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Lung function and asthma control with beclomethasone and formoterol in a single inhaler

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KEYWORDS
Corticosteroid;
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Combination therapy;
Extra-fine

Summary
Background: Lung deposition is crucial for asthma treatment. However, there is no study comparing the potential role of lung co-deposition of combination therapy (inhaled corticosteroid and long-acting β2 agonist) in the same inhaler. In moderate to severe asthmatics, an extra-fine hydrofluoroalkane combination of beclomethasone dipropionate and formoterol given via a single pressurised metered-dose inhaler (pMDI) was compared with beclomethasone dipropionate chlorofluorocarbon (CFC) pMDI and formoterol dry powder inhaler (DPI) given via separate inhalers.
Methods: In a double-blind, double-dummy, 24-week randomised clinical trial, 645 patients with moderate to severe asthma uncontrolled by regular treatment with inhaled corticosteroids received regular treatment with extra-fine fixed combination beclomethasone dipropionate 200 μg/formoterol 12 μg bid, or beclomethasone dipropionate (500 μg bid) via CFC pMDI and formoterol (12 μg bid) via DPI, or beclomethasone dipropionate (500 μg bid) via CFC pMDI.

List of abbreviations: ACTH, adrenocorticotropic hormone; ANCOVA, analysis of covariance; CI, confidence interval; CFC, chlorofluorocarbon; DPI, dry powder inhaler; ECG, electrocardiogram; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GINA, global initiative for asthma; HFA, hydrofluoroalkane; ITT, intention to treat; LSM, least squares mean; MDI, metered-dose inhaler; PEF, peak expiratory flow; pMDI, pressurised metered-dose inhaler; PP, per protocol; SD, standard deviation; SE, standard error.

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The primary outcome was morning peak expiratory flow (PEF). Secondary outcomes included lung function measured at clinic, asthma symptoms and control, exacerbations.
Results: Beclomethasone dipropionate/formoterol combination via single inhaler or via separate inhalers improved morning PEF. However, the combination via single inhaler was more effective than given via separate inhalers for asthma control. Both combination treatments were superior to beclomethasone dipropionate alone in improving lung function and asthma control. All treatments were well tolerated.
Interpretation: In patients with moderate to severe asthma, beclomethasone dipropionate/formoterol in a single inhaler was as effective as beclomethasone dipropionate plus formoterol and superior to beclomethasone dipropionate alone in improving lung function. For the first time with a single inhaler, beclomethasone dipropionate/formoterol was significantly superior to separate components for asthma control. *This trial is registered with* ClinicalTrials.gov, *number NCT00476268*.

Introduction

Asthma is a global health problem and patients with moderate to severe disease need optimal treatment to avoid severe exacerbations. All guidelines recommend combination therapy using an inhaled corticosteroid plus a long-acting β2 agonist for patients insufficiently controlled by inhaled corticosteroids alone.[1,2] Three preparations are commercially available: fluticasone propionate with salmeterol, or budesonide with formoterol or beclomethasone dipropionate with formoterol. The latter combination is formulated as a hydrofluoroalkane-134a (HFA-134a)-containing pressurised metered-dose inhaler (pMDI), developed using the Modulite® solution formulation technology.[3] It delivers extra-fine particles of 100 μg beclomethasone dipropionate and 6 μg formoterol[4] per actuation which are suitable for high lung deposition and homogeneous distribution throughout the lung.[5] In moderate to severe asthmatic patients, it was found to have a comparable efficacy to the two other fixed-dose combinations.[6,7]

Lung deposition is crucial for an optimal treatment of asthma. Inflammation of the small airways (internal diameter <2 mm) is an important feature of asthma and treatment of distal lung inflammation may be key for appropriate asthma pharmacotherapy.[8] Hydrofluoroalkane propelled metered-dose inhalers deliver fine particles which may target the lower airways. However, there is no study showing that the co-deposition via single inhaler of a corticosteroid and a long-acting β2 agonist in the distal lung improves the control of asthma better than the same drugs deposited via separate inhalers.

It was shown that the dose of 100 μg of beclomethasone dipropionate in the extra-fine formulation delivers a fine particle dose comparable to a 250 μg dose of beclomethasone dipropionate via a CFC-containing pMDI (ratio of 1:2.5).[4] Moreover, in adults with moderate asthma, beclomethasone dipropionate extra-fine HFA pMDI was clinically equivalent (peak expiratory flow rate), to beclomethasone dipropionate via a CFC-containing pMDI at a dose ratio of 1:2.5.[9,10]

This paper describes a multi-centre, multinational Phase III, double-blind, double-dummy, clinical trial designed to establish that this HFA extra-fine beclomethasone dipropionate 100 μg with formoterol 6 μg fixed combination is clinically non-inferior to CFC-beclomethasone dipropionate 250 μg and formoterol 6 μg administered via separate inhalers, and superior to CFC-beclomethasone dipropionate 250 μg alone, in patients eligible for inhaled corticosteroid/long-acting β2 agonist combination therapy according to current guidelines.[1,2]

Methods

Participants

This study recruited men and non-pregnant women (18–70 years), with a diagnosis of moderate to severe persistent asthma according to GINA 2005,[11] a forced expiratory volume in one second (FEV_1) ranging from 40% to 80% predicted values, and a positive reversibility test after salbutamol performed within the two years before screening (FEV_1 increase in FEV_1 over 12% baseline value and at least 200 ml).[12] Participants had received at least two-month treatment with CFC-beclomethasone dipropionate 750–1000 μg, or equivalent either alone or associated with a long-acting β2 agonist (formoterol 24 μg or salmeterol 100 μg per day), plus daily use of a short-acting beta-agonist. Asthma symptoms occurred over three times during the week before study entry.

Patients were excluded if they had smoked at least 20 cigarettes per day for ten years. The study recruited outpatients at 104 centres in Belgium (1), France (15), Hungary (5), Poland (15), Romania (14) and Russia (54).

Treatments

Participants were enrolled in a two-week run-in and continued their previous asthma treatments. If eligibility criteria were confirmed, participants were randomised to receive one of three treatments:

(1) pMDI containing beclomethasone dipropionate 100 μg and formoterol 6 μg per inhalation, with HFA-134a as a propellant (Foster®; Chiesi Farmaceutici).
(2) CFC pMDI containing beclomethasone dipropionate 250 μg per inhalation (Becloforte®; Allen & Hanburys),

plus a DPI containing formoterol 12 μg per capsule (Foradil® Aerolizer®; Novartis).
(3) CFC pMDI containing beclomethasone dipropionate 250 μg per inhalation (Becloforte®).

Each participant received three inhalers (containing active drug or placebo) to maintain blinding while using inhalers of different appearance. Patients were instructed to take their assigned study drug (plus alternative placebos) twice daily at 8.00 am and 8.00 pm as follows:

(1) two puffs beclomethasone dipropionate/formoterol (400 μg/24 μg per day), plus a placebo equivalent to one capsule formoterol DPI Aerolizer® and a placebo equivalent to two puffs beclomethasone dipropionate CFC pMDI.
(2) two puffs beclomethasone dipropionate CFC (1000 μg per day) plus one capsule formoterol DPI Aerolizer® (24 μg per day), plus a placebo equivalent to two puffs Foster® via pMDI.
(3) two puffs beclomethasone dipropionate CFC (1000 μg per day), plus a placebo equivalent to one capsule formoterol DPI Aerolizer® and a placebo equivalent to two puffs Foster® via pMDI.

Randomisation

Randomisation was performed according to a balanced block design with a centrally generated randomisation code. Blocks of three randomisation numbers were allocated to each centre.

Objectives

The primary objectives of this study were to demonstrate that a fixed-dose combination of beclomethasone dipropionate and formoterol was non-inferior to beclomethasone dipropionate and formoterol given separately, and superior to beclomethasone dipropionate alone, over 24 weeks in adults with moderate to severe persistent asthma.

Efficacy outcomes

Mean morning peak expiratory flow (PEF) measured by the patient before dosing during the last 14 days of treatment was the primary efficacy endpoint. Baseline morning PEF was the mean of all values recorded during the run-in period. Patients recorded their PEF with an electronic peak flow meter (Spirotel™, MIR, Italy).

Secondary efficacy endpoints included evening PEF, daily PEF variability, morning and evening FEV_1, day and night asthma symptom scores (cough, wheezing, chest tightness, breathlessness and attack) on a four-point scale where 0 = none, 1 = mild, 2 = moderate and 3 = severe, and salbutamol use. The percentage of days and/or nights without clinical symptoms and days with asthma control — defined as no or minimal clinical symptoms, no asthma-related unscheduled medical visits, less than three puffs/day SABA, no limitation on activities, daily PEF variability $\leq$20% and no drug-related adverse events (AEs) (GINA 2004) — was evaluated. Additionally, a post-hoc analysis was performed by assessing asthma control as: no nocturnal awakenings, no asthma symptoms and no rescue medication used.[13]

Spirometry was performed at each clinic visit (screening, baseline and after two, four, eight, 16 and 24-week treatment), and lung function tests (FEV_1, PEF, forced vital capacity [FVC] and forced expiratory flow between 25% and 75% of FVC [$FEF_{25-75\%}$]) were measured.

The occurrence of asthma exacerbations was recorded, according to pre-defined criteria, as follows:

Mild-to-moderate exacerbation: diurnal PEF variability >20% and $\leq$30%; SABA use between four and eight puffs per day; or nocturnal awakening due to asthma — all during at least two consecutive days.

Severe exacerbation: need for oral corticosteroid; asthma-related unscheduled medical visit or visit to an emergency department; hospital admission for asthma; diurnal PEF variability >30% or SABA inhalation of more than eight puffs per day during at least two consecutive days; or nocturnal awakening due to asthma during at least three consecutive 24-hour periods.

Safety outcomes

Adverse events were assessed by investigators at clinic visits and recorded by patients on paper diary cards. Vital signs, ECG (including QTc interval) and haematology/blood chemistry were evaluated during the treatment.

Morning serum cortisol (with adrenocorticotropic hormone [ACTH] stimulation test)[14] and overnight (12-hour) urinary cortisol/creatinine ratios were also measured at baseline and at week 24 in a subgroup of 93 patients.

Statistical methods and sample size

Efficacy data were analysed for both the intention to treat (ITT) and per-protocol (PP) populations. The ITT population included all participants who received at least one inhalation of study drug and had at least one post-baseline efficacy evaluation. Participants in the ITT population without major protocol deviations formed the PP population. The safety population included all patients who received at least one inhalation of study drug. The last available post-baseline values were carried forward to the end of treatment time point for missing data.

The non-inferiority of beclomethasone dipropionate/formoterol fixed combination versus beclomethasone dipropionate plus formoterol free combination, and its superiority versus beclomethasone dipropionate monotherapy, for morning pre-dose PEF (measured on the Spirotel®) and clinic FEV_1 were tested using an analysis of covariance (ANCOVA) model, including terms for treatment and centre as main effects and baseline value as covariates.

A sample size of $n = 191$ patients per group assured 80% power for the non-inferiority test of beclomethasone dipropionate/formoterol versus beclomethasone dipropionate plus formoterol, assuming an estimated difference on morning PEF (l/min) between beclomethasone dipropionate/formoterol versus beclomethasone dipropionate plus formoterol equal to zero, with a standard deviation of morning PEF equal to 60 l/min and a non-inferiority margin

fixed at 20 l/min. This sample size also provided more than 80% power to detect a clinically relevant difference (that is, larger than the non-inferiority margin) for the test of superiority of beclomethasone dipropionate/formoterol over beclomethasone dipropionate alone.

All secondary endpoint data were summarised and analysed for both ITT and PP populations. Continuous endpoints (evening PEF, daily PEF variability, morning and evening FEV_1, clinic-measured lung function tests, percentage of nights/days/complete days free of asthma symptoms, mean number of asthma exacerbations per patient, daily salbutamol use and percentage of days asthma was controlled) were summarised by treatment group and visit or period as appropriate, with analysis and presentation of results as for the primary efficacy endpoint. Morning and evening asthma clinical symptom scores were treated as continuous endpoints.

For the primary efficacy variable all the comparisons had to show statistical significance at the required level, therefore no formal adjustment for multiple comparisons was needed. For the secondary efficacy variables the adjustment was not considered necessary being these used for supportive purpose only.

Results

Participants

A total of 824 patients were screened and 645 were randomised to treatment, of whom 596 (92.4%) completed the 24-week study. The first patient entered the study on 7 February 2004 and the last patient completed the study on 28 January 2005.

Patient disposition is shown in Fig. 1. Baseline characteristics were similar between groups, as shown in Table 1.

Lung function

The primary outcome of the study, namely morning PEF, was significantly higher compared with baseline for both beclomethasone dipropionate/formoterol fixed combination and beclomethasone dipropionate plus formoterol free combination, but remained unchanged for beclomethasone dipropionate monotherapy (Fig. 2). Results in the ITT and PP populations were similar.

At the end of the treatment, non-inferiority of the fixed versus the free combination, and superiority versus beclomethasone dipropionate alone, were shown in both the ITT and PP populations. Analyses are presented in Table 2. FEV_1 measured at clinics confirmed the non-inferiority of the fixed versus the free combination and its superiority to beclomethasone dipropionate alone in both the ITT and PP populations (Table 2; Webfigure 1).

Results of other lung function variables (namely FVC and FEF_{25-75}) were consistent with the primary endpoint in both the ITT and PP populations (results for the ITT population are presented in Webtable1).

Asthma control measures

During the 24 weeks of the study, the percentage of days and/or nights and/or complete days free of asthma symptoms, and percentage of days with asthma control were unchanged on beclomethasone dipropionate alone, but increased from baseline on both the fixed and free combinations. Moreover, values at the end of the study were significantly higher in the fixed combination group than in the free combination ($p < 0.05$) or beclomethasone dipropionate monotherapy ($p < 0.01$) groups (Webfigure 2). A post-hoc analysis confirmed a significantly higher percentage of days with asthma control in the fixed combination group than in the free combination ($p < 0.005$) or beclomethasone dipropionate monotherapy ($p < 0.0001$) groups (Webtable 2 and Fig. 3). Accordingly, salbutamol use fell significantly from baseline to end of treatment in both combination groups (mean differences from baseline: −0.29, 95% CI [−0.44, −0.14] and −0.36, 95% CI [−0.52, −0.19] puffs/day, for fixed and free combination, respectively). There was no change from baseline in the beclomethasone dipropionate monotherapy group.

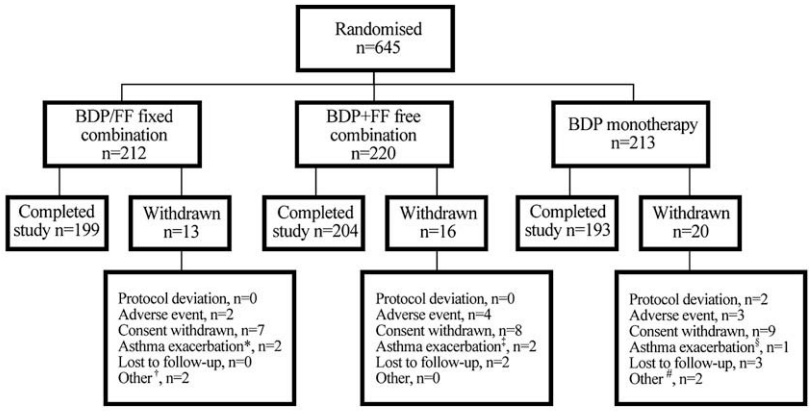

Figure 1 Patient disposition. BDP: beclomethasone dipropionate; FF: formoterol fumarate.

Table 1 Baseline patient characteristics

	BDP/formoterol fixed combination	BDP + formoterol free combination	BDP monotherapy
n (randomised)	212	220	213
Female/male [% female]	138/74 [65.1]	143/77 [65.0]	134/79 [62.9]
Mean age (years) ± SD	47.3 ± 12.31	47.4 ± 12.20	47.3 ± 13.05
Mean height (cm) ± SD	167.11 ± 8.822	166.97 ± 8.336	167.28 ± 8.548
Mean weight (kg) ± SD	74.41 ± 14.425	75.54 ± 15.451	74.87 ± 14.943
Morning PEF (l/min) ± SD	318.37 ± 109.29	310.26 ± 98.97	303.52 ± 105.73
FEV_1 (l) ± SD	1.95 ± 0.53	1.99 ± 0.56	1.97 ± 0.56
Mean FEV_1 (% predicted) ± SD	64.5 ± 10.79	66.2 ± 10.99	65.3 ± 10.64
Smoking history (*n*) [%]			
Never smoked	172 [81.1]	183 [83.2]	167 [78.4]
Former user	28 [13.2]	24 [10.9]	38 [17.8]
Smoker	12 [5.7]	13 [5.9]	8 [3.8]
Patients on inhaled corticosteroid/long-acting β2 agonist at entry (*n*)	104	104	102
Mean inhaled corticosteroid dose at entry (μg) ± SD[a]	658.79 ± 196.3	666.23 ± 215.1	681.45 ± 226.97
Daily SABA use (puffs/day) ± SD	0.65 ± 1.11	0.74 ± 1.40	0.57 ± 1.20
Days free of asthma symptoms (%) ± SD	21.2 ± 27.8	21.9 ± 28.1	25.6 ± 30.5
Nights free of asthma symptoms (%) ± SD	23.7 ± 29.9	26.9 ± 30.8	27.3 ± 31.9
Complete days free of asthma symptoms (%) ± SD	10.8 ± 21.2	11.9 ± 20.3	14.8 ± 24.4

BDP: beclomethasone dipropionate; FEV_1: forced expiratory volume in one second; FF: formoterol fumarate; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; PEF: peak expiratory flow; SABA: short-acting beta-agonist; SD: standard deviation.
[a] Mean of daily inhaled corticosteroid dose, irrespective of the type of inhaled corticosteroid.

A total of 280, 351 and 428 asthma exacerbations were reported in the beclomethasone dipropionate/formoterol fixed combination, beclomethasone dipropionate plus formoterol free combination and beclomethasone dipropionate monotherapy groups, respectively. Of these, 96, 145 and 160, respectively, were classified as severe. A post-hoc analysis showed that the number of events per patient was significantly lower ($p < 0.05$) on fixed combination compared with beclomethasone dipropionate monotherapy, and non-significant differences were observed versus the free combination (Table 3, Fig. 4). In particular, the overall number of exacerbations per patients was reduced by 35% with beclomethasone dipropionate/formoterol fixed combination versus BDP monotherapy. A minority of patients (3 subjects receiving the fixed combination, 8 on free combination and 9 with beclomethasone dipropionate alone) experienced exacerbations that required oral corticosteroid treatment.

Tolerability and safety outcomes

Similar numbers of patients reported treatment-related adverse events in each group (Webtable 3). The majority of treatment-related adverse events was mild in intensity and only very few patients were withdrawn due to adverse events (Fig. 1).

In the beclomethasone dipropionate plus formoterol free combination and beclomethasone dipropionate monotherapy groups, the analysis of morning serum cortisol levels and overnight urinary cortisol/creatinine ratios did not show any significant inhibition of adrenal function after 24 weeks of treatment compared with baseline. Conversely, a significant increase versus baseline ($p < 0.05$) in cortisol levels, which, however, has remained within the normal range, was observed in patients in the beclomethasone dipropionate/formoterol fixed combination group (Fig. 5). There were no patients with normal cortisol levels at baseline showing a decrease below normal range in the fixed combination group, while three patients in both the free combination and beclomethasone dipropionate monotherapy groups had a decrease of cortisol levels from

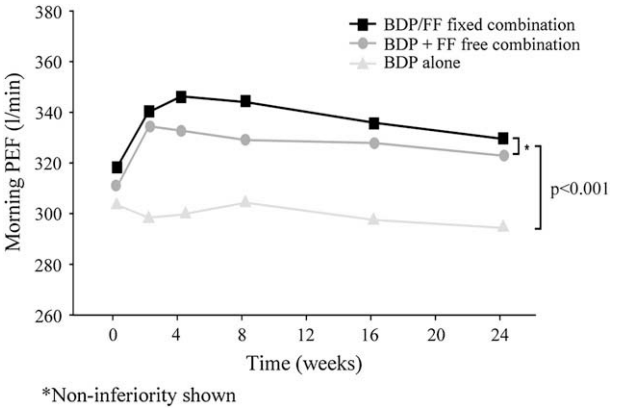

Figure 2 Morning peak expiratory flow rate (l/min) in ITT population. BDP: beclomethasone dipropionate; FF: formoterol fumarate; PEF: peak expiratory flow rate; ITT: intention to treat.

Table 2 Pulmonary function measures (morning pre-dose PEF and pre-dose FEV_1) at the end of treatment (study duration or at endpoint)

	Non-inferiority analysis[b] versus free combination				Superiority analysis versus BDP monotherapy				
	BDP/formoterol fixed combination	BDP + formoterol free combination	LS means difference (SE)	95% CI of difference	BDP/formoterol fixed combination	BDP monotherapy	LS means difference (SE)	95% CI of difference	*p* value
ITT population	$n = 211$	$n = 220$			$n = 211$	$n = 212$			
Morning PEF (l/min)[a]	339.64 (5.099)	332.37 (5.005)	7.27 (6.891)	−6.29, 20.82	339.64 (5.099)	309.41 (5.386)	30.22 (7.120)	16.22, 44.23	<0.001
FEV_1 at clinics (l)[a]	2.238 (0.0357)	2.222 (0.0347)	0.016 (0.0473)	−0.080, 0.109	2.238 (0.0357)	2.125 (0.0362)	0.113 (0.0475)	0.020, 0.206	0.018
PP population	$n = 179$	$n = 182$			$n = 179$	$n = 168$			
Morning PEF (l/min)[a]	339.46 (5.474)	335.96 (5.417)	3.49 (7.440)	−11.15, 18.14	339.46 (5.474)	312.78 (5.880)	26.68 (7.730)	11.46, 41.89	<0.001
FEV_1 at clinics (l)[a]	2.264 (0.0403)	2.290 (0.0396)	−0.026 (0.0537)	−0.130, 0.079	2.264 (0.0403)	2.129 (0.0419)	0.135 (0.0548)	0.028, 0.243	0.014

ANCOVA: analysis of covariance; BDP: beclomethasone dipropionate; CI: confidence interval; FEV_1: forced expiratory volume in one second; ITT: intention to treat; PEF: peak expiratory flow; PP: per protocol; SE: standard error.

[a] Non-inferiority margin of −20.0 l/min for morning PEF and −0.200 l for FEV_1 at clinics.

[b] Least squares mean (SE) at endpoint from the ANCOVA model with treatment and centre as factors and baseline value as covariate.

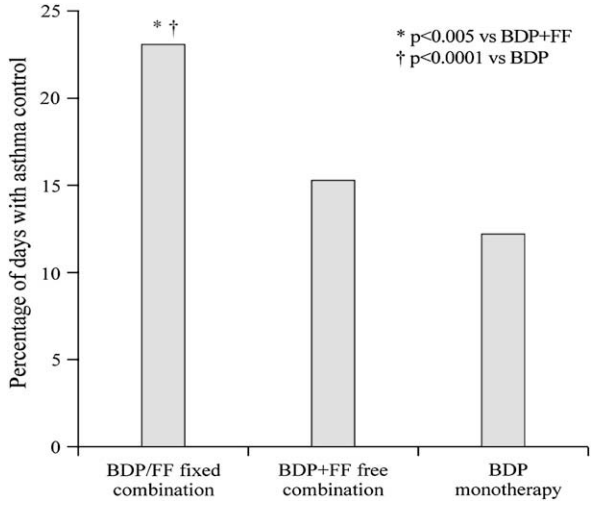

Figure 3 Percentage of days with asthma control in beclomethasone dipropionate/formoterol fixed combination, beclomethasone dipropionate plus formoterol free combination and beclomethasone dipropionate monotherapy groups (ITT population; post-hoc analysis). BDP: beclomethasone dipropionate; FF: formoterol fumarate; ITT: intention to treat. Asthma control was defined according to Zetterstrom et al.[13]

normal to below normal range. The ACTH stimulation test confirmed the lower inhibitory effect of the fixed combination on the hypothalamic-pituitary-adrenal axis, as the number of responders increased from baseline, while decreasing in both the comparator groups.

There was no variation over time of blood haematology and biochemistry results or ECG. Systolic and diastolic blood pressure (BP) and heart rate (HR) did not change over time.

Discussion

This study demonstrates that beclomethasone dipropionate/formoterol fixed combination is non-inferior to beclomethasone dipropionate and formoterol given via separate inhalers, and superior to beclomethasone dipropionate given alone, for the primary endpoint, morning PEF. Results were consistent in both the ITT and PP populations. As for asthma control, the fixed combination was superior to the two components given separately.

Randomised controlled studies of the two existing fixed-dose inhaled corticosteroid/long-acting β2 agonist combinations (budesonide/formoterol and fluticasone propionate/salmeterol) have demonstrated equivalence or non-inferiority to an inhaled corticosteroid plus a long-acting β2 agonist via separate inhalers, but failed to show any advantage over the equivalent combination of the separate components.[13,15–18]

The primary goal of the present study was to show that an extra-fine pMDI solution of a fixed combination of beclomethasone dipropionate/formoterol was non-inferior to the reference formulations of beclomethasone dipropionate and formoterol given via separate inhalers in improving lung function of patients with moderate to severe persistent asthma. This was confirmed for the

Table 3 Comparison between treatments for Asthma Exacerbations per patient

	BDP/formoterol fixed combination ($n = 211$)	BDP + formoterol free combination ($n = 220$)	p value	BDP/formoterol fixed combination ($n = 211$)	BDP monotherapy ($n = 212$)	p value
Overall exacerbations[a]	1.3 (1.92)	1.6 (2.34)	0.187	1.3 (1.92)	2.0 (2.69)	0.001
Mild-moderate exacerbations[a]	0.9 (1.37)	0.9 (1.69)	0.600	0.9 (1.37)	1.2 (2.29)	0.022
Severe exacerbations[a]	0.5 (0.98)	0.7 (1.30)	0.103	0.5 (0.98)	0.8 (1.48)	0.030

Statistical analysis performed by means of an ANCOVA model; BDP: beclomethasone dipropionate.
[a] Mean number of exacerbations per patient (SD). Evaluation performed on the intention to treat population.

primary outcome PEF and other secondary endpoints, such as FEV_1, FVC and $FEF_{25-75\%}$. These results are consistent with previous observations of other fixed combinations of a long-acting β2 agonist plus an inhaled corticosteroid.[17] Although the minimum dose required to achieve asthma control was not established in this study, previous randomised controlled trials confirmed the comparable efficacy and safety of beclomethasone dipropionate extra-fine HFA 400 μg and non extra-fine CFC 1000 μg daily.[9,10,19–21]

In this study different formulations of beclomethasone dipropionate and formoterol in a single inhaler versus the separate components were compared due to the limited market availability of extra-fine beclomethasone dipropionate HFA 100 μg pMDI and extra-fine formoterol 12 μg HFA pMDI at that time (2004–2005) and in the countries where the trial was carried out, as well as to technical difficulties in producing adequate dummy placebos.

However, the clinical validity of that result is assured by the fact that randomised clinical studies with the single components of beclomethasone/formoterol single inhaler had shown a similar efficacy in pulmonary function improvement between extra-fine beclomethasone HFA and CFC beclomethasone at 1:2.5 dose ratio,[9] as well as between extra-fine formoterol HFA pMDI and formoterol DPI Aerolizer™ at equivalent doses.[4] Indeed, in agreement with these findings, the present investigation confirmed that beclomethasone/formoterol fixed combination is able to provide lung function improvement comparable to the separate components.

In the present study, it was also observed that treatment with beclomethasone dipropionate/formoterol fixed combination was associated with significantly higher percentages of controlled days and nights and a better asthma control score than the administration of the two drugs separately or beclomethasone dipropionate alone. This is important because the control of asthma is the main therapeutic goal of asthma guidelines.[22] The control of asthma can be assessed using several methods and control questionnaires can be used.[22–24] We followed the method of Zetterstrom et al.[13] since it is found to be one of the most stringent ones and has been published in a randomised control trial. Furthermore, the beclomethasone dipropionate/formoterol treatment group experienced fewer overall and severe exacerbations than the free combination or beclomethasone dipropionate monotherapy groups, although only the comparison between beclomethasone dipropionate/formoterol fixed combination and beclomethasone dipropionate alone reached statistical significance (post-hoc analysis).

A meta-analysis indicated that the fluticasone propionate plus salmeterol combination offers the potential for increased clinical efficacy on PEF over concurrent use of the same doses of the two drugs.[25] However, this is the first observation in a randomised controlled trial of a difference in asthma control between an inhaled corticosteroid and a long-acting β2 agonist given as a fixed combination and via separate inhalers. The statistical relevance of this finding could be discussed since we used multiple comparisons, but, even using Bonferroni's correction, the results would still be significant for the control of asthma. This finding could be related to the lung deposition profile of beclomethasone/formoterol extra-fine formulation, which allows a distribution of the two drugs both in central and small airways.[5] Interestingly, *in vitro*, the two extra-fine components of beclomethasone dipropionate and formoterol in the combination investigated in this study show a comparable particle size distribution with the same fine particle fraction, suggesting *in vivo* potential for co-deposition throughout the entire bronchial tree.[26] The present study suggests that the synergistic effect of the two drug classes at various cellular types in the lungs[27] can be enhanced through their co-administration and consequent

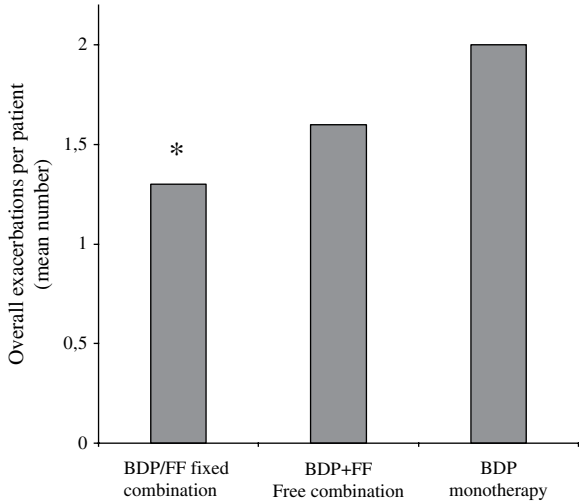

Figure 4 Overall asthma exacerbations per patient during the study (ITT population; post-hoc analysis). BDP: beclomethasone dipropionate; FF: formoterol fumarate; ITT: intention to treat.

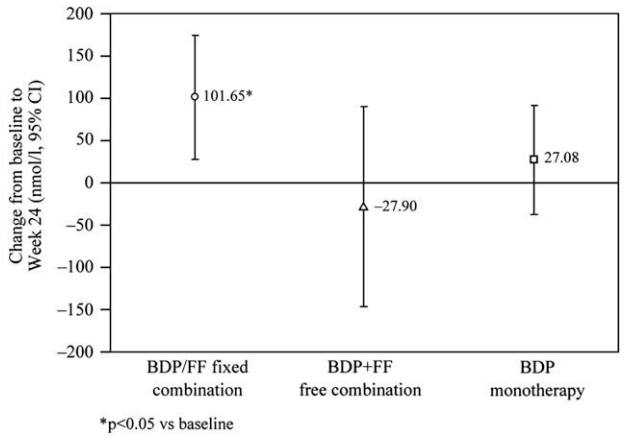

Figure 5 Change from baseline in mean morning serum cortisol (nmol/l). BDP: beclomethasone dipropionate; FF: formoterol fumarate.

co-deposition,[25] which might be favoured by the extra-fine formulation of the beclomethasone/formoterol combination. This could also explain the reason why such a difference in asthma control versus non-extra-fine combinations has been shown only when formoterol extra-fine is combined with an extra-fine corticosteroid in a single inhaler and not when administered alone.[28]

A well-established property of inhaled corticosteroid extra-fine formulations is the possibility of administering a lower nominal dose of corticosteroid, while maintaining the same clinical efficacy of their reference CFC formulations.[9,10,19–21] At the same time, adrenal function, measured through morning plasma cortisol levels, remained within the range of normality using both formulations.[20] In the present study, at the end of 24 weeks of treatment, morning serum cortisol levels increased significantly versus baseline with beclomethasone dipropionate/formoterol, but remained substantially unchanged in the beclomethasone dipropionate CFC plus formoterol DPI and beclomethasone dipropionate CFC alone groups. The lack of cortisol suppression observed with beclomethasone dipropionate/formoterol confirms its favourable safety profile compared with non-extra-fine formulations.

In conclusion, the present study demonstrates that beclomethasone dipropionate/formoterol fixed combination, an extra-fine HFA pMDI formulation containing beclomethasone dipropionate in combination with formoterol, offers at least similar efficacy and tolerability to beclomethasone dipropionate and formoterol delivered separately via CFC-containing MDIs and DPIs, respectively, and can be considered as a suitable therapeutic option for patients with moderate to severe persistent asthma. In addition, beclomethasone dipropionate/formoterol fixed combination is the first inhaled corticosteroid/long-acting β2 agonist single inhaler to show improved asthma control compared with corresponding doses delivered via separate inhalers. Further studies are needed to confirm this preliminary finding and assess the mechanisms through which this extra-fine inhaled corticosteroid/long-acting β2 agonist fixed combination may interfere with the pathophysiological process in asthma; this will potentially have consequent clinical implications.

Conflict of interest

G. Huchon has received grant funding from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer and Sanofi-Aventis and has also received honoraria for lecture or attended advisory boards from Chiesi, Boehringer Ingelheim, GlaxoSmithKline and Pfizer. H. Magnussen has no conflicts of interest; A. Chuchalin has no conflict of interest; L. Dymek has no conflict of interest; F. Bonnet Gonod (clinical study manager) is employed at Chiesi Farmaceutici; Research and Development, Paris site, France; J. Bousquet has received honorarium from Chiesi for lectures and advisory boards.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.rmed.2008.09.002.

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