

ORIGINAL ARTICLE

Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma

R. Aalbers¹, V. Backer², T. T. K. Kava³, E. R. Omenaas⁴,
T. Sandström⁵, C. Jorup⁶ and T. Welte⁷

¹Department of Pulmonology, Martini Hospital, Groningen, The Netherlands

²Respiratory Unit, Department of Internal Medicine, Bispebjerg Hospital, Copenhagen, Denmark

³Department of Respiratory Medicine, Central Hospital of Northern Karelia, Joensuu, Finland

⁴Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

⁵Department of Respiratory Medicine and Allergy, University Hospital, Umeå, Sweden

⁶AstraZeneca R&D Lund, Lund, Sweden

⁷Department of Pneumology and Intensive Care Medicine, University of Magdeburg, Magdeburg, Germany

Address for correspondence: Dr R. Aalbers, Department of Pulmonology, Martini Hospital, 9728 NZ Groningen, The Netherlands. Tel.: +31 50 524 59 30; Fax: +31 50 524 59 37; email: r.aalbers@mzh.nl

Key words: Adjustable maintenance dosing – Asthma control – Budesonide/formoterol – Exacerbations – Fixed dosing – Salmeterol/fluticasone

SUMMARY

Background: Current asthma guidelines recommend that patients are educated to adjust their medication according to their asthma severity using physician-guided self-management plans. However, many patients take a fixed dose of their controller medication and adjust their reliever medication according to asthma symptoms.

Objectives: This study examined whether asthma control improved if patients adjusted the maintenance dose of budesonide/formoterol (Symbicort Turbuhaler* 160/4.5 µg) according to

asthma severity compared with traditional fixed dosing (FD) regimens.

Methods: Symptomatic patients with asthma ($n = 658$, mean symptom score 1.5, mean inhaled corticosteroids 735 µg/day, mean forced expiratory volume in 1 second [FEV₁] 84% predicted) were randomised after 2 weeks' run-in to either: budesonide/formoterol adjustable maintenance dosing (AMD), budesonide/formoterol FD or salmeterol/fluticasone (Seretide Diskus† 50/250 µg) FD. In a 4-week double-blind period, both

* Symbicort and Turbuhaler are registered trademarks owned by the AstraZeneca group.

† Seretide and Diskus are trademarks of GlaxoSmithKline.

budesonide/formoterol AMD and FD groups received two inhalations twice daily (bid) and salmeterol/fluticasone FD patients received one inhalation bid. In the following 6-month open extension, both FD groups continued with the same treatment. Patients in the AMD group with well-controlled asthma stepped down to one inhalation bid; others continued with two inhalations bid. All AMD patients could increase to four inhalations bid for 7–14 days if symptoms worsened. All patients used terbutaline or salbutamol for symptom relief throughout. The primary variable was the odds of achieving a well-controlled asthma week (WCAW).

Results: The odds ratio for achieving a WCAW did not differ between the FD regimens; however, during the open period, budesonide/formoterol AMD increased the odds of achieving a WCAW vs. budesonide/formoterol FD (odds ratio 1.335; 95% CI: 1.001, 1.783; $p = 0.049$) despite a 15%

reduction in average study drug use.

Budesonide/formoterol AMD patients had a lower exacerbation rate over the study: 40% lower vs. salmeterol/fluticasone FD ($p = 0.018$); 32% lower vs. budesonide/formoterol FD (NS). During the double-blind period, there were no clinically relevant differences between the budesonide/formoterol FD and salmeterol/fluticasone FD groups. Budesonide/formoterol AMD patients used less reliever medication in the open extension: 0.58 vs. 0.92 occasions/day for budesonide/formoterol FD ($p = 0.001$) and 0.80 occasions/day for salmeterol/fluticasone FD ($p = 0.011$).

Conclusions: Adjustable maintenance dosing with budesonide/formoterol provides more effective asthma control by reducing exacerbations and reliever medication usage compared with fixed-dose salmeterol/fluticasone.

Introduction

The discovery in the last decade that the addition of a long-acting β_2 -agonist to low doses of inhaled corticosteroids (ICS) provides more effective asthma control than a higher dose of ICS alone has been a major step forward for asthma therapy^{1–4}. Nevertheless, many patients are still experiencing asthma symptoms and exacerbations and therefore further advances are required to ensure optimal asthma control is delivered using the lowest effective levels of treatment in accordance with asthma guidelines^{5,6}. Poor adherence to ICS is a significant problem hampering this aim⁷. The use of combination inhalers can overcome the potential for over-reliance on one controller therapy at the expense of the other, while making it easier for patients to adhere fully to their treatment. However, one suggested limitation of inhalers containing a fixed combination of long-acting β_2 -agonist and ICS is their lack of dosing flexibility⁸. This lack of flexibility is potentially important given the variable airway inflammation inherent to asthma. The variable nature of asthma means that asthma control fluctuates over time, even in patients whose asthma seems generally well controlled. As a result, international guidelines increasingly recommend a flexible approach to treatment that allows the dose of ICS to be increased in response to deterioration in asthma control^{5,6}.

Physician-guided self-management plans involving a patient–doctor partnership are increasingly advocated. Self-assessment of asthma severity can be combined with a subjective interpretation of asthma symptoms to influence treatment level. Studies have shown that action plans are beneficial in improving asthma control, while minimising the overall treatment level⁹ and the need for oral steroids^{10,11}. Action plans are also more cost-effective than fixed dosing^{12,13}.

A recent systematic review concluded that self-management with a written action plan – detailing how and when to adjust treatment and how to access healthcare resources when asthma worsened – and a regular medical review, improves health outcomes, exacerbation rates and hospitalisation in asthma¹⁴. Evidence suggests, however, that these recommendations are not being followed^{15,16}. Consequently, there are periods when patients are under- and overtreated on fixed dosing (FD) regimens. Another important problem with any FD regimen is that if a steady deterioration in asthma symptoms is treated with short-acting β_2 -agonists alone, anti-inflammatory treatment is delayed – resulting in increased potential for an exacerbation.

There are currently two combination products available in a single inhaler: budesonide/formoterol (Symbicort Turbuhaler*) and salmeterol/fluticasone (Seretide Diskus†). For salmeterol/fluticasone, a separate/additional inhaler must be used to increase the dose of ICS when required as the salmeterol dose–response curve is relatively flat above 50 μg ¹⁷. The dose of budesonide/formoterol in a single inhaler can be varied, however, by using 1–4 inhalations twice daily (bid), making it suitable for adjustable maintenance dosing (AMD) using a physician-guided self-management plan. The total daily doses of budesonide and formoterol when used as 1–4 inhalations bid are within the approved maximal daily doses¹⁸.

The efficacy and tolerability of an AMD regimen with budesonide/formoterol in providing a patient-focused, guideline-driven treatment approach with early intervention at the first sign of an asthma worsening have

* Symbicort and Turbuhaler are registered trademarks owned by the AstraZeneca group.

† Seretide and Diskus are trademarks of GlaxoSmithKline.

already been reported¹⁹. In this open-label study, budesonide/formoterol AMD resulted in a significant reduction in the number of severe exacerbations, despite using a 40% lower drug load, compared with a fixed higher dose of budesonide/formoterol. In another similar study, budesonide/formoterol AMD also significantly improved asthma control (reduced exacerbations and daily reliever use) compared with a significantly higher fixed dose of budesonide/formoterol²⁰. Budesonide/formoterol AMD has also been shown to result in lower drug costs than FD, making it a very cost-effective treatment approach²¹.

Although AMD with budesonide/formoterol has been proven to be more efficacious than fixed higher doses of budesonide/formoterol^{19,20}, AMD and FD with budesonide/formoterol have not, to date, been compared with salmeterol/fluticasone FD. Therefore we have compared the two treatment philosophies: AMD with budesonide/formoterol and FD with either budesonide/formoterol or salmeterol/fluticasone in a 7-month study to assess the effectiveness of each regimen in gaining and maintaining control of asthma. The hypothesis was to determine whether adjustable dosing with a combination inhaler had greater efficacy compared with FD regimens.

1 second (FEV₁) ≥ 50% of predicted normal, were enrolled into the study by the investigators. Patients were recruited by screening medical records and by advertisement. All patients had used ICS (any brand) for ≥ 3 months before study entry and the daily dose was constant in the last month before study entry at 500–1200 µg (for budesonide, based on metered dose) with or without concomitant long-acting β₂-agonist or other additional controller therapy. Exclusion criteria included respiratory infection affecting asthma within 1 month of study entry, smoking history ≥ 10 pack-years, use of systemic corticosteroids within 1 month of study entry and any significant disorder which, in the opinion of the investigator, may have put the patient at risk or influenced the study. The following medications were prohibited during the study: inhaled cromones; leukotriene modifiers; any β₂-agonist (except study medication); xanthines; any β-blocker medication (including eye drops); and inhaled anticholinergics.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol, patient information and consent form were approved by the local ethics committees. All patients provided written informed consent before starting the study.

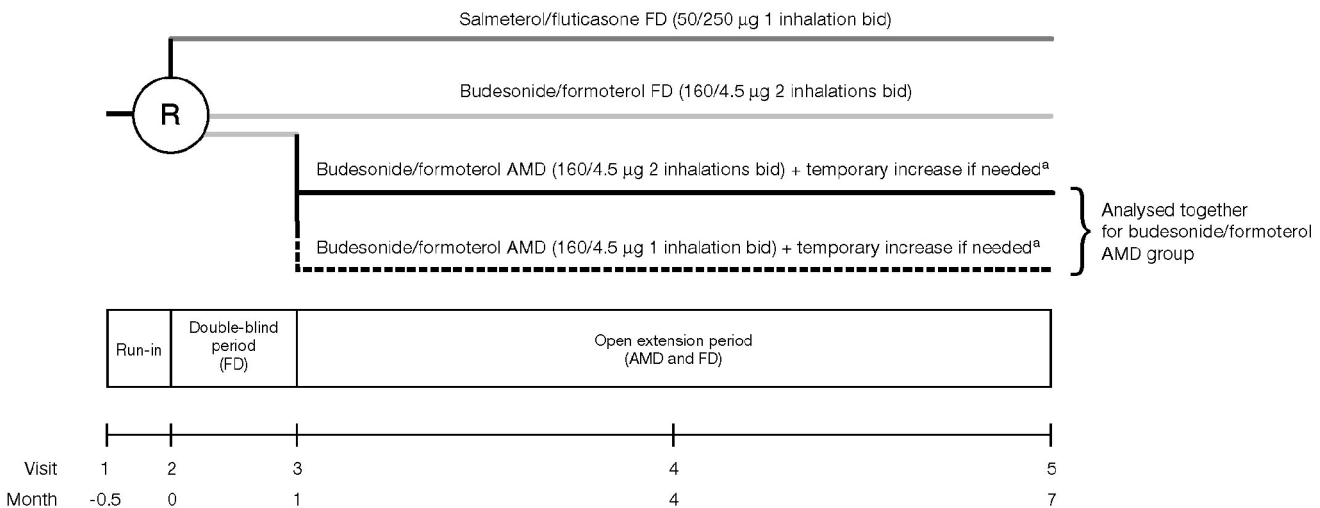
Study Design

This was a randomised, double-dummy, double-blind/open-extension, parallel-group study conducted at outpatient clinics in 93 centres in six countries: Denmark, Finland, Germany, Norway, Sweden and The Netherlands. The study consisted of three treatment periods: run-in, double-blind and open extension (Figure 1).

Methods

Patients

Male or female outpatients aged ≥ 12 years with asthma for a minimum of 6 months, as defined by the American Thoracic Society²², and a forced expiratory volume in



^aPatients increased to 4 inhalations of budesonide/formoterol 160/4.5 µg bid if asthma worsened.

Figure 1. Study design. All patients used terbutaline or salbutamol as needed for relief from asthma symptoms. AMD, adjustable maintenance dosing; bid, twice daily; FD, fixed dosing; R, randomisation

Run-in Period

During an open run-in period of 10–14 days, long-acting β_2 -agonists were not allowed and all patients continued treatment with the same dose of ICS that they had previously been using for the last month before study entry, with as-needed terbutaline sulphate (0.5 mg) for reliever medication (Bricanyl Turbuhaler; AstraZeneca Liquid Production, Södertälje, Sweden) or alternatively salbutamol (if preferred by the patient). The run-in period was used to confirm that patients needed additional controller treatment for their asthma in addition to the ICS allowed during run-in.

For randomisation, patients were required to have: a total asthma symptom score of ≥ 1 on at least 4 of the last 7 days of the run-in period; a mean morning peak expiratory flow (PEF) during the last 7 days of run-in of 50–85% of post-bronchodilatory PEF (obtained approximately 15 minutes after administration of inhaled terbutaline [2×0.5 mg]); and had to demonstrate the ability to use a peak flow meter and correctly record values in their diary. Morning PEF had to have been recorded on ≥ 8 of the last 10 days of the run-in period.

Double-blind Period

Eligible patients were randomised to one of three groups: budesonide/formoterol FD (160/4.5 μ g, Symbicort Turbuhaler; AstraZeneca Liquid Production, Södertälje, Sweden); budesonide/formoterol AMD; or salmeterol/fluticasone FD (50/250 μ g, Seretide Diskus; GlaxoSmithKline, UK). During the 1-month, double-blind period, patients in the budesonide/formoterol FD and AMD groups received budesonide/formoterol at a fixed dose (160/4.5 μ g, two inhalations bid; total daily dose: 640/18 μ g). Patients in the salmeterol/fluticasone FD group received standard doses of salmeterol/fluticasone (50/250 μ g, one inhalation bid; total daily dose: 100/500 μ g). All patients used terbutaline (or salbutamol if preferred) for as-needed reliever medication for the duration of the study.

Randomisation and Blinding

The randomisation schedule was generated using a computer program by a statistician independent of the study team. Patients were consecutively allocated to the lowest available patient number and were randomised strictly sequentially in blocks. Patients inhaled from both a Turbuhaler (budesonide/formoterol or lactose [placebo]) and a Diskus (salmeterol/fluticasone or empty [placebo]) during the double-blind, double-dummy period. Possible biases in treatment selection for the open extension period were avoided as all patients

were allocated to one of the three groups at the start of the double-blind period. The medication boxes dispensed for the open extension were sealed and were not opened until the treatment code envelopes were broken at the beginning of the open extension.

Open Extension Period

During the 6-month open extension, patients in the budesonide/formoterol FD group continued using two inhalations bid. Similarly, the salmeterol/fluticasone FD group continued with standard therapy (one inhalation bid). Patients in the budesonide/formoterol AMD group were instructed to use either one or two inhalations bid, both with increases to four inhalations bid, depending on their level of asthma control (see below).

All patients in the budesonide/formoterol AMD group also received oral and written instructions regarding the self-management plan and the actions to be taken in the event of asthma worsening, which was defined as 2 consecutive days with ≥ 3 occasions of reliever medication use/day or night-time awakenings due to asthma (Table 1). The asthma diary cards of patients randomised to the budesonide/formoterol AMD group were reviewed by the investigator after 1 month of fixed double-blind treatment and during the open extension period; well-controlled patients whose asthma met the criteria (detailed in Table 1) at the end of the double-blind period were stepped down to one inhalation bid. Patients not meeting these criteria continued on a minimum of two inhalations bid for the rest of the study. Without needing to consult their investigator, patients in the budesonide/formoterol AMD group were instructed to adjust their maintenance

Table 1. Dose adjustment criteria for budesonide/formoterol AMD patients during the open period

Adjustment	Criteria
Step down to one inhalation bid (only possible at end of double-blind period in consultation with the investigator)	During the last 7 days of the double-blind period: ≤ 1 occasion ^a of reliever medication use on no more than 2 days <i>and</i> no night-time awakenings due to asthma
Step up to four inhalations bid for 7–14 days ^b	≥ 3 occasions ^a of reliever medication use/day on 2 consecutive days <i>or</i> night-time awakenings due to asthma on 2 consecutive days

^aAn occasion was ≥ 1 inhalation taken at one time, without waiting for the maximal effect of each inhalation.

^bPatients returned to their previous dose if they had ≤ 1 occasion/day of reliever medication on 2 consecutive days and no night-time awakenings.

AMD = adjustable maintenance dosing; bid = twice daily.

dose (one or two inhalations) temporarily to four inhalations bid for 7–14 days if their asthma control was insufficient (as defined in Table 1).

All three groups could receive further treatments if required, at the discretion of the investigator.

Measurements

Patients recorded morning and evening PEF, daytime symptom score, night-time awakenings, daily number of occasions when as-needed reliever medication was used and intake of study medication on diary cards. PEF was measured using a Mini-Wright peak flow meter (Clement Clark, Harlow, UK); all patients were carefully instructed on its correct use.

Daytime asthma symptoms were recorded on a scale of 0–5, where 0 = no symptoms, 1 = symptoms for one short period, 2 = symptoms for two or more short periods, 3 = symptoms for most of the day that did not affect normal daily activities, 4 = symptoms for most of the day that did affect normal daily activities and 5 = symptoms so severe that normal daily activities could not be performed. Night-time asthma symptoms were scored as 0 (no symptoms) or 1 (symptoms caused an awakening or early waking).

FEV₁ was assessed by spirometry performed according to the European Respiratory Society recommendations²³ at study entry, at the end of run-in, after 1 month of double-blind treatment and after 6 months of open extension treatment.

A well-controlled asthma week (WCAW) (primary variable) was defined as a week with no night-time awakenings due to asthma, no exacerbations and no change in asthma treatment due to adverse events, plus at least two of the following: asthma symptom score of > 1 on ≤ 2 days; ≤ 2 days of reliever medication use (maximum four occasions/week); morning PEF ≥ 80% of the predicted normal value every day.

Total asthma control weeks (TACWs) were defined as a week with no daytime asthma symptoms, no night-time awakenings, no exacerbations, no reliever medication use, no change in asthma treatment due to adverse events, and a morning PEF ≥ 80% of the predicted normal value every day.

Exacerbations, defined as oral steroid treatment for ≥ 3 days, emergency room (ER) visits and/or hospitalisation, were recorded. If patients needed to use oral steroids for > 10 consecutive days, the eleventh day was considered to be a second exacerbation. Patients who experienced a third exacerbation were withdrawn from the study. Any patient in the budesonide/formoterol AMD group whose symptoms persisted after stepping up and who did not fulfil the criteria for a step-down of their maintenance dose after 14 days, contacted the investigator. The investigator instructed

the patient to step-down maintenance treatment (to the dose used before stepping up) and implemented alternative treatments as necessary.

Data on resource utilisation were not prospectively collected; however, study drug costs were compared for the three treatment arms.

Safety was assessed by recording adverse events at clinic visits. Spontaneously reported and/or observed adverse events, and the patient's response to a standard open-ended question, were recorded.

Data Analysis

The full analysis set was used in all efficacy analyses. The safety analysis included all patients who received at least one dose of the study drug. All hypothesis testing was done using two-sided alternative hypotheses, and *p*-values < 5% were considered statistically significant.

The double-blind period was a comparison between budesonide/formoterol FD and salmeterol/fluticasone FD. Data for the two budesonide/formoterol groups for the double-blind period were combined for analysis and presentation as these groups received identical doses during this period.

The primary efficacy variable was the odds of having a WCAW during the post-randomisation period (7 months); the primary comparison was between the two FD treatment groups over this period. A generalised estimating equation with a logistic link function, an exchangeable dependency model and subject as cluster was used to estimate the odds of having a WCAW and to compare treatments. Using normal approximation methods, there was 80% power to detect an odds ratio of 1.41, assuming the odds of a WCAW was 0.67 (i.e. an increase from 40% to 48.5%).

TACWs were analysed using similar methods to WCAWs.

Exacerbation data were analysed over the full post-randomisation period (7 months). The total number of asthma exacerbations was compared between groups using a Poisson regression model with the time in the study as an offset variable.

FEV₁ data at the end of the double-blind period and the average of values from the double-blind and open extension periods were analysed. Change in FEV₁ was analysed using additive analysis of variance (ANOVA) models with adjustments for country and baseline values.

Data for the double-blind and open extension periods were analysed separately for diary card variables using similar ANOVA models as for FEV₁. Reliever medication use was assessed as reliever occasions, which were defined as ≥ 1 inhalation of reliever medication, taken together, without waiting for the peak bronchodilator response to each individual inhalation.

Results

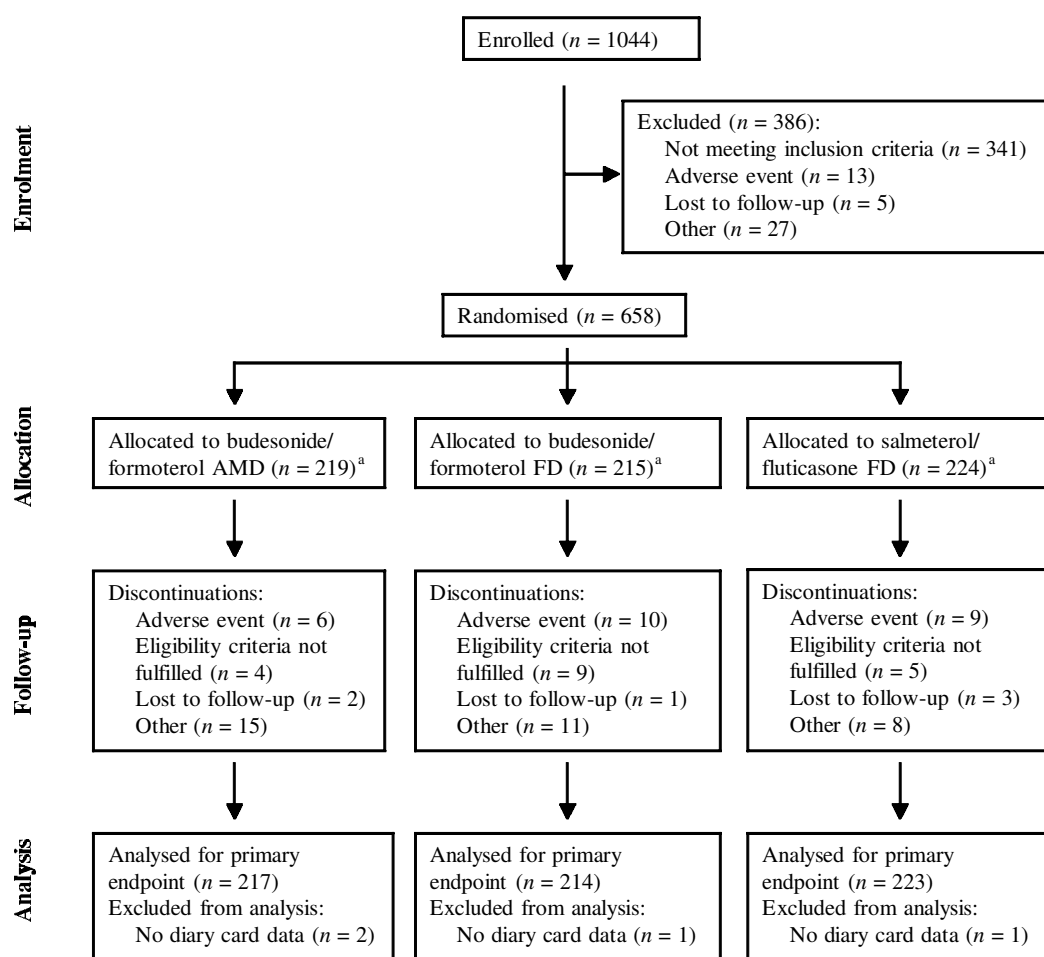
Patients

In total, 1044 patients were enrolled into the study. The first patient was recruited on 10th October 2001 and the last patient completed on 21st December 2002. After run-in, 658 patients were randomised to study treatment: 219, 215 and 224 patients to budesonide/formoterol AMD, budesonide/formoterol FD and salmeterol/fluticasone FD, respectively. Patient flow is shown in Figure 2. In total, 654 patients were analysed for the primary variable: 217, 214 and 223 patients in the budesonide/formoterol AMD, budesonide/formoterol FD and salmeterol/fluticasone FD groups, respectively. Four patients were excluded from the primary analysis because of a lack of diary card data. Data for all randomised patients were included in the safety analysis. There were 138 patients with ≥ 1 protocol deviation: 46, 48 and 44 patients in the budesonide/formoterol AMD, budesonide/formoterol FD and salmeterol/fluticasone FD groups, respectively. The most

common deviation was the use of systemic steroids (other than for exacerbation or emergency treatment), which was reported for 5, 15 and 12 patients in the budesonide/formoterol AMD, budesonide/formoterol FD and salmeterol/fluticasone FD groups, respectively. None of the protocol deviations justified exclusion from the analysis.

Overall, the three treatment groups were well balanced with regard to demography (Table 2). Patients enrolled had sub-optimal asthma control on their existing ICS therapy; 73% of all randomised patients (481/658) already used long-acting β_2 -agonists or combinations of ICS/long-acting β_2 -agonists at study entry. Patients in all groups had similarly low levels of WCAWs (10–12%) and TCAWs (0% for all groups) during the run-in period. Furthermore, patient diary data also indicated that 71% of patients experienced at least one night-time awakening due to asthma during the last 10 days of run-in; patients had a mean of 2.4 nights/week with an awakening due to asthma.

Patients' diary cards in all groups showed high self-recorded adherence to their maintenance medication (mean value of $> 99\%$ in all groups).



Total analysed for primary endpoint = 654
Total analysed for safety = 658

Figure 2. Patient flow. ^aAll patients received allocated treatment

Table 2. Patient characteristics at baseline

	Budesonide/ formoterol AMD (<i>n</i> = 219)	Budesonide/ formoterol FD (<i>n</i> = 215)	Salmeterol/ fluticasone FD (<i>n</i> = 224)
Male/female	94/125	96/119	109/115
Age, years (range)	47 (12–76)	46 (13–85)	46 (14–78)
Asthma duration, years (range)	13 (0–73)	12 (1–60)	12 (1–62)
Asthma daytime symptom score, scale 0–5 (range)	1.6 (0.1–5.0)	1.6 (0.0–4.1)	1.5 (0.0–4.3)
ICS dose at entry, µg (range)	725 (500–1600)	751 (500–1600)	729 (400–1200)
Long-acting β ₂ -agonist use at entry, <i>n</i> (%) ^a	59 (27)	64 (30)	60 (27)
Combinations of ICS/long-acting β ₂ -agonists at entry, <i>n</i> (%)	99 (45)	97 (45)	102 (46)
FEV ₁ , litre (range)	2.71 (0.98–6.11)	2.70 (1.03–4.94)	2.78 (1.20–5.76)
FEV ₁ , % of predicted normal (range)	84 (47–142)	84 (45–156)	85 (50–134)
PEF, l/min post-bronchodilator (range) ^b	465 (170–850)	461 (200–750)	475 (167–951)
Reliever use, number of occasions/day ^c (range)	1.7 (0.0–9.1)	1.9 (0.0–9.4)	1.8 (0.0–12.5)
Reliever-free days, % (range)	28 (0–100)	26 (0–100)	28 (0–100)

All values are presented as absolute numbers or as mean (range), except time since diagnosis (median).

^aPatients were also using ICS.

^bPEF obtained approximately 15 minutes after administration of inhaled terbutaline 2 × 0.5 mg.

^cAn occasion was ≥ 1 inhalation taken together, without waiting for peak bronchodilator response to each individual inhalation.

AMD = adjustable maintenance dosing; FD = fixed dosing; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; PEF = peak expiratory flow.

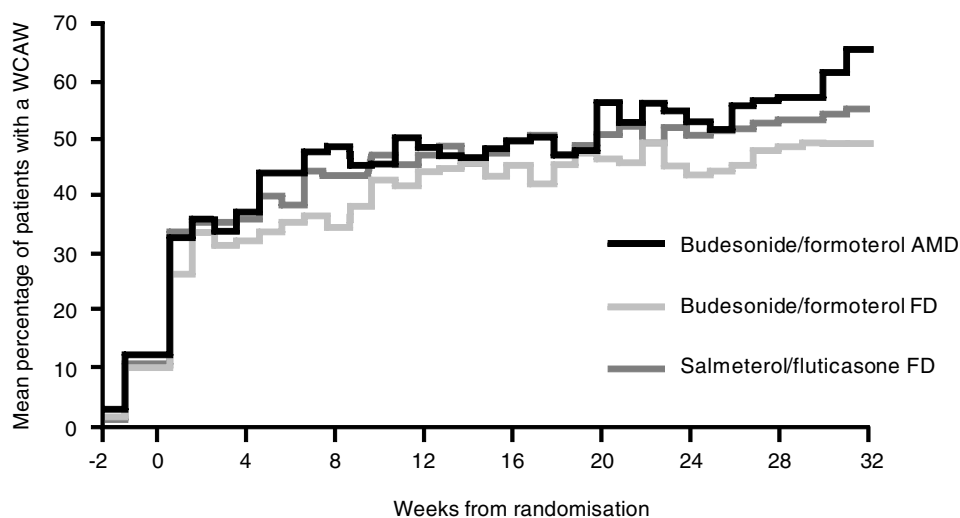


Figure 3. Mean percentage of patients with a well-controlled asthma week (WCAW) (defined as a week with no night-time awakenings due to asthma, no exacerbations, no change in asthma treatment due to adverse events, plus at least two from: asthma symptom score > 1 on ≤ 2 days; ≤ 2 days of reliever use [maximum four occasions/week]; morning peak expiratory flow (PEF) ≥ 80% of predicted normal value every day). Patients in the fixed dosing (FD) groups received budesonide/formoterol (160/4.5 µg, two inhalations bid) or salmeterol/fluticasone (50/250 µg, one inhalation bid) at a constant dose throughout the study. Patients receiving budesonide/formoterol (160/4.5 µg) adjustable maintenance dosing (AMD) received 1 month of double-blind treatment with budesonide/formoterol FD followed by budesonide/formoterol (160/4.5 µg, 1–4 inhalations bid) AMD during the 6-month open extension. During the open extension, there were significantly more WCAWs in the budesonide/formoterol group vs. budesonide/formoterol FD (*p* = 0.049); budesonide/formoterol AMD vs. salmeterol/fluticasone FD, NS

Asthma Control

Well-controlled Asthma Weeks

The odds of achieving a WCAW over the whole treatment period were similar for salmeterol/fluticasone FD and budesonide/formoterol FD (odds ratio 1.289; 95% confidence interval [CI]: 0.981, 1.694; NS); however, during the open extension there was an increase in the odds of achieving a WCAW in patients treated with budesonide/formoterol AMD compared

with budesonide/formoterol FD (odds ratio 1.335; 95% CI: 1.001, 1.783; *p* = 0.049) but no improvement compared with salmeterol/fluticasone FD (odds ratio 1.048; 95% CI: 0.791, 1.391; NS). Interestingly, a sizeable minority of patients – one fifth across all groups – failed to achieve a single WCAW throughout the study period. Mean percentages of patients with WCAWs are shown in Figure 3.

No treatment differences were observed for the composite measure of TACWs. TACWs were not experienced by any patients during the run-in period.

Over the 6-month extension period, only 18–21% of patients achieved a TACW in the three groups compared with 47–54% achieving a WCAW.

Exacerbations

The number and type of asthma exacerbations by treatment group are shown in Figure 4. Patients in the budesonide/formoterol AMD group had fewer exacerbations than patients in either the budesonide/formoterol FD or salmeterol/fluticasone groups: (35 vs. 50 and 59 exacerbations, respectively). The total rate of exacerbations over 7 months was 0.041/month for patients treated with salmeterol/fluticasone FD, 0.036/month for budesonide/formoterol FD and 0.024/month for budesonide/formoterol AMD. There was a statistically significant rate reduction of 39.7% (95% CI: 8.3, 60.3; $p = 0.018$) in favour of budesonide/formoterol AMD compared with salmeterol/fluticasone FD. Similarly, there was a 32.0% rate reduction for budesonide/formoterol AMD compared with budesonide/formoterol FD (95% CI: -4.8, 55.9); however, this did not achieve statistical significance (NS). The number needed to treat [NNT]

to avoid 1 exacerbation over 1 year with budesonide/formoterol AMD vs. salmeterol/fluticasone FD was 4.9. Over the last 100 days of treatment, the number of exacerbations seen was three for budesonide/formoterol AMD, 12 for budesonide/formoterol FD and 14 for salmeterol/fluticasone FD (Figure 5). Asthma symptoms and reliever medication use around exacerbations are shown in Figure 6. Both asthma symptoms and reliever use were lower during the exacerbation period for budesonide/formoterol AMD compared with the two FD regimens.

Other Efficacy Variables

Improvements in FEV₁ were significantly greater after 1 month of FD double-blind treatment with budesonide/formoterol (pooled data from both groups [0.175 litre]) than with salmeterol/fluticasone FD treatment (0.125 litre) (mean difference -0.050 litre; 95% CI: -0.099, -0.001; $p < 0.05$). No other differences were observed after 1 month of FD treatment with budesonide/formoterol or salmeterol/fluticasone (Table 3). The treatment difference in FEV₁ in favour of budesonide/formoterol FD vs. salmeterol/fluticasone FD

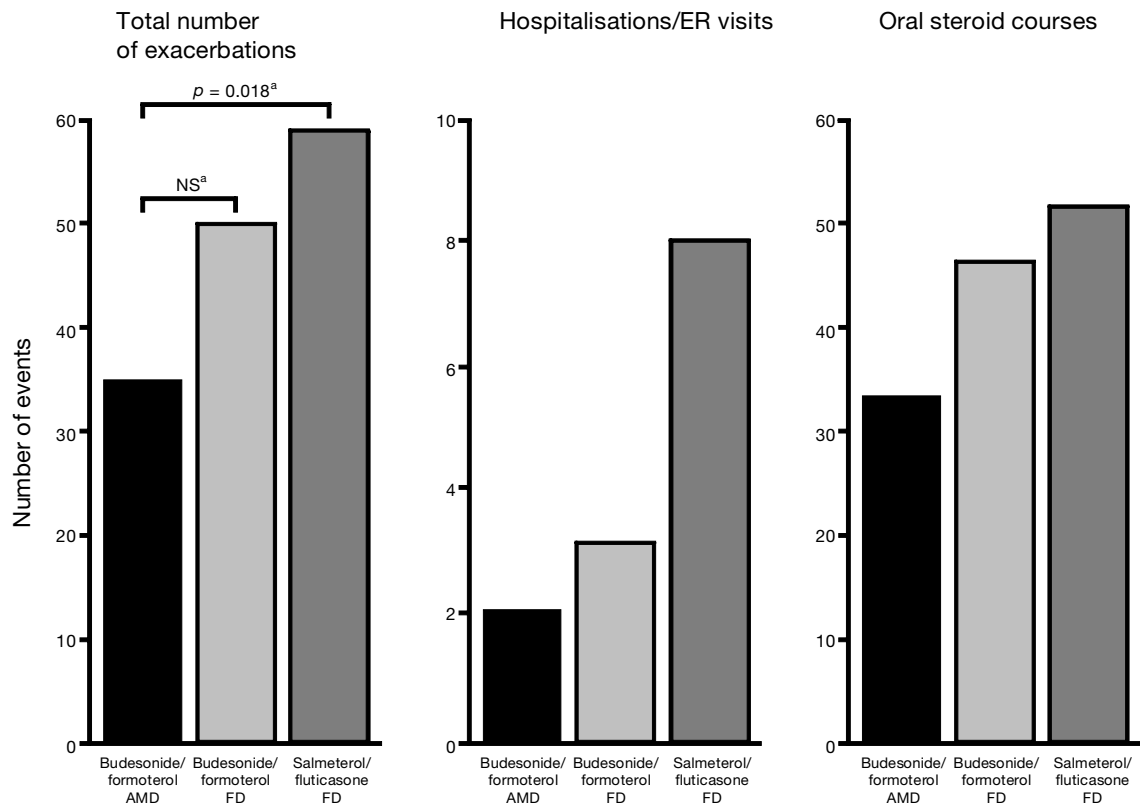


Figure 4. Exacerbations, defined as oral steroid treatment for ≥ 3 days, emergency room (ER) visits and/or hospitalisation. Total number of exacerbations is the sum of hospitalisation/ER visits and oral steroid courses. Patients in the fixed dosing (FD) groups received budesonide/formoterol (160/4.5 μg , two inhalations bid) or salmeterol/fluticasone (50/250 μg , one inhalation bid) at a constant dose throughout the study. Patients receiving budesonide/formoterol (160/4.5 μg) adjustable maintenance dosing (AMD) received 1 month of double-blind treatment with budesonide/formoterol FD followed by budesonide/formoterol (160/4.5 μg , 1–4 inhalations bid) AMD during the 6-month open extension. ^a39.7% rate reduction vs. salmeterol/fluticasone FD ($p = 0.018$) and 32.0% rate reduction vs. budesonide/formoterol FD (NS) (Poisson regression analysis)

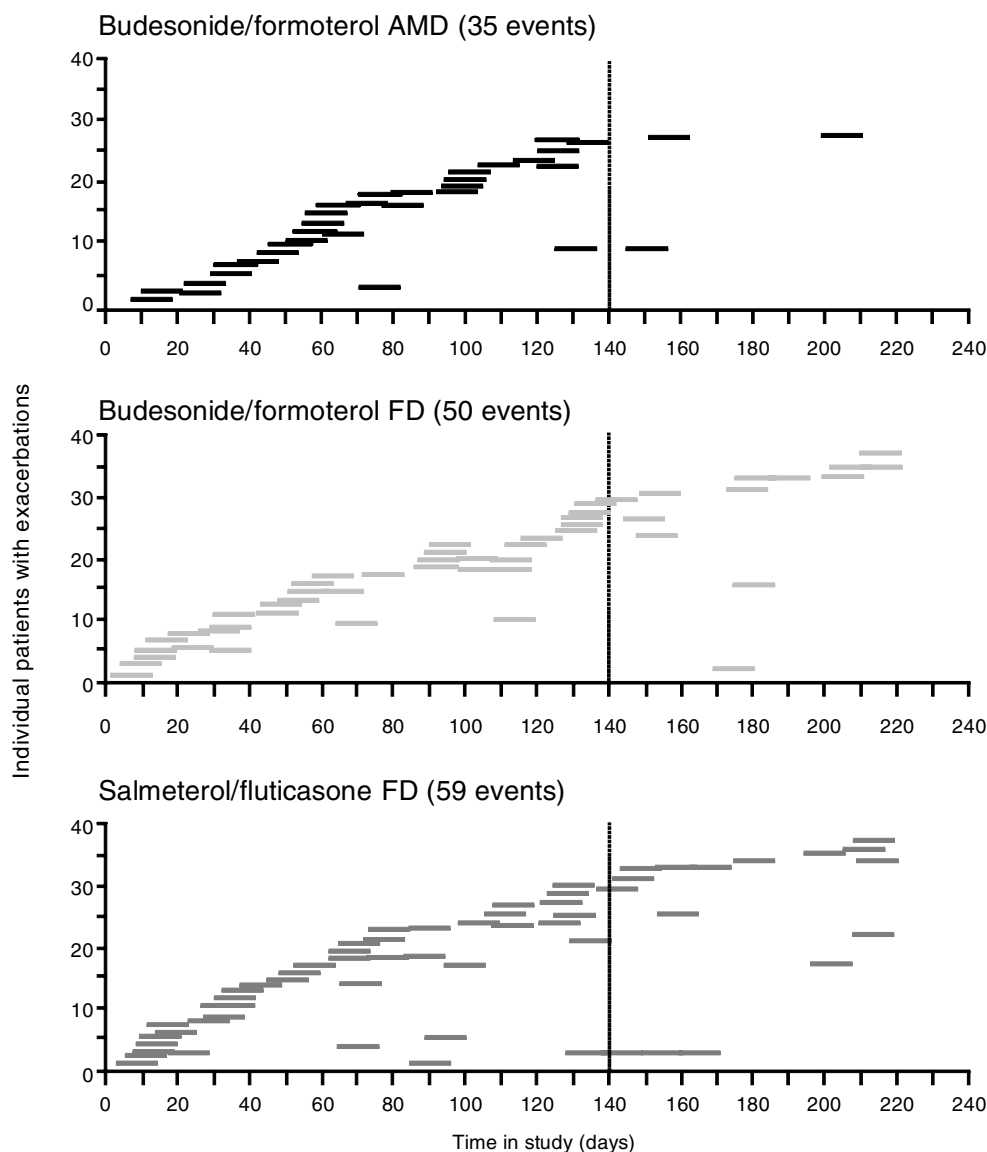


Figure 5. Incidence of exacerbations over time for individual patients. The x-axis represents time and each number on the y-axis represents an individual patient. Each single line represents one exacerbation for an individual patient. Exacerbations > 10 days in duration were considered as multiple events. Individual patients with > 1 exacerbation are shown as broken or extended lines in the same horizontal position. The dotted vertical line has been added to highlight the difference in exacerbations starting during the last 100 days of treatment. Patients in the fixed dosing (FD) groups received budesonide/formoterol (160/4.5 µg, two inhalations bid) or salmeterol/fluticasone (50/250 µg, one inhalation bid) at a constant dose throughout the study. Patients receiving budesonide/formoterol adjustable maintenance dosing (AMD) received 1 month of double-blind treatment with budesonide/formoterol (160/4.5 µg, two inhalations bid) FD followed by budesonide/formoterol (160/4.5 µg, 1–4 inhalations bid) AMD during the 6-month open extension

was maintained during the 6-month extension period (mean difference -0.058 litre; 95% CI: -0.113 , -0.002 ; $p < 0.05$).

Diary card variables during the 1-month FD double-blind period and the 6-month open extension are shown in Figure 7. After switching from an FD regimen to 6 months of AMD treatment in the open extension, patients in the budesonide/formoterol AMD group used their reliever medication less frequently than those continuing with an FD regimen: mean difference vs. salmeterol/fluticasone FD 0.23 occasions (95% CI: 0.05, 0.41; $p < 0.05$) and vs. budesonide/formoterol FD 0.30 occasions (95% CI: 0.12, 0.48; $p < 0.01$).

Night-time awakenings were also significantly reduced after switching from FD to AMD with budesonide/formoterol over the 6-month extension period (mean difference vs. budesonide/formoterol FD: 4.7%; 95% CI: 0.3, 9.2; $p < 0.05$). Other efficacy variables were comparable between groups during the open extension period, with the exception of evening PEF, which was significantly lower in the budesonide/formoterol AMD group compared with both FD regimens: mean difference 9.6 litre/min (95% CI: 1.8, 17.5; $p < 0.05$) and 8.4 litre/min (95% CI: 0.7, 16.1; $p < 0.05$) vs. budesonide/formoterol FD and salmeterol/fluticasone FD, respectively.

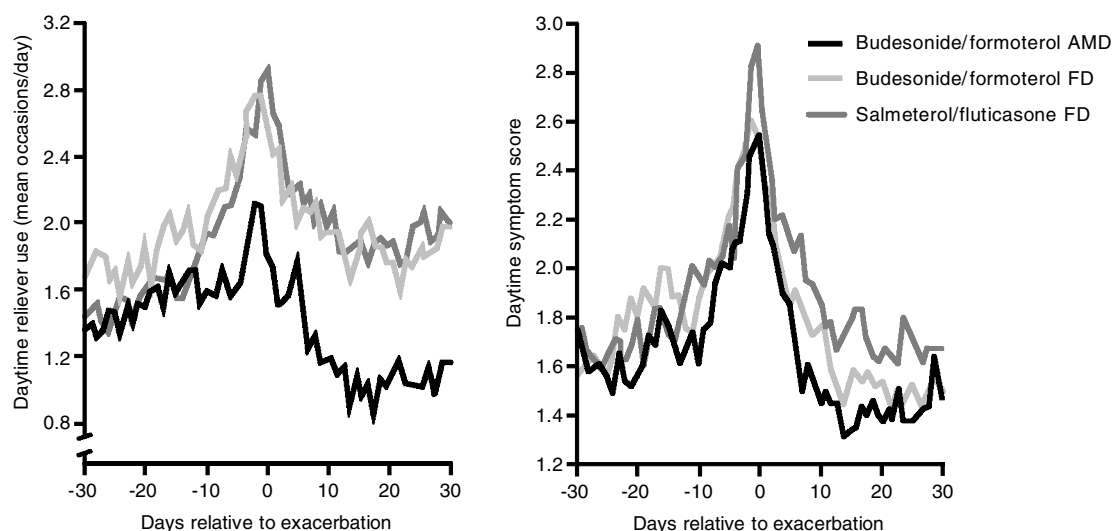


Figure 6. Mean daytime asthma symptom scores (scale 0–5, where 0 = no symptoms, 5 = symptoms so severe that normal daily activities could not be performed) and daytime reliever medication use (occasions defined as ≥ 1 inhalation taken together, without waiting for peak bronchodilator response to each individual inhalation) 30 days before and 30 days after exacerbations. Patients in the fixed dosing (FD) groups received budesonide/formoterol (160/4.5 μg , two inhalations bid) or salmeterol/fluticasone (50/250 μg , one inhalation bid) at a constant dose throughout the study. Patients receiving budesonide/formoterol adjustable maintenance dosing (AMD) received 1 month of double-blind treatment with budesonide/formoterol (160/4.5 μg , two inhalations bid) FD followed by budesonide/formoterol (160/4.5 μg , 1–4 inhalations bid) AMD during the 6-month open extension

Adjustable Dosing with Budesonide/Formoterol

In total, 45% of patients (95/211) in the budesonide/formoterol AMD group had gained sufficient control of their asthma after 1 month of double-blind treatment to

warrant a reduction in their maintenance treatment from two inhalations to one inhalation bid during the 6-month open extension period. Fifty-seven per cent of patients (120/211) in the budesonide/formoterol AMD group required no step-ups in treatment. Most patients who needed a temporary step-up in budesonide/formoterol

Table 3. Patient diary card variables and FEV₁ measured at clinic visits before and after 1 month of double-blind treatment with budesonide/formoterol FD or salmeterol/fluticasone FD

Variable	Budesonide/formoterol ^a		Salmeterol/fluticasone FD		Between-group mean difference (95% CI)
	Run-in ^b	Adjusted mean change ^c	Run-in ^b	Adjusted mean change ^c	
FEV ₁ , litre (range)	2.62 (0.97–5.76)	0.18	2.73 (1.18–5.65)	0.13	–0.05* (–0.099, –0.001)
Morning PEF, l/min (range)	372.2 (126–703)	24.3	385.7 (163–766)	24.9	0.6 (–4.6, 5.9)
Evening PEF, l/min (range)	391.6 (127–696)	14.5	402.8 (177–800)	17.6	3.1 (–1.9, 8.0)
Reliever use, number of occasions/day (range) ^d	1.83 (0.0–9.4)	–0.86	1.76 (0.0–12.5)	–0.81	0.04 (–0.12, 0.21)
Awakenings, % (range)	34.6 (0–100)	–11.3	32.9 (0–100)	–12.0	–0.7 (–4.4, 2.9)
Daytime symptom scores, scale 0–5 (range)	1.56 (0.0–5.0)	–0.49	1.50 (0.0–4.3)	–0.50	–0.01 (–0.11, 0.09)

* $p = 0.047$ in favour of budesonide/formoterol.

^aDuring the double-blind period, budesonide/formoterol AMD and FD groups were pooled as all received the standard dose (160/4.5 μg , two inhalations bid).

^bValues are means during the 10–14-day run-in period.

^cValues from analysis of variance (ANOVA) model.

^dAn occasion was ≥ 1 inhalation taken together, without waiting for peak bronchodilator response to each individual inhalation.

CI = confidence interval; FD = fixed dosing; FEV₁ = forced expiratory volume in 1 second; NS = not significant; PEF = peak expiratory flow.

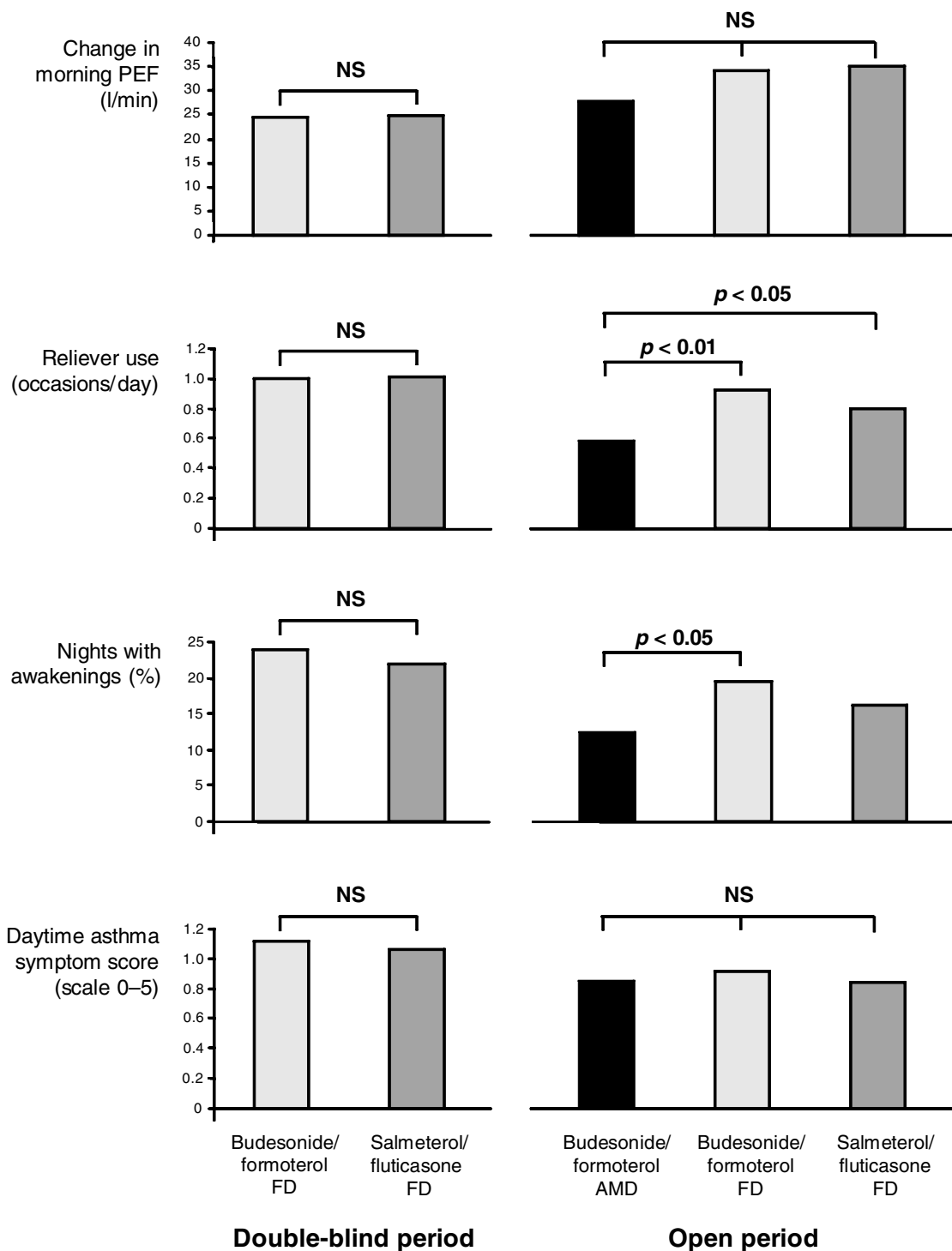


Figure 7. Diary card variables for patients receiving budesonide/formoterol (160/4.5 µg, 1–4 inhalations bid) adjustable maintenance dosing (AMD), fixed dosing (FD; 160/4.5 µg, two inhalations bid) or salmeterol/fluticasone (50/250 µg, one inhalation bid) FD. During the 1 month of double-blind treatment, the budesonide/formoterol AMD and FD groups received two inhalations bid (data were combined for analysis and presentation). NS = not significant; PEF = peak expiratory flow

treatment regained control of their asthma within 7 days (67% of the step-up periods).

During the 6-month open extension, budesonide/formoterol AMD patients used, on average, significantly fewer inhalations of study drug than those receiving budesonide/formoterol FD: 3.4 inhalations/day vs. 4.0 inhalations/day (adjusted mean difference 0.51

inhalations; 95% CI: 0.36, 0.66; $p < 0.001$). Overall, patients in the budesonide/formoterol AMD group used less ICS/long-acting β_2 -agonist: 544/15 µg/day vs. 640/18 µg/day for the budesonide/formoterol FD group. In contrast, patients in the salmeterol/fluticasone group used their long-acting β_2 -agonist/ICS medication at a dose of 100/500 µg/day.

Drug Costs

Costs for budesonide/formoterol AMD and salmeterol/fluticasone FD are shown in Table 4. There was no clear cost advantage for budesonide/formoterol FD or salmeterol/fluticasone FD. However, budesonide/formoterol AMD resulted in consistently lower drug costs than either FD regimen in five major European Union markets.

Safety

The incidence of adverse events was similar in all treatment groups: 57% (124/219), 58% (124/215) and 66% (147/224) of patients in the budesonide/formoterol AMD, budesonide/formoterol FD and salmeterol/fluticasone FD groups, respectively, had at least one adverse event. Most events were mild or moderate in severity. A lower incidence of dysphonia was observed during treatment with budesonide/formoterol AMD and FD compared with salmeterol/fluticasone (Table 5). A lower incidence of candidiasis was also observed in budesonide/formoterol AMD patients compared with salmeterol/fluticasone FD patients (1% vs. 3%, respectively).

A total of 31 serious adverse events were recorded for 24 patients: eight patients treated with budesonide/formoterol AMD; 11 patients treated with budesonide/formoterol FD; and five patients treated with salmeterol/fluticasone FD. Three serious adverse events were related to asthma: two patients in the budesonide/formoterol AMD group and one patient in

the budesonide/formoterol FD group had aggravated asthma events. None of the serious adverse events was considered by the investigator to be causally related to the study drugs.

Discussion

The goals of successful asthma management include achieving and maintaining control of symptoms, maintaining lung function as close to normal as possible, maintaining normal activity levels, avoiding adverse events from asthma medications, preventing irreversible airway remodelling and preventing exacerbations – optimal asthma control is not achieved until exacerbations are eliminated and the patient is symptom free. All these aims should be achieved at the lowest possible drug load. Indeed, asthma guidelines recommend that patients are educated to adjust their medication according to variations in asthma using physician-guided self-management plans. Previously, AMD has been compared with FD using budesonide/formoterol. The present study was the first to investigate the effect of these two different treatment approaches on prospectively defined targets of asthma control^{5,24} using the two available ICS/long-acting β_2 -agonist combination inhalers, budesonide/formoterol and salmeterol/fluticasone. Budesonide/formoterol AMD and FD were compared with salmeterol/fluticasone FD. Adjustable dosing with salmeterol/fluticasone is only possible by using a

Table 4. Costs (€) for budesonide/formoterol AMD and salmeterol/fluticasone FD regimens

Country	Pack price	Pack size ^a	Cost per dose	Daily cost ^b
Spain				
Symbicort	70.48	120 × 160	0.59	2.00
Seretide	66.97	250 × 60	1.12	2.23
UK ^c				
Symbicort	54.72	120 × 200	0.46	1.55
Seretide	56.75	260 × 60	0.95	1.89
Germany				
Symbicort	80.02	120 × 160	0.67	2.27
Seretide	80.02	250 × 60	1.33	2.67
France				
Symbicort	57.78	120 × 200	0.48	1.64
Seretide	52.41	250 × 60	0.87	1.75
Italy				
Symbicort	69.16	120 × 160	0.58	1.96
Seretide	64.6	250 × 60	1.08	2.15

^aSymbicort pack size is number of doses × strength; Seretide pack size is strength × number of doses.
^bCosts are for Symbicort AMD and Seretide FD.
^cGBP: euro exchange rate = 1:1.44.
AMD = adjustable maintenance dosing; FD = fixed dosing.

Table 5. Incidence of most commonly reported^a pharmacologically predictable adverse events

Adverse event	Budesonide/formoterol AMD (n = 219) (%)	Budesonide/formoterol FD (n = 215) (%)	Salmeterol/fluticasone FD (n = 224) (%)
Candidiasis	1	2	3
Dysphonia	1	1	7
Headache	3	2	4

^aOnly pharmacologically predictable adverse events reported for > 3% of the overall population are included.

AMD = adjustable maintenance dosing; FD = fixed dosing.

separate and additional inhaler to increase the dose of ICS; this is because the salmeterol dose–response curve is limited¹⁷.

The study comprised two treatment periods: a 4-week double-blind period comparing FD with budesonide/formoterol and salmeterol/fluticasone followed by a 6-month open extension period where AMD with budesonide/formoterol was compared with FD with budesonide/formoterol and salmeterol/fluticasone. In contrast to the EDICT study²⁵, where salmeterol/fluticasone was compared with budesonide and formoterol given via separate inhalers, the current study compared single inhaler products containing both ICS and long-acting β_2 -agonists at appropriate doses and used clinically relevant, prospectively defined markers of asthma control.

Previous studies have established that lung function, symptom control and reliever use reached near-maximal effects within 4 weeks with both budesonide/formoterol and salmeterol/fluticasone^{26,27}. Data from the double-blind period in this study confirmed that FD with budesonide/formoterol and salmeterol/fluticasone in a controlled setting delivered similar levels of efficacy, except for the small but statistically significantly higher FEV₁ observed with budesonide/formoterol, which was then maintained over the full treatment period.

In the present study, the definition of exacerbations was limited to clinically meaningful events – the need for oral steroid courses or ER visits/hospitalisation. Budesonide/formoterol AMD was significantly more effective at reducing exacerbations than traditional salmeterol/fluticasone FD. The rate of exacerbations was significantly lower by 40% in patients receiving budesonide/formoterol AMD than in those receiving salmeterol/fluticasone FD. This treatment difference relates to a reduction of 20 severe exacerbations per 100 patients/year (NNT = 4.9). The rate of exacerbations also tended to be reduced by 32% with budesonide/formoterol AMD vs. budesonide/formoterol FD; however, this reduction was not significant. Importantly, with increasing study duration, budesonide/formoterol AMD appeared to provide better asthma control: the difference in exacerbation

rates in favour of budesonide/formoterol AMD became more marked over time. During the last 100 days of treatment, there was a 4-fold higher incidence of exacerbations for both FD groups compared with the budesonide/formoterol AMD group. In addition, breakthrough daily symptoms, indicated by as-needed reliever medication use, were more commonly seen in both FD groups throughout the 6-month assessment period. Budesonide/formoterol AMD patients also used less study drug, had fewer night-time awakenings and had an increase in WCAWs compared with those using budesonide/formoterol FD. Although patients in both FD groups had larger increases in evening PEF than those in the budesonide/formoterol AMD group, these changes were neither consistent with asthma control measures nor considered to be clinically relevant, and may simply reflect the higher daily use of reliever medication in the FD groups.

Variability in asthma control is reduced over time with budesonide/formoterol AMD compared with traditional therapy using a higher fixed dose of budesonide/formoterol or salmeterol/fluticasone. These improvements in asthma control are gradual and do not appear to have peaked by the end of the study. Indeed, the trend for improvements in WCAW seen in all three treatment groups does not seem to have attained maximal effect during the 7-month study. Studies of a longer duration may therefore be needed to provide a more complete picture over time for WCAW.

The use of a composite measure of asthma control in the current study that takes into account subjective assessments of asthma symptoms and night-time awakenings in addition to traditional assessments of lung function, as well as the incidence of clinically relevant exacerbations, aimed to provide an overall assessment of asthma control. Composite measures of asthma control, such as WCAWs, have been advocated as important measures of long-term asthma control that require further assessment over longer periods²⁴. However, the present study indicated that the use of WCAWs alone will only present half the picture of a successful treatment outcome – the number of patients achieving or approaching target levels of asthma control. A

WCAW was not achieved during a single week of the study for a large proportion of the trial population and this outcome measure failed to take account of the greater variability in asthma control leading to severe exacerbations and the increased need for reliever medication for breakthrough symptoms in the FD groups. Furthermore, only a minority of patients achieved the more ambitious target for full control (TACWs); therefore, TACWs are probably too insensitive to be useful for assessing the effectiveness of different management approaches in patients with more moderate to severe asthma. The results of the present study highlight the need for studying multiple measures of asthma control before drawing conclusions on the effectiveness of treatment regimens.

An important guideline objective of asthma management is to minimise the patient's overall drug load while maintaining asthma control. This can be achieved by tailoring treatment to the individual patient's needs, which has implications for minimising adverse events and potentially improving patients' long-term adherence to treatment. In this study, patients' asthma was under sufficient control (patients had ≤ 1 occasion of reliever medication use on no more than 2 days and no night-time awakenings due to asthma) after 1 month of treatment with budesonide/formoterol for approximately half the patients in the AMD group to have their treatment reduced to one inhalation bid as instructed by their clinicians. The use of additional temporary step-ups to four inhalations bid was permitted in the budesonide/formoterol AMD group in accordance with the asthma management plan. Twice as many step-ups occurred in patients who were not able to step-down treatment at the end of the double-blind period. Consequently, although the mean dose of budesonide/formoterol was significantly lower than in the budesonide/formoterol FD group, the adjustable maintenance plan allowed greater flexibility to meet the differing needs of individual patients. Improved asthma control at an overall lower drug load for budesonide/formoterol AMD compared with budesonide/formoterol FD has been reported previously^{19,20}.

With the growing importance of economic evaluations in healthcare decision-making²⁸, it is also important to consider the costs of these different treatment approaches. A Swedish analysis has previously reported that budesonide/formoterol AMD leads to significantly lower healthcare costs than budesonide/formoterol FD²¹. In the current study, budesonide/formoterol AMD resulted in lower drug costs than FD with either salmeterol/fluticasone or budesonide/formoterol. This costing approach is considered conservative as the budesonide/formoterol AMD group had fewer exacerbations and used less reliever medication, implying that including these items would further lower

the costs for budesonide/formoterol AMD vs. budesonide/formoterol FD and salmeterol/fluticasone FD. The reduction in exacerbations and lower usage of reliever medication would further increase the difference in healthcare costs in favour of budesonide/formoterol AMD.

In the current study, promptly increasing the dose of ICS and long-acting β_2 -agonists at the first sign of asthma worsening provided an early intervention strategy for the reduction of exacerbations. This concept was first demonstrated for budesonide alone by Foresi *et al.*, who showed that in patients controlled on a low-maintenance dose of budesonide, asthma exacerbations could be prevented and limited in severity by early intervention with a short-term increase in the daily dose of ICS while using a lower overall dose compared with fixed high-dose treatment⁹. In this 6-month study, all treatment was blinded using one regular budesonide inhaler (200 μ g/day or 800 μ g/day) and an inhaler for treating asthma worsenings (7 days of budesonide 800 μ g/day or matching placebo), i.e. a total of two study inhalers. While the present study was conducted to the highest possible scientific and ethical standards, one limitation of the study design was the lack of blinding in the 6-month open-label extension. A double-blind, double-dummy design for the adjustable dosing in the present study would have required a highly complex design with at least four regular inhalers per treatment arm (e.g. one active vs. three placebo inhalers in both fixed-dose arms and three active inhalers and one placebo inhaler in the budesonide/formoterol AMD arm). A decision not to blind the study was therefore made in order to continue the single-inhaler approach to treatment in all groups. Thus, the second phase of the study focused on assessing two simple treatment philosophies in current practice using single inhalers – AMD with an action plan or FD without. The written action plan plus instruction on its use was an integral part of the AMD treatment philosophy. Any increased patient–doctor interaction that may have occurred due to instruction on the written action plan only happened at the end of the double-blind period and so is unlikely to have resulted in the beneficial outcomes of budesonide/formoterol AMD, which are evident throughout the 6-month open extension. The four-inhaler approach with action plans in all groups, although having greater scientific rigor, is less applicable to the real-life clinical situation, where patients ideally use one or possibly two inhalers for long-term maintenance treatment. In addition, four inhalers would introduce unnecessary complexity, which is undesirable because of the adverse effect this can have on patient adherence²⁹.

This and other studies^{9,19,20,30–33} confirm the benefits of a temporary increase in maintenance treatment to meet

the inherent variability in asthma. It is noteworthy that a 2-fold increase in ICS dose alone – as can be achieved with salmeterol/fluticasone by switching inhaler strength – is not effective during a period of worsening asthma³⁴. However, promptly increasing the dose of both ICS and long-acting β_2 -agonists 2- or 4-fold – as is possible with budesonide/formoterol – is effective and has been confirmed in several studies^{19,20}. Data from the present study confirm these findings.

Overall, the present study suggests that FD with budesonide/formoterol and salmeterol/fluticasone provides similar levels of guideline-defined asthma control. However, both treatments were associated with greater asthma variability, higher reliever use and more exacerbations than AMD with budesonide/formoterol. Furthermore, the goal of achieving better asthma control with the lowest possible drug load was easier to achieve with an adjustable dosing regimen because budesonide/formoterol AMD provides the patient with the ability to increase their dose when needed, while allowing them to use a lower drug load during periods of good control. Early intervention with budesonide/formoterol may prove to be more effective in managing the variations in asthma, which may increase the patients' confidence in their treatment, leading to improved adherence to treatment. In addition, budesonide/formoterol in a single inhaler has been shown to provide rapid relief from severe bronchoconstriction that patients can feel, faster than that of salmeterol/fluticasone³⁵, and is at least as effective and rapid acting as salbutamol in acute, severe asthma³⁶. Future studies may show that budesonide/formoterol can be used as both a controller and a reliever medication. Using budesonide/formoterol for symptom relief allows rapid adjustment in effective controller therapy if asthma worsens.

In conclusion, budesonide/formoterol adjustable maintenance dosing is well tolerated, providing more effective asthma control than traditional fixed dosing with budesonide/formoterol and salmeterol/fluticasone.

Acknowledgements

The study was sponsored by AstraZeneca, Lund, Sweden. The authors would like to thank all of the investigators and staff at the study sites for their valuable contribution to the study and are grateful to Ian Naya (AstraZeneca, Lund, Sweden) for editorial assistance.

References

- Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing ICS. *Lancet* 1994;344:219-24
- Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481-8
- Pauwels RA, Lofdahl C-G, Postma DS, Tattersfield AE, O'Byrne PM, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11
- O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1392-7
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. National Institutes of Health: National Heart, Lung, and Blood Institute. Bethesda, MD: National Institutes of Health; 2002 (publication No. NIH-NHLI 02-3659)
- British Thoracic Society (BTS)/Scottish Intercollegiate Guideline Network (SIGN). British Guideline on the management of asthma. *Thorax* 2003;58(Suppl. 1):1-94
- Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7
- Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting β_2 -agonists and corticosteroids. *Eur Respir J* 2002;19:182-91
- Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. *Chest* 2000;117:440-6
- Charlton I, Charlton G, Broomfield J, Mullee MA. Evaluation of peak flow and symptoms only self management plans for control of asthma in general practice. *BMJ* 1990;301:1355-9
- Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, Peramaki E, Poussa T, Saarelainen S, Svahn T. Randomised comparison of guided self-management and traditional treatment of asthma over one year. *BMJ* 1996;312:748-52
- Liljas B, Lahdensuo A. Is asthma self-management cost-effective? *Patient Educ Couns* 1997;32(Suppl. 1):S97-S104
- Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, Pekurinen M, Peramaki E, Saarelainen S, Svahn T, Liljas B. Randomised comparison of cost effectiveness of guided self management and traditional treatment of asthma in Finland. *BMJ* 1998;316:1138-9
- Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma (Cochrane review). In: *The Cochrane Library*, Issue 4. Oxford: The Cochrane Library; 2003
- National Asthma Campaign. Out in the open. A true picture of asthma in the United Kingdom today. *Asthma J* 2001;6(Suppl.):1-16
- Haughney J, Barnes G, Partridge M. Living and breathing – a national survey of patients' views of asthma and its treatment. *Thorax* 2001;56(Suppl. III):S51
- Palmqvist M, Ibsen T, Mellén A, Lötvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med* 1999;160:244-9
- British National Formulary. London: British Medical Association, Royal Pharmaceutical Society of Great Britain; 2003
- Stållberg B, Olsson P, Jörgensen LA, Lindarck N, Ekström T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. *Int J Clin Pract* 2003;57:656-61
- FitzGerald MJ, Sears MR, Boulet L-P, Becker AB, McIvor AR, Ernst P, Smiljanic-Georgijev NM, Lee JSM. Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with fixed dosing. A 5-month multicentre Canadian study. *Can Respir J* 2003;10 (in press)
- Olsson P, Karlsson G, Ekström T, Lindarck N. Adjustable dosing with budesonide/formoterol in a single inhaler reduces costs compared with a conventional fixed dosing regimen. *Eur Respir J* 2003;22(Suppl. 45):411s [Abstract No. P2643]

22. American Thoracic Society (ATS). Standards for the diagnosis and care of patients with chronic obstructive airway disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44
23. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Report of the Working Party: Standardisation of lung function tests. European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993;6(Suppl. 16):5-40
24. Bateman ED, Bousquet J, Braunstein GL. Is overall asthma control being achieved? A hypothesis-generating study. *Eur Respir J* 2001;17:589-95
25. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide™ (50/250 µg bd Diskus™ versus formoterol (12 µg bd) and budesonide (800 µg bd) given concurrently (both via Turbuhaler™) in patients with moderate-to-severe asthma. *Respir Med* 2002;96:851-61
26. Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S. Symbicort® (budesonide and formoterol in a single inhaler) improves asthma control in adults: a randomised controlled study. *Eur Respir J* 2001;18:262-8
27. Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 µg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J* 1999;6:45-51
28. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines – similarities, differences and some implications. *Values Health* 2001;4:225-50
29. van der Palen J, Klein JJ, van Herwaarden CLA, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. *Eur Respir J* 1999;14:1034-7
30. Gustafsson D, Olsson P, Stållberg B, Ekström T, Lindarck N. Budesonide/formoterol adjustable maintenance dosing and fixed dosing in adolescents with asthma: a Swedish study. *Eur Respir J* 2003;22(Suppl. 45):258s [Abstract No. P1697]
31. Leuppi JD, Salzberg M, Meyer L, Bucher SE, Nief M, Brutsche MH, Tamm M. An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. *Swiss Med Wkly* 2003;133:302-9
32. Moretti AM, Canonica GW, Sanguinetti CM, Mangrella M, Stabilini M, and the CAST Study Team. Adjustable maintenance dosing with budesonide/formoterol controls asthma symptom severity and maintains lung function with a lower overall dose than fixed dosing: results of an Italian study. *Eur Respir J* 2003;22(Suppl. 45):259s [Abstract No. P1703]
33. Sears MR, McOvor A, Becker A, Fitzgerald JM, Boulet LP, Ernst P, Goergijev NS, Lee J. Budesonide/formoterol adjustable maintenance dosing effectively improves asthma symptom severity: a multicentre Canadian study. *Eur Respir J* 2003;22(Suppl. 45):258s [Abstract No. P1695]
34. FitzGerald JM, Becker A, Chung K, Lee J. Randomised, controlled, multi-centre study to compare double-dose versus maintenance dose of inhaled corticosteroids (ICS) during asthma exacerbations. *Am J Respir Crit Care Med* 2000;161:A187
35. van der Woude HJ, Boorsma M, Bergqvist PBF, Winter TH, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. *Pulm Pharmacol Ther* 2004 (in press)
36. Balanag VM, Yunus F, Yang P-C, Jorup C. Budesonide/formoterol in a single inhaler is as effective and well tolerated as salbutamol in relieving acute asthma in adults and adolescents. *Eur Respir J* 2003;22(Suppl. 45):445s [Abstract No. P2836]

CrossRef links are available in the online published version of this paper:

<http://www.cmrojournal.com>

Paper CMRO-2502, Accepted for publication: 19 November 2003

Published Online: 12 December 2003

doi:10.1185/030079902125002928

Erratum

Since its original publication on-line on 12 December 2003, a correction has been made to this manuscript. On page 235, line 4 of paragraph 2 previously read:

3.4 inhalations bid vs. 4.0 inhalations bid

This has been corrected for both the on-line and print versions to:

3.4 inhalations/day vs. 4.0 inhalations/day