Adjustable maintenance dosing: suitability of budesonide/formoterol in a single inhaler and overview of a clinical study programme

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ABSTRACT

Inhaled budesonide/formoterol is effective and well tolerated in the treatment of asthma. Unlike salmeterol, formoterol is a full β_2-receptor agonist and exhibits dose-dependent bronchoprotection across a wide dose range. Budesonide/formoterol adjustable maintenance dosing (i.e. varying the number of inhalations from a single inhaler) is suitable for maintaining asthma control with an adequately low dose of medication. The first in a series of international, randomised, multicentre, open-label studies, evaluating adjustable maintenance dosing with budesonide/formoterol has been completed. Following 1-month run-in on budesonide/formoterol fixed dosing (two inhalations bid), patients either continued this regimen or received budesonide/formoterol adjustable maintenance dosing (2–8 inhalations daily) for 3–6 months. Doses were adjusted according to asthma control but varied between countries to reflect appropriate clinical practices. The studies evaluate a wide range of outcomes: exacerbations/treatment failure, health-related quality of life, health economic variables and tolerability, and will provide a robust evaluation of adjustable maintenance dosing with budesonide/formoterol.

Keywords: Study design; adjustable maintenance dosing; budesonide/formoterol; asthma

INTRODUCTION

Recent asthma management guidelines stress the importance of a treatment approach that is tailored to the needs of individual patients (1,2). The use of guided, personalised, management plans, with appropriate education and training, regular supervision and reinforcement by healthcare personnel, enables patients to take more responsibility for, and cope with, their asthma (3). Guided, personalised, management plans have been shown to lead to significant reductions in morbidity and use of healthcare services (4) (Table 1). However, variations in healthcare services between different countries will affect the level of patient autonomy when implementing such plans. The level of input and guidance that the physician would like to have will vary in each of the different countries, highlighting the need to tailor guided self-management strategies to the healthcare system in which it will be used.

Effective self-management requires the appropriate use of medication to gain and then maintain control of asthma with the lowest effective dose (1,2). For personalised management, patients need to recognise variations in their asthma symptom severity [indicators include cough, chest tightness, wheeze, breathing difficulty, sleep disturbance or peak expiratory flow (PEF) below personal best] and respond by appropriately and rapidly adjusting their medication dose to maintain asthma control and prevent a full-blown exacerbation from occurring. The best way to identify when a change in medication is required is through the use of objective measurements of lung function, such as peak flow measurements and/or symptoms (e.g. increased use of reliever medication or nocturnal wakening). Objective measures are preferable to subjective methods for assessing asthma control level, as patients do not otherwise detect changes in asthma severity reliably (5).

In order to respond appropriately to changes in asthma severity, personalised management plans rely upon a suitable medication that enables patients to adjust therapy quickly and easily. Suitable drugs should therefore have increased efficacy at higher doses, have a rapid onset of effect and be simple to use. The standard asthma maintenance treatment in patients who are uncontrolled with corticosteroids alone is a combination of inhaled corticosteroids (ICS) and a long-acting β_2-agonist (such as budesonide/formoterol) (1,2). Combinations of ICS and a long-acting β_2-agonist are now available in a single inhaler and can assist guided self-management by providing a simple and convenient means for patients to adjust their dose of maintenance medication.

In this article, we consider the suitability of budesonide/formoterol in a single inhaler (Symbicort®) for adjustable maintenance dosing in asthma and describe a series of studies

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Table 1 Effects of self-management education and regular practitioner review on morbidity and healthcare resource use in asthma patients [adapted from Gibson et al. (4)]

Outcomes	*Measures*	
	Reduction in relative risk	*95% CI*
Healthcare resources		
Hospitalisations	0.64	0.50–0.82
Emergency room visits	0.82	0.73–0.94
Unscheduled physician visits	0.68	0.56–0.81
Morbidity		
Days off work	0.79	0.67–0.93
Nocturnal asthma	0.67	0.56–0.79
Lung function	NS	–
Oral corticosteroids	NS	–
Standardised mean difference		
Health-related quality of life	0.29	0.11–0.47

CI, confidence intervals; NS, not significant.

comparing budesonide/formoterol adjustable maintenance dosing with traditional fixed dosing. These studies are the first to evaluate the concept of adjustable maintenance dosing with an ICS and a long-acting β_2-agonist.

CONSIDERATIONS IN ADJUSTABLE MAINTENANCE DOSING

Periodic changes in asthma control are normal in asthma, with exacerbations occurring even in the mildest form of the disease and in patients who are well controlled on current treatments. Adjustable maintenance dosing provides the means for patients to utilise a suitable, low dose of ICS and long-acting β_2-agonist during periods of good control but increase their medication at times of symptom worsening to maintain control. Flexible treatment approaches such as this require the use of drugs with dose–response profiles that have increased efficacy at higher doses. To optimise this effectiveness, patients need to have confidence in the medications they are using; the treatment regimens must be simple to understand and follow and the medications convenient to administer. Of the treatments currently available, budesonide/formoterol is the only suitable treatment for adjustable maintenance dosing for the reasons discussed below.

CLINICAL EXPERIENCE WITH BUDESONIDE AND FORMOTEROL

ICS suppress the chronic inflammation of asthma and reduce airway hyper-responsiveness. Budesonide is a well-established treatment that is effective and well tolerated for the long-term maintenance treatment of asthma in children and adults (6–8). Long-term treatment with once-daily, low-dose budesonide (400 μg adults or 200 μg children daily) decreased the risk of severe exacerbations and improved asthma control in patients with mild persistent asthma of recent onset (9). Furthermore, for patients taking low-dose budesonide (100 μg twice daily), increasing the dose to 1000 μg daily for 7 days significantly reduced the incidence of severe exacerbations requiring a course of oral corticosteroids as effectively as continuously high doses of budesonide (800 μg daily) (10).

Long-acting β_2-agonists provide sustained bronchodilation and bronchoprotection, inhibit release of inflammatory mediators and may reduce airway sensitivity. However, as long-acting β_2-agonists are not recommended for use as sole maintenance treatments, their use will be discussed in the more clinically relevant context of an add-on to ICS therapy. Indeed, there is a strong scientific rationale for the beneficial effects seen in clinical studies when these two agents are used together, because ICS and long-acting β_2-agonists exert their effects on different and complementary aspects of asthma pathophysiology (11). Furthermore, *in vitro* data support synergistic anti-inflammatory and smooth-muscle anti-proliferative effects for formoterol and budesonide (12,13).

In clinical studies, addition of formoterol to budesonide therapy has been shown to provide greater improvement in asthma symptom control and reduce the risk of severe exacerbations compared with increasing the dose of budesonide alone (14). In patients with mild asthma who were symptomatic on low or moderate doses of budesonide, adding formoterol established asthma control faster and allowed the ICS dose to be reduced, while decreasing the rate of mild exacerbations, compared with budesonide alone (15). Furthermore, when used as needed in addition to maintenance doses, formoterol reduced the risk of severe asthma exacerbations more than treatment with salbutamol in asthma patients receiving both ICS and a long-acting β_2-agonist as maintenance therapy (16).

Budesonide/formoterol in a single inhaler is as effective as delivery via separate inhalers (17,18) and more cost-effective over the long term (19,20). It is also well tolerated at high cumulative daily doses (up to 1920 μg budesonide and 54 μg formoterol) (21) and when used regularly (18).

DOSE–RESPONSE EFFECTS

The feasibility of adjustable maintenance dosing is dependent on the dose–response curves of the drugs used. Suitable medications need to demonstrate improved efficacy at higher doses and must have a good safety profile, characteristics that are both evident in budesonide. Indeed, Busse et al. (22) demonstrated increases in PEF (Figure 1) and forced expiratory volume in 1 s (FEV_1), with increased daily doses of budesonide between 200 μg and 1600 μg over 12 weeks. The dose–response profile of budesonide is similar to both fluticasone and beclometasone. All demonstrate a plateau in response at high doses, such that at doses above approximately 1000 μg for budesonide and beclometasone or 500 μg for fluticasone, the risk : benefit ratio increases considerably (7,11,23–25). In mild-to-moderate

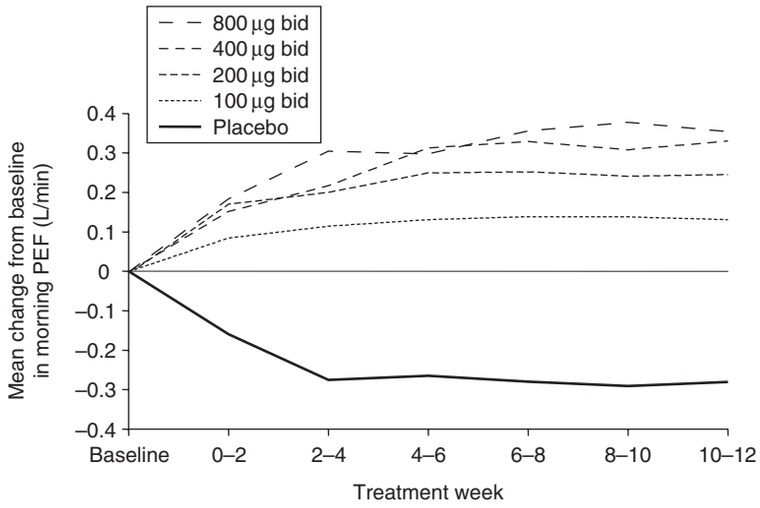

Figure 1 The effect of increasing dose of budesonide on peak expiratory flow (22). Reproduced with kind permission from the American Academy of Allergy, Asthma and Immunology (PEF, peak expiratory flow)

asthma, improvements in clinical effectiveness of budesonide with increasing dose have not been proven conclusively (25); however, dose-related effects of budesonide have been demonstrated on surrogate markers of inflammation (26).

In patients with moderate asthma, single doses of formoterol (6–48 μg, metered doses) produced sustained dose-dependent effects on parameters of lung function lasting ≥12 h (27) (results for specific airway resistance are shown in Figure 2). Palmqvist et al. (28) showed that formoterol had a dose-dependent protective effect on methacholine-induced bronchoconstriction at cumulative metered doses of 12, 60 and 120 μg (Figure 3). In healthy subjects, salmeterol and formoterol exhibit broadly similar, dose-related, systemic, class effects (29). Clinical studies comparing salmeterol and formoterol (metered doses of 50 μg and 12 μg, respectively, twice daily) have shown that formoterol is at least as effective as salmeterol, although more rapidly active in onset of bronchodilation and that both are well tolerated (30,31). However, formoterol is more appropriate for use in adjustable maintenance dosing regimens than salmeterol, as formoterol can provide greater levels of efficacy at higher doses (28,32,33), supported by the proven benefit of formoterol when used as needed in addition to maintenance doses for the control of exacerbations (16).

The dose–response profiles of budesonide and formoterol as outlined above mean that effective adjustment of the pulmonary activity of budesonide/formoterol can be made by simply changing the number of inhalations from a single inhaler. Furthermore, when administered in a single inhaler, doubling the dose of budesonide/formoterol provides better protection (2.4-fold difference) against an adenosine monophosphate bronchial challenge than doubling the dose of monocomponents (34).

ONSET OF ACTION

Although the duration of effect of formoterol is similar to salmeterol (>12 h), it has a rapid onset of action, similar to salbutamol (35). Formoterol provides significantly faster relief from severe bronchoconstriction and dyspnoea than salmeterol (36,37). The rapid bronchodilatory effect of formoterol allows

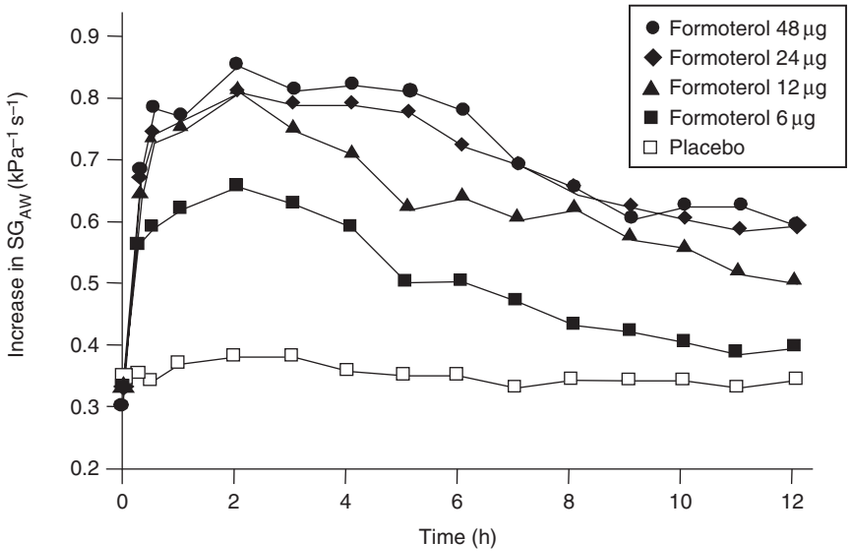

Figure 2 The effect of increasing formoterol dose on specific airway resistance (SG_{AW}) (27). Reproduced with kind permission from Elsevier Science

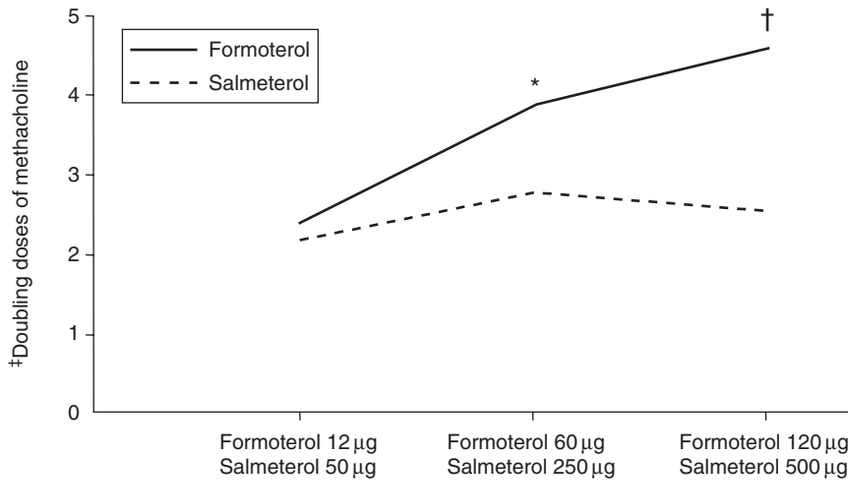

Figure 3 The effect of dose on the bronchoprotective effect of formoterol and salmeterol (28). Reproduced with kind permission from the American Lung Association. *p=0.002, †p=0.0001 vs. salmeterol, ‡The *y*-axis represents the mean shift in the number of doubling doses of methacholine required to produce ≥20% decrease in forced expiratory volume in 1 s (FEV_1) following inhalation of formoterol or salmeterol relative to placebo

patients to perceive the immediate effects of the medication. This addition of a long-acting β_2-agonist to maintenance ICS has been shown to improve adherence (38) because when used alone, ICS does not have such a strong perceived effect. This view is supported by a study in which the addition of long-acting β_2-agonists to ICS improved adherence with ICS therapy compared with corticosteroid treatment alone (39). Moreover, budesonide/formoterol in a single inhaler has been shown to have an onset of bronchodilatory action of <3 min (40).

EASE OF USE

A recent study of regular treatment with budesonide/formoterol in a single inhaler, compared with the components delivered by separate inhalers, demonstrated that single inhaler administration of budesonide/formoterol is at least as effective as separate inhaler delivery over a 1-year period (18). Budesonide/formoterol in a single inhaler offers a means of administering adjustable maintenance treatment of both ICS and long-acting β_2-agonist components without the need to change or add another maintenance inhaler to obtain the appropriate level of medication. Thus, use of a single inhaler provides greater convenience than the use of separate inhalers and reduces the complexity of treatment, which may improve adherence to treatment (41,42).

ADJUSTABLE MAINTENANCE DOSING CLINICAL STUDY PROGRAMME

An international series of multicentre studies was designed to test the concept of adjustable maintenance dosing with budesonide/formoterol in a real-life setting; these studies are the first to evaluate adjustable maintenance dosing with an ICS and a long-acting β_2-agonist in a single inhaler. Of these studies, the first seven [Switzerland (43), Belgium (44), Italy (45), Germany (46), Sweden (47), Canada (48) and the UK (49)], involving more than 10,000 patients with asthma recruited from a large number of primary care and hospital clinics, are complete and are reported in this supplement. Each of these studies compared an adjustable maintenance dosing regimen of budesonide/formoterol with a traditional fixed twice-daily regimen of budesonide/formoterol in adults, and in some cases children and/or adolescents, with asthma over a 4–7-month period. An additional European multinational study (50), comparing budesonide/formoterol fixed and adjustable maintenance dosing with fluticasone/salmeterol fixed dosing, will also be discussed in this article.

An open-label design was used in the studies as this was considered the most practical method for studying these treatment regimens in a way reflecting normal clinical practice; use of a double-dummy blinded approach would have required the use of multiple inhalers and added unrealistic complexity. Clinical characteristics and demographics were obtained at enrolment. A requirement of each study was that the patients were already receiving regular ICS maintenance therapy, however lung function criteria and whether or not patients were symptomatic while receiving long- or short-acting β_2-agonists varied between studies (Table 2). During a 1-month run-in period, patients received budesonide/formoterol fixed dosing (two inhalations, twice daily). In the European multinational study, patients continued their regular maintenance treatments for 10–14 days and then entered a 1-month, randomised, double-blind period with either budesonide/formoterol fixed dosing (two inhalations, twice daily) or fluticasone/salmeterol-fixed dosing (one inhalation, twice daily). Following run-in, patients were randomised to either fixed dosing or budesonide/formoterol adjustable maintenance dosing for a further 3 (Germany, Italy, Switzerland, UK), 4 (Belgium), 5 (Canada) or 6 (Sweden, European multinational study) months. An overview of the study designs is shown in Figure 4. Patients used the same strength of inhaler throughout the run-in and randomised treatment period. Where two strengths of inhalers were used in the study, the choice of budesonide/formoterol 80/4.5 μg or 160/4.5 μg (delivered doses equivalent to 100/6 μg or 200/6 μg metered doses) was made on the basis of pre-study ICS dose.

Table 2 Patients and study designs in the clinical study programme

Country	Belgium	Canada	Germany	Italy	Sweden	Switzerland	UK	European multinational study
Number of patients enrolled and entering run-in	1144	1193	3651	2358	1112	142	1719	1044
Duration of randomised treatment (months)	4	5	3	3	6	3	3	6 (+1 month following run-in)
Inclusion criteria*								
Age (years)	≥18	≥12	18–50	≥6	≥12	≥12	≥18	≥12
Daily pre-study ICS dose (μg)	≥500	250–1000	≤1000	≥400	400–1000	≥600	400–2000	500–1200
FEV_1 % predicted normal	≥50	≥70	Not specified	Not specified	≥70	Not specified	Not specified†	≥50
Asthma severity	Stable or symptomatic on ICS	Symptomatic on ICS	Symptomatic on ICS	Stable on ICS + LABA or symptomatic on ICS + SABA	Stable on ICS + LABA or symptomatic on ICS + SABA	Stable on ICS + LABA or symptomatic on ICS + SABA	Stable on ICS + LABA or symptomatic on ICS + SABA	Symptomatic on ICS
First step down‡	At randomisation (excluded if not stable during run-in)	At randomisation if step-down criteria met	At randomisation	At randomisation at physician's discretion	At randomisation if step-down criteria met	At randomisation at physician's discretion	At randomisation at physician's discretion	At start of open-label treatment period if step-down criteria met
Step up (if criteria met)§	To two inhalations qid	Directly to four inhalations bid	From one to two inhalations bid. From two to four inhalations bid if criteria still met after 1 week	Directly to four inhalations bid	Directly to four inhalations bid	Directly to four inhalations bid	Directly to four inhalations bid	Directly to four inhalations bid
Step down (if criteria met)	Directly to one inhalation bid	From four to previous dose	From four to two, or two to one inhalations bid	To one bid or two inhalations at night	To one inhalation bid	To one bid or two inhalations at night	From four to two, or two to one inhalations bid	To one or two inhalations bid
Criteria for dose adjustment	Night-time awakening, SABA	Night-time awakening, SABA use, PEF	Night-time awakening, SABA use, PEF	Night-time awakening, SABA use	Night-time awakening, SABA use, PEF	Night-time awakening, SABA use, PEF	Night-time awakening, SABA use	Night-time awakening, SABA use
Inhaler strength(s) used (delivered doses μg)	160/4.5	80/4.5 or 160/4.5	160/4.5	80/4.5 or 160/4.5	80/4.5 or 160/4.5	160/4.5	80/4.5 or 160/4.5	160/4.5 or 250/50 (salmeterol/fluticasone)

*Patients were required to have asthma for ≥6 months, as shown by reversibility to bronchodilators ($FEV_1 \geq 12\%$) and/or history of short-term variation in airway function and asthma symptoms responding to conventional asthma symptoms, unless otherwise mentioned. Patients were receiving regular ICS. Exclusion criteria included a respiratory infection during the last month and a recent history of exacerbations (criteria varied between studies) and the presence of cardiovascular disease or other significant disease. †PEF ≥ 50% predicted normal. ‡Patients used as-needed inhalations of salbutamol or terbutaline throughout the study. §Patients stepped up for a period of 7 days. Thereafter they could step down if criteria met or maintain a step-up dose for a maximum of 14 days. ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 s; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist; PEF, peak expiratory flow; bid, twice daily; qid, four-times daily.

Patients on adjustable maintenance dosing could step down their budesonide/formoterol inhaler to a minimum of two inhalations daily (either one inhalation in the morning and one in the evening or two inhalations in the evening) if asthma was controlled, according to their level of reliever usage, nocturnal awakenings and in some cases PEF measurements. Patients could step up their dose to a maximum of eight inhalations daily at signs of asthma worsening for 7–14 days, and step down their dose again when asthma was controlled, as exemplified by the Swedish study in Figure 5. The Swedish study in particular was chosen as an example as it was one of the larger studies to include step-ups directly to four inhalations twice daily, demonstrating the full effect of adjustable maintenance dosing.

In each study, the criteria for dosage adjustment and format for stepping up and down dosage were well defined. There are several different parameters that could be used to identify when treatment changes are required, yet this number was kept to a minimum so that patients could easily follow the regimen outlined, maximising adherence. The specific criteria for adjusting dosage also varied between studies to reflect usual clinical practice in the individual countries. All studies used twice-daily dosing throughout, with the exception of the Belgian study in which patients used a four-times-daily dose during step-up periods and the Italian and Swiss studies that allowed two inhalations at night as an alternative to one inhalation twice daily. Tables 2 and 3 summarise the key patient information, study design and the outcomes measured in each of the studies.

As a result of the range of countries involved, study endpoints differed in order to accommodate country-specific variations in healthcare systems and culture. However, all studies assessed the occurrence of either treatment failure or exacerbations (although the definitions differed, they included asthma-related serious adverse events, use of oral corticosteroids and hospitalisation/emergency treatment) as the primary efficacy variable with the exception of the German and European multinational studies in which treatment failure and/or the occurrence of severe exacerbations were secondary variables. Most studies also monitored treatment success, defined as maintenance or improvement of asthma severity according to modified National Heart, Lung and Blood Institute (NHLBI) severity levels (51). In Germany, health-related quality of life (HRQL) was the primary efficacy variable and was measured using the standardised asthma quality of life questionnaire (52). HRQL was a secondary variable in other studies. The primary variable in the European multinational study was the odds of having a well-controlled asthma week, based on symptoms, reliever use and PEF. Patient enablement, which reflects the patient's ability to understand and cope with their disease, was measured in the UK study (using a modified Patient Enablement Instrument).

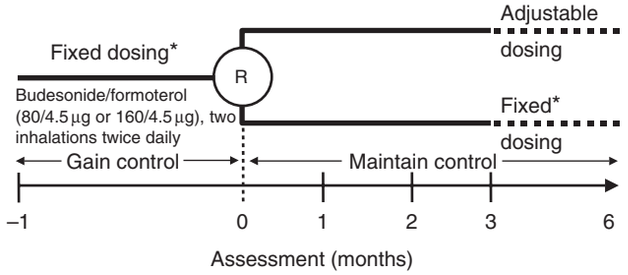

Figure 4 Overview of study design. Patients received either terbutaline or salbutamol as needed throughout the study. *In the European multinational study alternative fixed dosing with fluticasone/salmeterol of 250/50 μg (one inhalation twice daily) was also investigated (R, randomisation)

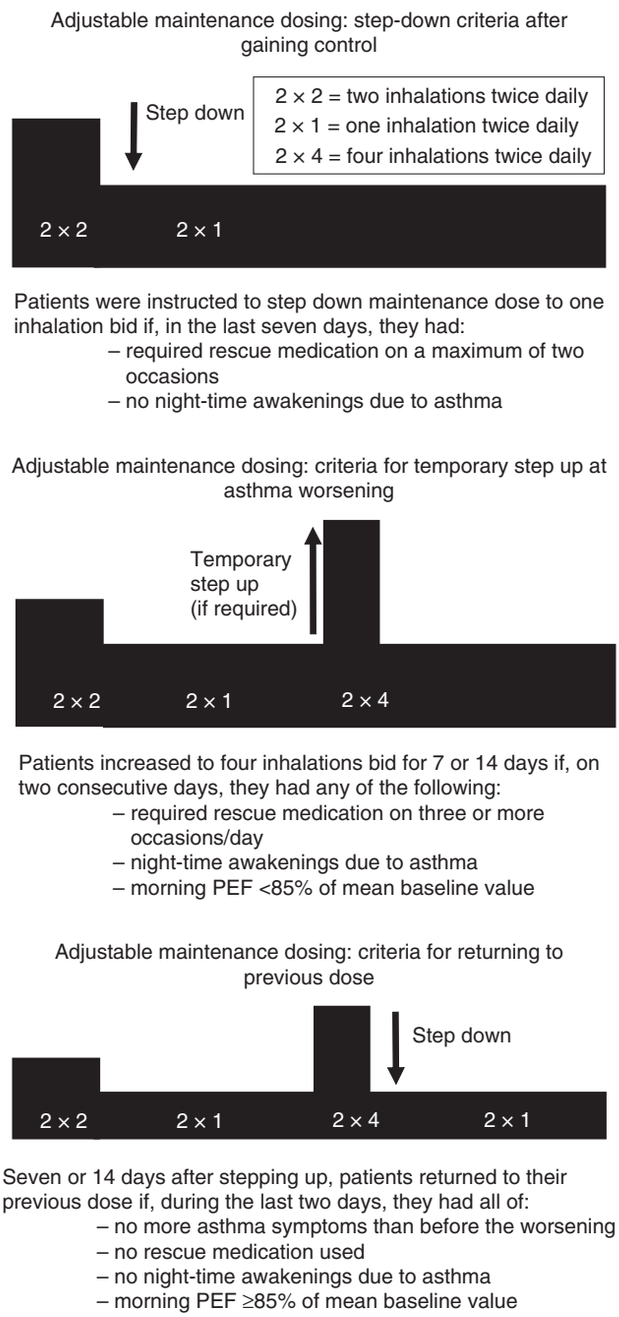

Figure 5 Patients on adjustable maintenance dosing stepped down their dose during period of control but stepped up their dose at first signs of worsening: the Swedish study adjustable maintenance dosing regimen

Table 3 Outcomes measured in the clinical study programme

Country	Belgium	Canada	Germany	Italy	Sweden	Switzerland	UK	European multinational study
Key efficacy variables*	Severe exacerbations	Exacerbations; treatment success	HRQL	Treatment failure and success	Exacerbations; treatment success	Treatment failure and success	Treatment failure and success	Asthma control weeks
HRQL measurements	MiniAQLQ, ACQ	None†	AQLQ (S), SF-36	None	None†	MiniAQLQ	MiniAQLQ	None†
Health economics	Direct costs	Direct and indirect costs	Direct and indirect costs	Direct and indirect costs	Direct and indirect costs	Data not captured	Direct and indirect costs	Data not captured
Adverse events recorded	All	All	All	All	SAEs, DAEs only	All	All	All

*Doses of study medication, reliever medication, frequency of nocturnal awakenings and PEF were monitored via diary records in all studies. Treatment success was monitored as the change in asthma severity according to NHLBI severity level (51). Categories of events used for defining treatment failure, exacerbations, or serious exacerbations included the following asthma-related events: SAEs; use of oral or additional ICS; hospitalisation or emergency department treatment, withdrawal because of the need for additional asthma maintenance medication. †Included a single question on overall treatment satisfaction. FEV_1, forced expiratory volume in 1 s, Asthma Quality of Life Questionnaire (standardised); SF-36, short form survey 36; ACQ, Asthma Control Questionnaire; SAE, serious adverse event; DAE, discontinuation due to adverse events.

Patients used daily diary cards to record symptoms, morning PEF, night-time awakenings and use of study and reliever medication in all studies. Patients also recorded any days off from work/school or unscheduled healthcare contacts associated with their asthma. In all studies except Switzerland and the European multinational study, drug and total healthcare costs (direct costs) were calculated. Additionally, costs of lost productivity (indirect costs) were estimated in Canada, Germany, Italy, Sweden and the UK. Through diary records and interviews at clinic visits, investigators identified and recorded on case report forms any adverse or serious adverse events.

Clinical findings for all of these budesonide/formoterol adjustable maintenance dosing studies are presented together for the first time in this supplement (53,54).

CONCLUSIONS

Adjustable maintenance dosing with budesonide/formoterol in a single inhaler offers a practical approach to maintaining control of asthma with an appropriately low dose of medication and an early intervention strategy when asthma worsens. This approach is consistent with international asthma treatment guidelines for long-term asthma management, which recommend guided self-management and the use of a minimal effective amount of medication for maintenance of asthma control.

Budesonide and formoterol both show proven efficacy and tolerability, which, in conjunction with their dose–response profile, makes them suitable for use in an adjustable maintenance dosing regimen with a single inhaler. Budesonide/formoterol in a single inhaler provides a convenient and simple means of adjusting dose by increasing and decreasing the number of inhalations from the same inhaler and avoids the need to use or add another inhaler to obtain the appropriate level of anti-inflammatory and bronchoprotective activity, a feature which is unique to this product. The rapid onset of action of formoterol in the product may also facilitate adherence to treatment.

A series of clinical studies, with essentially similar designs, has compared the efficacy of budesonide/formoterol in an adjustable maintenance dosing regimen with a fixed dosing strategy of either budesonide/formoterol or fluticasone/salmeterol. The studies included patients with a broad range of asthma severities, although all were regular users of ICS at entry, and used levels of dosage adjustment that reflected usual clinical practice in individual countries. The differences between studies enabled the robustness of the adjustable maintenance dosing concept to be tested (53,54).

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