



Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial

Alberto Papi*, Brunilda Marku*, Nicola Scichilone, Piero Maestrelli, Pierluigi Paggiaro, Marina Saetta, Stefano Nava, Ilenia Folletti, Giuseppina Bertorelli, Stefano Bertacco, Marco Contoli, Mario Plebani, Maria Pia Foschino Barbaro, Antonio Spanevello, Maria Aliani, Marco Pannacci, Paolo Morelli, Bianca Beghét, Leonardo M Fabbri†, for the AIFASMA Study Group‡

Summary

Background Treatment guidelines for patients with moderate persistent asthma recommend regular therapy with a combination of an inhaled corticosteroid and a longacting β_2 agonist plus as-needed rapid-acting bronchodilators. We investigated whether symptom-driven budesonide and formoterol combination therapy administered as needed would be as effective as regular treatment with this combination plus as-needed symptom-driven terbutaline for patients with moderate asthma.

Methods In this non-inferiority randomised clinical trial, we recruited adult patients (18–65 years of age) with stable moderate persistent asthma, according to 2006 Global Initiative for Asthma guidelines. Patients were recruited from outpatient clinics of secondary and tertiary referral hospitals and university centres. After a 6-week run-in period of inhaled regular budesonide and formoterol plus as-needed terbutaline, the patients were randomly assigned in a 1:1 ratio to receive placebo twice daily plus as-needed treatment with inhaled 160 μ g budesonide and 4·5 μ g formoterol (as-needed budesonide and formoterol therapy) or twice-daily 160 μ g budesonide and 4·5 μ g formoterol combination plus symptom-driven 500 μ g terbutaline (regular budesonide/formoterol therapy) for 1 year. Randomisation was done according to a list prepared with the use of a random number generator and a balanced-block design stratified by centre. Patients and investigators were masked to treatment assignment. The primary outcome was time to first treatment failure measured after 1 year of treatment using Kaplan-Meier estimates, and the power of the study was calculated based on the rate of treatment failure. Analyses were done on the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00849095.

Findings Between April 20, 2009, and March 31, 2012, we screened 1010 patients with moderate asthma and randomly assigned 866 eligible patients to the two treatment groups (424 to as-needed budesonide and formoterol therapy and 442 to regular budesonide and formoterol therapy). Compared with regular budesonide and formoterol therapy, as-needed budesonide and formoterol treatment was associated with a lower probability of patients having no treatment failure at 1 year (Kaplan-Meier estimates 53·6% for as-needed treatment vs 64·0% for regular treatment; difference 10·3% [95% CI 3·2–17·4], at a predefined non-inferiority limit of 9%). Patients in the as-needed budesonide and formoterol group had shorter time to first treatment failure than those in the regular therapy group (11·86 weeks vs 28·00 weeks for the first quartile [ie, the time until the first 25% of patients experienced treatment failure]). The difference in treatment failures was largely attributable to nocturnal awakenings (82 patients in the as-needed treatment group vs 44 in the regular treatment group). Both treatment regimens were well tolerated.

Interpretation In patients with moderate stable asthma, as-needed budesonide and formoterol therapy is less effective than is the guideline-recommended regular budesonide and formoterol treatment, even though the differences are small.

Funding Italian Medicines Agency.

Introduction

The 2014 revision of the Global Initiative for Asthma (GINA) guidelines recommends that patients with asthma should first be assessed for the level of asthma control and then treatment should be planned accordingly.¹ For patients whose asthma is not controlled by low-dose inhaled corticosteroids, guidelines recommend a combination of low-dose inhaled corticosteroids and a longacting β_2 agonist plus a rapid-acting β_2 agonist for symptom relief, or treatment with

inhaled corticosteroids and rapid-acting longacting β_2 agonist both regularly and for symptom relief. This approach, called same maintenance and reliever therapy (SMART), achieves similar levels of asthma control as inhaled corticosteroids and longacting β_2 agonists plus a rapid-acting β_2 agonist for symptom relief but more effective reduction of exacerbations in patients with moderate to severe asthma.^{2–10}

The symptom-driven use of an inhaled corticosteroid with a shortacting β_2 agonist or an inhaled corticosteroid

Lancet Respir Med 2015;
3: 109–19

Published Online
December 4, 2014
[http://dx.doi.org/10.1016/S2213-2600\(14\)70266-8](http://dx.doi.org/10.1016/S2213-2600(14)70266-8)
See [Comment](#) page 88

*Joint first authors

†Joint senior authors

‡Members of the AIFASMA Study Group are listed in the appendix

Department of Respiratory Medicine, University of Ferrara, Ferrara, Italy (Prof A Papi MD, B Marku MD, M Contoli MD); Biomedical Department of Internal and Experimental Medicine, University of Palermo, Palermo, Italy (N Scichilone MD); Department of Cardiology, Thoracic and Vascular Sciences (Prof P Maestrelli MD, Prof M Saetta MD) and Department of Laboratory Medicine (Prof M Plebani MD), University of Padova, Padova, Italy; Department of Respiratory Medicine, University of Pisa, Pisa, Italy (Prof P Paggiaro MD); Respiratory and Critical Care, Department of Specialist, Diagnostic, and Experimental Medicine, University of Bologna, Bologna, Italy (Prof S Nava MD); Department of Medicine, Section of Occupational and Environmental Allergy, University of Perugia, Perugia, Italy (I Folletti MD); Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy (G Bertorelli MD); Respiratory Medicine, Hospital of Bussolengo, Bussolengo (VR), Italy (S Bertacco MD); Respiratory Medicine, University of Foggia, Foggia, Italy (Prof M Pia Foschino Barbaro MD); Respiratory Medicine, Fondazione Salvatore Maugeri,

Tradate (VA), Italy
(Prof A Spanevello MD);
University of Varese, Varese,
Italy (Prof A Spanevello);
Respiratory Medicine,
Fondazione Salvatore Maugeri,
Cassano delle Murge (BA), Italy
(M Aliani MD); CROS NT, Verona,
Italy (M Pannacci MS,
P Morelli PhD); and Section of
Respiratory Disease,
Department of Oncology,
Haematology and Respiratory
Diseases, University of Modena
and Reggio Emilia, Modena,
Italy (B Beghé MD,
Prof L M Fabbri MD)

Correspondence to:
Prof Leonardo M Fabbri, Section
of Respiratory Disease,
Department of Oncology,
Haematology and Respiratory
Diseases, University of Modena
and Reggio Emilia, Largo del
Pozzo, 71-41124 Modena, Italy
leonardo.fabbri@unimore.it

and longacting β_2 agonist combination in the absence of any regular maintenance treatment are viewed as effective alternatives to regular inhaled corticosteroid plus as-needed shortacting β_2 agonist in patients with intermittent or mild asthma.^{11,12} In patients with mild persistent asthma that is controlled by regular low-dose inhaled corticosteroid, the as-needed combination of beclometasone and the short-acting β_2 agonist salbutamol with no regular treatment is non-inferior to regular low-dose beclometasone plus as-needed salbutamol.¹³ The rationale for use of a symptom-driven approach is that it allows titration of both the inhaled corticosteroid and the longacting β_2 agonist according to the patient's needs, it is associated with lower cumulative exposure to both bronchodilators and inhaled corticosteroids, and it might reduce the effect of low adherence to regular treatment that frequently occurs in real life.^{11,12,14} Additionally, treatment with a steroid together with a bronchodilator for symptom relief could be more effective than a bronchodilator alone, since it might reverse not only bronchoconstriction but also the transient acute airway inflammation^{15–18} associated with the development of symptoms.^{11,19–22} Therefore, it might improve asthma control and reduce the need for regular treatment.

No previous study has investigated whether moderate asthmatics—ie, patients whose asthma is not controlled by low-dose inhaled corticosteroids but is adequately controlled by an inhaled corticosteroid and longacting β_2 agonist combination—can be just as well controlled by a symptom-driven inhaled corticosteroid and longacting β_2 agonist combination therapy in the absence of regular maintenance treatment.

In this 1-year study, we investigated whether treatment failure could be prevented in patients with moderate asthma receiving regular placebo plus as-needed combination budesonide and formoterol versus regular treatment with budesonide and formoterol plus as-needed terbutaline.

Methods

Study design and participants

This trial was a multicentre, randomised, placebo-controlled, double-blind, parallel-group study (appendix p 9). The study population consisted of adults (18–65 years of age) with moderate persistent asthma, according to 2006 GINA guidelines,²³ whose symptoms were either not controlled by low-dose inhaled corticosteroids (≤ 500 μ g beclometasone per day or equivalent; 594 [73%] of 817 enrolled patients in the intention-to-treat population) or controlled by a fixed combination of low-dose inhaled corticosteroid and longacting β_2 agonist twice daily during the 2 months before the study (223 [27%] of 817 patients in the intention-to-treat population). Patients were recruited from outpatient clinics of secondary and tertiary referral hospitals and university centres. Asthma was judged to be not adequately controlled with low-dose inhaled corticosteroids if

patients reported more than two daytime symptoms per week, more than two occasions per week when they needed rescue treatment, any nocturnal symptoms or awakening, any limitation of activities, and use of oral corticosteroids in the month before enrolment. By contrast, asthma was regarded as adequately controlled in patients who had initiated low-dose inhaled corticosteroid and longacting β_2 agonist combination treatment in the past year because asthma was not controlled by low-dose inhaled corticosteroid, and if in the 2 months before the study they reported a maximum of two daytime symptoms in a week, a maximum of two occasions per week when they needed rescue treatment, no nocturnal symptoms or awakening, no limitation of activities, and no use of oral corticosteroids. The main exclusion criteria were: inability to undergo pulmonary function testing; moderately severe asthma associated with reduced lung function; history of near-fatal asthma, admission to the intensive care unit because of asthma, or both; three or more courses of oral corticosteroids or hospital admissions for asthma during the previous year; diagnosis of chronic obstructive pulmonary disease as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines; evidence of severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; current smoker or recent (<1 year) ex-smoker, defined as smoking at least ten pack-years; history of, or existing evidence of, heart failure, coronary artery disease, myocardial infarction, severe hypertension, or cardiac arrhythmias; and diabetes mellitus. Appendix p 6 provides further details of inclusion and exclusion criteria.

The protocol was approved by the institutional review board for each centre, and all participants provided written informed consent. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

Between April 20, 2009 and March 31, 2012, we recruited and enrolled 1010 eligible patients with moderate asthma. The patients entered a 6-week run-in period, during which they received an open-label combination of inhaled 160 μ g budesonide and 4.5 μ g formoterol twice daily, plus as-needed inhaled 500 μ g terbutaline. At the end of the run-in, 866 eligible patients with controlled asthma during the final 14 days of the run-in were randomly allocated in a 1:1 ratio to receive either twice-daily placebo plus as-needed inhaled 160 μ g budesonide and 4.5 μ g formoterol combination (as-needed budesonide and formoterol) or twice daily 160 μ g budesonide and 4.5 μ g formoterol combination plus as-needed inhaled 500 μ g terbutaline (regular budesonide and formoterol). Patients were not given a written plan of action to guide the as-needed use of study drugs but were merely verbally instructed to use them any time they were needed for relief of symptoms. Patients were not given oral corticosteroids or additional inhaled

See Online for appendix

corticosteroids to keep at home for self-administration in case of asthma deterioration, but were instructed, according to current clinical practice, to seek medical attention or investigator contact (unscheduled visits) in case of uncontrolled clinical condition. At the end of 1 year of treatment, patients underwent 6 weeks of follow-up open-label SMART therapy with 160 µg budesonide and 4·5 µg formoterol with the aim to assess whether maximising treatment would modify the level of asthma control recorded at the end of the study (appendix p 9). Up to eight additional as-needed inhalations of rescue medication (either budesonide and formoterol inhaled combination or inhaled salbutamol) per day were allowed for the entire study duration. No other anti-asthma drug was allowed. All drugs were prepared and given by the dry-powder inhaler Turbohaler (AstraZeneca S.p.a., Basiglio, Milan, Italy). Clinic visits took place at the beginning (visit 1) and end (visit 2) of the run-in period and thereafter on study weeks 4, 12, 20, 28, 36, 44, 52 (visit 9: end of treatment period) and 58 (visit 10: end of follow-up period) for a total of ten visits. Treatment compliance was assessed by the clinical investigator at each visit by asking the patients to return study drug devices and diary cards. Diary cards were reviewed and correct use of the device was assessed at each visit. Compliance to treatment was checked by counting the remaining doses (on the dose counter within the inhaler) in each returned dry powder inhaler at the end of the study period (visit 9) and reporting the number in the case report form. Compliance to treatment was expressed as the percentage of the expected number of doses actually taken in the previous 8 weeks.

As specified in the protocol, the investigators or the family doctor could give patients additional medication to treat worsening asthma, including additional open-label courses of inhaled twice-daily corticosteroids or oral or systemic corticosteroids. Patients were also recommended to stop study medication during exacerbations and restart afterwards. Investigators were asked to record in the case report form the treatments that the patients received for the exacerbations. Patients were not withdrawn from the study after an exacerbation, unless such a decision was made by the patient, family doctor, or investigator.

Randomisation and masking

Patients were randomly assigned to a treatment group according to a list prepared with the use of a random-number generator and a balanced permuted block design (block size of 4), stratified by centre.

Investigators and patients were masked to treatment assignment. Dry powder inhaler devices were identical in shape and used in all groups to ensure a double-blind design. The powder was odourless. The inhalation devices containing regular treatment (budesonide and formoterol combination or placebo) were white, whereas those for as-needed treatment (terbutaline or combined budesonide and formoterol) were yellow.

A package insert written in Italian containing the instructions for use was included in each test treatment inhaler. Patients were instructed to take one inhalation in the morning and one inhalation in the evening from the white device, and one or more inhalation when needed for symptom relief from the yellow device. Patients were individually instructed by the investigators to use the dry powder inhalers with the support of the package insert.

Outcomes

The primary outcome of the study was the time to treatment failure measured at 1 year. The power of the study was based on the rate of treatment failure at 1 year. Treatment failure was defined as the occurrence of one of the following: admission to hospital, unscheduled medical visits for asthma, use of systemic corticosteroids or open-label use of inhaled corticosteroids for asthma prescribed by a doctor, two nocturnal awakenings on 2 consecutive

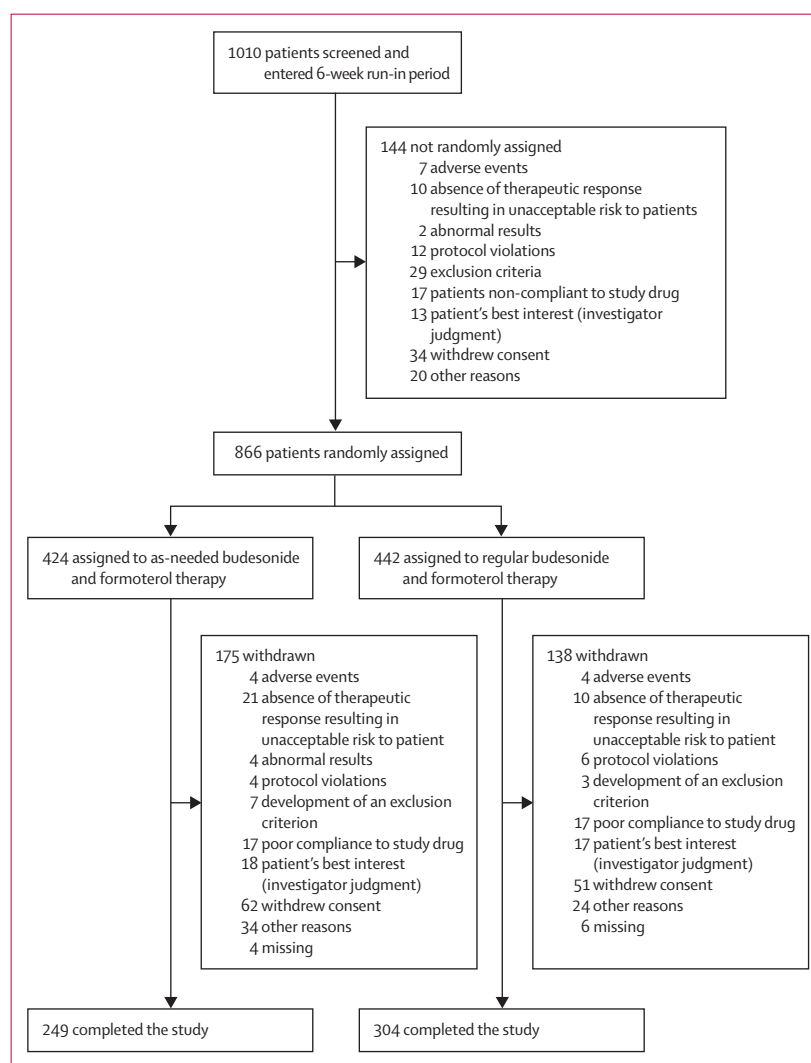


Figure 1: Trial profile

days, four or more additional puffs of as-needed medication per day compared with baseline on 2 consecutive days, patient refusal to continue because of dissatisfaction with treatment, or if treatment was stopped by the physician for safety reasons. Secondary outcomes were: time to treatment failure measured at other timepoints during the treatment period, time to dropout, use of rescue medication, asthma control, quality of life, daily morning and evening peak expiratory flow (measured

by the patient at home); pre-bronchodilator forced vital capacity; ratio of forced expiratory volume in 1 s to vital capacity; ratio of forced expiratory volume in 1 s to forced vital capacity; post-bronchodilator forced expiratory volume in 1 s; asthma symptom scores; rescue medications; Asthma Control Questionnaire;²⁴ and Asthma-Related Quality of Life Questionnaire.²⁵ Secondary safety outcomes were adverse events and morning serum cortisol (appendix p 4).

Statistical analysis

We estimated that the proportion of patients in the regular budesonide and formoterol group with treatment failure at 1 year would be 35%, and we judged a non-inferiority margin of 9% at 1 year to be clinically acceptable, based on an estimated effect size of 17%.^{7,26} A total of 355 treatment failures (in patients with at least one treatment failure) were needed to test the non-inferiority (one-sided test at 0.025 significance) of the time to treatment failure of the as-needed budesonide and formoterol therapy group versus the regular budesonide and formoterol therapy group, with a power of at least 80%. A total of 860 evaluable patients (430 in each treatment group) were needed to satisfy the aforementioned hypothesis.

We used Kaplan-Meier estimates to assess the time to treatment failure and the probability of patients with no treatment failure at 1 year. We also analysed time to treatment failure with a Cox proportional hazards regression model, in which treatment was the only term included in the model.

Methods for the sensitivity analyses of the primary outcome, and ANCOVA models for secondary quantitative endpoints, are described in appendix pp 4–5. We did a post-hoc analysis to assess the effects of baseline risk factors or covariates on the probability of treatment failure by means of a logistic analysis. The primary endpoint was assessed in both the intention-to-treat and per-protocol population. The intention-to-treat population included all randomly assigned patients who received at least one dose of the study drug and who had at least one available post-baseline efficacy evaluation. The per-protocol population comprised all patients from the intention-to-treat population without any major protocol deviations. All secondary endpoints were analysed in the intention-to-treat population. Safety outcomes were assessed in the safety population—ie, the number of patients who actually received treatment.

	As-needed budesonide and formoterol (n=394)	Regular budesonide and formoterol (n=423)
Sex		
Men	153 (39%)	185 (44%)
Women	241 (61%)	238 (56%)
Age (years)	42.1 (12.8; n=392)	43.2 (12.6; n=423)
Ethnic origin		
White	382 (97%)	415 (98%)
Asian	5 (1%)	3 (1%)
Black	4 (1%)	1 (<1%)
Other	3 (1%)	3 (1%)
Missing data	0	1 (<1%)
Weight (kg)	71.93 (16.33; n=393)	73.10 (16.01; n=422)
Height (cm)	166.6 (9.60; n=393)	166.5 (9.80; n=422)
Body-mass index (kg/m ²)	25.87 (5.35; n=393)	26.31 (5.09; n=422)
Asthma duration (years)	10.95 (10.27; n=393)	10.99 (10.68; n=419)
Morning peak expiratory flow (L/min)	402.02 (121.50; n=363)	414.11 (120.08; n=395)
Evening peak expiratory flow (L/min)	406.51 (121.66; n=362)	419.99 (121.03; n=393)
Pre-bronchodilator FEV ₁ (L)	2.91 (0.84; n=393)	2.95 (0.81; n=419)
Pre-bronchodilator FEV ₁ (% predicted)	93.59 (21.54; n=393)	94.58 (14.33; n=418)
Post-bronchodilator FEV ₁ (L)	3.01 (0.85; n=379)	3.06 (0.83; n=406)
Post-bronchodilator FEV ₁ (% predicted)	96.70 (22.00; n=379)	97.73 (14.76; n=405)
Pre-bronchodilator FVC (L)	3.86 (1.03; n=393)	3.92 (1.02; n=419)
Asthma symptoms score*	0.11 (0.30; n=364)	0.06 (0.18; n=388)
Rescue medication (puffs/day)	0.13 (0.52; n=352)	0.06 (0.21; n=377)
ACQ score	0.57 (0.68; n=375)	0.52 (0.64; n=401)
AQLQ score	6.03 (0.94; n=363)	6.00 (0.81; n=401)
Use of regular longacting β_2 agonist and inhaled corticosteroid combination therapy in the past year	104 (26%)	119 (28%)

Data are n (%) or mean (SD; number of patients), unless otherwise indicated. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. ACQ=Asthma Control Questionnaire. AQLQ=Asthma-Related Quality of Life Questionnaire. *Daytime asthma symptoms were assessed in the evening on a scale ranging from 0 (no symptoms) to 4 (symptoms for most of the day that affected normal daily activities), whereas night-time symptoms were assessed in the morning on a scale ranging from 0 (no symptoms during the night) to 4 (symptoms so severe that they did not allow the patient to sleep at all).

Table 1: Baseline demographics and clinical characteristics (intention-to-treat population)

	As-needed budesonide and formoterol group (n=394)	Regular budesonide and formoterol group (n=423)	Difference between groups (95% CI)	Time to treatment failure during treatment period, HR (95% CI)	p value
Probability of no treatment failure at 1 year, Kaplan-Meier estimate (SE)	0.536 (0.026)	0.640 (0.025)	0.103 (0.032–0.174)	1.491 (1.192–1.866)	0.0022
Patients with at least one treatment failure	170 (43.1%)	139 (32.9%)	0.103 (0.037–0.169)	..	0.0011

HR=hazard ratio

Table 2: Primary outcome results: time to treatment failure in the intention-to-treat population

All statistical analyses and data processing were done using Statistical Analysis Systems (SAS) software, version 9.2, on a Windows 7 operating system. This trial is registered with ClinicalTrials.gov, number NCT00849095.

Role of the funding source

Data were collected by the clinical investigators, analysed by CROS NT (Verona, Italy), and discussed by the clinical investigators. AstraZeneca, who donated the drugs, had no role in study design, data collection or analyses, or in drafting the report, nor were they informed of the results of the study. The first author and study coordinator (AP), the study manager (BM), and the corresponding author (LMF) oversaw all the data analyses. The first author and the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, 1010 patients were screened and entered the 6-week run-in period, and 866 eligible patients were randomly assigned to the two treatment groups (424 to the as-needed budesonide and formoterol group and 442 to the regular budesonide and formoterol group (figure 1). The 18 patient difference in allocation between treatment groups was because of uncompleted randomisation blocks opened by sites during the study. Because some patients withdrew from the study before treatment was started, the number of patients who actually received treatment (the safety population) was 419 in the as-needed treatment group and 437 in the regular treatment group. The intention-to-treat population comprised 394 patients in the as-needed group and 423 in the regular treatment group, and the per-protocol population, which excluded two patients with major protocol violations, included 393 and 422 patients, respectively. As figure 1 shows, 249 patients in the as-needed budesonide and formoterol group and 304 patients in the regular budesonide and formoterol group completed the study.

The treatment groups were well matched in demographic and clinical characteristics at baseline (table 1). Mean compliance to treatment at the end of the study period (visit 9) was 85% (SD 27) in the as-needed budesonide and formoterol group and 83% (26) in the regular budesonide and formoterol group.

Compared with regular budesonide and formoterol therapy, patients in the as-needed treatment group had shorter time to first treatment failure (table 2, figure 2) and a higher probability of treatment failure (Kaplan-Meier estimates 53.6% for regular treatment *vs* 64.0% for as-needed treatment; difference 10.3% [95% CI 3.2–17.4], predefined non-inferiority limit 9%; $p=0.0022$) at 1 year (table 2, figure 2) in the intention-to-treat population analysis. The hazard ratio between the two groups was 1.49 (95% CI 1.19–1.87). The curves of $\log(-\log[\text{survival}])$ versus $\log$ of survival time by intention-to-treat analysis show that the two curves for the two

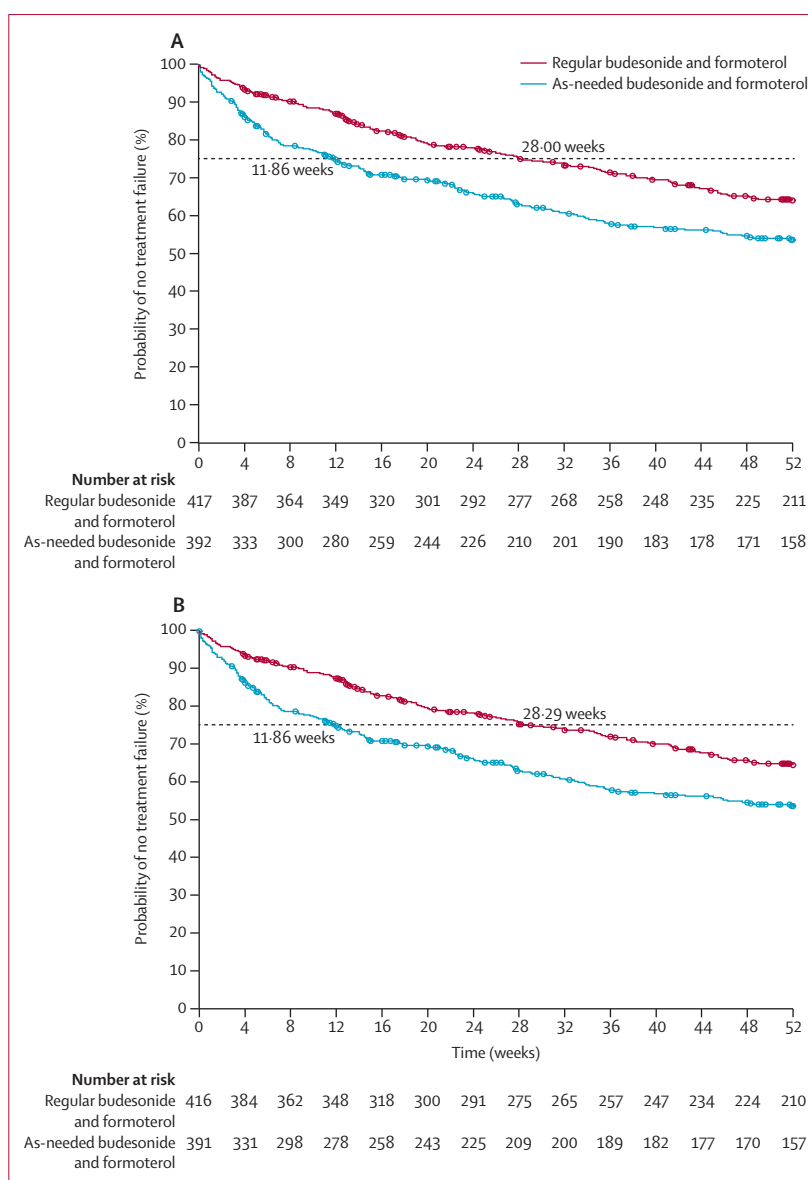


Figure 2: Time to treatment failure

(A) Kaplan-Meier curve for time to treatment failure by treatment group in the intention-to-treat population. (B) Kaplan-Meier curve for time to treatment failure by treatment group in the per-protocol population.

groups were parallel, which confirmed the proportional hazards assumption. We also tested the correlation of the scaled Schoenfeld residuals on functions of time for both the intention-to-treat and per-protocol population. The Pearson correlation was not statistically significant (Pearson correlation coefficient 0.02814, $p=0.5302$), indicating no violation of the proportional hazards assumption.

The cumulative number of patients who had at least one treatment failure during the 1-year study period was 170 (43.1%) of 394 in the as-needed budesonide and formoterol group and 139 (32.9%) of 423 in the regular budesonide and formoterol group (table 2); thus, this

number of treatment failures did not completely reach our sample size estimation assumption.

The results reported in the per-protocol analysis were consistent with those in the intention-to-treat population (appendix p 7). The pre-planned sensitivity analyses, which treated dropouts as treatment failures (appendix p 10), confirmed the robustness of the results of the primary outcome. The most common reason for treatment failure was two nocturnal awakenings on two consecutive days (82 patients in the as-needed budesonide and formoterol group and 44 in the regular budesonide and formoterol group). This outcome was the only component of the composite primary outcome that differed significantly between groups ($p<0.0001$) (table 3). The mean percentage of days with nocturnal awakenings was 16.17% (SD 23.94) in the as-needed budesonide and formoterol group and 7.94% (16.07) in the regular budesonide and formoterol group. Female sex in the as-needed budesonide and formoterol group, smoking habits overall and in the as-needed budesonide and formoterol group, and baseline Asthma Control Questionnaire score overall and in both groups, were the factors significantly associated with increased risk of treatment failure (figure 3).

The time to dropout, representing the time until at least 25% of the patients (ie, the first quartile) dropped out of the study, was shorter in the as-needed budesonide and formoterol group (28 days) than in the regular treatment group (48 days; $p=0.009$ between groups in the log-rank test). Appendix p 11 shows the Kaplan-Meier plot for the time to dropout in the intention-to-treat population. The cumulative number of patients who dropped out at the end of the randomised treatment phase was 133 (33.7%) of 394 patients in the as-needed

budesonide and formoterol group and 108 (25.5%) of 423 in the regular budesonide and formoterol group (Kaplan-Meier estimates 34.0% vs 25.9%; $p=0.009$).

Table 4 shows the results of the other secondary outcomes. From baseline to the end of treatment in the randomised phase of the study, significant differences were recorded between the two groups, in favour of regular budesonide and formoterol therapy.

After the follow-up period with open-label SMART budesonide and formoterol therapy (appendix p 8) only morning peak expiratory flow ($p=0.02$), number of puffs of rescue medication ($p=0.012$), and percentage of days without use of rescue medication ($p=0.004$) still differed significantly between the groups in favour of regular budesonide and formoterol therapy.

Patients on as-needed budesonide and formoterol combination treatment used significantly more rescue medications, and the difference, albeit small, remained significant even at the end of follow-up (table 4; appendix p 8). Unsurprisingly, the estimated cumulative dose of budesonide (116.8 vs 24.5 mg per year) and formoterol (3.2 mg vs 0.69 mg per year) was larger in patients treated with regular budesonide and formoterol combination than in those who received the treatment as needed.

Apart from the number of patients with oropharyngeal pain, the frequency of treatment-emergent adverse events did not differ between the two groups ($p=0.363$; table 5). Similarly, the number of patients with adverse reactions also did not differ between the groups ($p=0.815$). Worsening of asthma was the most common treatment-emergent adverse event: it was recorded in 48 patients (12%) in the as-needed group and 40 (9%) in the regular treatment group (table 5). From baseline to the end of the treatment period, morning serum cortisol showed no evidence of adrenal suppression in either group (data not shown).

Discussion

In this 1-year, randomised, double-blind, clinical trial in patients with moderate asthma, as-needed budesonide and formoterol was inferior to regular budesonide and formoterol combination treatment plus as-needed terbutaline in preventing treatment failure. Our results confirm that the regular longacting β_2 agonist combination treatment recommended in guidelines is effective for patients whose asthma is not adequately controlled by regular inhaled corticosteroids (panel).¹

Nocturnal awakenings were the only component of treatment failure that was not protected by the as-needed budesonide and formoterol therapy, most likely either because of absence of protection offered by the regular treatment or because of no prompt reversal of nocturnal symptoms by the as-needed treatment. The overall increased number of nocturnal awakenings in the as-needed budesonide and formoterol group was 38 episodes of nocturnal awakening in 2 consecutive

	As-needed budesonide and formoterol group (n=394)	Regular budesonide and formoterol group (n=423)	p value
Admission to hospital	0	3 (1%)	0.250
Treatment stopped for safety reasons (physician's judgment)	24 (6%)	23 (5%)	0.688
Refusal to continue because of patient dissatisfaction with treatment	6 (2%)	4 (1%)	0.534
Two episodes of nocturnal awakenings on 2 consecutive days	82 (21%)	44 (10%)	<0.0001
Unscheduled medical visit for asthma worsening	6 (2%)	8 (2%)	0.685
Use of rescue medication	17 (4%)	18 (4%)	0.967
Use of systemic corticosteroids or inhaled corticosteroids for asthma worsening	51 (13%)	59 (14%)	0.674
Use of systemic corticosteroids for asthma worsening	31 (8%)	31 (7%)	0.771
Use of inhaled corticosteroids for asthma worsening	20 (5%)	28 (7%)	0.349

Data are n (%).

Table 3: Reasons for treatment failure in the intention-to-treat population

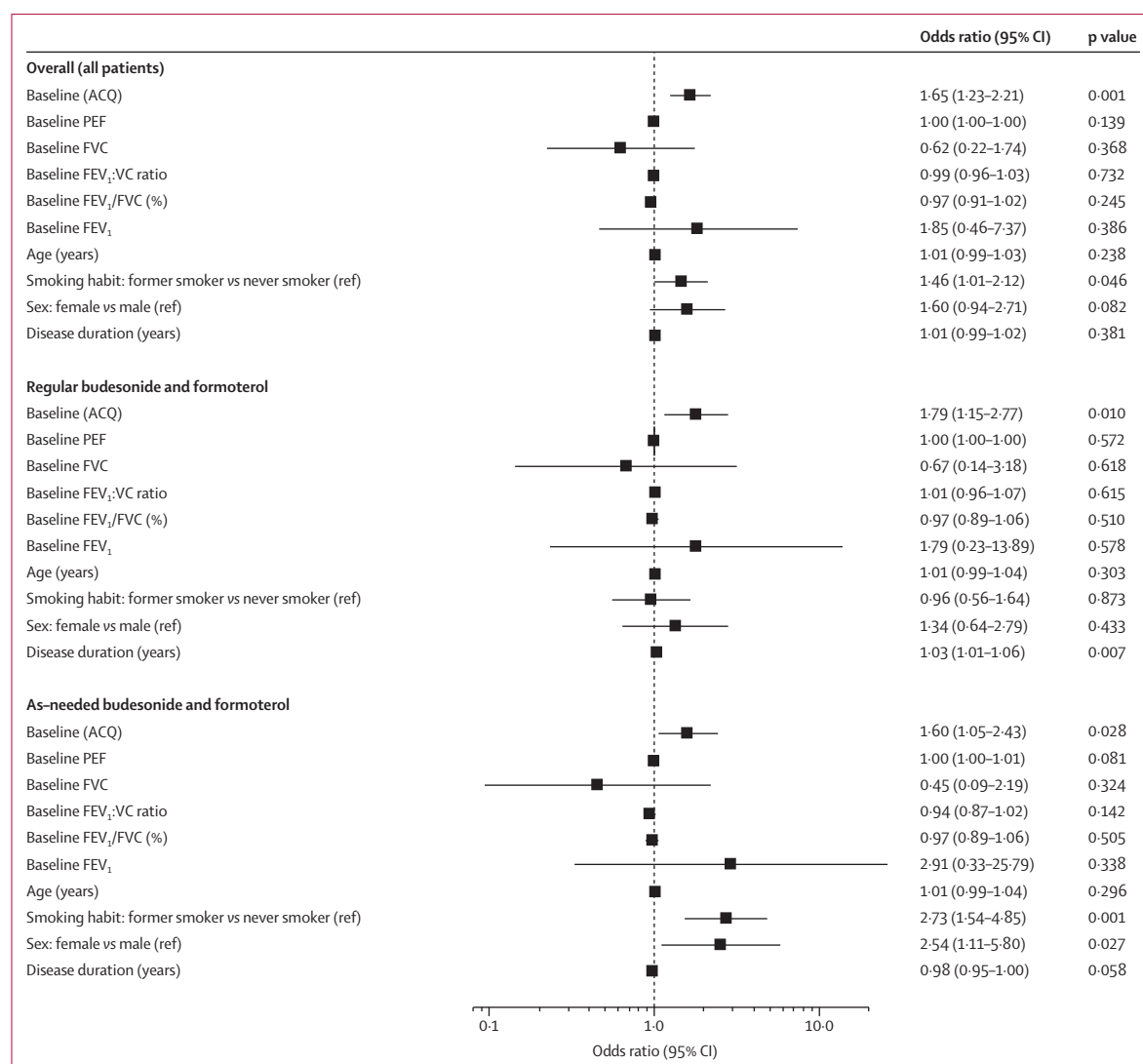


Figure 3: Effects of baseline risk factors or covariates on the probability of treatment failure overall and in the two groups (intention-to-treat population)
Data are odds ratios (95% CI) for probability of treatment failure (yes) vs probability of no treatment failure (no). Error bars are 95% CIs. The term (ref) indicates the reference level of the qualitative variable used in the calculation of the odds ratio. ACQ=Asthma Control Questionnaire. PEF=peak expiratory flow. FVC=forced vital capacity. FEV₁=forced expiratory volume in 1 s. VC=vital capacity.

nights in 1 year for the 394 patients in the intention-to-treat population—ie, an average increased risk of one episode of nocturnal awakening in two consecutive nights per patient in 10 years, which might be regarded as of low clinical relevance. The other difference between the two treatments was the higher rate of dropout from the study in patients on as-needed budesonide and formoterol treatment. The dropout was reported to be not related to efficacy or safety reasons, but mainly to withdrawal of consent (11.5% vs 14.6%) and other logistical reasons (5.4% vs 8.0%). In a young and actively working population, it is not surprising that the willingness (and possibility) to follow the strict rules and timing for multiple visits of a randomised controlled trial for a whole year might be too demanding, and thus

patients withdrew their consent (the main reason for dropout), especially in a non-sponsored study like this one, in which patients receive no payment or expense reimbursement for their participation. However, the difference in dropout rate between the two groups (5.4% vs 8.0%) further suggests inferiority of the as-needed treatment.

The results of the sensitivity analyses that took into account the study dropouts confirmed the results of the primary analysis, excluding that they might have been affected by the different dropout rates.

Because of the characteristics of the population analysed—ie, patients with moderate asthma well controlled by the regular inhaled corticosteroid and longacting β_2 agonist combination and thus not at high

	As-needed budesonide and formoterol (n=394)	Regular budesonide and formoterol (n=423)	Difference (95% CI) between adjusted means (regular vs as-needed)	p value
Pulmonary function				
Morning PEF (L/min)*	191	234	..	..
Mean change (SD; 95% CI)	-22.73 (55.26; -31.18 to -14.29)	-2.61 (41.89; -8.25 to 3.04)	23.127 (13.406 to 32.847)	<0.0001
Evening PEF (L/min)*	190	230	..	..
Mean change (SD; 95% CI)	-21.39 (56.27; -30.01 to -12.76)	-4.21 (43.62; -10.15 to 1.74)	19.882 (9.766 to 29.998)	0.0001
FEV ₁ (L)	244	305	..	..
Mean change (SD; 95% CI)	-0.16 (0.37; -0.20 to -0.11)	-0.01 (0.34; -0.05 to 0.03)	0.146 (0.088 to 0.204)	<0.0001
FEV ₁ (% predicted)	244	305	..	..
Mean change (SD; 95% CI)	-3.47 (12.40; -5.03 to -1.91)	-0.02 (11.95; -1.38 to 1.33)	3.605 (1.715 to 5.494)	<0.0002
Post-bronchodilator FEV ₁ (L)	232	294	..	..
Mean change (SD; 95% CI)	-0.08 (0.31; -0.12 to -0.04)	0.06 (0.34; 0.02 to 0.10)	0.137 (0.080 to 0.194)	<0.0001
Post-bronchodilator FEV ₁ (% predicted)	232	293	..	..
Mean change (SD; 95% CI)	-0.81 (12.76; -2.48 to 0.86)	2.33 (12.65; 0.85 to 3.81)	3.082 (0.998 to 5.166)	0.0038
FVC (L)	244	305	..	..
Mean change (SD; 95% CI)	-0.10 (0.39; -0.15 to -0.05)	-0.02 (0.38; -0.06 to 0.03)	0.079 (0.015 to 0.142)	0.0148
PEF (L/min)†	244	305	..	..
Mean change (SD; 95% CI)	-33.96 (97.22; -46.22 to -21.70)	-13.64 (99.40; -24.91 to -2.36)	20.863 (6.921 to 34.804)	0.0034
Asthma symptoms				
Symptoms score*	194	225	..	..
Mean change (SD; 95% CI)	0.14 (0.43; 0.07 to 0.20)	0.05 (0.29; 0.01 to 0.10)	-0.103 (-0.177 to -0.029)	0.0064
% of days without symptoms*	194	225	..	..
Mean change (SD; 95% CI)	-15.46 (37.29; -21.14 to -9.78)	-4.95 (27.75; -8.81 to -1.09)	11.886 (5.409 to 18.363)	<0.0004
Use of rescue medication				
Rescue medication (puffs per day)*	187	219	..	..
Mean change (SD; 95% CI)	0.42 (0.82; 0.29 to 0.55)	0.12 (0.52; 0.05 to 0.19)	-0.304 (-0.499 to -0.159)	<0.0001
% of days without rescue*	187	219	..	..
Mean change (SD; 95% CI)	-23.80 (38.51; -29.83 to -17.77)	-6.38 (25.33; -9.95 to -2.82)	18.036 (11.292 to 24.779)	<0.0001
Asthma control				
ACQ score	231	293	..	..
Mean change (SD; 95% CI)	0.25 (0.92; 0.12 to 0.37)	0.06 (0.74; -0.03 to 0.15)	-0.207 (-0.337 to -0.077)	0.0019
% of days of asthma control*	185	217	..	..
Mean change (SD; 95% CI)	-21.65 (40.85; -28.07 to -15.23)	-6.53 (29.67; -10.74 to -2.32)	16.859 (9.646 to 24.072)	<0.0001
Quality of life				
AQLQ score	236	292	..	..
Mean change (SD; 95% CI)	-0.11 (1.01; -0.25 to 0.02)	0.07 (0.75; -0.02 to 0.16)	0.220 (0.086 to 0.354)	0.0013

Numbers for each outcome are the number of patients (n) in whom the outcome was assessed; mean change values are expressed as changes from baseline to the end of randomised treatment (week 52). All measurements were done pre-bronchodilator, unless otherwise indicated. Morning PEF, evening PEF, asthma symptoms score, % of days without symptoms, rescue medication, and % of days without rescue medication are analysed excluding from the analysis the diary card measurements in which the patients entered less than 75% data in the final 2 weeks before the visit (ie, <10 days over the 2 weeks preceding a study visit). n=number of patients. PEF=peak expiratory flow. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. ACQ=Asthma Control Questionnaire. AQLQ=Asthma-Related Quality of Life Questionnaire. *In the 2 weeks preceding the medical visit. †Measured at sites.

Table 4: Secondary outcomes in the intention-to-treat population

risk of exacerbations—the primary outcome of our study was time to treatment failure. Indeed, only 117 severe exacerbations (defined as treatment with steroids and/or admission to the emergency room or hospital⁷) occurred in 817 patients during the 1-year study (0.143 per patient per year); 53 (none of whom were admitted to hospital) in the as-needed budesonide and formoterol group (0.135 per patient per year) and 64 (four admitted to hospital) in the regular budesonide and formoterol group (0.151 per patient per year). Therefore, both therapies were associated with a very low incidence of severe

exacerbations, possibly because they were both effective in controlling exacerbations.

Poor adherence to the regular treatment might have reduced the difference in medication use between the two groups, thereby contributing to the small differences in outcomes at the end of the study. In fact, Patel and colleagues⁸ recently reported that adherence to regular treatment is lower than to SMART treatment and decreases progressively over 6 and 12 months, suggesting that poor adherence to regular maintenance treatment might have affected the small differences in outcomes that we reported

	As-needed budesonide and formoterol (n=419)	Regular budesonide and formoterol (n=437)	p value
Worsening of asthma	48 (11%)	40 (9%)	0.268
Headache	27 (6%)	30 (7%)	0.805
Rhinitis	25 (6%)	25 (6%)	0.878
Bronchitis	23 (5%)	24 (6%)	0.999
Pyrexia	21 (5%)	18 (4%)	0.531
Influenza	17 (4%)	19 (4%)	0.832
Nasopharyngitis	11 (3%)	22 (5%)	0.067
Cough	15 (4%)	16 (4%)	0.949
Oropharyngeal pain	6 (1%)	16 (4%)	0.039
Back pain	11 (3%)	10 (2%)	0.750
Pharyngitis	9 (2%)	5 (1%)	0.247
Arthralgia	6 (1%)	9 (2%)	0.484

Data are n (%).

Table 5: Treatment-emergent adverse events reported in 2% or more of patients in either group

in our study. However, the differences in our study probably represent what would happen in real life with use of the two different treatment strategies that we compared.

After the 1-year randomised treatment, both groups of patients received 6 weeks of SMART treatment with both maintenance and reliever budesonide and formoterol therapy to reverse uncontrolled components of asthma, if any. Both groups improved clinically and in most measurements of lung function (forced vital capacity, forced expiratory volume in 1 s, and peak expiratory flow) taken in the clinic. These values returned to baseline, which suggests that no irreversible decline in lung function had occurred. However, morning peak expiratory flow measured by the patient at home decreased significantly in the as-needed budesonide and formoterol group and did not return to baseline after 6 weeks of SMART treatment. The reasons for the discrepancy between measurements of lung function made by the patient and in the clinic remain unclear.²⁷ Although the decrease in morning peak expiratory flow might suggest that the as-needed budesonide and formoterol therapy could be associated with a decline in pulmonary function that was not reversible even after 6 weeks of SMART treatment with budesonide and formoterol, the fact that such a decline was not recorded in clinically assessed peak expiratory flow, forced vital capacity, and forced expiratory volume in 1 s is reassuring.

The use of rescue medication and the percentage of days without the use of rescue medication remained significantly different between groups at the end of the 6-week SMART follow-up therapy, which suggests that long-term use of as-needed therapy might be associated with some persistent small reduction of control.

As expected, the number of patients with adverse reactions was low in both groups and, apart from the

Panel: Research in context

Systematic review

We systematically searched Medline to identify trials of single inhaler maintenance and reliever therapy (SMART) and rescue or as-needed medication in asthma, using the search terms: ("single inhaler", "Symbicort", "Seretide", "Advair", "Viani", "Fostair", or "Clenil Forte") OR ("inhaled corticosteroid", "ICS", "fluticasone", "FP", "Flixotide", "budesonide", "BUD", "Pulmicort", "beclomethasone", or "Becotide") AND ("long acting beta agonist", "beta-agonist", "LABA", "salmeterol", "Serevent", "formoterol", "Oxis", "Foradil", or "Atimos"). We began our search before we designed the study or wrote the protocol, and we searched for articles published from Jan 1, 1950, until Aug 31, 2014, with at least the abstract written in English. We supplemented our Medline search with hand-searches of respiratory journals and meeting abstracts. Of the complete list of references obtained, we selected those relevant to our study, including those about rescue inhaled corticosteroid and longacting β_2 agonist combinations in a single inhaler for mild asthma. To the best of our knowledge, our study is the first trial of rescue budesonide and formoterol combination treatment in a single inhaler for moderate asthma. However, we reviewed all 28 original studies of as-needed inhaled corticosteroid and formoterol combinations in a single inhaler for mild asthma and inhaled corticosteroid and formoterol used as SMART therapy for moderate to severe asthma and we have referenced the most important of these in the Article. Previous studies have shown that inhaled as-needed shortacting β_2 agonist and inhaled corticosteroid or inhaled as-needed longacting β_2 agonist and inhaled corticosteroid combination were effective in controlling intermittent or mild asthma, respectively, and that the SMART therapy was more effective than regular longacting β_2 agonist and inhaled corticosteroid therapy in moderate to severe asthma.

Interpretation

Current guidelines recommend regular inhaled longacting β_2 agonist and inhaled corticosteroid plus as-needed symptom-driven therapy with rapid-acting β_2 agonists or inhaled corticosteroid and formoterol for the treatment of moderate asthma not controlled by regular inhaled corticosteroids. In this study, we investigated whether a simpler as-needed symptom-driven budesonide and formoterol combination would be as effective as regular budesonide and formoterol plus as-needed terbutaline. The findings of our trial confirm guideline recommendations by showing that the as-needed inhaled therapy is less effective than the regular treatment in patients with moderate asthma not controlled by inhaled corticosteroids alone or adequately controlled by longacting β_2 agonist and inhaled corticosteroid combination treatment. However, because the differences were small and the level of control remained above that of partially controlled asthma,^{1,23} we speculate that in recommending the regular combination treatment according to guidelines, the results of this study could be discussed with the individual patient.

predictable oropharyngeal pain possibly related to the regular use of inhaled steroids, no other differences between groups were recorded, suggesting that safety is not an issue in considerations of the two alternative therapies, at least from a 1-year perspective. In particular, the use of a less intensive regimen in the as-needed budesonide and formoterol group did not result in a lower risk of adverse events compared with the regular budesonide and formoterol group.

The study had some limitations. Two centres (Genova and Cava de' Tirreni) that had initially agreed to participate in the study later withdrew their willingness to participate because of logistical or local reasons. Therefore, no patients from these centres were enrolled, randomised, or included in the analysis. Furthermore, owing to the limited budget, monitoring of the centres was mainly

done via teleconferences or the internet and not through direct site visits as is usually done in pharmaceutically sponsored randomised clinical trials. Moreover, the use of paper diary cards was a limitation for the completeness of the data related to peak expiratory flow or symptoms. This problem is well known in clinical research and electronic patient-reported outcomes are generally used to limit this problem. However, budget restrictions did not allow us to use this approach.

In conclusion, our results show that as-needed budesonide and formoterol is inferior to regular budesonide and formoterol plus as-needed terbutaline in preventing treatment failure and in maintaining asthma control. However, because the differences were small and the level of control remained above that of partially controlled asthma,^{1,23} we speculate that in recommending the regular combination treatment according to guidelines, the results of this study could be discussed with the individual patient. The regular treatment approach could be especially strongly recommended to female patients and to those with a substantial smoking history who have a raised risk of loss of asthma control with as-needed combination treatment.²⁸ Other patients that in our study had a lower risk of treatment failure could be presented with the advantages of as-needed treatment (convenience, lower cumulative dose of drugs, and potential long-term safety) and could weigh these up against the disadvantages (lower level of asthma control with occasional nocturnal awakening, and increased use of rescue medication).

Contributors

AP (study coordinator) and LMF designed the study, assisted by BM (study manager) and BB. Data were collected by the clinical investigators (listed in the appendix), analysed by PMo and MPa (CROS NT, Verona, Italy), who also contributed to the study design and to the statistical analysis. NS, PMa, PP, MS, SN, IF, GB, SB, MC, MPFB, AS, and MA recruited the patients and contributed to the study design. MPI did the laboratory analyses. The first draft of the report was written by AP and LMF, assisted by BM and BB. All authors discussed and approved all drafts of the report and agreed to submit it for publication. All authors had access to all the data and vouch for the accuracy of the reported data and for the fidelity of this report to the study protocol.

Declaration of interests

LMF has received grants from the University of Ferrara as part of the Agenzia Italiana del Farmaco (AIFA) grant during the conduct of the study; grants, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini, Novartis, Takeda, Almirall, Laboratori Guidotti, and MDS; personal fees and non-financial support from TEVA Pharmaceutical Industries, Pearl Therapeutics, Boston Scientific, Mundipharma, Bayer, Day Pharma, Elevation Pharmaceutical, Grunenthal, Kyorin Pharmaceutical, Hybrid NJ, and OM Pharma; personal fees from HBE Solutions; and grants from Gilead, Sanofi, Amgen, Jansen, Roche, Dompé, Pfizer, and Vree Health Italia. AP has received grants from AIFA during the conduct of the study; and grants, personal fees, and non-financial support from AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Menarini, Novartis, Zambon, Pfizer, Takeda, and Mundipharma. MS has received grants from the University of Ferrara as part of the AIFA grant during the conduct of the study; and grants from Takeda, Chiesi Farmaceutici, and Fondazione Cassa di Risparmio di Padova e Rovigo. BB, GB, MPI, MPFB, MA, PMa, BM, SN, NS, IF, AS, and SB have received grants

from the University of Ferrara as part of the AIFA grant during the conduct of the study. MC has received grants from AIFA during the conduct of the study; grants from Chiesi; and personal fees from Chiesi, AstraZeneca, Boehringer Ingelheim, Novartis, Menarini, and Mundipharma. PP has received grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, MSD, Menarini, Novartis, and Takeda; personal fees from Zambon and GlaxoSmithKline; and grants from the University of Ferrara as part of the AIFA grant, during the conduct of the study. MPa and PMo declare no competing interests.

Acknowledgments

This study was funded by the Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]), grant number FARM6BWSF9) of the Italian Ministry of Health. All drugs were donated by AstraZeneca (AstraZeneca S.p.A. Basiglio, Milan, Italy). We thank Luca Cantini (Rosignano Marittimo, Livorno, Italy), Mary McKenney (Menominee, MI, USA), and Elisa Veratelli (University of Ferrara, Ferrara, Italy) for scientific editorial assistance in the preparation of the report.

References

- 1 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Revised 2014. <http://www.ginasthma.org/documents/4> (accessed Sept 1, 2014).
- 2 Humbert M, Andersson TL, Buhl R. Budesonide/formoterol for maintenance and reliever therapy in the management of moderate to severe asthma. *Allergy* 2008; **63**: 1567–80.
- 3 Peters M. Single-inhaler combination therapy for maintenance and relief of asthma: a new strategy in disease management. *Drugs* 2009; **69**: 137–50.
- 4 Patel M, Pilcher J, Beasley R. Combination ICS/fast-onset LABA inhaler as maintenance and reliever therapy: the future for uncontrolled adult asthma? *Expert Rev Respir Med* 2013; **7**: 451–54.
- 5 Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013; **12**: CD009019.
- 6 O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; **171**: 129–36.
- 7 Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; **368**: 744–53.
- 8 Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; **1**: 32–42.
- 9 Papi A, Corradi M, Pigeon-Francisco C, et al. Beclomethasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; **1**: 23–31.
- 10 Aalbers R. Single inhaler as maintenance and reliever therapy—is it SMART? *Lancet Respir Med* 2013; **1**: 2–3.
- 11 Papi A, Caramori G, Adcock IM, Barnes PJ. Rescue treatment in asthma. More than as-needed bronchodilation. *Chest* 2009; **135**: 1628–33.
- 12 Beasley R, Weatherall M, Shirtcliffe P, Hancox R, Reddel HK. Combination corticosteroid/ β -agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? *J Allergy Clin Immunol* 2014; **133**: 39–41.
- 13 Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; **356**: 2040–52.
- 14 Corrigan CJ. Asthma therapy: there are guidelines, and then there is real life. *Prim Care Respir J* 2011; **20**: 13–14.
- 15 Djukanovic R, Wilson JW, Britten KM, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992; **145**: 669–74.
- 16 Duong M, Gauvreau G, Watson R, et al. The effects of inhaled budesonide and formoterol in combination and alone when given directly after allergen challenge. *J Allergy Clin Immunol* 2007; **119**: 322–27.

- 17 Sears MR, Boulet LP, Laviolette M, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. *Eur Respir J* 2008; **31**: 982–89.
- 18 Pavord ID, Jeffery PK, Qiu Y, et al. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. *J Allergy Clin Immunol* 2009; **123**: 1083–89.
- 19 Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990; **323**: 1033–39.
- 20 Gibson PG, Wong BJ, Hepperle MJ, et al. A research method to induce and examine a mild exacerbation of asthma by withdrawal of inhaled corticosteroid. *Clin Exp Allergy* 1992; **22**: 525–32.
- 21 Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000; **161**: 64–72.
- 22 Romagnoli M, Vachier I, Tarodo de la Fuente P, et al. Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002; **20**: 1370–77.
- 23 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: NHLBI/WHO workshop report. 2006. http://www.ginasthma.org/documents/5/documents_variants/31 (accessed June 6, 2007).
- 24 Juniper EF, O'Byrne PM, Gujatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14**: 902–07.
- 25 Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest* 1999; **115**: 1265–70.
- 26 The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007; **356**: 2027–39.
- 27 Brouwer AF, Roorda RJ, Brand PL. Comparison between peak expiratory flow and FEV₁ measurements on a home spirometer and on a pneumotachograph in children with asthma. *Pediatr Pulmonol* 2007; **42**: 813–18.
- 28 van Schayck OC, Haughney J, Aubier M, et al. Do asthmatic smokers benefit as much as non-smokers on budesonide/formoterol maintenance and reliever therapy? Results of an open label study. *Respir Med* 2012; **106**: 189–96.