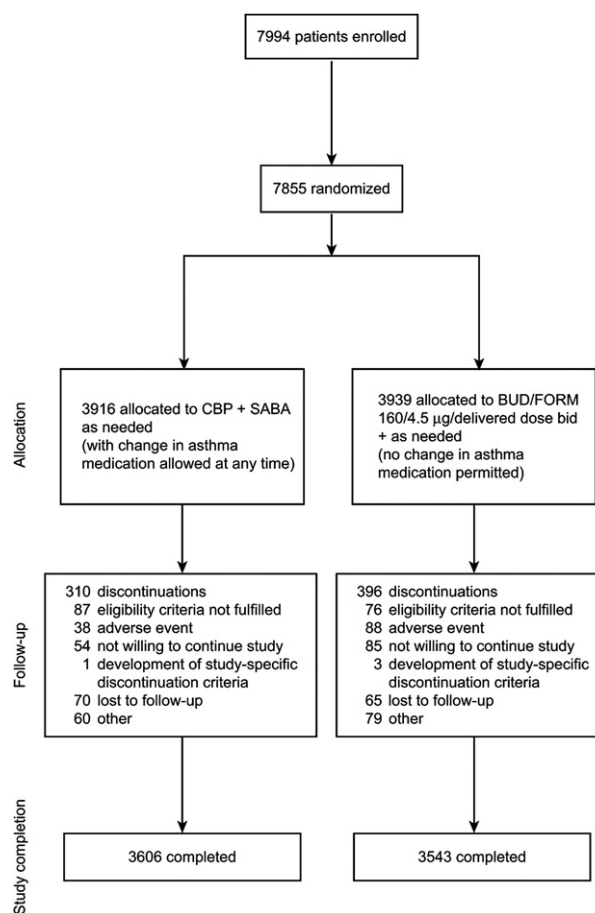


Figure 1 Patient flow diagram. bid = twice daily; BUD/FORM = budesonide/formoterol; CBP = conventional best practice; SABA = short-acting β_2 -agonist.

separate countries in one study (D5890L00014, Chile $n = 60$, Croatia $n = 102$, Czech Republic $n = 72$, Greece $n = 142$, Iceland $n = 100$, Latvia $n = 110$, Lithuania $n = 111$, Portugal $n = 110$, Slovakia $n = 121$ and Slovenia $n = 80$ [total $n = 1008$]).

The baseline demographics and measures of clinical control prior to randomization were comparable between treatment groups (Table 1). Based on the baseline ACQ-5 scores, 29–31% of all patients had well-controlled asthma, 30–31% had intermediate control and 40% uncontrolled asthma (Table 1). The proportion of patients at study entry using Steps 2, 3 and 4 of GINA guideline-based treatment was comparable between treatment groups, with the majority of patients (68–69%) at Step 3 (Table 1).

Prescribed medications during treatment

Maintenance medication in the budesonide/formoterol maintenance and reliever therapy arm was fixed by protocol. All patients in the CBP arm were prescribed maintenance ICS (100%); 87% with LABA in a single combination inhaler. Additional controller therapies in the CBP group in addition to ICS

Table 1 Patient characteristics and baseline demographics.

Characteristic	Conventional best practice	BUD/FORM maintenance and reliever therapy
<i>N</i>	3864	3883
Male, %	40	40
Age, years (range)	44 (12–94)	44 (12–92)
ICS BDP equivalent, $\mu\text{g/day}$ (SD)	992 (576)	966 (520)
GINA treatment step, <i>n</i> (%) ^a		
Step 2	234 (6)	259 (7)
Step 3	2624 (68)	2700 (69)
Step 4	974 (25)	891 (23)
Not defined	32 (1)	33 (1)
LABA use at study entry, %	83	82
Rescue <4 inhalations/week, % ^b	55	54
ACQ-5 total score, %		
≤ 0.75 (well controlled)	31	29
0.76–1.49 (intermediate control)	30	31
≥ 1.50 (uncontrolled)	40	40

Mean data unless stated otherwise. ACQ-5 = five-item asthma control questionnaire; BDP = beclomethasone dipropionate; BUD/FORM = budesonide/formoterol; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; SD = standard deviation.

^a Patients prescribed different levels of asthma medication at study entry: low-dose ICS alone, Step 2 patient; medium- or high-dose ICS alone or a low- to moderate-dose ICS in combination with another controller, Step 3 patient; two separate controllers including high-dose ICS or ≥ 3 controller therapies at any ICS dose, Step 4 patient.¹

^b Data missing from one of the six studies (study D5890L00014) (representing 13% of the pooled patient population).

or ICS/LABA therapy included a separate LABA for maintenance or relief (15%), leukotriene modifiers (14%), xanthines/oral bronchodilators (5%), inhaled anticholinergics (2%) and disodium cromoglycate or nedocromil sodium (1%).

Overall asthma control

Exacerbations

A trend towards a prolongation in the time to first exacerbation was seen with budesonide/formoterol maintenance and reliever therapy compared with CBP, although this difference was not statistically significant (Cox hazard ratio 0.86 [95% confidence interval (CI): 0.74–1.01] $P = 0.062$) (Fig. 2A).

Including repeat events, patients in the budesonide/formoterol maintenance and reliever therapy arm experienced 15% fewer exacerbations compared with CBP (0.20 versus 0.24 per patient/year; rate ratio 0.85 [95% CI: 0.74–0.98] $P = 0.021$) (Fig. 2B). The total number of days with exacerbations was 28% lower in the budesonide/formoterol maintenance and reliever therapy group compared with CBP (2753 versus 3801 days; $P = 0.022$).

The majority of exacerbations required courses of oral corticosteroids and this was 18% lower with budesonide/formoterol maintenance and reliever therapy compared with CBP (0.15 per patient/year versus 0.18 per patient/year; odds ratio [OR] 0.82 [95% CI: 0.70–0.95] $P = 0.01$). No significant difference in the rate of hospitalization/ER treatment was observed (0.055 versus 0.064 per patient/year respectively; $P = 0.18$).

In both treatment groups, there was a trend showing increasing exacerbation rates on treatment with increasing

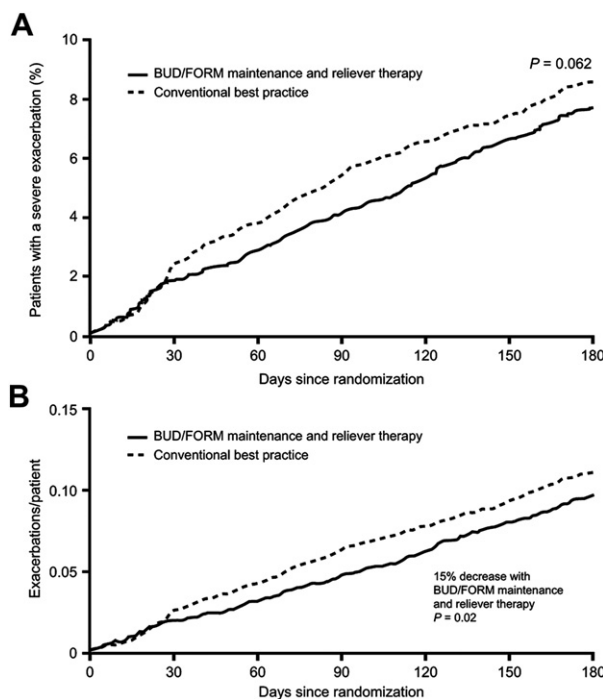


Figure 2 Kaplan–Meier plots of (A) time to first severe exacerbation and (B) exacerbation rate per patient. BUD/FORM = budesonide/formoterol.

GINA treatment steps at study entry (Table 2). The exacerbation rates tended to be lower in the budesonide/formoterol maintenance and reliever therapy group at all three steps; this was most apparent in patients recruited at treatment Step 4, where the exacerbation rates were 0.24 and 0.31 events/patient/year in the budesonide/formoterol maintenance and reliever therapy and CBP arms, respectively.

Asthma control

The likelihood of patients having well-controlled asthma over the assessment period, based on their individual ACQ-5 score, was 29% higher with budesonide/formoterol maintenance and reliever therapy compared with CBP (45% versus 41%; OR 1.29 [95% CI: 1.15–1.43] $P < 0.01$) and the risk of being uncontrolled was 19% lower (25% versus 29%; OR 0.81 [95% CI: 0.71–0.91] $P < 0.01$) (Fig. 3A). Similar proportions of patients with intermediate control were observed in both treatment arms (30%).

The proportion of patients well controlled in the CBP group varied according to the treatment prescribed based on physicians' free choice. Nevertheless, no combination of therapies was more effective than budesonide/formoterol maintenance and reliever therapy in achieving well-controlled asthma. Compared with the 45% of patients well controlled with budesonide/formoterol maintenance and reliever therapy, patients using ICS alone or ICS/LABA, at any approved range of doses, were well controlled in 38% and 42% of cases in the CBP group, respectively. Patients using LTRAs and xanthines, in addition to ICS or ICS/LABA therapy, were well controlled in only 35% and 33% of cases respectively. Similarly, in the CBP group, no combination of therapies was more effective in reducing uncontrolled asthma than was seen with budesonide/formoterol maintenance and reliever therapy (data not shown).

Levels of clinical control over time assessed by group mean ACQ-5 values were consistently improved with budesonide/formoterol maintenance and reliever therapy

compared with CBP from the 4-week assessment to the final assessment at 6 months (Fig. 3B, Table 3; $P < 0.001$).

When patients in each treatment group were stratified according to GINA treatment levels at study entry, descriptive analyses showed a trend towards improved levels of clinical control in the budesonide/formoterol maintenance and reliever therapy treatment group compared with CBP at Steps 2 and 3 (Table 2). At Step 4, the likelihood of asthma control was lower in both treatment groups than at Steps 2 and 3; likewise, the number of patients with uncontrolled asthma was higher. The proportions of patients with well-controlled and uncontrolled asthma who entered the study at Step 4 were similar in both treatment groups (Table 2).

As-needed reliever use

There was no significant difference in the mean number of daily inhalations of as-needed therapy or the number of patients using <4 inhalations/week between budesonide/formoterol maintenance and reliever therapy and CBP groups (Table 3; $P = 0.22$ and $P = 0.56$, respectively).

The number of days free of as-needed medication was 63% with CBP and 60% with budesonide/formoterol maintenance and reliever therapy (Table 3; $P = 0.008$). Although patients in the CBP group recorded fewer days with reliever use, patients in the CBP group were more likely to use a higher overall dose of reliever on days with use, based on numerically higher mean daily values and the number of days with high use; for example, only 80 patients (2%) with budesonide/formoterol maintenance and reliever therapy reported using >8 inhalations on a single day, compared with 138 patients (4%) in the CBP arm.

Lung function

Budesonide/formoterol maintenance and reliever therapy resulted in a small but statistically significant increase in pre-bronchodilator PEF compared with CBP (Table 3;

Table 2 Overall asthma control according to GINA treatment level at study entry.^a

Treatment groups, <i>n</i> (% at each step)	Exacerbations/ patient-year (95% CI)	Patient control status based on ACQ-5 scores (%)		
		Well controlled ≤ 0.75	Intermediate control 0.76–1.49	Uncontrolled ≥ 1.50
GINA Step 2				
CBP, 234 (6)	0.11 (0.07–0.19)	42	34	24
BUD/FORM maintenance and reliever therapy, 259 (7)	0.09 (0.05–0.16)	48	30	22
GINA Step 3				
CBP, 2624 (68)	0.14 (0.12–0.16)	43	34	23
BUD/FORM maintenance and reliever therapy, 2700 (69)	0.12 (0.11–0.14)	46	33	21
GINA Step 4				
CBP, 974 (25)	0.31 (0.27–0.35)	36	31	33
BUD/FORM maintenance and reliever therapy, 891 (23)	0.24 (0.20–0.28)	36	32	32

ACQ-5 = five-item asthma control questionnaire; BUD/FORM = budesonide/formoterol; CBP = conventional best practice; CI = confidence interval; GINA = Global Initiative for Asthma.

^a Patients prescribed different levels of asthma medication at study entry: low-dose inhaled corticosteroids (ICS) alone, Step 2 patient; medium- or high-dose ICS alone or a low- to moderate-dose ICS in combination with another controller, Step 3 patient; two separate controllers including high-dose ICS or ≥ 3 controller therapies at any ICS dose, Step 4 patient.

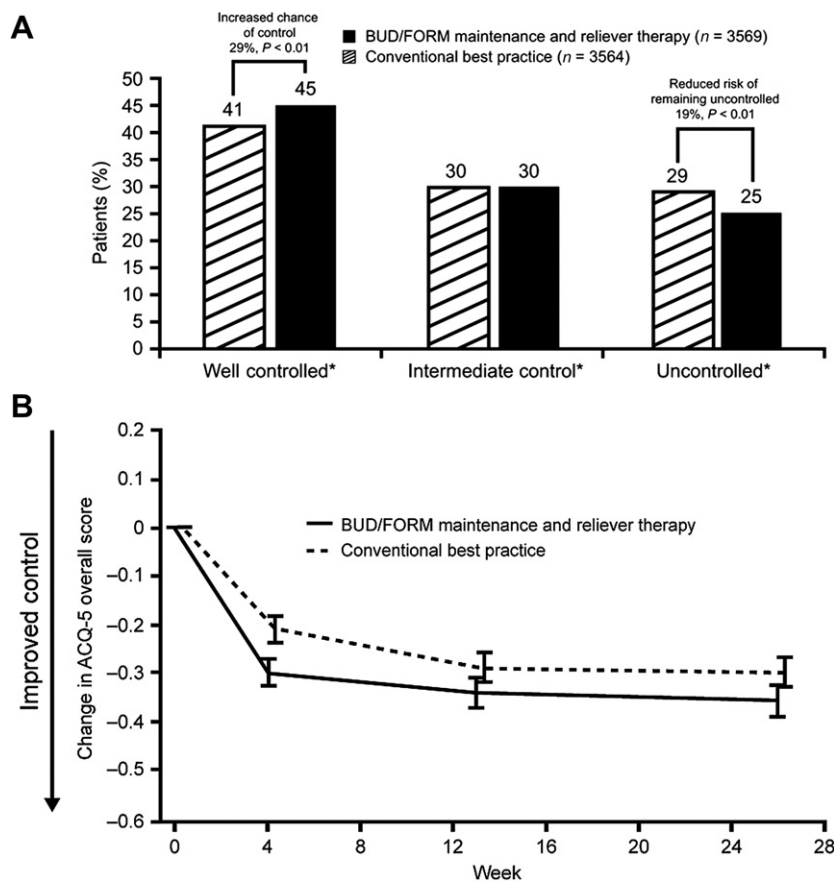


Figure 3 Asthma control assessed using ACQ-5. (A) Percentage of patients with well-controlled, intermediate controlled and uncontrolled asthma randomized to budesonide/formoterol maintenance and reliever therapy or conventional best practice and (B) change in ACQ-5 score over time in each of the treatment arms (error bars: 95% CI). *Asthma control questionnaire (ACQ-5) cut-points: ≤ 0.75 , well controlled; $0.76-1.49$, intermediate control; ≥ 1.5 , uncontrolled.

11.1 l/min versus 7.8 l/min increase from baseline; $P = 0.025$).

Corticosteroid load

The overall mean daily dose of ICS (expressed in beclomethasone dipropionate [BDP] equivalents)¹ was 27% lower with budesonide/formoterol maintenance and reliever therapy compared with CBP ($P < 0.0001$; Fig. 4). Most patients randomized to budesonide/formoterol maintenance and reliever therapy (66%) took a medium daily dose of ICS (501–1000 $\mu\text{g}/\text{day}$ BDP equivalent) (maintenance plus as needed) compared with 49% in the CBP group. Fewer budesonide/formoterol maintenance and reliever therapy patients were on a low (≤ 500 $\mu\text{g}/\text{day}$; 19% versus 31%) or high (> 1000 $\mu\text{g}/\text{day}$; 16% versus 21%) daily dose compared with patients in the CBP arm. The total number of courses with systemic corticosteroids to treat asthma exacerbations was also lower among patients using budesonide/formoterol maintenance and reliever therapy compared with CBP (Fig. 4).

Tolerability

Tolerability was similar in both treatment groups. Seven deaths occurred during the studies; four in the budesonide/

formoterol maintenance and reliever therapy group (due to a farming accident, sudden death, myocardial infarction and suicide) and three in the CBP group (due to heart attack, myopericarditis and sudden coronary death). Serious adverse events were uncommon and their incidence was comparable in both treatment groups: 98 patients (2.5%) in the budesonide/formoterol maintenance and reliever therapy group and 88 patients (2.3%) in the CBP treatment group. The most frequent serious adverse events by type were asthma (0.36% versus 0.44%) and pneumonia (0.08% versus 0.13%). There were 91 (2.3%) discontinuations due to adverse events in the budesonide/formoterol maintenance and reliever therapy group and 33 (0.9%) in the CBP group.

Discussion

This pooled analysis evaluated budesonide/formoterol maintenance and reliever therapy as a treatment alternative to physicians' free choice of guideline-based CBP. Although this analysis failed to show that budesonide/formoterol maintenance and reliever therapy prolonged the time to first severe exacerbation (primary variable) compared with CBP, the single inhaler maintenance and reliever approach resulted in significantly fewer exacerbations, fewer days with exacerbation

Table 3 ACQ-5, reliever use, as-needed free days and lung function with budesonide/formoterol maintenance and reliever therapy compared with CBP.

	CBP	BUD/FORM maintenance and reliever therapy	P-value
ACQ-5 score, range 0–6	1.11	1.06	<0.001
No. of as-needed inhalations/day ^a	0.95	0.91	0.22
Patients using <4 as-needed inhalations of rescue/week, %	57	57	0.56
As-needed-free days, % ^a	63	60	0.008
Increase in PEF from baseline, l/min			
Pre-bronchodilator	7.8	11.1	0.025
Post-bronchodilator	1.7	2.0	0.837

ACQ-5 = five-item asthma control questionnaire; BUD/FORM = budesonide/formoterol; CBP = conventional best practice; PEF = peak expiratory flow.

^a Data missing from one of the six studies (study D5890L00014).

treatment, a reduction in the number of patients with uncontrolled asthma, and enabled more patients to achieve or maintain target levels of well-controlled asthma compared with physicians' choice of CBP. These improvements in overall asthma control were achieved

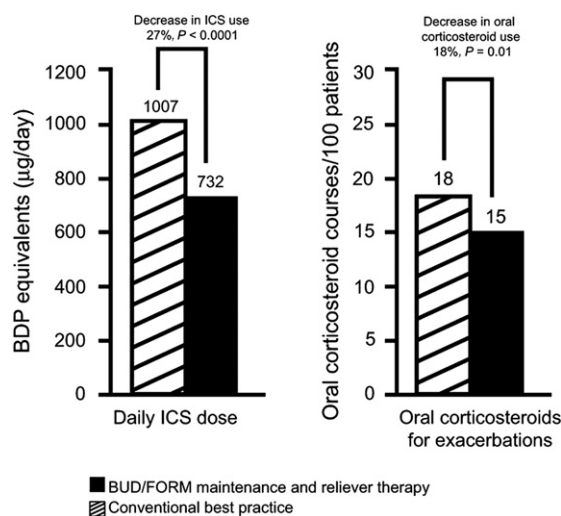


Figure 4 Corticosteroid load on treatment with either regimen. Use of inhaled corticosteroids (ICS) for day-to-day control and oral corticosteroids for exacerbations. Mean difference in daily beclomethasone dipropionate (BDP)-equivalent dose (95% confidence interval): budesonide/formoterol (BUD/FORM) maintenance and reliever therapy versus conventional best practice = $-273.08 \mu\text{g}$ ($-294.1, -252.1$); $P < 0.0001$.

with budesonide/formoterol maintenance and reliever therapy despite switching patients from higher levels of existing maintenance therapy at study entry, i.e. at Step 4 of GINA guidelines, and also removing the ability of physicians to increase maintenance treatment in the budesonide/formoterol maintenance and reliever therapy group in contrast to the CBP arm. As a result, improvements in overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy also occurred at a lower corticosteroid load.

Budesonide/formoterol maintenance and reliever therapy was compared here with the pragmatic management approach of allowing physicians free choice of alternative treatments, thus increasing the applicability of these findings to everyday clinical practice. Interestingly, all possible combinations of controller therapy used in CBP-treated patients, i.e. ICS plus LTRA and ICS/LABA plus LTRA at any approved doses, were associated with less satisfactory asthma control than that achieved in the budesonide/formoterol maintenance and reliever therapy arm.

Importantly, our findings suggest that budesonide/formoterol maintenance and reliever therapy is associated with better overall asthma control than physicians' choice of guideline-based therapy in patients who were recruited at GINA treatment Steps 2–4.¹ Benefits were seen in terms of both asthma control (based on ACQ-5 cut-points) and exacerbation rates with budesonide/formoterol maintenance and reliever therapy, which delivered different facets of control based on the patient's pre-existing treatment level, i.e. the greatest improvement in symptom control occurred in the small subgroup of patients recruited at Step 2 while the greatest benefit on reducing the rate of exacerbations occurred in patients at Step 4. These findings suggest that a disparity can exist between daily control and exacerbations in patients already receiving high levels of maintenance therapy, i.e. a reduction in the rate of exacerbations is not associated with an improvement in well-controlled asthma in Step 4 patients. In the Gaining Optimal Asthma control (GOAL) study, prior use of any maintenance dose of ICS doubled the risk of not achieving well-controlled asthma²² and, as patients on high-dose ICS were excluded from the GOAL study, this disconnect between exacerbations and asthma control in more severe asthma was less evident.¹⁵

As this present study was a pooled analysis of open-label trials, in contrast to the previous double-blind studies,^{5–7,18–20} these findings in isolation should be viewed with some caution. However, given the wealth of data from the previous highly controlled trials,^{5–7,18–20} these results, in comparison to physicians' free choice of CBP, complement the more rigorous efficacy studies. The reduction in exacerbations was of lower magnitude than in the six previous double-blind studies,^{5–7,18–20} likely reflecting the greater number of therapeutic options available to manage the CBP group compared with options in the double-blind trials. Further, the majority of patients recruited to each of the six studies in this pooled analysis had better asthma control compared with patients in the double-blind studies.

More patients in the budesonide/formoterol maintenance and reliever therapy arm discontinued treatment due to an adverse event. In the open-label RELIEF study,²³ which included 18,000 patients, discontinuation rates were 1.3% when patients continued on the same maintenance

and reliever therapy versus 2.4% when randomized to a new reliever and inhaler device. The increase in discontinuations in our pooled dataset was of similar magnitude to that seen in the RELIEF study and, as in that study, occurred despite no increase in overall adverse event reporting. It is probable that open-label studies, where a new treatment regimen is introduced in one group but not to the control group who continue to be treated as before, may bias reports of discontinuations even when overall adverse event reports are similar. It is not possible to know if our findings and those in other open-label studies reflect an inherent bias against the selective introduction of a novel regimen in only one group, or whether they reflect a real difference. Whatever the reason, these findings did not appear to have any clinical implications.

The significant reduction in exacerbations in this analysis on low maintenance plus as-needed budesonide/formoterol versus CBP in patients previously at Step 4, as defined by the GINA guidelines,¹ further endorses the value of this new management approach in severe asthma. In this subgroup the rate reduction in exacerbations with budesonide/formoterol maintenance and reliever therapy versus CBP (0.24 versus 0.31 events/patient/year) was very similar to that previously reported with budesonide/formoterol maintenance and reliever therapy versus alternative control groups in two previous studies, which both allowed maximum fixed-dose salmeterol/fluticasone therapy (100/1000 µg/day) to be used in the control arm.^{7,16} In the double-blind study by Bousquet and colleagues⁷ exacerbations in the high-dose salmeterol/fluticasone group correlated strongly with episodes of high reliever use. These episodes, more commonly seen on high-dose salmeterol/fluticasone than on budesonide/formoterol maintenance and reliever therapy, accounted for the excess in exacerbations.⁷ Thus, delivering as-needed anti-inflammatory therapy in line with increases in disease activity is a rational approach to prevent exacerbations even in patients using high-dose maintenance therapy.

Although there was no significant difference in the primary efficacy variable (time to first exacerbation) a similar percentage reduction in the rate of exacerbations with budesonide/formoterol maintenance and reliever therapy compared with CBP did reach statistical significance. The study had additional limitations when comparing drug load as not all physicians may have decreased or increased treatment in accordance with best practice in the CBP arm, due to a failure to recognize good or poor control or because there were few additional treatment options available. Had investigators been prompted to reduce or increase therapy according to a validated tool, the level of treatment in the CBP arm may have been higher or lower than that reported here. However, the assessment of individual patients' level of control using the ACQ-5 score was not fully validated when the study was initiated, although validation has since occurred and so it was included retrospectively in the analysis. In the present analysis, the budesonide/formoterol maintenance and reliever therapy group, by protocol, had enforced reductions in maintenance therapy in some patients from study entry and physicians did not have the option to increase maintenance therapy (including extra ICS, xanthines or LTRAs) compared with the CBP arm.

Nevertheless, the rate of uncontrolled asthma and exacerbations, key factors that drive the need for increased maintenance,²⁴ were significantly reduced. The need for increasing maintenance therapy, particularly in patients who entered at Step 4, with budesonide/formoterol maintenance and reliever therapy cannot be excluded as we did not investigate how this affected overall asthma control in the current study design. This question is, however, being addressed in the large, parallel-group, dose-comparison study, EUROSMART.²⁵

In the present analysis, the assessment of guideline-defined asthma control with a cut-point of <0.75 on the ACQ-5 also had limitations. Whilst it discriminated between the regimens tested, it is likely to be a conservative estimate of total levels of well-controlled asthma on both regimens because a large minority of patients with intermediate scores (0.76–1.5) will also have had well-controlled asthma.¹¹ Finally, it is important to note that the cost of implementing budesonide/formoterol maintenance and reliever therapy versus CBP in all studies was not assessed. Nevertheless, analyses from two of the six studies included (Canada and Belgium plus Luxembourg) have reported that this simplified treatment approach can also significantly reduce direct costs versus CBP.^{8,9}

Use of medication in this study was self-reported. The inhalers dispensed were not counted and therefore the exact dose administered in each arm could not be known. Self-reporting of medication use is, however, a common feature of many studies in asthma.^{26–28}

In conclusion, this large pooled analysis of six studies performed in a setting reflecting normal clinical practice, showed that budesonide/formoterol maintenance and reliever therapy was well tolerated and was associated with a greater likelihood of improving overall asthma control, reducing exacerbations and improving symptoms, compared with physicians' free choice of maintenance therapy in accordance with local CBP.

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Conflicts of interest

P. Demoly is on the speakers' bureau for GlaxoSmithKline, Schering-Plough, UCB Pharma, Allergo-ALK, Stallergenes and AstraZeneca and has received research support from Schering-Plough, Sanofi-Aventis, GlaxoSmithKline and Pierre Fabre Medicament.

R. Louis received unrestricted research grants from GlaxoSmithKline, AstraZeneca, Novartis and UCB. He is on national advisory boards for GlaxoSmithKline, Novartis and UCB and is on an international advisory board for UCB and GlaxoSmithKline as well as in the speakers' bureau for UCB.

U. Søes-Petersen is on national advisory boards for AstraZeneca, GlaxoSmithKline and Novartis.

H. Worth is on national advisory boards for AstraZeneca, Chiesi, Janssen Cilag and Novartis. He is on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Janssen Cilag and Pfizer.

J. Almeida is on the speakers' bureau of AstraZeneca and Boehringer Ingelheim.

M. Sears has received research grants from Merck Frosst Canada and AstraZeneca, is on the speakers' bureau for Merck Frosst Canada, Merck Sharp Dohme, AstraZeneca and Altana Pharma (Nycomed), and holds a Chair in Respiratory Epidemiology jointly endowed by AstraZeneca and McMaster University.

Å. Carlsheimer and I. Naya are both in full-time employment with AstraZeneca, Lund, Sweden, and hold stock in this company.

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