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Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option?

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ABSTRACT: This 12-month dose-titration study assessed the effectiveness of budesonide/formoterol for maintenance plus relief with a control group using salmeterol/fluticasone for maintenance plus salbutamol for relief.

Adolescents and adults (n=2,143; mean forced expiratory volume in one second (FEV_1) 73% predicted; mean inhaled corticosteroid (ICS) 884 μg·day^{-1}) were randomised to budesonide/formoterol 160/4.5 μg two inhalations *b.i.d.* plus additional inhalations as needed, or salmeterol/fluticasone 50/250 μg *b.i.d.* plus salbutamol as needed. Treatment was prescribed open label; after 4 weeks, physicians could titrate maintenance doses in accordance with normal clinical practice.

Maintenance plus as-needed budesonide/formoterol prolonged the time to first severe exacerbation *versus* salmeterol/fluticasone (25% risk reduction). The total number of severe exacerbations was significantly reduced in the budesonide/formoterol group (255 *versus* 329). Both regimens provided sustained improvements in symptoms, as-needed use, quality of life and FEV_1, with differences in favour of the budesonide/formoterol group for as-needed use (0.58 *versus* 0.93 inhalations·day^{-1}) and FEV_1 (post-β_2-agonist values). Mean ICS dose during treatment was similar in both groups (653 μg budesonide·day^{-1} (maintenance plus as-needed) *versus* 583 μg fluticasone·day^{-1}).

The simplified strategy using budesonide/formoterol for maintenance and reliever therapy is feasible, safe and at least as effective as salmeterol/fluticasone plus salbutamol.

KEYWORDS: Asthma, budesonide/formoterol, salmeterol/fluticasone, Seretide®/Advair®, Symbicort®

Combination therapy with inhaled corticosteroids (ICS) and a long-acting β_2-agonist (LABA) represents a major improvement in the treatment of asthma [1–4], and is now used increasingly as fixed-combination therapy [5]. In addition to being more convenient than separate inhalers, combination inhalers control asthma at lower doses of ICS compared with ICS alone [6, 7] and may prevent patients from over-relying on their LABA or short-acting β_2-agonist (SABA) at the expense of ICS therapy. Currently, there are two ICS/LABA combination inhalers available: budesonide/formoterol and salmeterol/fluticasone. In normal clinical practice, a maintenance dose appropriate to the severity of the patient's asthma of either combination is prescribed twice daily, and a separate SABA is used as needed to relieve breakthrough symptoms.

A further simplification of this treatment concept is the use of budesonide/formoterol for both maintenance therapy and as-needed symptom relief, without the requirement for a separate rescue medication, such as salbutamol. This treatment approach enables patients to adjust their anti-inflammatory and LABA medication according to their level of symptoms. Patients take additional inhalations immediately during periods of suboptimal control for relief and to improve control, while relying only on the maintenance dose of budesonide/formoterol when symptom free. This novel management strategy, which is possible with budesonide/formoterol owing to its rapid onset of action [8, 9] and dose–response profile [10, 11], is closely in line with normal patient behaviour, as patients tend to take more as-needed medication as their asthma control declines [12]. A recent 1-yr

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double-blind study involving >2,500 patients with persistent asthma compared budesonide/formoterol for maintenance plus as needed with an equivalent maintenance dose of budesonide/formoterol plus SABA as needed [13]. Although both treatment regimens substantially improved all efficacy outcomes, budesonide/formoterol for maintenance plus as needed reduced the incidence of severe exacerbations, reduced as-needed medication use and progressively increased lung function compared with the fixed-dose budesonide/formoterol regimen [13]. Furthermore, patients using maintenance plus as-needed budesonide/formoterol required no additional as-needed inhalations on the majority of days [13].

The use of one inhaler for both maintenance and as needed simplifies asthma therapy, which is likely to improve patient adherence. However, there is still a need to assess the effectiveness of this approach in a setting mirroring clinical practice to establish whether this management strategy is at least as effective as alternative regimens allowing dose titration of combination therapy [14, 15].

The aim of this 12-month study was to compare the effectiveness of budesonide/formoterol for maintenance plus as needed with that of a regimen using maintenance salmeterol/fluticasone plus salbutamol as rescue medication. To mirror normal clinical practice and minimise patient withdrawal, physicians were free to titrate the level of maintenance treatment in both groups. Furthermore, patients were not required to keep daily diaries and reversibility was not a requirement for inclusion, thereby avoiding the selection of a population primed to respond to increases in LABA therapy [16]. The study was run open label, enabling the appropriate maintenance doses of the combinations to be titrated up or down following any scheduled or unscheduled clinic contact. The open-label design also allowed a single inhaler to be used in the budesonide/formoterol group, excluding the need for separate blinded as-needed medication. The study focused on severe exacerbations to assess effectiveness because of the clinically relevant burden these events place on both patients' quality of life and healthcare resources.

METHODS

Patients

Outpatients aged ⩾12 yrs with a diagnosis of asthma (as defined by the American Thoracic Society [17]) for ⩾6 months were eligible for inclusion in the study (0691) if they had used ⩾500 μg·day^{-1} of budesonide or fluticasone (or ⩾1,000 μg of another ICS) for at least 1 month before study entry. Patients were enrolled if they had a pre-terbutaline forced expiratory volume in one second (FEV_1) 40–90% of predicted and at least one severe exacerbation >2 weeks but ⩽12 months before study entry. To be eligible for randomisation, patients had to have used as-needed medication on ⩾4 of the last 7 days of run-in. The use of either budesonide/formoterol or salmeterol/fluticasone during the last 3 months excluded patients from the study.

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

Study design

This was a 12-month, randomised, open-label, parallel-group study conducted at 246 centres in 16 countries. Patients attended clinic visits at the beginning and end of run-in, and after 1, 3, 6 and 12 months of treatment (visits 1–6). Additional patient-initiated contacts (unscheduled visits/telephone contacts) were permitted throughout the study and the addition of other asthma controller medication was allowed after randomisation, if necessary.

After a 2-week run-in period, during which patients used their existing ICS (and LABA, if appropriate) and as-needed medication, patients were randomised to treatment with either budesonide/formoterol (Symbicort® Turbuhaler®; AstraZeneca, Lund, Sweden) 160/4.5 μg two inhalations *b.i.d.* plus additional inhalations as needed (budesonide/formoterol single inhaler therapy) or salmeterol/fluticasone (Seretide® Diskus®; GlaxoSmithKline, Middlesex, UK) 50/250 μg *b.i.d.* plus salbutamol for rescue medication (*via* dry-powder inhaler or pressurised metered-dose inhaler; Ventolin®; GlaxoSmithKline). Patients were randomised in chronological order at each centre according to a computer-generated code, and treatment was communicated *via* an Interactive Voice Response System.

The starting maintenance doses for each combination were selected to reflect a moderate dose of ICS in both groups, in accordance with guidelines [18]. From week 4 onwards, treatment in both groups was assessed by physicians (either at scheduled clinic visits or unscheduled contacts). In accordance with normal clinical practice, maintenance treatment was titrated up or down to improve control or to attain the lowest dose at which effective control of symptoms was maintained in order to minimise drug load (fig. 1). The maintenance dose of budesonide/formoterol could be down-titrated from 160/4.5 μg 4 inhalations·day^{-1} to 2 inhalations·day^{-1} to maintain a low maintenance dose of budesonide/formoterol [18]. In the salmeterol/fluticasone group, downwards titration from 50/250 μg *b.i.d.* to 50/100 μg *b.i.d.* was also allowed. Furthermore, in this group, physicians had the additional option to step up treatment to a high maintenance dose of salmeterol/fluticasone 50/500 μg *b.i.d.* (fig. 1).

As an additional safety precaution, patients in both groups who required >12 inhalations of study medication·day^{-1} (maintenance plus as needed) were asked to contact their physician for reassessment.

Efficacy

Exacerbations

The primary end point was time to first severe exacerbation. A severe exacerbation was defined as a deterioration in asthma, resulting in hospitalisation/emergency room (ER) treatment, oral steroids for ⩾3 days or an unscheduled visit (*i.e.* patient initiated) leading to treatment change. Further *a priori* analysis considered severe exacerbations excluding unscheduled patient-initiated visits not resulting in hospitalisation/ER treatment or oral steroid therapy, as well as hospitalisation/ER treatment alone. The total number of severe exacerbations, number of days with exacerbations and days with oral steroids due to exacerbations were recorded.

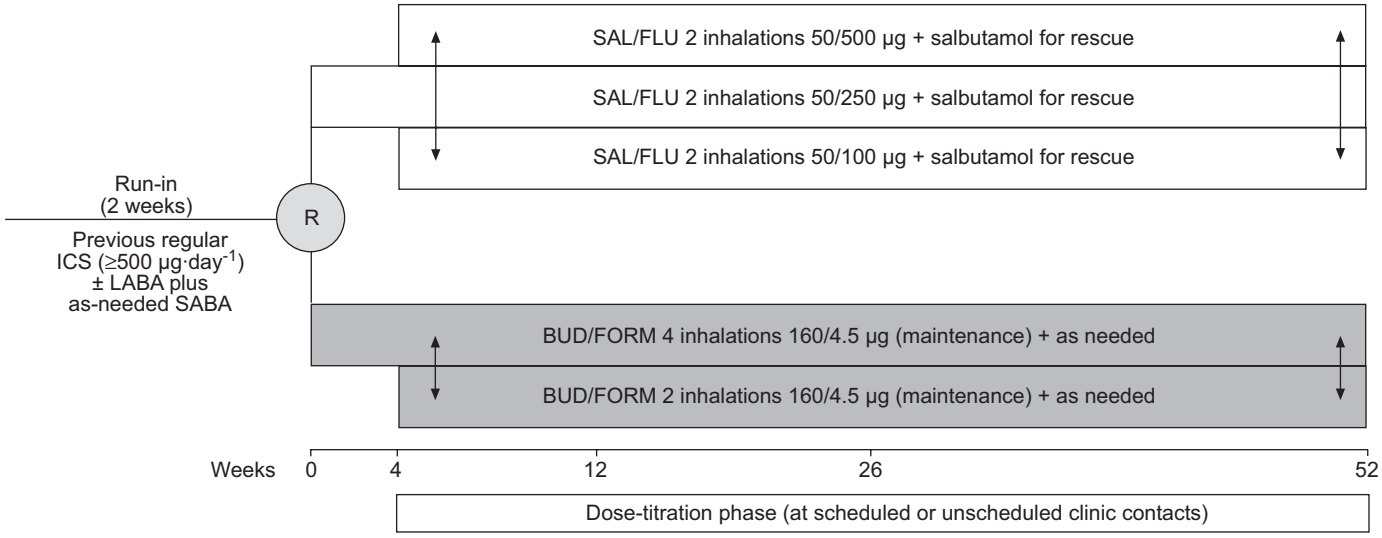

FIGURE 1. Study design. SAL/FLU: salmeterol/fluticasone; BUD/FORM: budesonide/formoterol; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; SABA: short-acting β_2-agonist; R: randomisation.

Other assessments

Clinic spirometry was determined both pre- and post-terbutaline 1.0 mg (Bricanyl® Turbuhaler®; AstraZeneca). The best of three satisfactory FEV1 tests was recorded [19].

At each clinic visit, patient-reported maintenance and as-needed medication use during the preceding 2 weeks was recorded. Total ICS use was calculated from the prescribed maintenance dose; self-reported as-needed medication use was also included for the budesonide/formoterol group.

The Asthma Control Questionnaire (five-item version; ACQ-5) [20] was completed by patients at each clinic visit. This included five questions on the burden of symptoms. Each question was scored on a scale of 0–6, where 0 represents no symptoms. Health-related quality of life was assessed at each clinic visit using the standardised version of the Asthma Quality of Life Questionnaire (AQLQ(S)), consisting of 32 questions [21]. Each of the 32 questions was scored on a scale of 1–7, where 7 represented the least impairment; scores were summed to obtain an overall score. A change in ACQ-5 and AQLQ(S) overall scores of $\geqslant 0.5$ is considered clinically relevant [22, 23].

Adverse events (AEs) reported spontaneously and in response to a standard question at visits 2–6 were recorded.

Statistical analysis

The intent-to-treat population was used for all analyses. A total of 1,000 patients·group^{-1} was required to have a 90% chance of detecting a reduction from 15% to 10% in the proportion of patients with severe exacerbations (at the two-sided 5% significance level).

Time to first severe exacerbation was compared between groups using a log-rank test and further described using a Cox proportional hazards model stratified for country with treatment as factor. The rate of severe exacerbations·patient^{-1}·yr^{-1} was compared between treatment groups using a Poisson regression model with treatment and country as factors and time in the study as an offset variable.

Mean use of as-needed medication was calculated from all patient estimates during the treatment period. The treatment groups were compared using an ANOVA with treatment and country as factors. A *post hoc* analysis was performed at the final visit to assess patients' as-needed use during the last 2 weeks of the study to define good symptom control. The odds of using $\leqslant 4$ as-needed inhalations·week^{-1} were compared between treatments using a logistic regression model with treatment and country as factors.

FEV1 and overall ACQ-5 score were analysed as change from baseline using the average of all measurements during the treatment period. Overall AQLQ(S) was analysed as change from baseline to visit 6. Analyses were performed using ANOVA with treatment and country as factors and the baseline value as a covariate.

RESULTS

Of the 2,509 patients enrolled, 2,143 were randomised to receive maintenance plus as-needed budesonide/formoterol (n=1,067) or salmeterol/fluticasone plus salbutamol for rescue (n=1,076). A total of 2,135 patients were included in the efficacy and safety analyses (no data were available for eight patients following randomisation). A total of 269 patients (119 budesonide/formoterol patients and 150 salmeterol/fluticasone patients) discontinued the study: 83 because eligibility criteria were violated (37 *versus* 46, respectively); 34 because of AEs (13 *versus* 21, respectively); 34 were lost to follow-up (15 *versus* 19, respectively) and 118 for other miscellaneous reasons (54 *versus* 64, respectively). Baseline characteristics were comparable between groups (table 1).

Exacerbations

The time to first severe exacerbation was prolonged in patients using maintenance plus as-needed budesonide/formoterol

TABLE 1 Patients' baseline characteristics

Characteristic	SAL/FLU + salbutamol	BUD/FORM maintenance + as needed
Patients n	1076	1067
Sex M:F	429:647	451:616
Age yrs	45 (12–84)	45 (12–80)
Asthma duration yrs	12 (0–74)	13 (1–75)
FEV1 (pre-terbutaline) % predicted	73 (28¶–100¶)	73 (39¶–115¶)
FEV1 reversibility %	13	13
ICS dose at entry μg·day^{-1}#	881 (400¶–3000)	888 (50¶–2000)
Baseline ICS medication type % patients BUD/FLU/BDP	63/24/13	60/25/15
Inhaled LABA use at study entry n (%) patients	409 (38)	402 (38)
Reliever use inhalations·24 h^{-1}	2.7 (0.3¶–33.7)	2.6 (0.2¶–10.7)
Use of ⩽4 inhalations of as-needed medication·week^{-1} % patients	5	5
Overall ACQ-5 score	1.87 (0.00–5.00)	1.86 (0.00–5.20)
Overall AQLQ(S) score	4.95 (1.19–7.00)	4.97 (1.75–7.00)

Data are presented as mean (range), unless otherwise stated. SAL/FLU: salmeterol/fluticasone; BUD/FORM: budesonide/formoterol; FEV1: forced expiratory volume in one second; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate; LABA: Long-acting β_2-agonist; ACQ-5: Asthma Control Questionnaire 5-item score; AQLQ(S): Asthma Quality of Life Questionnaire (Standardised). #: mean not adjusted for type of ICS or inhaler choice; minimum doses of ICS stipulated at entry were: BUD 500 μg·day^{-1}, FLU 500 μg·day^{-1} and BDP 1,000 μg·day^{-1} for either metered or delivered doses; ¶: deviation from inclusion criteria (included in the intention-to-treat population).

versus salmeterol/fluticasone plus salbutamol (p=0.0051). The instantaneous risk of having a severe exacerbation was 25% lower in the budesonide/formoterol group (95% confidence intervals (CI) 7–39%; p=0.0076). The risk of a severe exacerbation excluding unscheduled visits was reduced by a comparable extent (23%; 95% CI 3–39%; p=0.025). The total rate of severe exacerbations was 22% lower with maintenance plus as-needed budesonide/formoterol *versus* salmeterol/fluticasone (95% CI 9–44%; p=0.0025), with annual rates of 0.24 *versus* 0.31 events·patient^{-1}·yr^{-1}, for the two groups, respectively. By extrapolation, treating 100 patients for a year with the budesonide/formoterol regimen *versus* the salmeterol/fluticasone regimen would prevent seven severe exacerbations (number needed to treat=14). A small between-group difference in the total number of severe exacerbations emerged before the start of the dose-titration phase and continued to increase thereafter (fig. 2). The overall reduction in severe exacerbation rate between the budesonide/formoterol and salmeterol/fluticasone groups, seven severe exacerbations·100 patients^{-1}·year^{-1}, largely reflected the size of the efficacy difference observed between the groups in the 11-month dose-titration period (six severe exacerbations·100 patients^{-1}·yr^{-1}). A small treatment benefit (although not significant; p=0.38) was apparent for severe exacerbations requiring emergency treatment (fig. 3). The overall exacerbation burden was reduced in patients treated with budesonide/formoterol compared with salmeterol/fluticasone-treated patients, as demonstrated by the following (descriptive statistics): 36% reduction in the total number of days with severe exacerbations of any type (2,053 *versus* 3,200, respectively); 24% reduction in unscheduled visits (117 *versus* 154, respectively); 34% reduction in oral steroid days due to severe exacerbations (1,980 *versus* 2,978, respectively); 16% reduction in ER visits (38 *versus* 45, respectively) and 37% reduction in hospital days (59 *versus* 94, respectively).

Lung function

An early improvement in pre- and post-terbutaline FEV1 was observed in both groups during the first 4 weeks of treatment and these improvements were sustained throughout the dose-titration phase. A small statistically significant difference in post-terbutaline FEV1 was observed in favour of patients in the budesonide/formoterol group (table 2).

As-needed medication use

The use of as-needed medication was substantially reduced during the first 4 weeks of the study in both groups, with additional modest reductions throughout the dose-titration phase. The budesonide/formoterol group used 45% less as-needed medication than those receiving salmeterol/fluticasone plus salbutamol before dose titration (0.59 *versus* 1.07 inhalations·day^{-1}) and 35% less at study completion (0.51 *versus* 0.79 inhalations·day^{-1}). Over the entire treatment period, patients receiving budesonide/formoterol for maintenance plus as needed used 38% less as-needed medication than those

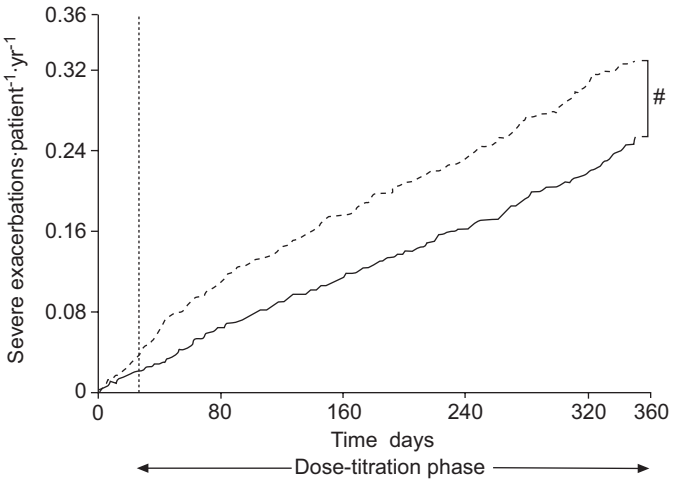

FIGURE 2. Cumulative rate plot of time to first and repeat severe asthma exacerbations in both treatment groups (----: salmeterol/fluticasone and salbutamol for rescue; ——: budesonide/formoterol maintenance and as needed). The vertical dotted line marks the start of the dose-titration phase. #: p=0.0025 (Poisson regression analysis of the rate of exacerbations).

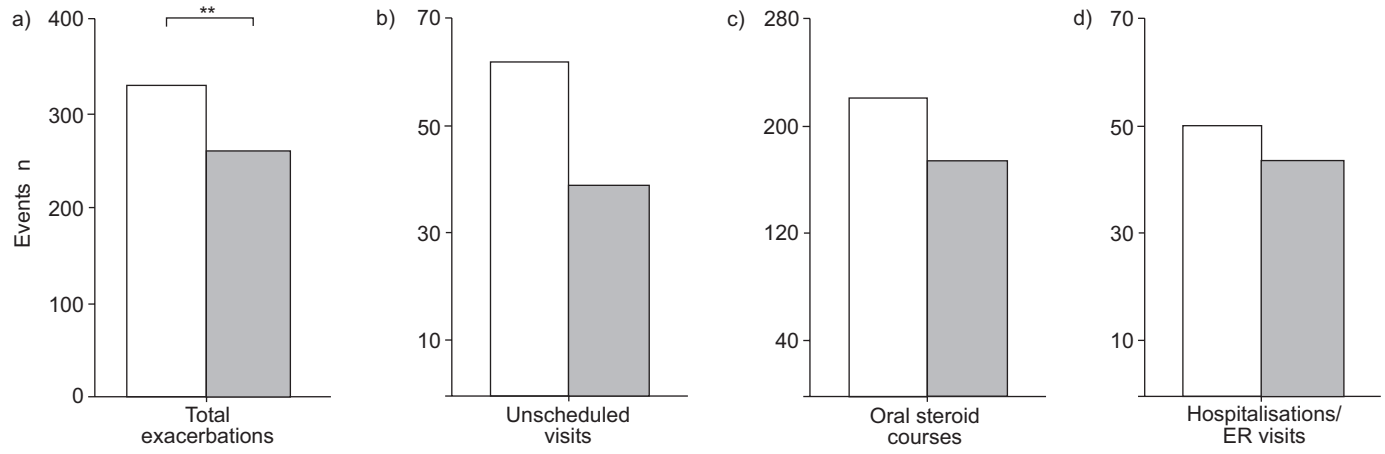

FIGURE 3. Total number of all severe exacerbations (a) and exacerbations by subtype (b–d). Subtypes are presented here as mutually exclusive categories and were defined in order of increasing severity as follows: unscheduled visits; oral steroid courses; hospitalisation/emergency room (ER) visits. Exacerbations fulfilling ⩾1 subtype were categorised by the most severe criterion. □: salmeterol/fluticasone and salbutamol for rescue; ■: budesonide/formoterol maintenance and as needed. **: $p<0.01$, statistically significant between-group difference derived from Poisson regression analysis of the rate of exacerbations.

receiving salmeterol/fluticasone plus salbutamol (0.58 *versus* 0.93 inhalations·day^{-1}; $p<0.001$). Figure 4 shows the proportion of patients using a maximum of 4 as-needed inhalations·week^{-1} or >4 as-needed inhalations·week^{-1} in the last 2 weeks of the study. Overall, the majority of patients in both groups used a maximum of 4 as-needed inhalations·week^{-1} (76% and 66% of the budesonide/formoterol and salmeterol/fluticasone groups, respectively) compared with 5% of patients in both groups during run-in. The odds of using a maximum of four as-needed inhalations·week^{-1} was higher in the budesonide/formoterol group compared with the salmeterol/fluticasone group (odds ratio 1.68; 95% CI 1.38–2.05; $p<0.001$).

TABLE 2 Clinical outcomes

Variable	SAL/FLU + salbutamol	BUD/FORM maintenance + as needed	p-value
Patients n	1076	1067	
All severe exacerbations			
Patients with event n (%)	204 (19)	159 (15)	0.0076#
Rate events·patient^{-1}·yr^{-1}	0.31	0.24	0.0025¶
Severe exacerbations excluding unscheduled clinic visits			
Patients with event n (%)	167 (16)	132 (12)	0.025#
Rate events·patient^{-1}·yr^{-1}	0.23	0.19	0.023¶
Severe exacerbations due to ER visits/ hospitalisations			
Patients with event n (%)	46 (4)	31 (3)	0.18#
Rate events·patient^{-1}·yr^{-1}	0.05	0.04	0.38¶
Adjusted mean change in FEV_1 (pre-terbutaline) from baseline	0.14	0.17	0.066
Adjusted mean change in FEV_1 (post-terbutaline) from baseline	0.04	0.07	0.045
Mean as-needed use inhalations·day^{-1}	0.93	0.58	<0.001
Adjusted mean change in overall ACQ-5 score from baseline	-0.58	-0.64	0.069
Adjusted mean change in overall AQLQ(S) score from baseline	0.57	0.60	0.51

SAL/FLU: salmeterol/fluticasone; BUD/FORM: budesonide/formoterol; ER: emergency room; FEV_1: forced expiratory volume in one second; ACQ-5: Asthma Control Questionnaire 5-item score; AQLQ(S): Asthma Quality of Life Questionnaire (Standardised). #: p-values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazards model); ¶: p-values based on relative rate analysis (Poisson regression).

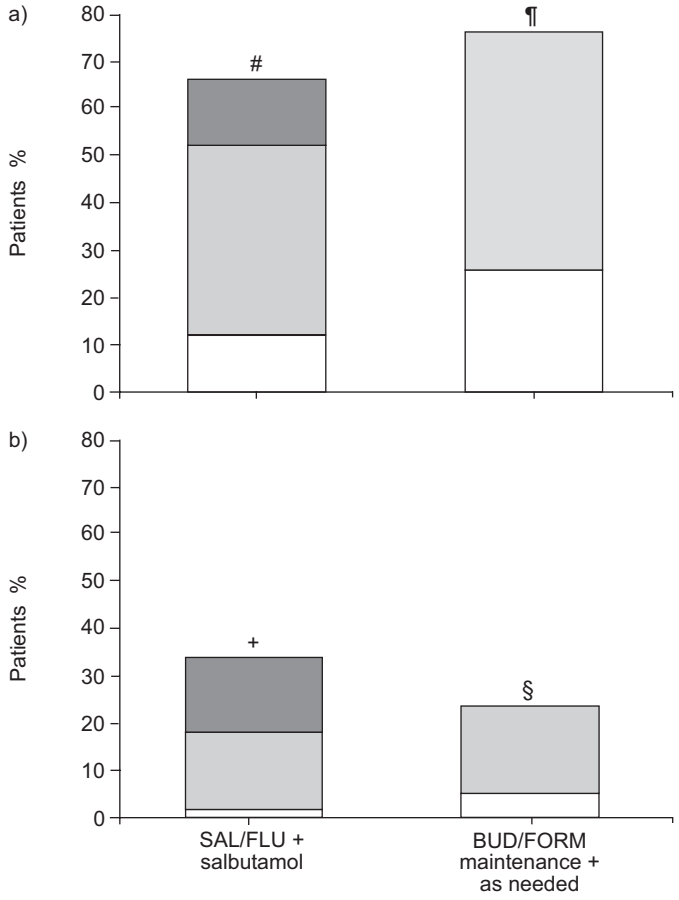

FIGURE 4. The proportion of patients in the last 2 weeks of the study using a) low levels of as-needed medication (a maximum of 4 as-needed inhalations·week^{-1}) or b) higher levels (>4 as-needed inhalations·week^{-1}). Data are split by the average daily maintenance inhaled corticosteroid (ICS) dose, defined by guidelines [18] as: low or moderate dose, or high dose (for fluticasone patients only). SAL/FLU: salmeterol/fluticasone; BUD/FORM: budesonide/formoterol. ■: high maintenance ICS dose; ■: moderate maintenance ICS dose; □: low maintenance ICS dose. #: n=688; ¶: n=787; +: n=350; §: n=247.

Overall study drug use

Patients in both groups used a similar total microgram dose of budesonide or fluticasone, averaged over the whole treatment period (mean daily dose: 562 μg (maintenance) + 91 μg (as-needed) for budesonide/formoterol patients *versus* 583 μg (maintenance only) for salmeterol/fluticasone patients). The corresponding values expressed as equivalent beclomethasone dipropionate (BDP) doses [18] were 1,019 μg·day^{-1} for budesonide/formoterol (maintenance and as-needed) *versus* 1166 μg·day^{-1} for salmeterol/fluticasone (maintenance only). When subdividing patients by as-needed medication use at study completion (fig. 4), the total mean daily ICS dose in low as-needed users was: budesonide 537 μg·day^{-1} (BDP equivalent 838 μg·day^{-1}) *versus* fluticasone 547 μg·day^{-1} (BDP equivalent 1,094 μg·day^{-1}). The total mean daily ICS dose in patients with high as-needed use (>4 inhalations·week^{-1}) was: budesonide 910 μg·day^{-1} (BDP equivalent 1,420 μg·day^{-1}) *versus* fluticasone 701 μg·day^{-1} (BDP equivalent 1,402 μg·day^{-1}).

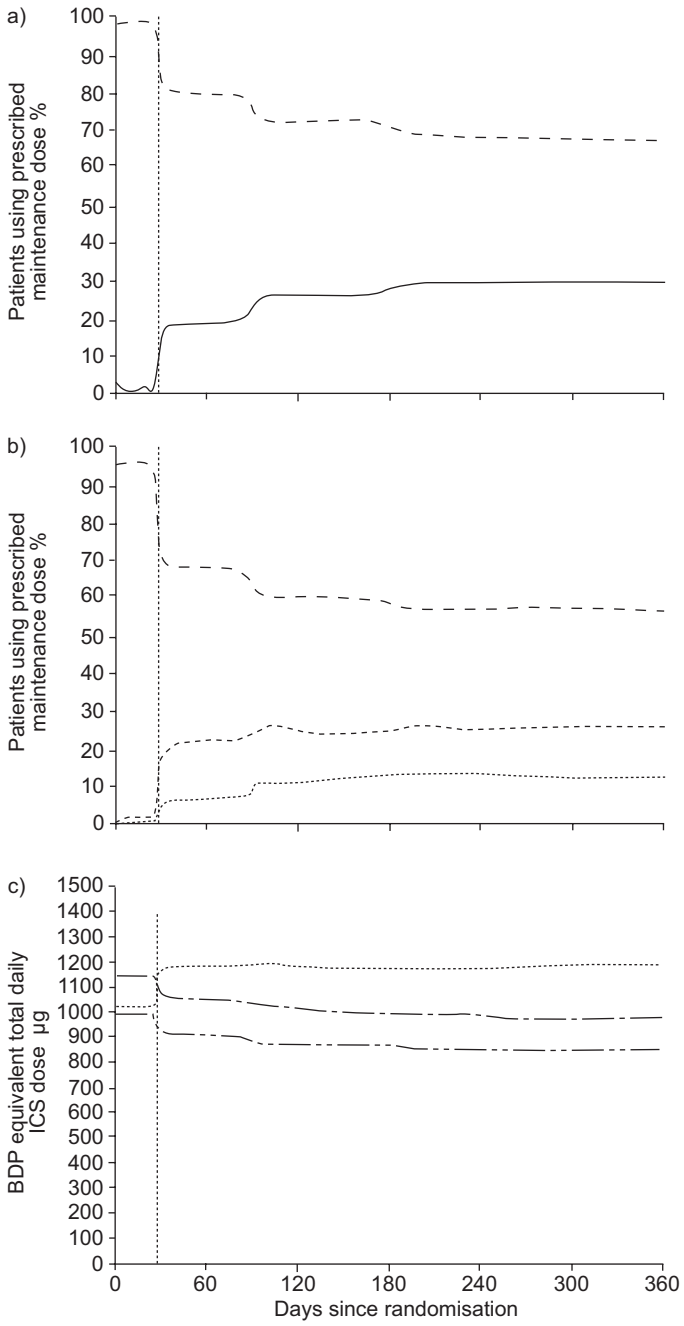

FIGURE 5. The changes in maintenance medication levels over time. a) Percentage of patients using 2 (——) or 4 (– – –) inhalations·day^{-1} of budesonide (BUD)/formoterol (FORM) (160/4.5 μg); b) percentage of patients using each strength of salmeterol (SAL)/fluticasone (FLU) (50/100 μg 2 inhalations·day^{-1} (·····), 50/250 μg 2 inhalations·day^{-1} (– – –) and 50/500 μg 2 inhalations·day^{-1} (- - -)); c) mean total daily inhaled corticosteroid (ICS) dose shown graphically as equivalent beclomethasone dipropionate (BDP) dose (BUD 640 μg·day^{-1} or FLU 500 μg·day^{-1}= BDP 1,000 μg·day^{-1} [18]) (·····: SAL/FLU + salbutamol for rescue; – – –: BUD/FORM (maintenance and as needed); – - - –: BUD/FORM (maintenance only)). The vertical dotted line marks the start of the dose-titration phase.

Approximately 40% of salmeterol/fluticasone patients received the maximum maintenance dose (100/1,000 μg·day^{-1}) at some time during the study and 27% completed the study on

TABLE 3 Study drug cost (€[#]) per patient per yr[¶]

Country	SAL/FLU + salbutamol			BUD/FORM maintenance + as needed		Between-group difference (95% CI)	% difference
	Cost·inhalation^{-1} SAL/FLU 50/100–50/500 μg	Cost·inhalation^{-1} salbutamol[+]	Total cost·yr^{-1}	Cost·inhalation^{-1}	Total cost·yr^{-1}		
Italy	0.77–1.45	0.02	815	0.58	835	20 (1–40)	+2
France	0.71–1.17	0.03	665	0.48	691	26 (11–43)	+3
UK	0.81–1.06	0.03	701	0.46	668	-33 (-48– -17)	-5
Germany	0.81–1.72	0.07	910	0.57	821	-89 (-111– -67)	-10

SAL/FLU: salmeterol/fluticasone; BUD/FORM: budesonide/formoterol; CI: confidence interval. [#]: GBP 1=€1.45 (December 3, 2004); [¶]: the costs presented relate to drugs only and do not include healthcare utilisation; [+]: patients were allowed to use salbutamol *via* dry-powder inhaler in some countries and *via* pressurised metered-dose inhaler in other countries. The cost used in this estimation is based on the relative use of dry-powder inhaler and pressurised metered-dose inhaler in the respective countries.

this dose. Overall, 32% of salmeterol/fluticasone patients had their dose stepped down at some point during the study (13% from the maximum dose), with 14% completing the study on the lowest dose.

In the budesonide/formoterol group, 39% of patients halved their maintenance dose from 640/18 μg·day^{-1} to 320/9 μg·day^{-1} (4 *versus* 2 maintenance inhalations·day^{-1}) during the study and 31% completed the study on this dose. Dose titration occurred early in the study, predominantly at the week 4 post-randomisation visit (fig. 5a, b). From week 4, the mean total dose of ICS decreased in the budesonide/formoterol group with a contrasting increase in the salmeterol/fluticasone group (fig. 5c).

The mean total number of inhalers/patient prescribed during the study was 12.7 in the budesonide/formoterol group compared with 16.6 in the salmeterol/fluticasone group (11.6 maintenance (up to three separate strengths) plus 5.0 salbutamol inhalers). The majority of patients (55%) in the salmeterol/fluticasone group used two different strengths of their maintenance inhaler plus one salbutamol inhaler; patients receiving budesonide/formoterol used one type of inhaler (of the same strength) for both maintenance and as-needed throughout the study.

Study drug cost·patient^{-1}·yr^{-1} was estimated for four major European Union countries participating in the study. The cost of medication was similar between the two groups (table 3).

Health-related quality of life

Total ACQ-5 scores improved from baseline in both groups, indicating improvement in daily symptoms, but there was no statistically significant difference between groups (table 2). A clinically relevant change from baseline ($\geqslant$0.5 unit decrease) in overall score was reported in ~50% of patients in both groups. Overall AQLQ(S) scores also improved from baseline to a similar extent in both groups (table 2).

Safety

Both treatments were well tolerated and there were no notable differences between the groups in the number or severity of AEs. There were 168 serious AEs (80 *versus* 88 for budesonide/formoterol *versus* salmeterol/fluticasone patients, respectively). Overall, one patient in the budesonide/formoterol group and two patients receiving salmeterol/fluticasone had serious AEs that were considered by the investigator to be causally related to study medication. Although a comparable number of patients discontinued the study due to AEs (27 budesonide/formoterol patients *versus* 28 salmeterol/fluticasone patients), a greater number of salmeterol/fluticasone patients withdrew owing to asthma *versus* budesonide/formoterol patients (11 *versus* three patients, respectively). Two deaths occurred during the treatment period in the salmeterol/fluticasone group, but these were not judged to be causally related to the investigational products.

DISCUSSION

In this randomised 12-month study, the current treatment paradigm for the management of persistent asthma (daily maintenance combination therapy plus salbutamol as rescue medication) was compared with a simplified strategy using budesonide/formoterol for both maintenance and as-needed symptom relief. The open-label design enabled the current authors to establish the overall treatment benefits of this approach in conditions closely mirroring routine clinical practice.

Both budesonide/formoterol for maintenance plus as-needed and the salmeterol/fluticasone regimen (both titrated in line with physician judgment) improved all efficacy variables compared with baseline, and both treatments were well tolerated. Maintenance plus as-needed budesonide/formoterol was, however, associated with a reduced risk of severe exacerbations compared with the salmeterol/fluticasone plus salbutamol regimen.

The definition of a severe exacerbation included unscheduled clinic visits, which may have been due to patients only requiring their maintenance dose to be altered in response to poor symptom control. Importantly, the reduced risk of a severe exacerbation in the budesonide/formoterol group was similar regardless of whether unscheduled clinic visits were included, emphasising that the primary end point was a robust measure both including and excluding this criterion. The

reduction in severe exacerbations associated with the use of budesonide/formoterol for maintenance and reliever therapy was reflected by fewer oral steroid days (~1,000 fewer) and hospital days (35 fewer) compared with the salmeterol/fluticasone regimen. The findings from the current study support the favourable efficacy and safety profiles of budesonide/formoterol maintenance and reliever therapy reported in three recent double-blind studies including >5,000 patients [13, 24, 25] and further validate the effectiveness of this simplified asthma treatment strategy.

The additional control observed in the budesonide/formoterol group was not achieved as a result of patients over-relying on their as-needed medication. The use of as-needed medication was reduced by 38% during the 12-month study with the budesonide/formoterol regimen *versus* salmeterol/fluticasone plus salbutamol. Previous studies where a short-acting bronchodilator rescue medication, such as salbutamol or terbutaline, was replaced by formoterol in patients receiving combination therapy have reported ~10% reductions in as-needed medication use [26, 27]. Thus, the greater reduction in as-needed medication use observed in the present study with the budesonide/formoterol regimen may reflect the improved asthma control provided by as-needed budesonide when used in combination with as-needed formoterol.

Patients' symptomatic improvement was similar in both groups, as reflected by ACQ-5 and AQLQ scores. The symptom-based ACQ-5 questionnaire used in the present study excludes as-needed medication use, which is included in the ACQ-6. However, it may be speculated that the ACQ-6 would have provided increased sensitivity compared with the ACQ-5, given that differences in as-needed medication use were observed in favour of the budesonide/formoterol regimen. The majority of patients in both groups (76% *versus* 66% for the budesonide/formoterol and salmeterol/fluticasone groups, respectively) used a maximum of 4 as-needed inhalations·week^{-1} at study completion, one of the guideline criteria for ''well-controlled asthma'' in the Gaining Optimal Asthma controL (GOAL) study [15] and other studies [28–30]. The budesonide/formoterol regimen achieved this outcome using a low or moderate daily maintenance ICS dose, in accordance with guidelines [18].

In the present study, the inclusion of a dose-titration phase ensured that all patients could have their maintenance therapy decreased or increased as required. It was hypothesised that the use of as-needed budesonide/formoterol would reduce exacerbations and improve asthma control without the need for high maintenance doses (>640/18 μg·day^{-1}). Consequently, although the dose of salmeterol/fluticasone could be increased to the highest maintenance dose available (100/1,000 μg·day^{-1}; ~40% of patients used this dose and 27% completed the study on this dose), there was no option to step up to high maintenance doses of budesonide/formoterol in the study protocol. The findings that exacerbation rate and as-needed use were reduced and FEV1 improved in the budesonide/formoterol group compared with the salmeterol/fluticasone group support the hypothesis.

A recent study involving >3,000 patients aimed to improve asthma control by progressively up-titrating the maintenance ICS dose in patients receiving either salmeterol/fluticasone or fluticasone alone [15]. The majority of salmeterol/fluticasone patients previously prescribed moderate maintenance doses of ICS (Stratum 3), achieved a high level of asthma control (''well-controlled'' asthma) at the starting maintenance dose (100/500 μg·day^{-1}) [15]. However, only one in four patients who did not attain control at the starting dose achieved control when the ICS dose was doubled [15]. The present study, although focusing on self-reported as-needed medication to define symptom control instead of a composite measure [15], also confirmed that more patients achieve good symptom control with low or moderate doses of salmeterol/fluticasone, compared with the highest dose (fig. 4) [18]. This provides additional evidence that a treatment regimen involving an increase of the maintenance ICS dose alone has limited additional benefit in improving symptom control in most patients [7, 15, 31–34]. Such a regimen may result in over-treatment with ICS, potentially increasing the risk of long-term side-effects [33, 35].

A key treatment benefit of the budesonide/formoterol regimen exemplified in the present study was the use of one inhaler for maintenance plus as-needed treatment. Most patients (55%) receiving the salmeterol/fluticasone plus salbutamol regimen required three different inhalers (two different maintenance strengths plus one salbutamol inhaler). As a result of these contrasting treatment regimens, budesonide/formoterol patients were prescribed approximately four fewer inhalers·patient^{-1}·yr^{-1} compared with the salmeterol/fluticasone group. Further studies are needed to determine whether the simplicity of using a single inhaler for both maintenance and as needed also improves patient adherence. Importantly, the findings from the current study indicate that the budesonide/formoterol regimen did not add to the overall drug cost *versus* the salmeterol/fluticasone regimen. Given the reduction in exacerbations observed with the budesonide/formoterol regimen, further analysis of the cost-effectiveness of this management approach may be warranted.

Both treatment regimens were found to be similarly well tolerated over the 12-month study. A concern of using an ICS/LABA inhaler for both maintenance and as-needed relief is that patients may overuse their medication. However, in addition to reducing as-needed medication use, the budesonide/formoterol regimen resulted in a greater number of patients having their maintenance dose stepped down at the end of the study compared with those receiving salmeterol/fluticasone (31% *versus* 14% of patients, respectively). These findings suggest that this simplified treatment approach is unlikely to result in the overuse of medication in clinical practice.

As the aim of the present study was to closely replicate the real-life clinical setting, physicians were not blinded to treatment. The open-label design was the best method to investigate the effectiveness of the contrasting treatment regimens, enabling the budesonide/formoterol single inhaler regimen to be followed without a separate as-needed inhaler, as would occur in real life. This design also allowed the physicians to titrate maintenance doses up or down easily, as appropriate, to adapt the dose to the clinical situation without the need for a complex double-dummy study design. Clinically relevant exacerbations and as-needed medication use were the

key effectiveness measures, as often used in clinical practice. In addition, patients were not excluded from the study based on reversibility criteria as in standard efficacy trials of LABA therapy [7, 13, 15], a factor potentially reducing the applicability of clinical trial findings to routine clinical practice [16].

Although greater improvements in exacerbation rate and as-needed medication use were demonstrated with budesonide/formoterol *versus* salmeterol/fluticasone, caution should be used when interpreting the differences given the open-label design used in this study. A further potential limitation of the study design was that, as titration of maintenance medication was left to physician judgement and was not protocol driven, patients could have been inadvertently undertreated, especially given that the salmeterol/fluticasone group used only salbutamol for as-needed relief. However, there was no evidence that patients were undertreated with maintenance medication in the present study. The rate of exacerbations defined by oral steroid courses and emergency treatments was 0.23 events·patient^{-1}·yr^{-1} with salmeterol/fluticasone, and the proportion of salmeterol/fluticasone patients defined as having well-controlled asthma based on rescue use, increased from 5% during run-in to 66% at study completion. In a recent study, patients receiving salmeterol/fluticasone 100/500 μg·day^{-1} with upwards protocol-driven dose titration (without downward titration) had an exacerbation rate (using the same definition) of 0.27 events·patient^{-1}·yr^{-1}, and less than two-thirds of patients achieved a well-controlled status based on a composite measure of asthma control [15]. Indeed, a comparison with the study by BATEMAN *et al*. [15], in which patients' asthma was of a similar or lower severity to that in the current study, highlights the extent to which asthma control improved in both treatment groups in the present study. In conclusion, the current study provides evidence that treating asthma with a novel regimen of maintenance plus as-needed budesonide/formoterol is both highly effective and safe in a study setting mirroring normal clinical practice.

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