Adjustable maintenance dosing with budesonide/formoterol in a single inhaler – efficacy and safety

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SUMMARY

Asthma guidelines support adjustable maintenance dosing and the use of guided self-management for long-term asthma management and advocate the use of inhaled corticosteroids and long-acting β_2-agonists to control symptoms. In this context, budesonide/formoterol in a single inhaler may be used with either a fixed-dosing or adjustable maintenance dosing treatment regimen. Eight randomised studies compared the efficacy and tolerability of budesonide/formoterol adjustable maintenance dosing (one to two inhalations bid with a temporary step-up to four inhalations bid maximum) with fixed-dosing (two inhalations bid). In three studies ($\geq$6 months in duration), a reduced incidence of exacerbations was reported with adjustable maintenance dosing compared with fixed-dosing. In all studies, adjustable maintenance dosing reduced the mean number of inhalations of budesonide/formoterol per patient per day compared with fixed-dosing while maintaining or improving asthma control. Adjustable maintenance dosing with budesonide/formoterol is well tolerated and has proven to be a more effective treatment strategy for asthma management, despite using less amount of drug compared with fixed-dosing.

Keywords: Asthma; budesonide/formoterol; adjustable maintenance dosing; efficacy; tolerability

INTRODUCTION

The objective of asthma treatment to gain and maintain effective control of asthma, allowing patients to live as normally as possible (1,2), is feasible with an adjustable maintenance dosing strategy. Adjustable maintenance dosing coupled with a personalised asthma action plan is a realistic approach to treating patients with asthma and has many potential benefits (3). A key aim is to individualise treatment so that control of asthma is achieved without under- or over-treating the patient. This aspect of asthma management can be resolved with an adjustable maintenance dosing regimen. As discussed by Fabbri and colleagues (4), the alternative is traditional, fixed dosing; however, this treatment approach may not be the optimal solution for controlling asthma in all situations. Fixed-dose regimens are limited in their ability to maintain overall asthma control (5), and patients considered well controlled on these regimens still experience occasional worsening of symptoms, exacerbations or both, caused by the natural variability of asthma (6). Therefore, the use of guided self-management with adjustable maintenance dosing has been proposed as an alternative treatment approach for improved long-term asthma management.

Not all treatments are suitable for, and compatible with, this flexible approach to asthma management using only one maintenance inhaler. The suitability of Symbicort® (budesonide/formoterol in a single inhaler) for an adjustable maintenance dosing approach has been discussed in detail elsewhere in this supplement (3). As well as proven efficacy and safety at different doses (7–11), the main attribute of budesonide/formoterol that allows it to be considered for this flexible programme (where patients adjust their treatment dose according to their symptoms), is the clear dose–response profiles of both formoterol and budesonide in patients with increasing asthma severity (3). Thus, increased use of budesonide/formoterol during periods of asthma worsening should result in increased effectiveness relative to a fixed dose. As a result of these unique dosing properties with one inhaler, with an approved dose range of one to four inhalations bid in Europe and Canada, budesonide/formoterol is the only currently available combination treatment that can be considered for use in a symptom-driven adjustable maintenance dosing regimen.

Here, we review the results from the first national and international studies in the Symbicort Adjustable Maintenance Dosing (SAMD) programme. The efficacy and tolerability of adjustable maintenance dosing with budesonide/formoterol in a single inhaler, fixed dosing with budesonide/formoterol and fixed dosing with fluticasone/salmeterol are evaluated.

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ADJUSTABLE MAINTENANCE DOSING STUDY PROGRAMME

An overview of the SAMD study designs and patient characteristics are summarised in Table 1, with additional details provided elsewhere in this supplement (3). Seven national, 4–7-month randomised studies compared budesonide/formoterol adjustable maintenance dosing with traditional fixed dosing in Switzerland, Belgium, Italy, Germany, Sweden, Canada and the UK. An additional European multinational study also compared budesonide/formoterol adjustable maintenance dosing and fixed dosing with fluticasone/salmeterol fixed dosing. All of the studies were open label, to reflect the real-life situation of using a single inhaler for adjustable maintenance dosing (the alternative double-dummy, placebo-controlled design, to allow dose adjustments up and down, would have required three to four study inhalers per treatment arm plus an additional reliever medication). The SAMD study programme is the first to look in detail at guided self-management using an inhaled corticosteroid and a long-acting β_2-agonist in a single inhaler. This article presents the first overview of the SAMD study programme.

Patients

In the eight studies considered in this review, over 10,000 patients were randomised to adjustable maintenance dosing or fixed dosing. With the exception of the European multinational study, all patients entered a 1-month run-in period where they received two inhalations bid of budesonide/formoterol (80/4.5 μg or 160/4.5 μg). Patients were then randomised to treatment with adjustable maintenance dosing (budesonide/formoterol one to eight inhalations daily, based on their level of asthma control) or fixed dosing (budesonide/formoterol two inhalations bid) for a further 3–6 months. In the European multinational study, a fixed-dose fluticasone/salmeterol arm (250/50 μg bid) was also included.

In all eight studies, patients were able to increase their maintenance dose, temporarily, to a maximum of eight inhalations daily for 7 or 14 days based on clinical need, in accordance with their action plan. In the European multinational study, patients used their regular inhaled corticosteroid treatment during a 10–14-day run-in and were then randomised, double-blind, into one of three groups for a 1-month fixed-treatment period: two groups received budesonide/formoterol of 160/4.5 μg bid and the other group received fluticasone/salmeterol of 250/50 μg bid. On commencing the 6-month, open-label treatment period, one of the two budesonide/formoterol groups was allocated to adjustable maintenance dosing and the other to fixed dosing.

Within the SAMD programme, variations in the asthma action plan were incorporated to reflect usual, real-life clinical practice in the individual countries (Table 1) (12–19).

Efficacy assessments

Measurements used to assess efficacy are summarised elsewhere in this supplement (3). However, it should be noted that the primary and secondary efficacy measures varied according to the individual study (3). Primary variables included: total dose of inhaled budesonide/formoterol in the randomised study period (Belgian study), treatment failure/exacerbation (Belgian, Italian, UK, Canadian, Swedish and Swiss studies) and odds ratio of having a well-controlled asthma week (European multinational study). Treatment failure was also a secondary variable in the German study, in which the primary variable was health-related quality of life (HRQL). Although the definitions varied between studies, exacerbations (treatment failures) were generally defined as one or more of the following: asthma-related serious adverse events (SAEs), use of oral corticosteroids or hospitalisation/emergency treatment. In several studies, including the Canadian study, any increase in maintenance asthma medication needed to maintain asthma control was also included; protocol increases as part of the adjustable maintenance dosing plan were not classified as exacerbations. Treatment success was measured as the change in the proportion of patients meeting each category of control, intermittent, mild persistent, moderate persistent and severe persistent according to the National Institutes of Health, National Heart, Lung and Blood Institute (NHLBI) criteria (20). The Canadian study used a modification of the NHLBI severity stage definitions (17). Investigators assessed other efficacy variables during visits and from patient diaries. Those common to all of the studies are presented in Table 2.

Safety

Adverse events (AEs), SAEs and discontinuations due to AEs (DAEs) were recorded in patient diaries and assessed by investigators during patient visits.

RESULTS

Demographic data and the size of the eight studies are summarised in Table 1. The total number of patients included in this review was 5285 for adjustable maintenance dosing with budesonide/formoterol, 5198 for fixed dosing with budesonide/formoterol and 224 for fixed dosing with fluticasone/salmeterol. Asthma severity, based on lung-function tests [forced expiratory volume in 1 s (FEV_1)] and pre-study doses of inhaled corticosteroids, indicated that patients were well balanced across all studies in both the fixed and adjustable maintenance dosing groups.

Efficacy

In the 6–7-month studies (Canadian, Swedish and European multinational), there were significant differences in exacerbation control in favour of the adjustable maintenance dosing groups compared with the fixed-dosing groups. Exacerbation data were expressed as the proportion of patients experiencing

Table 1 Study design

Reference (in order of first publication)	*Country (number of randomised patients)*	*Study duration (months)*	*B/F inhaler strength (μg)*	*Number of inhalations used during step-up**	*Mean FEV_1 (% predicted normal)*	*Mean pre-study ICS (μg/day)*
Leuppi et al. 2003 (12)	Switzerland ($n=127$) Adjustable ($n=69$) Fixed ($n=58$)	4	160/4.5	Two or four bid	79	≥600†
Michils et al. 2003 (13)	Belgium ($n=980$) Adjustable ($n=490$) Fixed ($n=490$)	5	160/4.5	Two qid	73	≥400†
Canonica et al. 2004 (14)	Italy ($n=2063$) Adjustable ($n=1030$) Fixed ($n=1033$)	4	80/4.5 and 160/4.5	Four bid	85	715
Buhl et al. 2004 (15)	Germany ($n=3297$) Adjustable ($n=1679$) Fixed ($n=1618$)	4	160/4.5	Two or four bid	N/A	<1000†
Ställberg et al. 2003 (16)	Sweden (1034) Adjustable ($n=517$) Fixed ($n=517$)	7	80/4.5 and 160/4.5	Four bid	96	603
FitzGerald et al. 2003 (17)	Canada (995) Adjustable ($n=499$) Fixed ($n=496$)	6	80/4.5 and 160/4.5	Four bid	93	582
Aalbers et al. 2004 (18)	European (658) Adjustable (B/F) ($n=219$) Fixed (B/F) ($n=215$) Fixed (F/S) ($n=224$)	7	160/4.5 and 250/50	Four bid	84	735
Ind et al. 2004 (19)	UK (1553) Adjustable ($n=782$) Fixed ($n=771$)	4	80/4.5 and 160/4.5	Four bid	N/A	672

*Adjustable maintenance group only; †Mean not recorded. FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; bid, twice daily; qid, four-times daily; B/F, budesonide/formoterol 160/4.5 μg two inhalations bid (fixed) or one to four inhalations bid (adjustable); F/S, fluticasone/salmeterol 250/50 μg bid; N/A, not applicable.

Table 2 Common asthma control variables assessed during treatment with budesonide/formoterol adjustable maintenance dosing and fixed dosing with budesonide/formoterol and fluticasone/salmeterol*

Country	*Improved asthma symptom severity NHLBI (20)*	*Decrease in awakenings*	*Decrease in daytime symptoms*	*Increase in morning PEF*	*Decrease in reliever use*	*Decrease in study drug use*
Switzerland	AMD > FD	AMD > FD	Not assessed	AMD = FD	AMD > FD	AMD > FD
Belgium	Not assessed	AMD = FD	Not assessed	Not assessed	AMD = FD	AMD > FD
Italy	AMD = FD	AMD = FD	AMD = FD	AMD = FD	AMD = FD	AMD > FD
Germany	Not assessed	AMD = F D	AMD = FD	AMD = FD	AMD = FD	AMD > FD
Sweden	AMD = FD	AMD < FD	Not assessed	Not assessed	AMD < FD	AMD > FD
Canada	AMD = FD	AMD = FD	Not assessed	Not assessed	AMD = FD	AMD > FD
European* multinational	Not assessed	AMD > FD	AMD = FD	AMD = FD	AMD > FD	AMD > FD
UK	AMD = FD	AMD = FD	AMD = FD	AMD > FD	AMD > FD	AMD > FD

*The European multinational study included both a budesonide/formoterol and a fluticasone/salmeterol fixed dosing group. AMD > FD, AMD was significantly more effective than FD; AMD = FD, AMD was equally as effective as FD; AMD < FD, AMD was significantly less effective than FD; AMD, adjustable maintenance dosing; FD, fixed dosing; PEF, peak expiratory flow; NHLBI, National Institutes of Health, National Heart, Lung and Blood Institute.

an exacerbation (Canada, Sweden) or the rate of exacerbations (European multinational).

In the Canadian study, the proportion of patients with an exacerbation was 4.0% (adjustable maintenance dosing) vs. 8.9% [fixed dosing; odds ratio 0.43 (95% CI: 0.25, 0.75); p = 0.002 Figure 1], while the corresponding figures from the Swedish study were 6.2% vs. 9.5% [odds ratio 0.63 (95% CI: 0.40, 1.00); p = 0.049, Figure 1]. In the European multinational study, adjustable maintenance dosing with budesonide/formoterol reduced the rate of an exacerbation by 32% (95% CI: −5 to 55%; p = 0.08) vs. fixed dosing with budesonide/formoterol, and by 40% (95% CI: 8–60%; p = 0.018) vs. fixed dosing with fluticasone/salmeterol.

In the Canadian and Swedish studies, despite using an average of 36–40% less study medication, adjustable maintenance dosing with budesonide/formoterol reduced the risk of an exacerbation compared with fixed dosing by 57% and by 35%, respectively. The enhanced beneficial effect of adjustable maintenance dosing with budesonide/formoterol became more apparent with increased study duration (Figure 2).

The longer studies (≥4 months) had the advantage of a higher incidence of exacerbations than in most of the other studies. This observation was also true in the smallest study, performed in Switzerland, where the overall exacerbation incidence was high in both groups (17% with adjustable maintenance dosing and 24% with fixed dosing). However, in this study, repeat exacerbations were reduced by almost 3-fold in the adjustable maintenance dosing group compared with the fixed dosing group (5% vs. 12% of patients, respectively), but the small study was under-powered to detect significant differences. No statistically significant differences between the adjustable maintenance dosing and fixed-dosing groups were observed in the other studies of shorter duration, where low exacerbation rates were reported.

Reduction in asthma severity with budesonide/formoterol treatment ranged from 41.0% (Italy) to 63.5% (Canada) with similar improvements in adjustable maintenance and fixed-dosing treatment groups in all studies where this was assessed.

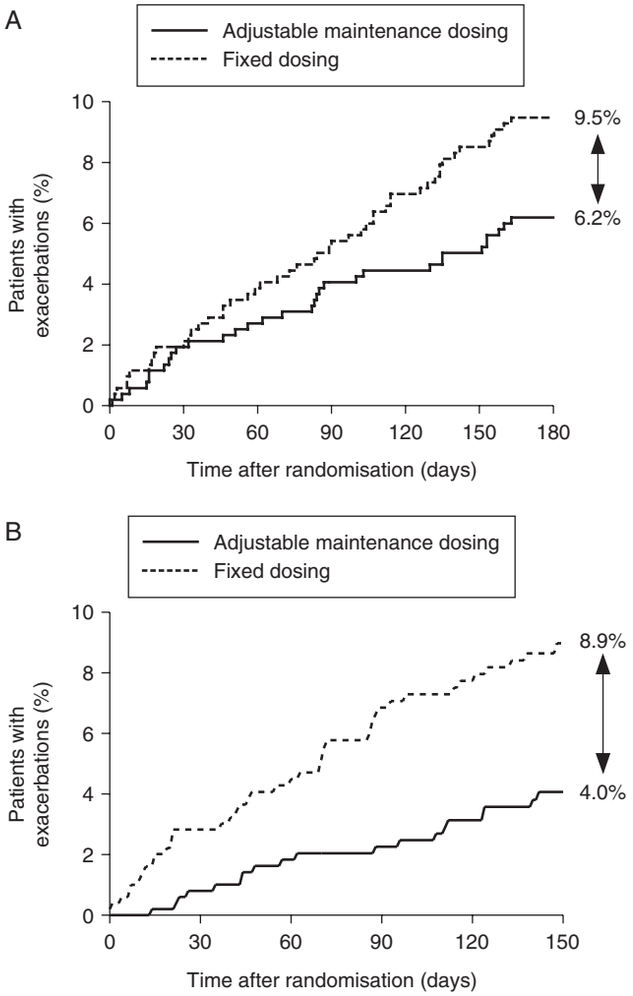

Figure 1 Kaplan–Meier curves showing an increased proportion of patients with exacerbations in the budesonide/formoterol fixed-dosing group vs. adjustable maintenance dosing group in (A) Swedish study, p = 0.049 adjustable maintenance dosing vs. fixed dosing (16) reproduced with kind permission from Blackwell Publishing. (B) Canadian study, p = 0.0021 adjustable maintenance dosing vs. fixed dosing. This information was originally published in the *Canadian Respiratory Journal* 2003; **10**(8): 431

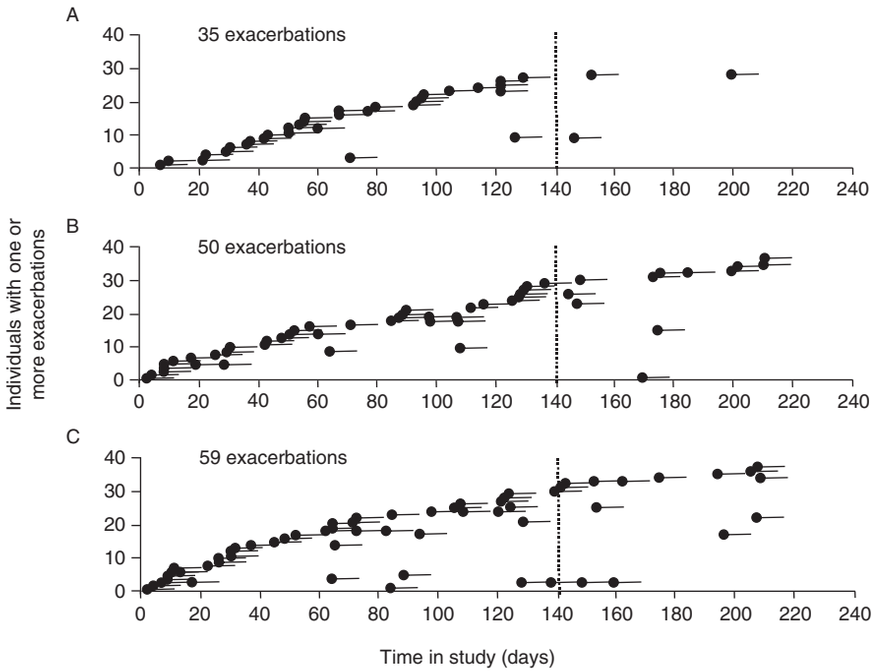

Figure 2 Incidence of exacerbations over time for individual patients in the European multinational study (18) reproduced with kind permission from Librapharm. (A) Adjustable maintenance dosing with budesonide/formoterol, (B) fixed dosing with budesonide/formoterol, (C) fixed dosing with fluticasone/salmeterol. The *x*-axis represents time and each number on the *y*-axis represents an individual patient. Each single line represents one exacerbation for an individual patient. Exacerbations >10 days in duration were classed as multiple events. Individual patients with >1 exacerbation are shown as extended horizontal lines. The dotted vertical line highlights the 4-fold difference in exacerbations starting during the last 100 days of treatment between patients in the fixed-dosing groups receiving budesonide/formoterol (160/4.5 μg, two inhalations bid) or fluticasone/salmeterol (250/50 μg, one inhalation bid) and those in the adjustable maintenance dosing group, receiving budesonide/formoterol (160/4.5 μg, one to two inhalations bid) plus four inhalations bid for 1 or 2 weeks during a period with worsening asthma. The rate of exacerbations over 7 months was 40% lower in the budesonide/formoterol adjustable maintenance dosing group than with fluticasone/salmeterol fixed-dosing ($p = 0.018$) and 32% lower than with budesonide/formoterol fixed-dosing ($p = 0.08$)

In all the studies analysed, ≥81% of patients either reduced or maintained the same level of asthma severity achieved during run-in. At the end of the treatment period in the Canadian study, approximately half of the patients in both treatment groups were categorised as having mild intermittent asthma (Figure 3).

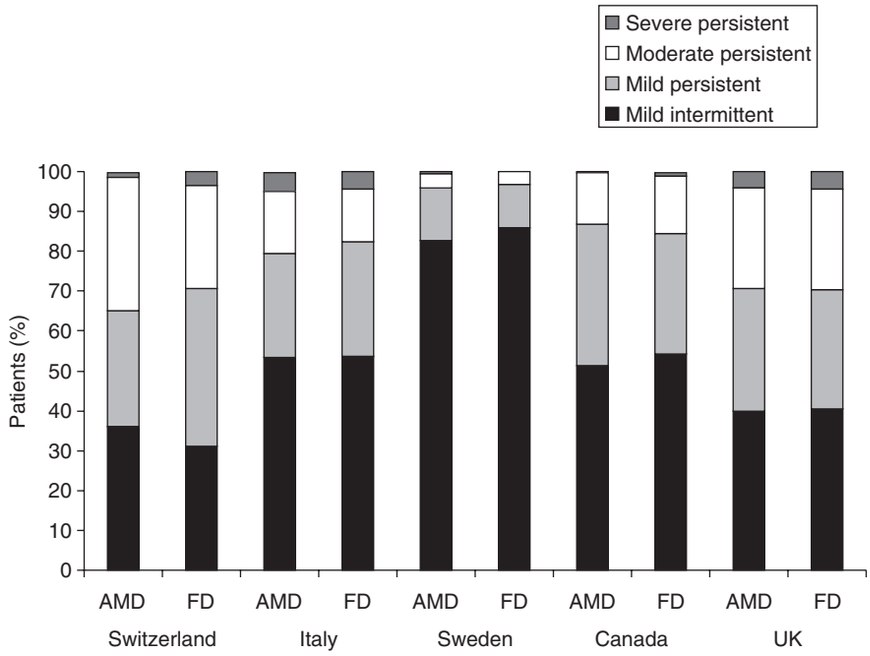

Figure 3 Comparable symptom severity based on National Institutes of Health, National Heart, Lung and Blood Institute (NHLBI) classification (20) with adjustable maintenance dosing (AMD) and fixed dosing (FD) at final clinic visits

In the European multinational study, the odds ratio of having a well-controlled asthma week was the primary efficacy measure. There was a significant increase in the odds ratio of achieving a well-controlled asthma week with budesonide/formoterol adjustable maintenance dosing vs. budesonide/formoterol fixed dosing, but the difference vs. fluticasone/salmeterol did not achieve statistical significance. Increased asthma control with adjustable maintenance dosing was achieved using an average of 15% less medication than the budesonide/formoterol fixed-dosing group.

Adjustable maintenance dosing significantly ($p < 0.05$) reduced the number of nocturnal awakenings in both the Swiss and European multinational studies and was shown to be as effective as fixed dosing in all other studies, except for the Swedish study (Table 2). In those studies where daytime symptoms were assessed, mean scores were consistent, with no significant differences in any studies between adjustable maintenance dosing and fixed dosing (Table 2). The mean use of reliever therapy with adjustable maintenance dosing was significantly ($p < 0.05$) reduced in the Swiss, UK and European multinational studies compared with fixed dosing (Table 2) (12,18,19).

In all eight studies, the use of budesonide/formoterol was consistently reduced by 13–40% compared with fixed dosing (Table 2, Figure 4). In all studies, there were no clinically relevant differences in lung function between the adjustable maintenance dosing and fixed-dosing groups during treatment. HRQL and cost-effectiveness analysis of the adjustable maintenance dosing approach are discussed elsewhere in this supplement (21,22).

Safety

Both regimens were well tolerated and were associated with few SAEs or DAEs (Table 3). The most commonly reported AEs, which were seen in a similar proportion of patients in both study groups, were bronchitis, respiratory tract infection and asthma exacerbation. Few patients experienced an SAE ($\leq$4% adjustable, $\leq$5% fixed) and the DAE rate was also low ($\leq$3% adjustable, $\leq$5% fixed). Only one death was recorded, which the investigator considered to be unrelated to the study medication.

In the European multinational study, no difference in AE reporting occurred between the budesonide/formoterol regimens (Table 3). The incidence of pharmacologically predictable side effects, e.g. dysphonia and candidiasis, was increased in the fluticasone/salmeterol fixed-dosing group compared with the budesonide/formoterol adjustable maintenance dosing group.

DISCUSSION

Results from eight studies with budesonide/formoterol (Symbicort®) used as adjustable maintenance dosing show that this approach to treatment, which allows patients to respond to changes in their asthma symptoms, is more appropriate than fixed-dosing regimens. Adjustable maintenance dosing was found to be a more effective strategy for reducing exacerbation rates compared with fixed dosing in the longer-term studies conducted in Canada, Sweden and in the European multinational study but not in the shorter-term studies, where the exacerbation rate was low in both groups.

In all the longer-term studies ($\geq$6 months), patients in the adjustable maintenance dosing groups had greater exacerbation control over time. Furthermore, in all of these studies patients were allowed to step-up temporarily to a maximum of four inhalations bid during a period of worsening symptoms. This step-up occurred in 20–49% of patients. This step-up strategy differed from the Belgian, German and Swiss studies, in which patients initially stepped up to two inhalations bid. However, no reduction in exacerbation rate was seen in the adjustable maintenance dosing groups in these shorter studies or in the UK and Italian studies. It is possible that the lack of effect of budesonide/formoterol on exacerbation rate is attributable to the study duration not being sufficiently long to detect a change, or to the lack of immediate availability of all budesonide/formoterol doses during an asthma worsening. This result emphasises that further, long-term studies are required to demonstrate the full effect of adjustable maintenance dosing on exacerbation and to

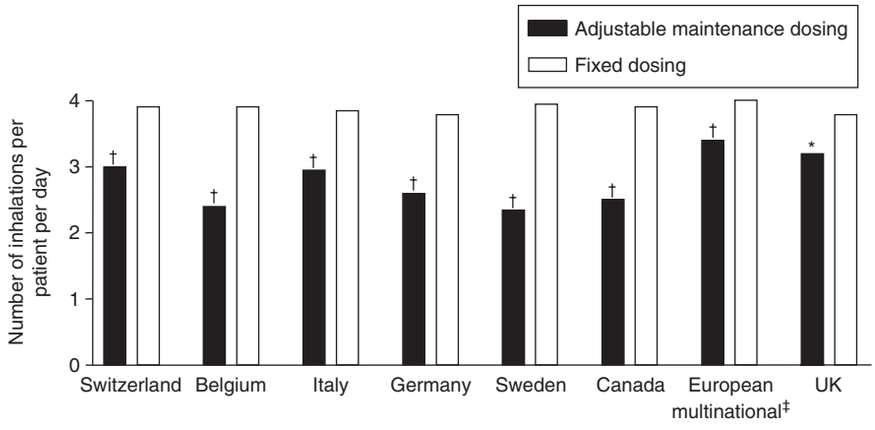

Figure 4 Comparison of mean budesonide/formoterol doses (number of inhalations per patient per day) by adjustable maintenance dosing or fixed dosing, after patient randomisation. *$p < 0.05$, †$p < 0.001$ adjustable vs. fixed dosing, ‡For fixed dosing and adjustable maintenance dosing with budesonide/formoterol only

Table 3 Summary of total numbers of adverse events for budesonide/formoterol adjustable maintenance and fixed dosing in all studies

Country (number of randomised points)	*Any AE [n (%)]*		*SAE [n (%)]*		*DAE [n (%)]*	
	Adjustable maintenance dosing	*Fixed dosing*	*Adjustable maintenance dosing*	*Fixed dosing*	*Adjustable maintenance dosing*	*Fixed dosing*
Switzerland ($n=127$)	29 (37.7)	25 (38.5)	0 (0)	3 (4.6)	2 (2.6)	1 (1.5)
Belgium ($n=980$)	238 (48.6)	264 (53.9)	8 (1.6)	12 (2.5)	4 (0.8)	10 (2.0)
Italy ($n=2358$)	233 (19.8)	233 (20.1)	8 (0.7)	10 (0.9)	37 (1.3)	41 (3.5)
Germany ($n=3297$)	587 (34.4)	577 (35.7)	17 (1.0)	24 (1,5)	29 (1.7)	18 (1.1)
Sweden ($n=1034$)	Not assessed	Not assessed	15 (2.9)	10 (1.9)	14 (2.7)	14 (2.7)
Canada ($n=995$)	345 (69.1)	357 (72.0)	5 (1.0)	7 (1.4)	11 (2.2)	19 (3.8)
European multinational* ($n=658$)	124 (57.0)	124 (58.0)	8 (4.0)	11 (5.0)	6 (3.0)	10 (5.0)
UK ($n=1553$)	448 (57.0)	440 (57.0)	24 (3.0)	28 (4.0)	15 (2.0)	19 (2.0)

*For fixed dosing and adjustable maintenance dosing with budesonide/formoterol only. AE, adverse event; SAE, serious adverse event; DAE, discontinuation due to adverse event.

confirm that the increasing benefit over time, which was apparent in all longer-term studies is sustainable over 1 or 2 years.

In the three long-term budesonide/formoterol adjustable maintenance dosing studies, a 2–4-fold step-up in dose of both budesonide and formoterol, resulted in better exacerbation control and a reduced overall average treatment level over the entire study. This observation is all the more impressive given that fixed-dosing regimens, with both budesonide/formoterol and fluticasone/salmeterol are themselves excellent treatments for asthma, with proven efficacy and safety (7,9,10,23–25). Moreover, in all eight studies, patients in the adjustable maintenance dosing group used less study drug than the fixed-dosing group to control their asthma while achieving at least similar levels of asthma control (Figure 3, Table 2), thus reducing costs (22). Results from adjustable maintenance dosing studies with Symbicort have shown that even further improvements in asthma control can be made with optimal use of therapies with clinical effectiveness. These further improvements can be realised when the timing of increased use becomes an essential part of treatment, i.e. knowing when to step-up and step-down effectively.

An adjustable maintenance dosing plan aims to empower patients with the ability to increase their treatment earlier than would otherwise be possible if they relied on an unscheduled visit to see their physician. The effectiveness of budesonide/formoterol as part of an adjustable maintenance dosing plan may, however, be reduced somewhat if patients do not understand the purpose and have confidence in their treatment. Also, this may subsequently lead to reduced adherence to the asthma management plan. In the Canadian study, despite the significant reduction in exacerbations, 50% of patients did not adjust their dose at all despite worsening symptoms, which leads to speculation that further improvements may have been seen if these patients had adhered fully to their asthma management plan. This outcome implies that adjustable maintenance dosing is not a perfect solution to increasing treatment early in response to symptoms. It may not be appropriate for all patients, and there may be a subpopulation who would either choose not to follow a plan or who cannot manage their own disease. For adjustable maintenance dosing to facilitate improvements in asthma control, patients need to adhere to their written plans. This is where the role of physicians should not be underestimated, as it is their responsibility to educate patients about the importance of their treatment. Clear communication between physicians and patients is crucial to ensure that patients understand the role of both their treatment and themselves in long-term asthma management. Understanding, through good education, is the key to enhancing adherence.

In summary, the clinical objective of the adjustable maintenance dosing studies with budesonide/formoterol was to demonstrate the advantages of a more effective treatment strategy for the management of asthma compared with fixed dosing in terms of equal or superior efficacy with lower drug load and consequently a decrease in costs. Taken together, these findings indicate that adjustable maintenance dosing with budesonide/formoterol has the potential to further increase asthma control above that seen with traditional fixed-dose combination therapies.

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