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Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone ☆

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Summary
Background: Budesonide/formoterol maintenance and reliever therapy (Symbicort SMART®) improves asthma control compared with fixed-dose inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) regimens, but its efficacy has not been assessed in comparison with sustained high-dose salmeterol/fluticasone (Seretide™) plus a short-acting β_2-agonist (SABA).
Methods: Patients ($N = 2309$) with symptomatic asthma (aged $\geqslant 12$ years; forced expiratory volume in 1 s $\geqslant 50\%$ predicted), who had experienced an asthma exacerbation in the previous year, were randomised to receive budesonide/formoterol 160/4.5 μg two inhalations twice daily and as needed, or one inhalation of salmeterol/fluticasone 50/500 μg twice daily plus terbutaline as needed, for 6 months.
Results: Time to first severe exacerbation, the pre-specified primary outcome, was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05). Budesonide/formoterol maintenance and reliever therapy reduced total exacerbations from 31 to 25 events/100 patients/year ($P = 0.039$), and exacerbations requiring hospitalisation/emergency room (ER) treatment from 13 to 9 events/100 patients/year ($P = 0.046$).

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The treatments showed no difference in measures of lung function or asthma symptoms. The mean dose of ICS received was lower using budesonide/formoterol maintenance and reliever therapy (792 μg/day budesonide [1238 μg/day beclomethasone dipropionate (BDP) equivalent] versus 1000 μg/day fluticasone [2000 μg/day BDP equivalent] with salmeterol/fluticasone therapy; $P<0.0001$). Both treatments were well tolerated.
Conclusion: In the treatment of uncontrolled asthma, budesonide/formoterol maintenance and reliever therapy reduces the incidence of severe asthma exacerbations and hospitalisation/ER treatment with similar daily symptom control compared with sustained high-dose salmeterol/fluticasone plus SABA. This benefit is achieved with substantially less ICS exposure.

Introduction

The aim of modern asthma management is to improve control of the disease. This is reflected in guidance produced for healthcare professionals with the intention of improving patient care.[1,2] Furthermore, it should provide patients with an effective means of addressing deteriorations in asthma, so that severe exacerbations can be averted.[3–6]

When control of asthma is not achieved in adults using low-dose inhaled corticosteroids (ICS), ICS/long-acting β_2-agonist (LABA) combination therapy is the recommended treatment approach.[6–11] Surveys of asthma, however, have shown that the majority of patients using an ICS/LABA combination or ICS alone still require daily short-acting β_2-agonist (SABA) therapy, with high proportions reporting daytime symptoms, awakenings and hospital admissions due to asthma.[3–5,12]

The challenge of residual symptoms in adults using ICS/LABA combinations can now be managed in two ways. One option is to increase the maintenance dose of the fixed-dose ICS/LABA combination (budesonide/formoterol or salmeterol/fluticasone), with the aim of progressively stabilising the underlying disease process to minimise the need for short-acting reliever therapy.[7,13,14] An alternative, more patient-centred option, is the use of budesonide/formoterol for both maintenance and relief. This approach is possible because the rapid onset of formoterol[15] allows its use for relief, unlike combination products containing the slower-acting bronchodilator, salmeterol.[16]

Use of budesonide/formoterol maintenance and reliever therapy (Symbicort SMART®) relies on rapid as-needed adjustments in ICS/LABA, as opposed to SABA therapy, to fine-tune asthma control. This approach has the advantage over fixed-dose ICS/LABA plus SABA of substantially reducing severe exacerbations.[17–20] This new management approach is now endorsed in the updated Global Initiative for Asthma (GINA) guidelines as an effective treatment strategy for preventing asthma exacerbations and improving asthma control.[6]

In a large, 6-month, double-blind study, treatment with budesonide/formoterol 160/4.5 μg twice daily (bid) plus as needed reduced exacerbation rates by 28–39% compared with either budesonide/formoterol 320/9 μg bid or salmeterol/fluticasone 250/50 μg bid plus SABA as needed.[20] This result was also replicated in a 1-year, open-label, randomised study performed in a clinical setting, mirroring normal treatment practice, which showed that dose titration of salmeterol/fluticasone combination therapy was less effective than budesonide/formoterol maintenance and reliever therapy, with the latter approach reducing the rate of severe asthma exacerbations by 22%.[19] Although the open-label study allowed maintenance doses to be adjusted in line with clinician judgement, only 40% of salmeterol/fluticasone-treated patients were titrated to the highest possible dose (50/500 μg bid), which may have resulted in less than optimal control. In the Gaining Optimal Asthma Control (GOAL) study, across all strata, 68% of patients receiving salmeterol/fluticasone were on the highest dose at the end of treatment.[7] However, as budesonide/formoterol maintenance and reliever therapy has not been tested against sustained high-dose salmeterol/fluticasone therapy, a direct comparison is warranted.

This study assessed the efficacy of budesonide/formoterol $2 \times 160/4.5$ μg bid plus as needed, compared with salmeterol/fluticasone (50/500 μg bid) plus SABA as needed, in a double-blind setting.

Methods

Study design

This was a 6-month, randomised, double-blind, parallel-group, multinational study (study code D589 0C00002), comprising 184 centres in 17 countries. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by independent ethics committees. Written consent was obtained from all patients, and parents or guardians of adolescents. The first patient was enrolled on 2 May 2005 and the last patient completed the study on 29 May 2006.

Patients visited the clinic at the beginning and end of run-in (visits 1–2), and after 4, 13 and 26 weeks of treatment (visits 3–5). During the 2-week run-in period, patients used their regular maintenance dose of ICS (in combination with a LABA if used as maintenance prior to study entry), plus terbutaline (Bricanyl® Turbuhaler®, AstraZeneca, Sweden) as needed. After run-in, eligible patients were randomised to receive either budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca, Sweden) $2 \times 160/4.5$ μg bid, plus as needed (budesonide/formoterol maintenance and

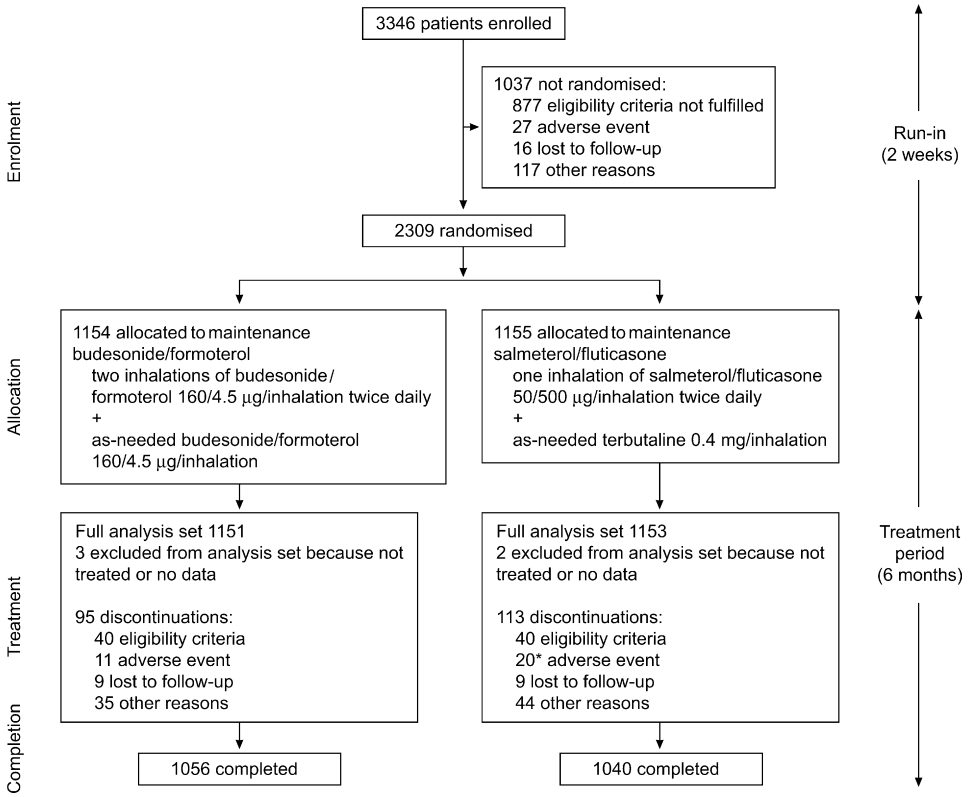

Figure 1 Patient flow. *One patient discontinued treatment but continued in the study; all data from this patient are included in the efficacy analysis in accordance with the full analysis set principle.

reliever therapy), or salmeterol/fluticasone (Seretide™ Diskus™, GlaxoSmithKline, UK) 50/500 μg bid, plus terbutaline 0.4 mg/inhalation for symptom relief (Figure 1). Randomisation codes were sequentially assigned in balanced blocks from a computer-generated list at AstraZeneca R&D, Lund, Sweden. Patients were randomised strictly sequentially as they became eligible. Maintenance and as-needed medication were administered in a blinded double-dummy fashion, with each subject receiving two inhalers for maintenance (one Turbuhaler [red dot], containing budesonide/formoterol or placebo; one Diskus™, containing salmeterol/fluticasone or placebo) and one Turbuhaler® (white) containing budesonide/formoterol or terbutaline for relief.

Study subjects

Outpatients aged 12 years or more, with persistent asthma, who had been treated with ICS alone (800–1600 μg/day) or ICS (400–1000 μg/day) in combination with LABA for at least 3 months prior to study entry, were eligible for inclusion. All eligible patients had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) $\geqslant$50% of predicted normal value, with $\geqslant$12% reversibility following 1.0 mg terbutaline, and had experienced one or more clinically important asthma exacerbations (as judged by the clinician) in the previous 12 months (but none in the month before enrolment). To be eligible for randomisation at the end of run-in, patients had to have used as-needed terbutaline on $\geqslant$5 of the previous 7 days, with no more than eight inhalations in any single day. Exclusion criteria included recent respiratory infection, use of systemic corticosteroids within 30 days of study entry, use of any β-blocking agent (including eye drops) and a smoking history of $\geqslant$10 pack-years.

Assessments

The primary outcome was time to first severe exacerbation, defined as deterioration in asthma leading to hospitalisation/emergency room (ER) treatment and/or oral corticosteroid treatment for at least 3 days.[21] Secondary outcomes included the rate of severe exacerbations (as the same composite), the time to first hospitalisation/ER treatment and the rate of hospitalisation/ER treatments.

Measures of daily asthma control, including peak expiratory flow, reliever use, asthma symptoms and nights with awakenings due to asthma symptoms, were recorded by patients in daily asthma diaries. From these assessments, a composite measure of asthma control days (day and night with no asthma symptoms, no awakenings due to asthma symptoms and no use of as-needed medication) was derived. At clinic visits, adherence was checked by investigators, spirometry (FEV_1) was performed and patients completed an Asthma Control Questionnaire (5-item version; ACQ-5), consisting of five questions on symptom control (excluding responses based on FEV_1 and as-needed medication use, which are included in the ACQ-7), each scored on a scale of 0–6, where 0 represents good control and 6 represents poor control. The overall score from the ACQ-5 was the mean of the five responses.

Total use of as-needed inhalations recorded in patient diaries was also used to evaluate the mean daily dose of ICS with budesonide/formoterol maintenance and reliever therapy in delivered budesonide and beclomethasone dipropionate (BDP)-equivalent doses.[6]

Statistical analysis

The primary objective was to compare the time to first severe asthma exacerbation between treatment groups. A total of 985 randomised and evaluable patients per treatment group were required for a log-rank test (at the two-sided 5% significance level) to have a 90% chance of detecting a between-group difference, assuming a true difference of 11% versus 16% in the patients who experienced a severe asthma exacerbation. All patients for whom data were collected after randomisation were included in the full analysis set. Safety analyses were based on all patients taking at least one dose of study medication.

Time to first severe exacerbation was described using Kaplan–Meier curves, and treatment groups were compared using a Cox proportional hazards model, stratified by country, with treatment as a factor. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model with treatment and country as factors, and time in study as an offset variable. The same methods were used to perform an additional *post hoc* analysis comparing differences in exacerbation risk between the two groups in relation to single days with >2, >4, >6 and >8 inhalations of as-needed reliever medication. Other efficacy measures, including spirometry, peak expiratory flow, asthma symptoms, as-needed medication use and ACQ-5 score, were compared between groups as changes from baseline using analysis of variance, with treatment and country as factors and baseline as a covariate.

Results

Patient profile

Of the 3346 patients enrolled, 2309 were randomised and 2304 were included in the full analysis set (see Figure 1 for patient flow). Baseline characteristics were comparable between the two treatment groups (Table 1). Self-reported adherence to maintenance medication was high (mean use was 98% according to patient diary cards in both groups).

Exacerbations

Time to first exacerbation was not significantly different between treatment groups (hazard ratio 0.82; $P = 0.12$). However, Kaplan–Meier plots of time to first and second exacerbation (Figure 2) show that budesonide/formoterol maintenance and reliever therapy tended to prolong the time to the first and repeat exacerbations. This was reflected in a 21% reduction in overall exacerbation rate versus high-dose salmeterol/fluticasone (25 versus 31 events/100 patients/year; $P = 0.039$; Table 2). The risk of a hospitalisation/ER treatment for asthma was also decreased versus high-dose salmeterol/fluticasone plus SABA (hazard ratio 0.64; $P = 0.031$), and a 31% reduction in the rate of hospitalisation/ER treatment was seen with budesonide/formoterol maintenance and reliever therapy (9 versus 13 events/100 patients/year, respectively; $P = 0.046$; Table 2). The 21% reduction in the rate of exacerbations seen with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone was consistent ($\pm$1%) for patients pre-exposed or not exposed to LABA at study entry.

Table 1 Baseline characteristics of patients.

Characteristic	Budesonide/formoterol maintenance and reliever therapy ($N = 1154$)	High-dose salmeterol/fluticasone + SABA ($N = 1155$)
Male, *n* (%)	443 (38)	444 (38)
Mean age, years (range)	40 (12–80)	39 (12–80)
Time since diagnosis*, years (range)	14 (1–67)	13 (1–77)
Exacerbations during last 12 months (range)	1.8 (1–10)	1.9 (1–24)
FEV_1, l (range)	2.08 (0.60–4.65)	2.10 (0.72–4.89)
FEV_1, % predicted normal (range)	70.2 (45–114)	71.0 (45–222)
FEV_1 reversibility, % (range)	23.9 (7–103)	23.9 (7–95)
Smoking status		
Never, *n* (%)	949 (82)	952 (82)
Previous, *n* (%)	154 (13)	151 (13)
Smokers, *n* (%)	51 (4)	52 (5)
ICS use at entry, μg/day delivered dose (range)	705 (250–1600)	720 (200–2000)
Inhaled LABA use at entry, *n* (%)	645 (56)	622 (54)

Data are means unless otherwise indicated; *median value.
SABA = short-acting β_2-agonist.
FEV_1 = forced expiratory volume in 1 s.
ICS = inhaled corticosteroid.
LABA = long-acting β_2-agonist.

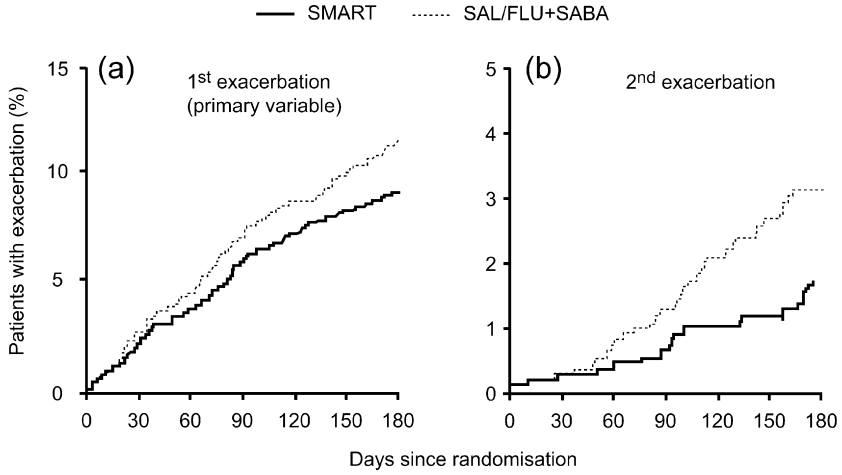

Figure 2 Kaplan–Meier plots of (a) time to first severe asthma exacerbation and (b) time to second severe exacerbation. The risk of a first exacerbation was not different between the treatments with statistical significance ($P = 0.12$). SMART = budesonide/formoterol maintenance and reliever therapy. SAL/FLU+SABA = high-dose salmeterol/fluticasone + short-acting β_2-agonist.

Table 2 Burden of severe asthma exacerbations.

	Treatment group		Reduction in the risk and rate (%) of exacerbations with budesonide/formoterol maintenance and reliever therapy (95% CI); *P*-value
	Budesonide/formoterol maintenance and reliever therapy ($N = 1151$)	High-dose salmeterol/fluticasone + SABA ($N = 1153$)	
All patients (intention-to-treat population)			
Severe asthma exacerbations (all definitions)			
Patients with event, *n* (%)	108 (9.4)	130 (11.3)	18[a] (–5, 37); $P = 0.12$*
Rate, events/100 patients/year	25	31	21[b] (1, 37); $P = 0.039$*
Total number of events[#]	137	173	
ER visits or hospitalisations			
Patients with event, *n* (%)	39 (3.4)	59 (5.1)	36[a] (4, 57); $P = 0.031$*
Rate, events/100 patients/year	9	13	31[b] (1, 51); $P = 0.046$*
Total events[#]	51	73	
Patient subgroup with use of >4 inhalations of reliever medication on at least one study day			
Number within subgroup, *n* (%)	305 (26.5)	333 (28.9)	
Severe asthma exacerbations following the first use of >4 inhalations/day (all definitions)			
Patients with event, *n* (% of subgroup)	46 (15.1)	80 (24.0)	
Rate, events/100 patients/year in subgroup	54	92	41[b] (19, 57); $P = 0.0012$[†]
ER visits or hospitalisations following the first use of >4 inhalations/day			
Patients with event, *n* (% of subgroup)	17 (5.6)	39 (11.7)	
Rate, events/100 patients/year in subgroup	20	42	53[b] (22, 72); $P = 0.0037$[†]

[a]Treatment comparisons from a Cox proportional hazards model of time to first severe asthma exacerbation.
[b]Comparison of relative rates from a Poisson regression; **a priori* analysis; [†]*post hoc* analysis; [#]descriptive statistics only.

Pattern of reliever use in relation to exacerbations

Days with a high number of as-needed inhalations of >4, >6 and >8 reliever inhalations/day (indicating periods with poorly controlled asthma) occurred with salmeterol/fluticasone plus SABA in 333 (29%), 151 (13%) and 49 (4%) patients, and with budesonide/formoterol maintenance and reliever therapy in 305 (27%), 106 (9%) and 32 (3%) patients, respectively. The incidence of severe exacerbations in association with this pattern of high as-needed use was reduced with budesonide/formoterol maintenance and reliever therapy more than with high-dose salmeterol/fluticasone plus SABA. Kaplan–Meier plots in Figure 3 show the time to first severe exacerbation in the 28-day period after the first day of high reliever use, revealing that, at times of increasingly poor asthma control, budesonide/formoterol maintenance and reliever therapy provided added protection from exacerbations compared with high-dose

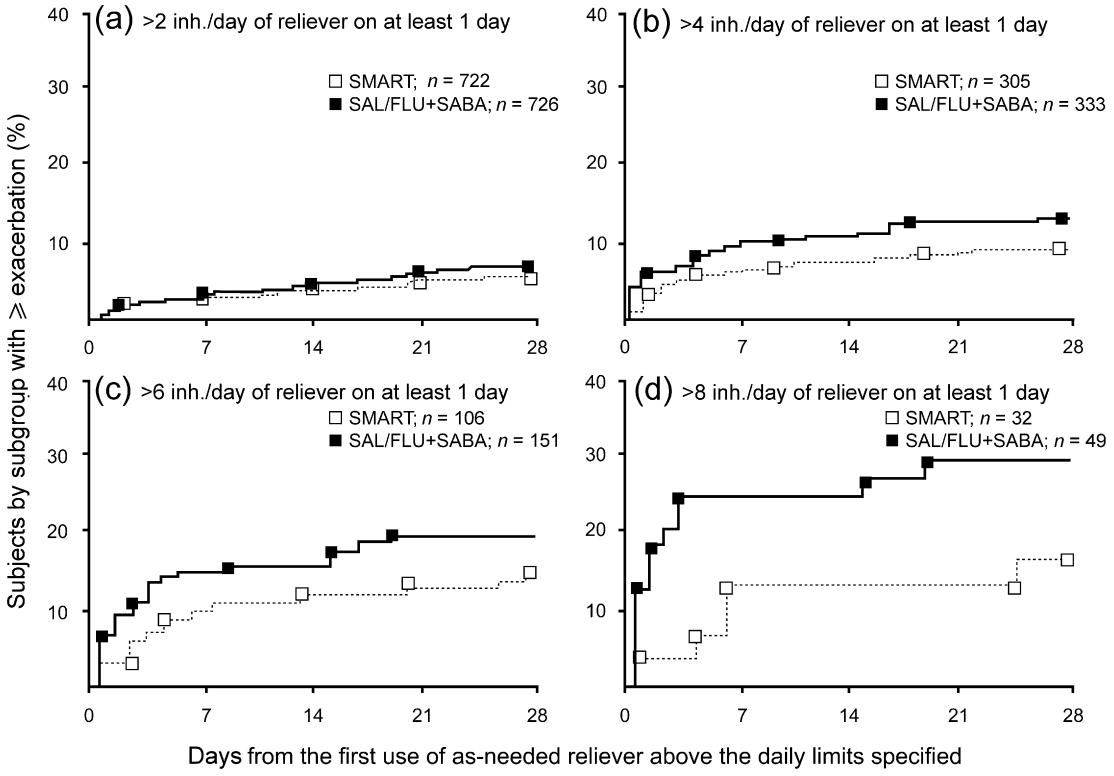

Figure 3 Kaplan–Meier plots showing the percentage of patients with ⩾1 exacerbation in the month following the first day with (a) >2, (b) >4, (c) >6 and (d) >8 inhalations/day of as-needed medication. SMART = budesonide/formoterol maintenance and reliever therapy. SAL/FLU + SABA = high-dose salmeterol/fluticasone + short-acting β_2-agonist. inh. = inhalations.

salmeterol/fluticasone plus SABA. The incidence of exacerbations following the first day with >4 inhalations of reliever therapy are shown in Table 2.

Measures of control

Table 3 shows similar improvements in daily symptom control. Asthma control days increased in both treatment groups, from 6.3% and 5.8% at baseline to 44.0% and 44.9% in the budesonide/formoterol and high-dose salmeterol/fluticasone groups, respectively. Similarly, ACQ-5 scores decreased in both groups with no significant difference between groups, indicating similar clinically relevant improvements in asthma control (Table 3).[22]

FEV_1 increased in both groups, from 2.29 to 2.52 l with budesonide/formoterol and from 2.27 to 2.49 l with high-dose salmeterol/fluticasone, with no difference between the treatments.

Study drug use and treatment cost

No as-needed medication use occurred on 59% of days in both treatment groups, although patients used a mean of 0.95 and 1.01 inhalations/day in the budesonide/formoterol and salmeterol/fluticasone groups, respectively. Mean daily doses of ICS were substantially lower in the budesonide/formoterol group than in the high-dose salmeterol/fluticasone group. With salmeterol/fluticasone, the fluticasone dose was fixed at 1000 μg/day (2000 μg BDP equivalent), and in the budesonide/formoterol maintenance and reliever therapy group, the mean budesonide dose was 792 μg/day (1238 μg BDP equivalent), representing an average 38% reduction in BDP-equivalent dose ($P<0.0001$).

There were 764 days of oral steroid use due to exacerbations among 88 (7.6%) of the patients in the budesonide/formoterol group, compared with 990 days among 108 (9.4%) patients in the salmeterol/fluticasone group. This indicates a substantial overall reduction in the necessity for oral steroid use due to exacerbation in the budesonide/formoterol group.

Study drug costs/patient/year were estimated for five countries participating in the study. The reduced drug load was associated with reduced drug costs for budesonide/formoterol maintenance and reliever therapy versus high-dose salmeterol/fluticasone plus SABA, although this benefit varied by country. In four of the five countries assessed (Germany, Spain, Australia and Canada), costs were significantly reduced, by 4%, 5%, 11% and 24%, respectively (all $P<0.001$ versus salmeterol/fluticasone). No decrease in cost was seen with budesonide/formoterol maintenance and reliever therapy in France (1% increase versus salmeterol/fluticasone; $P = 0.10$).

Safety

The number of patients reporting adverse events (39% with budesonide/formoterol, 40% with salmeterol/fluticasone) and serious adverse events (3% with budesonide/formoterol,

Table 3 Mean outcome measures of daily control and ACQ assessed during run-in and on-treatment.

	Treatment group		Treatment comparison (95% CI); *P*-value[a]
	Budesonide/formoterol maintenance and reliever therapy ($N = 1144$)	High-dose salmeterol/ fluticasone + SABA ($N = 1145$)	
Use of as-needed medication			
Total inhalations daily			
Run-in	2.23	2.29	–0.04 (–0.12, 0.04);
On-treatment	0.95	1.01	$P = 0.36$
As-needed free days, %			
Run-in	10.3	9.3	–0.80 (–3.6, 1.9);
On-treatment	58.2	58.4	$P = 0.56$
Asthma symptoms			
Total symptom score, 0–6 scale			
Run-in	1.87	1.89	0.00 (–0.06, 0.07);
On-treatment	0.98	0.98	$P = 0.92$
Symptom-free days, %			
Run-in	10.7	11.2	–0.50 (–3.3, 2.3);
On-treatment	47.2	48.1	$P = 0.73$
Awakenings, %			
Run-in	32.1	32.2	–1.30 (–2.8, 0.3);
On-treatment	12.0	13.3	$P = 0.11$
Asthma control days, %			
Run-in	6.3	5.8	–1.30 (–4.1, 1.5);
On-treatment	44.0	44.9	$P = 0.37$
ACQ-5 (0–6 scale)			
Run-in	1.84	1.89	–0.02 (–0.07, 0.04);
On-treatment	1.08	1.12	$P = 0.59$
PEF (l/min)			
Morning			
Run-in	330.1	329.0	–0.8 (–4.4, 2.8);
On-treatment	359.5	359.4	$P = 0.67$
Evening			
Run-in	336.7	337.7	1.4 (–2.1, 4.9);
On-treatment	362.3	361.7	$P = 0.42$

Asthma control day = a day and night with no asthma symptoms, no awakenings due to asthma symptoms and no use of as-needed medication; PEF = peak expiratory flow.

[a]Treatment comparison using an analysis of variance model with country and treatment as factors and run-in included as a covariate.

3% with salmeterol/fluticasone) were similar in both treatment groups. Discontinuations were rare in both treatment groups; there were 31 in total (11 with budesonide/formoterol, 20 with salmeterol/fluticasone). Discontinuations in the salmeterol/fluticasone group included eight reports of events associated with the class effects of ICS or β_2-agonists (dysphonia, oral candidiasis, oral fungal infection, tremor, tachycardia and palpitations), compared with only one such report in the budesonide/formoterol group (headache). One death occurred during the study (in the budesonide/formoterol group; severe typhoid fever) but was not considered by the investigator to be causally related to the study drug.

Discussion

This study compared two highly effective asthma treatment strategies, budesonide/formoterol as maintenance and reliever therapy, and high-dose salmeterol/fluticasone (100/1000 μg/day) supplemented with terbutaline as needed. In both of the study arms, symptoms, lung function and reliever use all improved, and there was not a significant difference in the pre-specified primary outcome, time to first severe exacerbation. There were, however, significantly greater, and clinically important, reductions in the overall number of exacerbations and in exacerbations specified by hospitalisation or ER treatments, by 21% and

31% with budesonide/formoterol maintenance and reliever therapy versus high-dose salmeterol/fluticasone, respectively. The lack of difference between treatments in time to first severe exacerbation, in spite of significant differences in the secondary outcome parameters for severe exacerbations, may be the result of the short duration of the study; increasing the duration to 12 months may have permitted a difference to be observed, as has been seen elsewhere.[19]

In patients randomised to budesonide/formoterol maintenance and reliever therapy, 59% of days were free of any reliever use, which is identical to the percentage of reliever-free days in those subjects randomised to high-dose salmeterol/fluticasone. On these days, patients treated with budesonide/formoterol maintenance and reliever therapy were managed with half the daily dose of ICS used by the salmeterol/fluticasone group, i.e. 1000 μg/day versus 2000 μg/day BDP equivalents. However, overall, patients treated with budesonide/formoterol maintenance and reliever therapy used a mean of 762 μg/day less than those in the salmeterol/fluticasone group. The average reliever use overall was also similar in the two treatment groups, at approximately one dose/day. The number of days of high reliever use was small, and was similar in the two study arms. The absence of overuse and the overall pattern of reliever use replicate findings in other budesonide/formoterol studies. This randomised, blinded study demonstrates that there is no basis to favour the alternative approach of high-dose salmeterol/fluticasone treatment on the grounds that it will improve symptoms and eliminate the inconvenience associated with reliever use.

This study has shown that budesonide/formoterol maintenance and reliever therapy provides an effective intervention during periods of unstable asthma. Days with an increased number of as-needed inhalations (>2, >4, >6 and >8 inhalations/day) were used to identify periods of worsening asthma. The pattern of severe exacerbations following these high-use days revealed that the budesonide/formoterol maintenance and reliever therapy approach provided patients with greater protection from severe exacerbations at times of asthma worsening (Figure 3). The numbers of exacerbations increased more strikingly with the level of as-needed use in the high-dose salmeterol/fluticasone plus SABA group than with budesonide/formoterol maintenance and reliever therapy. In both treatment groups, patients who had used more than four reliever doses on any single day had a higher than average risk for severe exacerbation. However, the proportional reduction in severe exacerbations in those patients using more than four reliever doses per day was greater in the budesonide/formoterol group. In this group the use of salmeterol/fluticasone treatment, rather than budesonide/formoterol maintenance and reliever therapy (Table 2), was associated with more than double the rate of hospitalisations/ER treatments.

This study demonstrates that, despite using moderate to high doses of ICS/LABA in both treatment groups, episodes of high reliever use on a single day are still common and can often be associated with a high risk of imminent exacerbation, but that these exacerbations are not inevitable. The most common intervention advised in asthma action plans for such episodes is doubling of ICS, but this often proves ineffective.[23,24] This study has shown that budesonide/formoterol maintenance and reliever therapy, in periods of increased exacerbation risk, increases ICS/LABA doses in line with disease activity, which is associated with clear efficacy benefits.

Taken together, these findings suggest that the greater the exacerbation risk, the greater the benefit of budesonide/formoterol. It is therefore important to educate patients about the importance of using their budesonide/formoterol reliever when asthma symptoms occur.

Reassuringly, despite the substantial reduction in ICS dose with budesonide/formoterol maintenance and reliever therapy, no difference was shown between the two regimens in any aspect of daily symptom control or asthma control assessed by questionnaire. This reflects the observation that both treatment groups had effective asthma treatment, with visible increases in asthma control from run-in. Full clinical control of symptoms (asthma control days) occurred in approximately half of the treatment days in both groups (44–45%); this was nevertheless substantially higher than the 6% of asthma control days at baseline in both groups. Both treatment strategies were equally well tolerated, confirming the favourable safety profiles of the two treatment approaches, as seen in previous studies.[19,20]

The reduction in the rate of exacerbations with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone was consistently observed (range 21–22% reduction), whether patients used ICS alone or ICS plus LABA at study entry. This finding therefore negates the need for a prior trial of ICS/LABA ahead of implementing the budesonide/formoterol maintenance and reliever therapy approach. In addition, the convenience of ICS/LABA combined in one inhaler is increased further when the same inhaler can be used for maintenance and relief. These features, coupled with reduced ICS load and potential savings in treatment costs with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone, should not be overlooked when deciding which treatment approach to utilise.

The exact mechanisms for increased exacerbation control with budesonide/formoterol maintenance and reliever therapy have yet to be fully determined. A detailed discussion of the potential contribution made by budesonide and formoterol is beyond the scope of the present article and readers are referred to a recent review article.[25] However, one important factor, supported by current findings in high as-needed users, is the early increase in anti-inflammatory treatment provided by as-needed inhalations of budesonide/formoterol during periods of deteriorating symptoms. Indeed, use of high-dose budesonide has been shown to reduce eosinophilic inflammation within a 6-h period.[26] Additional non-genomic effects of as-needed budesonide have been reported, including rapid airway vasoconstriction leading to a reduction in airway oedema.[25,27,28] Single doses of budesonide/formoterol have also been shown to provide complete protection from late-phase bronchoconstrictor responses provoked by allergens, an effect not fully obtained with budesonide or formoterol monotherapy.[29]

When considering as-needed formoterol, switching patients from terbutaline to formoterol as needed has been shown to be effective in reducing asthma exacerbations in

patients already using budesonide/formoterol combination therapy.[18] Thus, increasing doses of formoterol in the presence of ICS is associated with increased protection from exacerbations.[18,30] Higher doses are not recommended with salmeterol, a partial β_2-agonist, which has a plateau in its efficacy at around 100 μg/day.[31,32] In a recent systematic review of over 4000 patients, comparing single inhaler combinations containing formoterol or salmeterol at equivalent fixed ICS doses, it was found that exacerbations occur to the same extent with both combinations but fewer result in hospitalisation/ER treatment with budesonide/formoterol compared with salmeterol/fluticasone.[33] Thus, the greater intrinsic efficacy of formoterol may result in it being more effective in protecting patients during periods of increased bronchial challenge compared with salmeterol.[31,34]

Additional beneficial effects on neutrophilic inflammation with formoterol compared with salmeterol have also been shown *in vitro*.[35] Whether these effects play any role in preventing severe exacerbations caused by the viral or bacterial infections that are associated with neutrophilic rather than eosinophilic inflammation is currently uncertain.

A potential limitation of the study is the accuracy level of self-reported medication use. However, a similar pattern of recorded reliever use occurred in both treatment groups, with a rapid reduction in reliever use at the start of study treatment and a further, gradual decline in use during the 6-month treatment period. This pattern of use was consistent with improvement in objective assessments of asthma control at clinic visits, and reported episodic high use of reliever was corroborated by higher rates of exacerbations. Thus, it appears that self-reported use of medication was in line with other treatment outcomes.

The reduced rate of severe exacerbations, including hospitalisations/ER treatments, with budesonide/formoterol maintenance and reliever therapy versus high-dose salmeterol/fluticasone confirms the findings of a recent study conducted by Kuna and colleagues, in which budesonide/formoterol 160/4.5 μg bid plus as needed reduced the rate of severe exacerbations by 39% and hospitalisations/ER treatment by 39% compared with salmeterol/fluticasone (100/500 μg daily).[20] The Kuna study was also a double-blind, double-dummy study of 6 months' duration, with similar populations in terms of FEV_1 (percent predicted) and steroid dose at entry. The present study differs in that the design allowed budesonide/formoterol maintenance and reliever therapy to be tested against the maximum approved dose of salmeterol/fluticasone (100/1000 μg daily), which had been used by the majority of patients in the GOAL study when aiming for total control.[7] Our study showed no difference in any measure of daily symptom control between this same maximum dose of salmeterol/fluticasone and budesonide/formoterol maintenance and reliever therapy. The resulting significantly lower severe exacerbation rate seen with budesonide/formoterol maintenance and reliever therapy without any difference in daily asthma control suggests that better overall asthma control may be gained without resorting to up-titration of maintenance medication and increasing exposure to steroids if the budesonide/formoterol maintenance and reliever therapy approach is adopted.

In conclusion, compared with the highest approved dose of salmeterol/fluticasone plus SABA, treatment with budesonide/formoterol as both maintenance and reliever therapy reduces the incidence of severe asthma exacerbations and hospitalisation/ER treatment. Furthermore, this treatment approach provides added protection for patients who still have episodes of deteriorating asthma. Other measures of asthma control were similar in the two treatment groups, but budesonide/formoterol maintenance and reliever therapy is associated with substantially less ICS exposure and is cost effective. These results confirm that budesonide/formoterol maintenance and reliever therapy is the most effective management approach in patients with moderate to severe asthma.

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