Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial

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Summary

Background According to international treatment guidelines, inhaled rapid-acting β_2 agonists should be used for the control of symptoms in patients with asthma. We compared the efficacy and safety of an extrafine combination inhaler containing a corticosteroid (beclometasone) plus a rapid-onset, long-acting β_2 agonist (formoterol) with a short-acting β_2 agonist (salbutamol) as reliever strategies in patients taking beclometasone–formoterol combination as maintenance treatment.

Methods In a double-blind trial undertaken in 183 centres in 14 European countries over 48 weeks, patients (aged ≥18 years) with asthma that was not fully controlled, with a forced expiratory volume in 1 s (FEV_1) of at least 60% predicted, had a 2-week run in. During this period, patients were treated with a combination of beclometasone 100 µg and formoterol 6 µg per one inhalation twice daily plus salbutamol 100 µg as required delivered by use of a pressurised metered-dose inhaler. They were then randomly assigned in a 1:1 ratio with a computer-generated randomisation list to receive beclometasone 100 µg plus formoterol 6 µg or salbutamol 100 µg as reliever in addition to maintenance with beclometasone 100 µg plus formoterol 6 µg twice daily. Primary outcome was the time to first severe exacerbation (admission to hospital or visit to emergency department, or use of systemic steroids for ≥3 consecutive days). Secondary outcomes were number of severe exacerbations (events per 100 patients per year), time to and number of mild exacerbations, additional exacerbation variables, lung function, symptom scores, and asthma control. Analysis was by intention to treat. The study is registered with ClinicalTrials.gov, number NCT00861926.

Findings 1714 patients were randomly assigned to the as-needed beclometasone–formoterol (n=857) and as-needed salbutamol groups (n=857), and 1701 were analysed (852 and 849, respectively). 326 severe exacerbations were reported by 251 patients during the study, and 99 versus 152 patients had at least one exacerbation during the 48 weeks, respectively. Compared with beclometasone–formoterol plus salbutamol as needed, beclometasone–formoterol for both maintenance and reliever treatment significantly increased the time to first exacerbation (209 days *vs* 134 days) by 75 days, with a 36% reduction in risk (hazard ratio 0·64 [95% CI 0·49 to 0·82]; p=0·0005), and the estimated probability was 12% and 18%, respectively (p=0·0003). The number of days with mild asthma exacerbations was also lower with as-needed beclometasone–formoterol than with as-needed salbutamol (56·04 days per patient per year *vs* 65·11 days per patient per year; 0·86 [0·76 to 0·98]; p=0·021). From the run-in period to week 48, both treatments improved symptoms (mean change –1·59 [–1·94 to –1·25] in the as-needed beclometasone–formoterol group *vs* –1·44 [–1·78 to –1·10] in the as-needed salbutamol group, difference –0·15 [–0·60 to 0·30]; p=0·507), percentage of asthma control days (9·5% [7·3 to 11·8] *vs* 10·9% [8·7 to 13·1], respectively, –1·4 [–4·3 to 1·6]; p=0·359), use of reliever (–0·29 [–0·38 to –0·20] *vs* –0·27 [–0·36 to –0·19], respectively, –0·02 [–0·13 to 0·10]; p=0·794), and lung function (FEV_1, 0·090 [0·060 to 0·120] *vs* 0·090 [0·060–0·120], respectively, 0·001 [–0·040 to 0·040]; p=0·969), and were well tolerated (patients with serious adverse events, 32 [4%] and 41 [5%], respectively).

Interpretation Our results lend support to the use of the combination of a single inhaled corticosteroid plus a rapid-onset, long-acting β_2 agonist for maintenance and relief in patients with moderate to severe asthma and provide encouraging data for the formulation of beclometasone–formoterol for this use.

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Introduction

International treatment guidelines for asthma[1,2] recommend the combination of an inhaled corticosteroid and a long-acting β_2 agonist with the addition of a short-acting β_2 agonist for relief of symptoms in patients who are not adequately controlled with an inhaled corticosteroid alone. All available combinations of inhaled corticosteroid plus long-acting β_2 agonist have similar efficacies in patients with moderate-to-severe asthma when given with a short-acting β_2 agonist as reliever.[3,4]

Budesonide–formoterol is more effective in reducing asthma exacerbations when given as maintenance and reliever than when given regularly as maintenance with a short-acting β_2 agonist terbutaline or the rapid-onset,

long-acting β_2 agonist formoterol as reliever.[5,6] These findings suggest that treatment of symptoms with an inhaled corticosteroid and rapid-onset, long-acting β_2 agonist combination might provide better clinical control than a short-acting β_2 agonist alone for symptom relief. Whether patients should be left in need of rescue medication is debatable,[7] partly because of concerns about the safety of a long-acting β_2 agonist in asthma.[8]

The use of regular inhaled beclometasone dipropionate–formoterol combination in an extrafine hydrofluoroalkane formulation plus salbutamol as a reliever is non-inferior to equivalent doses of both regular inhaled budesonide–formoterol[3] or fluticasone–salmeterol combinations plus salbutamol as reliever[4] in improving lung function in patients with asthma uncontrolled with inhaled corticosteroid alone. The clinical effectiveness of low-dose extrafine beclometasone–formoterol combination in a single pressurised metered-dose inhaler (pMDI) as maintenance led us to speculate that a similar effectiveness could also be shown if this combination was used as a reliever medication, particularly considering the increased penetration of particles in the peripheral airways, a site of important acute inflammation during exacerbations. This method of treating asthma, initially introduced as SMART (Single inhaler Maintenance And Reliever Therapy), seems to be a generally effective management strategy in patients with asthma, with particular effectiveness in the prevention of exacerbations. It might also have ramifications for the development of other affordable formulations worldwide. However, whether the extrafine beclometasone–formoterol combination is suitable as both maintenance and relief of asthma exacerbations has never been tested.

The main objective in our study was to investigate whether the inhaled extrafine hydrofluoroalkane fixed combination of beclometasone 100 μg and formoterol 6 μg was more effective when given as both maintenance and reliever than when given as maintenance with a short-acting β_2 agonist as reliever in adults with asthma that was not fully controlled by inhaled corticosteroid alone or low-dose inhaled corticosteroid plus a long-acting β_2 agonist.

Methods

Study design and patients

The study was a multinational, multicentre, double-blind, randomised, parallel group, active-controlled trial. Additional details about the study design are provided in the appendix p 3. Patients were recruited between March 20, and Nov 20, 2009, in 183 centres in 14 European countries (appendix p 2). They were eligible for inclusion if they were aged 18 years or older, and had a clinical diagnosis of asthma for at least 6 months, pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of at least 60% predicted, increase in FEV_1 of at least 12% and 200 mL after inhaled salbutamol 400 μg, and a history of at least one severe exacerbation in the 12 months before study entry (but not in the past month). Patients whose asthma had been treated regularly with inhaled corticosteroid (beclometasone equivalent ≥1000 μg/day) or inhaled corticosteroid (beclometasone equivalent ≥500 μg/day) plus long-acting β_2 agonist for the previous 2 months were also eligible. Respiratory exclusion criteria included use of systemic steroids in the past month; other lung disease—eg, chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung diseases, or any other clinically or functionally significant lung disorder; treatment with slow-release corticosteroids (eg, injections of slow-release triamcinolone acetonide, betamethasone, or methylprednisolone) in the 3 months before the screening visit or with long-acting β_2 agonist or inhaled corticosteroid plus long-acting β_2 agonist fixed combination in the 24 h before visit 1; severe asthma exacerbation in the past month before the screening visit or during the run-in period; and lower respiratory tract infection affecting their asthma within 30 days of screening. A complete and detailed list of exclusion criteria is provided in the appendix pp 4–5.

The study protocol was approved by the institutional review board at each site and by the central or local ethics committees according to the country's law. All patients provided written informed consent.

Randomisation and masking

At the end of the run-in period, in each centre, patients were assigned in a double-blind manner to one of two treatments in a 1:1 ratio through an interactive voice or internet response system according to a computer-generated randomisation list (generated by ALMAC Clinical Technologies, Yardely, PA, USA). This list was generated for 20 strata with a block size of four (country was a stratification factor) and sent on request to the investigator who assigned patients to the study groups. Based on 1748 patients being randomly assigned, 1748 randomisation numbers and 437 blocks were generated per stratum.

Procedures

After screening, patients whose asthma was not fully controlled during the previous month entered a 2-week run in. Not fully controlled asthma was defined as having at least one of the following: use of rescue medication more than twice a week; any limitation of activities; any nocturnal symptoms or awakenings; daytime symptoms more than twice a week; or FEV_1 less than 80% predicted.[1] During the run-in period, all patients received a fixed combination of beclometasone 100 μg and formoterol 6 μg in a single pMDI (Foster, Chiesi Farmaceutici, Parma, Italy), as one inhalation twice daily plus salbutamol 100 μg through a pMDI (Ventolin, GlaxoSmithKline, Middlesex, UK) on an as-needed basis for the relief of symptoms. Peak expiratory flow (PEF), asthma symptoms, and the number of reliever medications were assessed as described in the appendix pp 3–4.

See Online for appendix

If asthma was not fully controlled after the run-in period, patients continued regular use of beclometasone 100 µg and formoterol 6 µg in a single inhaler, one inhalation twice daily, and were randomly assigned to receive reliever medication for 48 weeks, consisting of either salbutamol 100 µg through a pMDI or a fixed combination of beclometasone 100 µg and formoterol 6 µg through a pMDI (for which patients used the same extrafine combination both as regular and as-needed medication).

Patients were advised to use the same maintenance beclometasone dipropionate–formoterol combination for the entire study, with reliever medication as needed for up to a maximum of six extra inhalations per day. No specific step-up or step-down instructions were given to patients. They were instructed to take one inhalation in response to symptoms; however, if symptoms persisted, additional inhalations were allowed. The maximum daily dose allowed as reliever was six inhalations. In the patients assigned to beclometasone–formoterol as both maintenance and reliever, the use of six inhalations as reliever medication (plus one inhalation in the morning and one inhalation in the evening taken as maintenance) corresponds to a total daily dose of non-extrafine beclometasone dipropionate 2000 µg equivalent and to formoterol 48 µg—ie, the highest daily dose of beclometasone dipropionate to be used as maintenance according to the Global Initiative for Asthma (GINA)[1] guidelines and the therapeutic daily dose of inhaled formoterol, respectively.

Clinic visits took place at the beginning (visit 1) and end (visit 2) of the 2-week run in and thereafter at weeks 4, 12, 24, 36, and 48. A pocket spirometer (Spirotel, Medical International Research, Rome, Italy), was used to record daily spirometric data, asthma symptom scores, and the use of rescue medication.

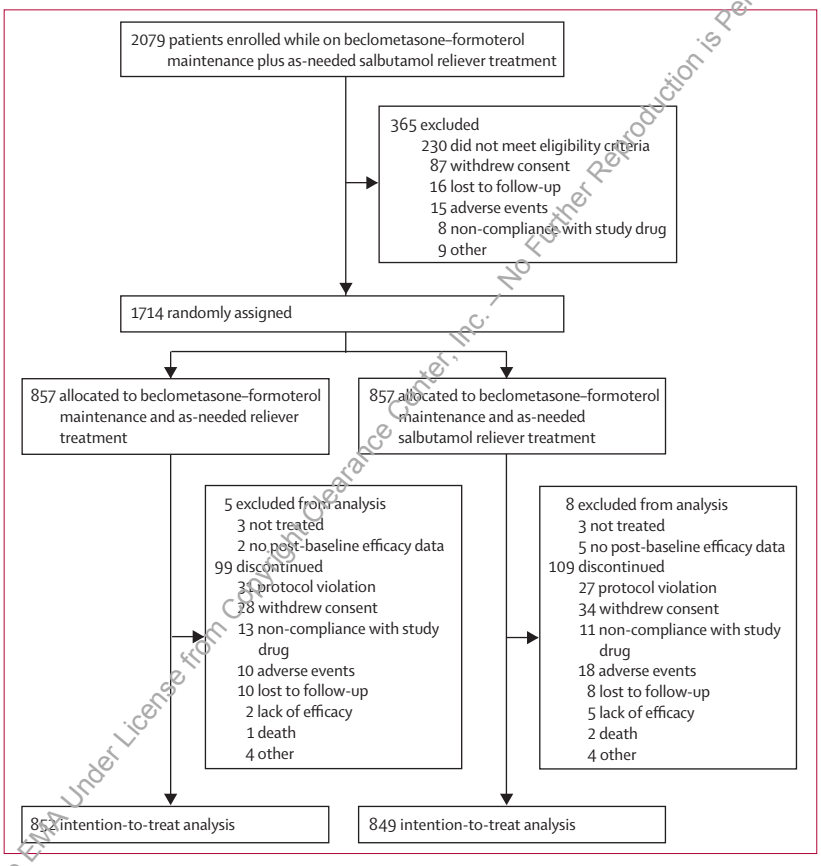

Figure 1: **Trial profile**

Outcomes

The primary outcome was the time to first severe asthma exacerbation, defined as deterioration in asthma resulting in admission to hospital or visit to the emergency department, or requiring systemic steroids for at least 3 days.

Secondary outcomes were number of severe exacerbations (events per 100 patients per year), and time to first and number of mild exacerbations. A mild exacerbation day was defined as the occurrence of one of the following: use of two or more inhalations of as-needed reliever in addition to the baseline in 24 h; morning PEF less than the baseline by at least 20%; or a night awakening due to asthma. Other secondary endpoints included additional exacerbation variables (different ways of expressing exacerbations), lung function, symptom scores, and asthma control (appendix pp 6–7).

Statistical analysis

Because of the importance of exacerbations in the natural history of asthma and the use of health-care services, the study was powered on the basis of time to first exacerbation and as a result planned for 1 year—ie, more than the minimum 6 months recommended for trials powered on the basis of exacerbations.[9] We calculated that 673 patients per group would need to be enrolled (log-rank test, two-sided 5% significance level) to have 80% power for the detection of a difference between treatments in the primary outcome, assuming 22% of patients in the beclometasone–formoterol plus salbutamol as-needed group and 16% of patients in the beclometasone–formoterol maintenance and reliever group had a severe asthma exacerbation. This difference corresponds to a hazard ratio of 0·69, and is in agreement with published data.[6]

Efficacy analyses were done on the intention-to-treat population—ie, included all randomly assigned patients who received at least one dose of study treatment and with at least one available evaluation of efficacy after baseline.

The mean of the last seven measurable values during the run-in period before visit 2 was defined as the baseline; for the other variables measured at the clinic visits, baseline was judged to be the value recorded at visit 2 before administration of treatment.

Time to first severe asthma exacerbation was analysed by use of Kaplan-Meier curves. A log-rank test was used

	As-needed beclometasone–formoterol (n=852)	As-needed salbutamol (n=849)
Sex		
Male	331 (39%)	321 (38%)
Female	521 (61%)	528 (62%)
Age (years)	49 (18 to 83)	47 (18 to 77)
Asthma duration (years; median, 95% CI)	9 (0·5 to 62·0)	9 (0·5 to 61·0)
Lung function		
FEV_1 (L)	2·21 (0·88 to 5·04)	2·27 (1·00 to 4·74)
FEV_1 (% predicted)	74 (29* to 127*)	75 (50* to 127)
FEV_1 reversibility	22·0% (–8·4* to 100·0)	22·3% (–1·5* to 98·6)
FVC (L)	3·22 (1·25 to 6·88)	3·26 (1·23 to 6·65)
FVC (% predicted)	83 (42 to 133)	82 (48 to 128)
Morning PEF (L/min)†	365 (131 to 744)	364 (104 to 729)
Evening PEF (L/min)†	373 (150 to 755)	373 (125 to 778)
Inhaled corticosteroid daily dose at study entry (µg/day)		
Beclometasone dipropionate (non-extrafine‡) equivalent	1128 (250 to 4000*)	1139 (200 to 4000*)
Use of inhaled long-acting β_2 agonist at study entry	707 (83%)	671 (79%)
Mean daily asthma control measures		
Total asthma symptom score†	6·63 (0·00 to 24·00)	6·44 (0·00 to 22·70)
Reliever use (inhalations per 24 h)	0·98 (0·00 to 8·71)	0·97 (0·00 to 9·43)
Asthma-control days§	8·30% (0·00 to 100·00)	8·87% (0·00 to 100·00)
ACQ-7¶	1·92 (0·00 to 4·14)	1·85 (0·00 to 3·86)

Data are number (%) or mean (range), unless otherwise indicated. Baseline was defined as the mean of the last seven measurable values during the run-in period before visit 2 for the variables recorded by use of a pocket spirometer; for other variables, baseline was the value recorded at visit 2 before treatment administration. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. PEF=peak expiratory flow. ACQ-7=Asthma Control Questionnaire-7. *Deviation from inclusion criteria (included in all statistical analyses). †Sum of the symptom scores recorded in the morning and evening (scale 0–3 used for each of the symptoms breathlessness, chest tightness, cough, and wheeze). ‡According to the Global Initiative for Asthma guidelines.[1] §Day with no asthma symptoms (symptom score 0) and no use of as-needed medication. ¶Mean scores from the seven questions measured at visit 2.

Table 1: **Baseline characteristics of patients receiving beclometasone–formoterol maintenance and as-needed beclometasone–formoterol or salbutamol reliever**

to assess the superiority of beclometasone–formoterol combination for maintenance and relief compared with beclometasone–formoterol combination plus as-needed salbutamol. A Cox proportional hazard model with country and treatment as factors was used to further describe any treatment differences. Total number of severe exacerbations, expressed as events per 100 patients per year, was compared by use of a Poisson regression model. Identical analyses were done for data for mild exacerbations. Methods for the analysis of other efficacy variables are reported in the appendix p 7.

A post-hoc analysis was done to assess the occurrence of exacerbations when patients were grouped on the basis of the dose of inhaled corticosteroid before study entry, with a beclometasone (non-extrafine) 500 µg/day or equivalent cutoff. This cutoff was chosen on the basis of a previous demonstration that the extrafine formulation allows a 2·5 times reduction in the dose of inhaled corticosteroid without compromising clinical efficacy,[1,2] so that the 500 µg/day (non-extrafine beclometasone) cutoff is equivalent to the inhaled corticosteroid maintenance dose of the beclometasone–formoterol extrafine combination administered during the study (beclometasone extrafine 200 µg/day). Thus, one subgroup of patients (beclometasone equivalent <500 µg/day before study entry) increased the maintenance treatment during the study and the other (beclometasone equivalent ≥500 µg/day before study entry) reduced or did not change the inhaled corticosteroid maintenance dose during the study.

All hypothesis testing was done with an α of 0·05 (two-sided) for comparisons between treatment groups. Statistical analysis was with SAS (version 9.2) on a Windows XP Pro operating system.

The study is registered with ClinicalTrials.gov, number NCT00861926.

Role of the funding source

Chiesi Farmaceutici assisted the investigators in the design of the study. SP and RB were employed by Chiesi Farmaceutici and participated in the collection, analysis, and interpretation of the data and writing of the report. AP, MC, CP-F, RB, ZS, SP, LMF, and KFR had full access to the raw data. The corresponding author had the final responsibility to submit the report for publication.

Results

The start and end dates for the study were March 20, 2009, and Dec 7, 2010, respectively. Figure 1 shows the trial profile; 2079 patients signed the informed consent and entered the study, 1714 were randomly assigned to the as-needed beclometasone–formoterol and as-needed salbutamol groups, and 1701 patients were included in the efficacy analysis (intention-to-treat population). The safety population consisted of all randomly assigned patients who took at least one dose of study medication (854 patients in each group). Table 1 shows that the baseline characteristics were similar between the treatment groups. Total self-reported mean use of maintenance medication during the study was 1·95 inhalations per day in the two groups (mean number of puffs 1·94 [SD 0·21] in the as-needed beclometasone–formoterol combination group and 1·96 [0·19]) in the as-needed salbutamol group); 95% of patients had a mean use of at least 1·5 maintenance inhalations per day (806 patients [95%] and 813 [96%], respectively). 326 severe exacerbations were reported by 251 patients during the study; 99 and 152 patients had at least one exacerbation during the 48 weeks in the as-needed beclometasone-formoterol and as-needed salbutamol groups, respectively (table 2). Compared with beclometasone–formoterol plus salbutamol as needed, beclometasone–formoterol for both maintenance and reliever treatment significantly increased the time to first exacerbation by 75 days (209 days *vs* 134 days), with a 36% reduction in risk (hazard ratio 0·64, 95% CI 0·49–0·82; p=0·0005; table 2), and an estimated probability of 12%

and 18%, respectively, by use of the Kaplan-Meier method (log-rank p=0·0003; figure 2). Thus, beclometasone–formoterol for maintenance and reliever was associated with a 36% (95% CI 18–51; p=0·0005; table 2) reduction in risk versus as-needed salbutamol in patients having a severe exacerbation; 34% reduction (20–45) in the yearly rate of severe exacerbations per patient (table 2); and 33% (16–46) reduction in the rate of exacerbations requiring admission to hospital or visit to the emergency department (table 2). Fewer patients receiving as-needed beclometasone–formoterol required at least one course of systemic corticosteroids (ie, ≥3 days) to prevent worsening of asthma than did those receiving as-needed salbutamol (35% reduction, 20–46; table 2).

The proportion of patients with more than one severe exacerbation was lower in the as-needed beclometasone–formoterol group than in the as-needed salbutamol group, but the difference was slight (25 [3%] of 852 *vs* 32 [4%] of 849).

22 hospital admissions were reported for 20 patients during the study: five in the as-needed beclometasone–formoterol group and 17 in the as-needed salbutamol group. The treatment difference was significant (1·18, 95% CI 0·2–2·2; p=0·03). No severe exacerbations requiring intubation were recorded.

No significant difference was noted between treatments in the time to first mild asthma exacerbation (table 2); however, the rate of mild exacerbations was reduced by 14% in patients treated with beclometasone–formoterol as maintenance and reliever treatment (table 2).

Post-hoc analyses showed that the time to first severe exacerbation was significantly prolonged (appendix p 13) and the yearly rate of severe exacerbations was reduced (appendix p 13) in patients using as-needed beclometasone–formoterol compared with as-needed salbutamol irrespective of the changes in or maintenance of the dose of inhaled corticosteroid.

Mean FEV_1 improved in all patients during the run-in period. After randomisation, further improvements were noted in both treatment groups with a change from baseline to the end of the study (week 48) of 0·090 L in both treatment groups; the difference between groups was not significant (table 3).

Mean asthma symptom scores significantly decreased from run in to week 48 in the as-needed beclometasone–formoterol and as-needed salbutamol groups, but the difference between the groups was not significant (p=0·51; table 3). Asthma-control days (days without symptoms or reliever use) increased in both groups from run in to week 48, with no significant difference between groups (table 3). Improvements in mean Asthma Control Questionnaire-7 (ACQ-7) scores from baseline were slightly but not significantly greater with as-needed beclometasone–formoterol than with as-needed salbutamol, but were not significantly different between the groups (table 3).

	As-needed beclometasone–formoterol (n=852)	As-needed salbutamol (n=849)	Hazard ratio (95% CI)	p value
Severe exacerbations (all definitions)				
Patients with event	99 (12%)	152 (18%)	0·64* (0·49–0·82)	0·0005
Total events	130	196	..	..
Rate (events per 100 patients per year)	14·76	22·39	0·66† (0·55–0·80)	<0·0001
Visit to emergency department or admission to hospital due to asthma				
Patients with event	53 (6%)	77 (9%)	..	..
Total events	67	99	..	..
Rate (events per 100 patients per year)	6·14	9·11	0·67† (0·54–0·84)	0·0003
Systemic corticosteroid for more than 3 days for asthma				
Patients with use of systemic corticosteroids	89 (10%)	143 (17%)	..	..
Use of systemic corticosteroids (total events)	125	190	..	..
Rate (events per 100 patients per year)	14·69	22·47	0·65† (0·54–0·80)	<0·0001
Mild exacerbations				
Patients with event	610 (72%)	607 (71%)	0·97* (0·86–1·08)	0·565
Total events	2847	2789	..	..
Rate (days per patient per year)	56·04	65·11	0·86† (0·76–0·98)	0·021

Data are number (%), unless otherwise indicated. All patients received beclometasone 100 µg plus formoterol 6 µg combination, per one inhalation twice daily for maintenance. *Treatment comparison of hazard ratios from a Cox proportional hazards model of time-to-first severe (or mild) exacerbation. †Comparisons of relative rates from a Poisson regression model.

Table 2: **Severe and mild exacerbations in patients in the as-needed beclometasone–formoterol and as-needed salbutamol groups**

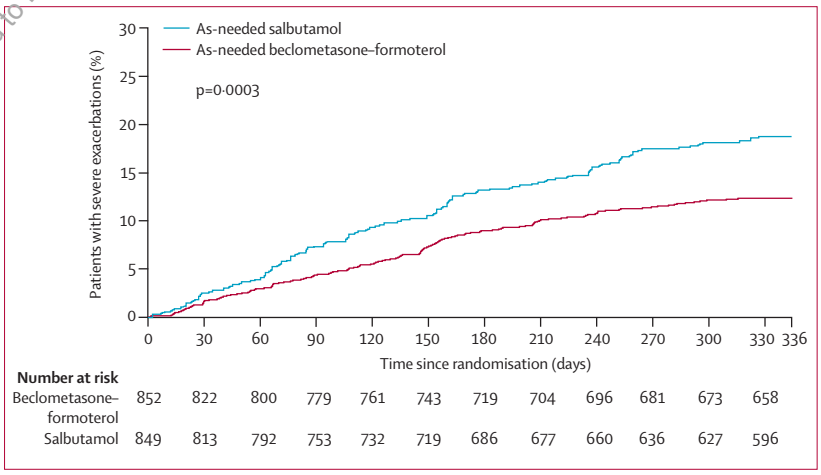

Figure 2: **Kaplan-Meier plot of time to first severe asthma exacerbation (primary outcome)**
Significant between-group differences were ascertained by use of the log-rank test.

At the end of the treatment period, mean daily reliever use had decreased by a similar amount in both groups (p<0·0001 for each group); the difference between the groups was not significant (table 3).

Overall, there was a net improvement in asthma control during the study. The number of patients with asthma not fully controlled (as defined by an ACQ-7 score at baseline ≥1·5) was 550 (65%) of 852 in the

	As-needed beclometasone–formoterol (n=852)			As-needed salbutamol (n=849)			Difference (95% CI)*	p value
	Baseline (visit 2)	Week 48	Mean change (95% CI)*	Baseline (visit 2)	Week 48	Mean change (95% CI)*		
Lung function								
FEV_1 (L)	2·21 (0·73)	2·41 (0·78)	0·090 (0·060 to 0·120)	2·27 (0·71)	2·47 (0·80)	0·090 (0·060 to 0·120)	0·001 (–0·040 to 0·040)	0·969
FVC (L)	3·22 (0·99)	3·44 (1·04)	0·11 (0·07 to 0·15)	3·26 (0·97)	3·48 (1·06)	0·12 (0·08 to 0·16)	–0·01 (–0·07 to 0·04)	0·587
Morning PEF (L/min)†	365·1 (115·0)	343·4 (112·0)	–9·07 (–14·64 to –3·49)	364·4 (113·8)	351·0 (113·2)	–12·75 (–18·29 to –7·22)	3·69 (–3·51 to 10·88)	0·315
Evening PEF (L/min)†	372·9 (114·7)	348·6 (107·4)	–11·37 (–16·79 to –5·95)	373·1 (112·7)	358·2 (112·2)	–15·09 (–20·56 to –9·62)	3·72 (–3·39 to 10·84)	0·305
Symptom control								
Total asthma symptom score†‡	6·63 (4·62)	5·06 (4·90)	–1·59 (–1·94 to –1·25)	6·44 (4·69)	4·99 (4·90)	–1·44 (–1·78 to –1·10)	–0·15 (–0·60 to 0·30)	0·507
Reliever use (inhalations per 24 h)†	0·98 (1·39)	0·73 (1·13)	–0·29 (–0·38 to –0·20)	0·97(1·44)	0·70 (1·18)	–0·27 (–0·36 to –0·19)	–0·02 (–0·13 to 0·10)	0·794
Asthma-control days†§	8·3 (20·1)	17·7 (29·3)	9·5% (7·3 to 11·8)	8·9 (19·9)	19·2 (31·6)	10·9% (8·7 to 13·1)	–1·4 (–4·3 to 1·6)	0·359
ACQ-7¶	1·92 (0·69)	1·39 (0·80)	–0·48 (–0·54 to –0·42)	1·85 (0·71)	1·41 (0·82)	–0·42 (–0·48 to –0·37)	–0·06 (–0·13 to 0·02)	0·137

Data are mean (SD), unless otherwise indicated. All patients received combined beclometasone 100 µg and formoterol 6 µg, per one inhalation twice daily for maintenance. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. PEF=peak expiratory flow. ACQ-7=Asthma Control Questionnaire-7. *Calculated by use of a mixed model for repeated measurements; maximum likelihood method was applied for missing data. †Mean of the last seven measurable values before the clinic visit. ‡Sum of the symptom scores recorded in the morning and evening (scale 0–3 used for each of the symptoms breathlessness, chest tightness, cough, and wheeze). §Day with no asthma symptoms (symptom score 0) and no use of as-needed medication. ¶Mean scores from the seven questions measured at visit 2.

Table 3: **Lung function and symptom control in patients in the as-needed beclometasone–formoterol and as-needed salbutamol groups**

as-needed beclometasone–formoterol group and 510 (60%) of 849 in the as-needed salbutamol group. Of the patients with uncontrolled disease, 287 (52%) of 550 in the as-needed beclometasone–formoterol group and 244 (48%) of 510 in the as-needed salbutamol group had partly controlled disease (ACQ-7 <1·5) at study end.

The mean additional dose of beclometasone used by patients in the beclometasone–formoterol group for maintenance and reliever treatment was 86 µg/day (SD 12). Compared with prescreening treatment, there was a decrease in the mean daily non-extrafine beclometasone dipropionate-equivalent dose from 1128 µg (508) to 701 µg (293) in the as-needed beclometasone–formoterol group, and from 1139 µg (505) to 489 µg (48) in the as-needed salbutamol group during the whole study. With the 1:2·5 equivalent dose ratio of beclometasone extrafine to non-extrafine, the difference of 212 µg in the dose of beclometasone non-extrafine noted at the end of the study between the two groups, corresponds to extrafine beclometasone 84·8 µg.

All treatments were well tolerated (appendix p 8). Similar numbers of patients in the as-needed beclometasone–formoterol and salbutamol groups had serious adverse events (32 [4%] and 41 [5%], respectively; appendix p 14). The occurrence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroid or β_2 agonists was low in both treatment groups, with the exception of adverse drug reactions that were significantly (p=0·01) higher in the beclometasone–formoterol group for maintenance and reliever treatment (appendix pp 14–15).

Discussion

We have shown that an extrafine inhaled combination of beclometasone 100 µg and formoterol 6 µg is more effective in reducing asthma exacerbations when given as both maintenance and reliever treatment than when given only as maintenance with salbutamol 100 µg as needed to patients who do not have fully controlled asthma. The two treatment regimens are equally safe and well tolerated. These findings confirm the efficacy of the inhaled corticosteroid (beclometasone) given as reliever with a rapid-onset, long-acting bronchodilator (formoterol) and extend the results of previous studies showing the effectiveness of another inhaled corticosteroid plus long-acting β_2 agonist combination (budesonide–formoterol) for both maintenance and reliever medication (panel).[5,6,10,11]

Prevention of asthma exacerbations is recognised in all current asthma guidelines as an important component of treatment[1,2] because exacerbations result in substantial reductions in work productivity and school or university attendance and represent the greatest cost to health-care systems.[12] Most exacerbations are managed in the outpatient setting, with only the most severe resulting in hospital admission, and represent about a third of the total expenditure per year on asthma-related health-care.[9,12,13] Furthermore, exacerbations have been shown to be an independent risk factor for an increase in the deterioration in lung function.[14] Therefore, prevention of severe exacerbations might be viewed as complementary to disease control in the overall management of asthma.

The findings of studies in unselected patient populations with asthma—ie, a real-life setting, show that patients will increase the dose of rescue inhalers as their asthma progresses; indeed, one of the most sensitive indices of asthma worsening is the increased use of rescue medication.[15] Overuse of short-acting β_2 agonist reliever can delay the start of effective treatment because it only provides temporary relief and does not improve the underlying bronchial inflammation. By contrast, the mechanism of action of the combination of inhaled

corticosteroid plus rapid-onset, long-acting bronchodilator provides rapid bronchodilation and reduction in acute airway inflammation, with the suggestion the drugs are having a synergistic effect.[16] This interaction is likely to be highly relevant in the use of inhaled corticosteroid and rapid-onset, long-acting β_2 agonist combination for both maintenance and reliever treatment and provides more advantages than does the use of short-acting β_2 agonist alone as a reliever treatment.

The strategy of using inhaled corticosteroid and long-acting β_2 agonist as both maintenance and reliever treatment has been recognised in the international asthma management guidelines (GINA).[1] In 2010, the efficacy of this approach with the combination of budesonide–formoterol was questioned, particularly in relation to the level of asthma control that is achievable;[7] however, the conclusions of this appraisal were heavily criticised.[7,17]

The reduction in exacerbation rate with beclometasone–formoterol as maintenance and reliever could be due to the additional dose of beclometasone extrafine (86 µg/day) taken by patients in this group. This reduction raises a question about the importance of a rapid-onset, long-acting β_2 agonist in the rescue treatment, and the possibility that the additional dose of inhaled corticosteroid and not of the rapid-onset, long-acting β_2 agonist (formoterol) accounts for the reduction in exacerbations. Indeed, in a previous study, we reported the efficacy of a combination of beclometasone with a short-acting β_2 agonist, and not a long-acting β_2 agonist, in a single inhaler as rescue treatment for patients with asthma.[18] Whether the reduction in exacerbation frequency noted in this study would occur if the extra inhaled corticosteroid were given regularly rather than as needed has to be tested properly. However, this explanation seems rather unlikely because the findings of early studies showed that even doubling of the dose of inhaled corticosteroid does not reduce the frequency of asthma exacerbations.

In previous trials, eligible patients had inadequately controlled asthma and a high use of inhaled reliever medication at baseline (up to 1·9 inhalations per day).[5,6] In our study, patients had a lower requirement for reliever medication at baseline (less than one inhalation per day), and this was further reduced during the treatment. These results provide evidence that the benefits of an as-needed combination of inhaled corticosteroid and rapid-onset, long-acting β_2 agonist over short-acting β_2 agonist as reliever medication for the reduction of severe exacerbations are maintained even in patients with a lower need for rescue medication. We believe that our study population is representative of most patients with asthma, who are affected by moderate persistent asthma and are not adequately controlled.[19] However, additional studies in patients with more severe asthma would be needed to prove that the extrafine beclometasone dipropionate–formoterol combination is equally effective as the budesonide–formoterol combination.

To address the specific concerns related to the level of asthma control in patients recruited to this study, post-hoc analyses were done in patients whose maintenance dose of inhaled corticosteroid was either increased during the study (step up, 281 [17%] of 1701) or stepped down or unchanged (1420 [83%] of 1701). These post-hoc analyses confirmed the superiority of as-needed beclometasone–formoterol compared with the as-needed salbutamol in reducing the risk of exacerbation irrespective of whether the dose of inhaled corticosteroid administered before study entry is stepped up or down. Therefore, compared with the results of previous studies, our findings might have a broader applicability to the general population with asthma.

Unlike the significant benefit in preventing severe exacerbations (table 2), the improvements in ACQ-7 scores were only slightly greater in the as-needed beclometasone–formoterol group than in the as-needed salbutamol group, due to the items of the ACQ-7 generally relating to different daily components of asthma control rather than specifically to episodes of acute exacerbation. Furthermore, in our study, FEV_1 and asthma control significantly improved in both treatment groups despite a substantial reduction in the daily dose of inhaled corticosteroid. Thus, the benefit in the active treatment group with as-needed beclometasone–formoterol occurred in patients with effective combination treatment for maintenance (so not undertreated). Although we cannot exclude that the

***Panel:* Research in context**

Systematic review

We identified trials of the Single inhaler Maintenance and Reliever Therapy (SMART) in asthma with a systematic search of Medline and handsearching of respiratory journals and meeting abstracts. We searched for ("single inhaler", "Symbicort", "Seretide", "Advair", "Viani", "Fostair", or "Clenil Forte") or ("steroid", "corticosteroid", "ICS", "fluticasone", "FP", "Flixotide", "budesonide", "BUD", "Pulmicort", "beclomethasone", "Beclo", or "Becotide") and ("long acting beta agonist", "beta-agonist", "LABA", "salmeterol", "Serevent", "formoterol", "eformoterol", "Oxis", "Foradil", or "Atimos"). Searches started before the study was designed and the writing of the protocol, and the search dates were from Jan 1, 1950, until Jan 30, 2013. Of the complete list of references obtained, we selected those relevant to our study. Since our study is the first, to the best of our knowledge, of the beclometasone–formoterol combination in a single inhaler for SMART, no specific reference was found.

Interpretation

Current guidelines recommend inhaled rapid-acting β_2 agonists for the control of asthma symptoms. However, the findings of our trial suggest that an extrafine combination of the corticosteroid (beclometasone) with the rapid-onset, long-acting β_2 agonist (formoterol) is more effective than a short-acting β_2 agonist (salbutamol) alone as reliever medication in patients with asthma that is not fully controlled receiving beclometasone–formoterol combination as maintenance treatment. This idea, initially introduced as SMART seems to be a generally effective management strategy for the treatment of asthma, with particular effectiveness to prevent exacerbations. Our results might also have ramifications for the development of other affordable formulations worldwide.

increase in FEV_1 might be a trial effect related to study participation, the reduction in use of inhaled corticosteroid could also be related to the beclometasone–formoterol formulation. We used an extrafine formulation with a hydrofluoroalkane propellant, which is characterised by high drug deposition in the peripheral airways, a primary site of inflammation in asthma.[20–22] Greater peripheral drug deposition as a result of smaller particle size increases the efficacy of inhaled treatment[23] and reduces the overall systemic exposure to inhaled corticosteroid.[24] Indeed, in previous studies with beclometasone alone or in fixed combination with formoterol, the use of the extrafine formulation allowed a 2·5 times reduction in the dose of inhaled corticosteroid without compromising clinical efficacy.[25,26] Furthermore, the pMDI inhalation technique for formulations that produce extrafine particles has been suggested as being less important than the other pMDIs[27] because lung deposition is less affected by inhalation flow[28] and coordination.[29] Even though the superiority of inhaled corticosteroid and rapid-onset, long-acting β_2 agonist combination for maintenance and relief of asthma is debated,[7] this approach is accepted in major treatment guidelines[1] and is approved in several countries but, notably, not in the USA.[30] The concerns are likely related to a negative perception of long-acting β-adrenoceptor agonists in asthma, although the evidence seems to indicate that the class of drug is safe when used in combination with steroids, and that an increase in maintenance doses of steroids will suffice in the achievement of asthma control. Furthermore, the proven efficacy of long-acting β-adrenoceptor agonists in children is less convincing than in adults with asthma.

The number of hospital admissions was significantly lower in patients treated with beclometasone dipropionate–formoterol as maintenance and reliever medication, an important effect that was consistent with the results obtained with budesonide–formoterol in previous studies in patients with more severe asthma.[6,11]

Equally important, in terms of concerns about the use of long-acting β_2 agonist in patients with asthma,[8] our results show that the inhaled corticosteroid and rapid-onset, long-acting β_2 agonist combination for maintenance and relief is safe and well tolerated. Our study was not planned to address pharmacoeconomical considerations. However, we believe that the additional cost of inhaled corticosteroid and rapid-onset, long-acting β_2 agonist combination (29 Eurocents per patient per day) is justifiable because of the significant reduction in severe exacerbations, and specifically hospital admissions, known to have a huge effect on health-care costs in asthma.

Taken together with the results of previous trials, our findings further support the notion of a single inhaled corticosteroid and a rapid-onset, long-acting β_2 agonist combination for maintenance and relief in patients with moderate to severe asthma.

Contributors
All authors contributed equally to the study design, data collection and analysis, and writing of the report.

Conflicts of interest
KFR has received consultancy and speaker fees for Chiesi Farmaceutici and has participated in review activities including data monitoring boards, statistical analysis, and endpoint committees. AP and ZS have received consultancy fees for Chiesi Farmaceutici and have participated in review activities including data monitoring boards, statistical analysis, and endpoint committees. MC has received consultancy fees for Chiesi Farmaceutici. CP-F is an employee of Chiesi SA, France. SP and RB are employees of Chiesi Farmaceutici, Italy. LMF has received consultancy fees and grants for Chiesi Farmaceutici.

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