



Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma

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ABSTRACT: The present study was designed to compare the fixed combination of beclomethasone and formoterol in a hydrofluoroalkane Modulite[®] (Chiesi Farmaceutici, Parma, Italy) pressurised metered-dose inhaler (pMDI), with a combination of budesonide and formoterol administered via a Turbuhaler[®] (AstraZeneca, Lund, Sweden) dry powder inhaler (DPI).

This was a phase III, multinational, multicentre, double-blind, double-dummy, randomised, two-arm parallel groups, controlled study design. After a 2-week run-in period, 219 patients with moderate-to-severe asthma were randomised to a 12-week treatment with beclomethasone 200 µg plus formoterol 12 µg *b.i.d.* delivered via a pMDI or budesonide 400 µg plus formoterol 12 µg *b.i.d.* delivered via a DPI.

The analysis of noninferiority on primary outcome, morning peak expiratory flow in the last 2 weeks of treatment, showed no difference between groups. A statistically significant improvement from baseline in lung function, symptoms and rescue medication use was observed in both groups at all time-points. No differences were observed between treatments in either rate of asthma exacerbations or frequency of adverse events.

The new fixed combination of beclomethasone and formoterol in hydrofluoroalkane Modulite[®] pressurised metered-dose inhaler is equivalent to the marketed combination of budesonide and formoterol in terms of efficacy and tolerability profile.

KEYWORDS: Asthma, beclomethasone, budesonide, combined therapy, extrafine, formoterol

International guidelines recommend the addition of a long-acting β_2 -agonist (LABA) to a low-to-medium dose of inhaled corticosteroids (ICS) in patients whose asthma is not fully controlled by ICS alone [1]. Several clinical trials have shown that the addition of a LABA to ICS is more beneficial than increasing the dose of ICS alone in terms of both symptom control and pulmonary function [2–6]. Treatment with an ICS/LABA combination in a single inhaler, with the same efficacy and safety profile as the two drugs given separately, may also produce a better adherence to treatment [7–9].

Beclomethasone dipropionate (BDP) is a widely used ICS with a favourable risk/efficacy profile [10]. BDP has been recently developed as an extra-fine formulation with hydrofluoroalkane (HFA) propellant, which has been shown to be effective in controlling asthma symptoms in both adults and children at a 2.5-fold lower daily dose as compared with chlorofluorocarbon-BDP [11–13].

The rationale behind an extra-fine formulation of an ICS is mainly based on accumulating evidence that in asthma the inflammation and remodelling process takes place in all parts of the airways, including peripheral bronchioles [14–20]. Since extra-fine formulations result in drug delivery to both central and peripheral airways [21], airway inflammation could be treated uniformly throughout the lower respiratory tract. A reduced ICS dose implies a lower systemic exposure and a lower overall risk of steroid-specific side-effects [22]. A new technology called Modulite[®] (Chiesi Farmaceutici, Parma, Italy), which uses the HFA-134a propellant, has been recently developed to obtain an extra-fine formulation of new drugs, as well as reformulation of pre-existing drugs in a pressurised metered-dose inhaler (pMDI) [23]. This technology has been used to develop the first fixed combination containing extra-fine BDP and formoterol (F) in HFA solution with a pMDI device.

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The main aim of the present study was to assess whether the efficacy and tolerability of the fixed combination BDP/F pMDI HFA Modulite® were noninferior when compared with those of a budesonide (BUD)/F Turbuhaler® (AstraZeneca, Lund, Sweden) dry powder inhaler (DPI) in patients with moderate-to-severe asthma whose symptoms were not controlled with ICS alone.

BUD/F combination has been selected as a comparator since it contains the same LABA, *i.e.* formoterol. As the extra-fine BDP formulation allows for a higher percentage of the nominal dose to be delivered to the lungs, the BDP dose used in the present study is half the BUD dose and, in accordance with the Global Initiative for Asthma (GINA) international guidelines, daily doses of 400 µg extra-fine BDP and 800 µg BUD are equivalent [1].

PATIENTS AND METHODS

Patients

The present study was carried out in 13 centres in Europe. Adult patients aged 18–65 yrs with moderate-to-severe persistent asthma and with a forced expiratory volume in one second (FEV₁) 50–80% of predicted normal values were eligible to take part in the study. All patients were previously treated with ICS at a daily dose ≤1,000 µg of BDP-equivalent and had asthma symptoms not adequately controlled. The lack of adequate control can be defined as: presence of daily asthma symptoms more than once a week, night-time asthma symptoms more than twice a month and daily use of short-acting β₂-agonists. Thus, as these patients were not controlled by moderate-to-high doses of ICS according to international guidelines [1], they were classified as moderate persistent asthmatics. These findings were based on recent medical history and were to be confirmed in the 2-week run-in period.

Patients satisfying any of the following criteria were excluded from the study: chronic obstructive pulmonary disease; current or ex-smokers (≥10 pack-yrs); severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; three or more courses of oral corticosteroids or hospitalisation due to asthma in the previous 6 months; treatment with LABAs, anticholinergics or antihistamines in the previous 2 weeks, and/or with topical or intra-nasal corticosteroids and leukotriene antagonists in the previous 4 weeks; and change of ICS dose in the previous 4 weeks. Patients with asthma exacerbation during the run-in period did not enter the treatment phase. Moreover, patients with an increase in peak expiratory flow (PEF) >15%, as compared with values measured in the screening visit, after 2 weeks run-in treatment with ≤1,000 µg daily BDP equivalent, were not randomised. This cut-off value was taken as an indicator of the positive response to ICS suggesting that they might not require combination therapy.

The study was performed in accordance with the Good Clinical Practice guidelines recommended by the International Conference on Harmonization of Technical Requirements. The protocol was approved by the institutional review board of each centre and written informed consent was obtained from each participant prior to study initiation.

Study design

The study was designed to evaluate the noninferiority of BDP/F combination *versus* equipotent doses of the combination of BUD/F.

The present study was a phase III, multinational, multicentre, double-blind, double-dummy, randomised, two-arm parallel groups, controlled study design. Enrolled patients entered a 2-week run-in period before being randomised to study groups. Inhaled rescue salbutamol was permitted at any time but ≥6 h before pulmonary function tests (PFT). Oral corticosteroids were permitted only in the case of asthma exacerbations. Inhaled or oral sodium cromoglycate or nedocromil sodium and theophyllines taken at study entry were permitted at a constant dose throughout the study period. ICS were continued at an unchanged dose during the run-in period, while all the other anti-asthma medications were not permitted at any time.

At the end of the run-in period, symptoms and rescue medication use were reviewed and patients whose asthma was not adequately controlled were randomised to the 12-week treatment phase with BDP/F 100/6 µg pMDI (FOSTER™; Chiesi Farmaceutici) or BUD/F 200/6 µg DPI (Symbicort® Turbuhaler®; AstraZeneca). Both study drugs were administered in two inhalations *b.i.d.* (morning and evening) to obtain daily doses of 400/24 µg BDP/F or 800/24 µg BUD/F. As the formulation of the study drugs differed, patients from each group were also given placebo inhalers of the respective pMDI and DPI devices to ensure the double-blind (double-dummy) design. Devices and respective placebo were identical in shape and colour and patients were instructed to take two inhalations from each device in the morning and in the evening.

Patients were asked to visit the clinic six times at the following scheduled times: study entry (visit 1, beginning of the run-in period), end of run-in period/start of treatment period (visit 2, randomisation) and after 2, 4, 8 and 12 weeks of treatment (visits 3, 4, 5 and 6).

Protocol outcome measures

The primary outcome variable was morning pre-dose PEF measured by patients, at least 12 h after the previous evening dose, in the last 2 weeks of the treatment period (weeks 11–12). PFT were performed at each visit before study drug intake at least 12 h after the previous evening dose, meaning that the morning dose of study drug was taken on-site after PFT. The following PFT were measured in accordance with standard procedure [24]: FEV₁, forced vital capacity (FVC), PEF and mid-expiratory flow at 50% vital capacity (MEF_{50%}). The best of three values was used for analysis.

Patients used a portable flow meter (Piko-1; Qubisoft, Padova, Italy), in compliance with the 2004 American Thoracic Society standard, to measure their pre-dose morning and evening PEF and FEV₁. The best of three readings was used for data analysis. Patients recorded asthma symptom scores and rescue salbutamol intake *b.i.d.* (in the morning for night-time and in the evening for daytime) on a diary card [5]. The percentage of symptom-free and salbutamol-free days (*i.e.* without 24-h symptoms or without use of salbutamol) was calculated.

The occurrence of asthma exacerbations was evaluated at all post-baseline visits and exacerbations were categorised as mild, moderate or severe as previously described elsewhere [4].

Adverse events (AEs) were reported throughout the study period. Vital signs (cardiac frequency and blood pressure) were also measured at all visits. A 12-lead ECG with measurement of the corrected QT (QTc) interval was performed at baseline and at the end of the study. Patients recorded their *b.i.d.* intake of study drugs on diary cards. A 75–125% range of scheduled administrations was considered as adequate for a satisfactory level of adherence.

Statistics

The present study was designed to evaluate the noninferiority of BDP/F *versus* BUD/F. The sample size calculation was made by defining the limit for noninferiority as the lower limit of the unilateral 97.5% confidence interval (CI) for the difference between least square means (LSMs) of morning PEF being ≥ -20 L·min⁻¹. To estimate a SD of 45 L·min⁻¹ and an expected difference between means equal to zero, a total of 90 patients in each group were required to have >80% power for satisfying the aforementioned hypothesis [25]. BDP/F was defined as noninferior to BUD/F if the lower limit of the unilateral 97.5% CI for the difference between LSMs was ≥ -20 L·min⁻¹.

Data analysis was carried out in the following populations: safety population (SAF), defined as all randomised patients for which there was evidence of drug intake; intention-to-treat (ITT) population, *i.e.* all randomised patients who received at least one dose of study drug and with post-baseline data; modified ITT (mITT) population, *i.e.* excluding data measured in the 30 days after the intake of oral corticosteroids for asthma exacerbation; and per-protocol (PP) population, *i.e.* all patients in the ITT analysis set without major protocol violations (*e.g.* poor compliance to study drug or procedures, use of nonpermitted medications). Post-baseline missing values were replaced with the “last observation carried forward method”. The same method was used to replace data measured in the 30 days after the intake of oral corticosteroids for the mITT population.

Baseline values were the mean values of the last week of the run-in period for variables recorded daily by patients on diary

cards and values measured at the end of the run-in visit for variables measured at clinics. Biweekly means were also calculated during the entire study period for variables recorded on diary cards. Demographic and baseline characteristics were summarised by means of descriptive statistics (number of subjects, mean \pm SD, median, minimum and maximum) or frequency distributions (number and percentage), as appropriate. For the primary efficacy analysis, the one-sided 97.5% CI for the difference between BDP/F and BUD/F in final PEF recorded by patients into diary cards was used in order to demonstrate the noninferiority. An ANCOVA model with terms for treatment, geographic region and baseline value as covariate was used. For the secondary efficacy variables, the same ANCOVA model was used.

The number of patients with asthma exacerbation in the two groups was summarised by means of frequency distribution and a Chi-squared test was used to compare the two treatment groups. Time to first exacerbation was compared using Kaplan–Meier curves. The number of patients with AEs that occurred during the treatment period was summarised by means of frequency distribution. Differences between treatment groups were evaluated using a Chi-squared test or two-tailed Fisher’s exact test. The results of the ECG were presented in terms of normal/abnormal findings, while QTc interval was analysed using the 95% CI for the final values from an ANCOVA model.

RESULTS

Patient flow and baseline characteristics are shown in figure 1 and table 1. In total, 240 patients were screened and 219 were randomised, while 21 were considered not eligible. A total of 109 (47.8%) patients were randomly assigned to the BDP/F arm and 110 (52.2%) to the BUD/F arm. Six patients in the BDP/F group and 13 patients in the BUD/F group were withdrawn from the study, and 103 patients in the BDP/F group and 97 patients in the BUD/F group completed the 3 months study period. One patient in the BUD/F group did not show intake of study drug, thus the SAF included 218 patients (109 in each group). Two BDP/F-treated patients did

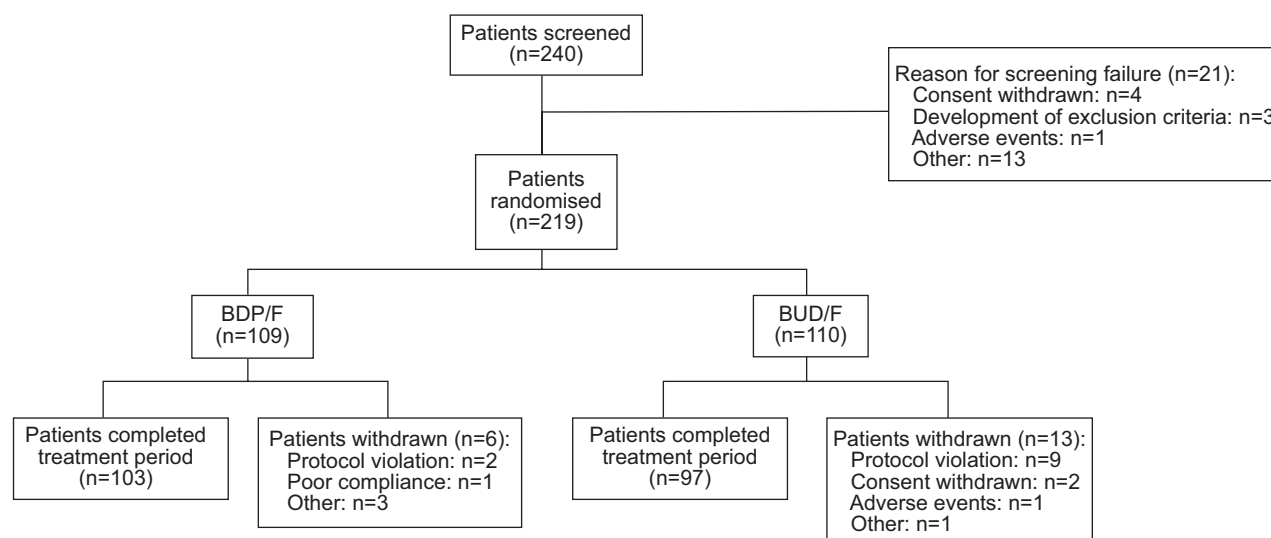


FIGURE 1. A flow-chart representing patient flow. BDP/F: beclomethasone/formoterol; BUD/F: budesonide/formoterol.

TABLE 1 Baseline characteristics of the two groups

	BDP/F [#]	BUD/F
Male	45 (42.1)	46 (42.2)
Female	62 (57.9)	63 (57.8)
Age yrs	43.4±12.3	46.0±11.1
Weight kg	72.2±12.9	75.6±16.3
Height cm	168.8±9.6	168.7±9.8
Allergies	69 (64.5)	70 (64.2)
ICS dose µg BDP equivalent	787.9±257.2	808.0±262.7
Time from first diagnosis yrs	11.8±9.5	12.4±10.4
FEV₁ % pred	70.5±10.7	69.3±9.7
FEV₁ L	2.30±0.71	2.21±0.64
FEV₁ % change in reversibility test	23.6±10.1	26.5±12.1
Morning PEF L·min⁻¹	308.9±106.6	305.2±100.0
Evening PEF L·min⁻¹	317.5±112.1	315.0±98.5

Data are presented as n (%) and mean±SD. BDP/F: Beclomethasone/formoterol; BUD/F: budesonide/formoterol; ICS: inhaled corticosteroids; FEV₁: forced expiratory volume in one second; % pred: % predicted; PEF: peak expiratory flow. The p-values were considered nonsignificant between groups for all comparisons. [#]: two patients were excluded from the intention-to-treat population due to missing post-baseline data.

not have post-baseline data and were excluded from the ITT analysis set. Four patients in the BDP/F group and 10 in the BUD/F group were also excluded from the PP analysis due to major protocol violation. Considering the small difference in the number of patients in the ITT and PP populations (table 2), results are shown for the ITT population only.

Baseline data (table 1) of the two groups were well matched in terms of demographics, pulmonary function, symptoms and

time from first asthma diagnosis. The two groups had comparable baseline asthma severity and there were no differences between groups in mean ICS dose.

Patient compliance in both groups was similar, with mean percentage of administered drug $96.8 \pm 3.2\%$ and $95.6 \pm 7.8\%$ in the BDP/F and BUD/F groups, respectively.

EFFICACY

Lung function

With respect to the primary outcome, morning pre-dose PEF during the last 2 weeks of the treatment period, the difference between adjusted means (LSMs) of the BDP/F group ($338.3 \text{ L} \cdot \text{min}^{-1}$) and the BUD/F group ($337.8 \text{ L} \cdot \text{min}^{-1}$) was $0.49 \text{ L} \cdot \text{min}^{-1}$. The 97.5% unilateral CI for this difference was -11.97 , which was within the pre-specified limit of $-20 \text{ L} \cdot \text{min}^{-1}$, thus showing that BDP/F was noninferior to BUD/F. Moreover, the 95% bilateral CI for the difference between LSMs was -11.97 – 12.95 .

When compared with the baseline, both groups showed marked and significant improvements in morning PEF; the mean increases from baseline to end-point were $29.43 \pm 52.8 \text{ L} \cdot \text{min}^{-1}$ (95% CI: 19.31 – 39.54) and $28.63 \pm 43.4 \text{ L} \cdot \text{min}^{-1}$ (20.39 – 36.87) in the BDP/F and BUD/F groups, respectively (fig. 2). Similarly, no significant difference between groups was observed in evening PEF at the end of treatment and a significant increase as compared with baseline was shown in both groups. The mean improvements in the final 2-week period were $27.50 \pm 53.35 \text{ L} \cdot \text{min}^{-1}$ and $27.43 \pm 39.39 \text{ L} \cdot \text{min}^{-1}$ in the BDP/F and BUD/F groups, respectively (95% CI for the difference between LSMs: -12.26 – 11.94). A significant increase *versus* baseline was shown in daily FEV₁ measured by patients in both groups with no significant difference between groups at the end of treatment.

TABLE 2 Populations for analysis

	BDP/F	BUD/F
Randomised	n=109	n=110
SAF	n=109	n=109
		One patient had no evidence of drug intake (randomised and immediately withdrawn, the diary card was not filled in)
ITT	n=107	n=109
	Two patients had no post-baseline data for the primary efficacy variable	
m-ITT	n=107	n=109
PP	n=103: four patients excluded	n=99: 10 patients excluded
	Two patients due to an increase >20% in PEF at visit 2 with respect to visit 1	Four patients due to an increase >20% in PEF at visit 2 with respect to visit 1
	Two patients had a time window >5 days between the last two visits	
	One patient had no intake of salbutamol for >5 days during the run-in period	Three patients due to poor compliance with study medication
		Two patients had no intake of salbutamol for >5 days during the run-in period
		One patient due to significant and unreliable discrepancies between pulmonary function tests, i.e. FEV ₁ and PEF, monitored daily by patients and measured at sites
		One patient due to study drug exposure <2 weeks

BDP/F: beclomethasone/formoterol; BUD/F: budesonide/formoterol; SAF: safety population; ITT: intention-to-treat population; m-ITT: modified ITT; PP: per-protocol population; PEF: peak expiratory flow; FEV₁: forced expiratory volume in one second. Patients can have more than one reason for exclusion.

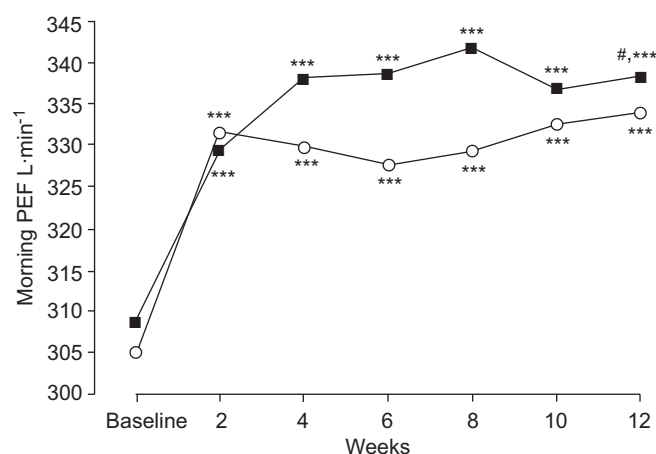


FIGURE 2. Mean morning peak expiratory flow (PEF) measured daily by patients in the two groups. ■: Beclomethasone/formoterol; ○: budesonide/formoterol. #: *p*=nonsignificant between treatments. ***: *p*<0.001 versus baseline.

The results of the PFT measured at the on-site visits (FEV₁, FVC, PEF and MEF₅₀%) are shown in table 3 and figure 3. Statistically significant improvements from baseline were found in both groups from week 2 onwards in all lung function parameters, with no significant difference between groups at the end of treatment.

Symptoms

Clinical symptoms' scores significantly decreased from baseline in both groups from the first 2-week period onwards, as well as daily use of rescue salbutamol, with no significant difference between groups at the end of treatment. The mean decreases from baseline to end-point (weeks 11–12) in daytime symptoms' scores were -0.93 ± 0.78 U and -0.86 ± 0.86 U in the BDP/F and BUD/F groups, respectively (*p*<0.001 versus baseline). The mean changes from baseline to the end of treatment in night-time symptoms' score were -0.73 ± 0.75 U and -0.66 ± 0.84 U in the BDP/F and BUD/F groups, respectively (*p*<0.001 versus baseline). Daily use of rescue medication significantly decreased from 2.16 ± 1.15 puffs·day⁻¹ in the last week of run-in to 0.76 ± 0.92 puffs·day⁻¹ in the last 2 weeks of

treatment period in the BDP/F group, and from 2.28 ± 1.50 to 0.87 ± 1.04 puffs·day⁻¹ in the BUD/F group.

The mean percentages of symptom-free days and of days without need of rescue salbutamol over the entire treatment period are shown in figure 4. As can be seen, there are no significant differences between the two groups, but statistical significance is reached in both groups when the data are compared with baseline (*p*<0.001).

Exacerbations

Asthma exacerbations occurred in 29 patients, 17 (15.9%) in the BDP/F group and 12 (11.0%) in the BUD/F group. No severe exacerbations occurred, while moderate exacerbations requiring one course of oral corticosteroids were reported only in two patients in each group. The ratio of days of exacerbation to days of exposure was 0.013 ± 0.04 in the BDP/F group and 0.023 ± 0.11 in the BUD/F group (*p*=0.38), *i.e.* not statistically different. The time (median (range)) to the first exacerbation was 29 (1–77) days in the BDP/F group and 24 (1–69) days in the BUD/F group (*p*=0.342 between groups in the Kaplan–Meier estimate for survival curves).

Tolerability

No significant differences were observed between the two treatment groups as reported in table 4. AEs were reported by 15 (13.8%) patients in the BDP/F group and 18 (16.5%) in the BUD/F group (*p*=nonsignificant), but none were classified as serious. Only one patient in the BUD/F group discontinued the study due to throat pain, palpitations and hand tremors.

No changes in blood pressure were observed in either group during the study period. A small but significant increase in cardiac frequency was observed only at visit 3 in the BUD/F group (1.67 ± 6.71 bpm; 95% CI: 0.39–2.95). No other significant changes were observed in either group. No evidence of ECG changes or QTc interval prolongation was reported in either group.

DISCUSSION

In the present study, the effects of the new pMDI containing the BDP/F combination were compared with those of the DPI Turbuhaler® containing combined BUD/F in moderate-to-severe

TABLE 3 Pulmonary function tests in the two groups measured at the on-site visits[#]

Measure	Group	Week 2	Week 4	Week 8	Week 12	p-value
FEV ₁ L	BDP/F	0.26 ± 0.38	0.29 ± 0.46	0.33 ± 0.49	0.28 ± 0.47	0.354
	BUD/F	0.33 ± 0.41	0.37 ± 0.44	0.40 ± 0.44	0.33 ± 0.44	
FVC L	BDP/F	0.23 ± 0.47	0.27 ± 0.53	0.33 ± 0.54	0.26 ± 0.52	0.557
	BUD/F	0.26 ± 0.49	0.31 ± 0.53	0.34 ± 0.52	0.21 ± 0.52	
PEF L·min ⁻¹	BDP/F	52.29 ± 72.81	59.99 ± 74.03	63.66 ± 74.28	56.04 ± 72.97	0.806
	BUD/F	55.71 ± 74.35	57.47 ± 71.25	64.36 ± 75.94	53.16 ± 77.29	
MEF ₅₀ L·s ⁻¹	BDP/F	0.42 ± 0.66	0.43 ± 0.71	0.48 ± 0.84	0.43 ± 0.82	0.512
	BUD/F	0.48 ± 0.69	0.53 ± 0.75	0.63 ± 0.86	0.50 ± 0.80	

Data are presented as mean ± SD, unless otherwise stated. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; MEF₅₀: mid-expiratory flow at 50% vital capacity; BDP/F: beclomethasone/formoterol; BUD/F: budesonide/formoterol. The p-values refer to comparison between groups in final values (week 12, last visit). #: mean changes from baseline (intention-to-treat population)

asthma patients over a 3-month period. The results of the study showed that BDP/F pMDI 400/24 $\mu\text{g}\cdot\text{day}^{-1}$ was as effective as BUD/F 800/24 $\mu\text{g}\cdot\text{day}^{-1}$ in morning PEF in the last 2 weeks of treatment period. This was also confirmed by the other lung function and clinical efficacy variables evaluated.

The two treatment groups were well matched in terms of asthma severity and baseline values of all outcome measures evaluated. The population in both treatment groups had a real potential to improve from baseline to end-point, as demonstrated by increases in lung function during the course of the study, showing real equivalence between the two study treatments. In addition, reassurance is provided that the equivalence was not due to lack of efficacy for both treatments or to maximal lung function potential already being present prior to dosing [26]. The increases obtained in both groups in the primary efficacy variable were both statistically and clinically significant, supporting the fact that the present study had the potential to detect any differences between groups.

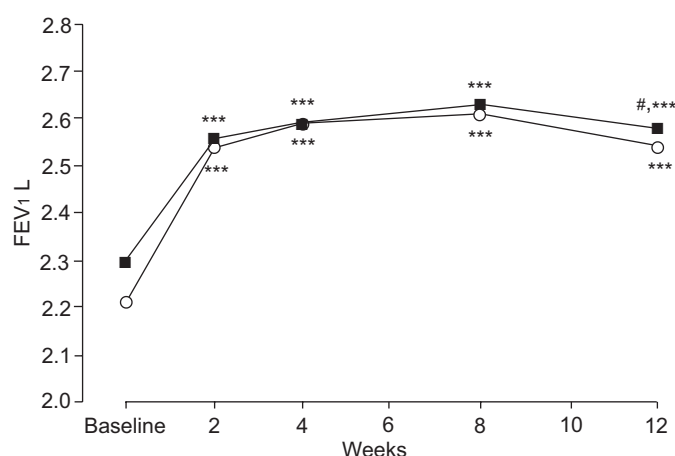


FIGURE 3. Forced expiratory volume in one second (FEV₁) measured at clinics in the two groups. ■: beclomethasone/formoterol; ○: budesonide/formoterol. #: p=non-significant between treatments. ***: p<0.001 versus baseline.

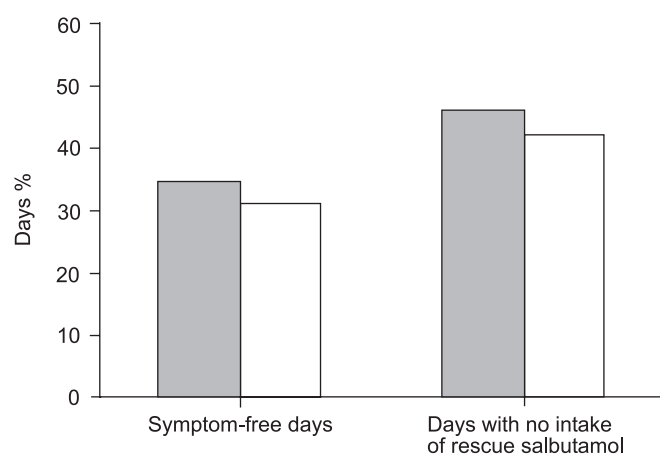


FIGURE 4. Percentage of symptom-free days and of days with no intake of rescue salbutamol in the treatment phase. ■: Beclomethasone/formoterol; □: budesonide/formoterol. p=non-significant in the comparisons between groups.

The results of the other pulmonary function parameters, either measured by patients twice daily or measured at the site visits, showed comparable increases in the two groups, with no significant differences between treatments being observed. Comparable improvements in the two groups were also observed in the assessment of clinical symptoms and in the use of rescue salbutamol, which significantly decreased from baseline with no difference between groups. Similarly, no difference was found in the rates of asthma exacerbations and in time to first exacerbation. However, it was not possible to treat exacerbation rate as a primary end-point in the present study, since exposure time was limited and more patients are needed in order to detect potential differences between treatments.

The two combination treatments showed similar tolerability profile. During the 3-month study period, the new BDP/F combination was at least as well tolerated as the standard combination containing BUD, an ICS that exhibits low systemic activity [27]. Worsening of asthma and upper/lower respiratory tract infections were the most common events, likely due to seasonal affections rather than to drug tolerability concerns as suggested by their similar frequency in the two groups. No evidence of detrimental effects on ECG or QTc interval prolongation, a potential cardiovascular effect of β_2 -adrenergic drugs [28], was reported.

Both patient compliance and long-term pulmonary function benefit from single inhaler treatment with LABA and ICS [3, 29]. This treatment regimen allows the patient to perceive the relief of symptoms provided by the LABA, thus enhancing compliance, while receiving a maintenance dose of the ICS that acts on the chronic airways inflammation, hence improving disease control. Moreover, the use of fixed combinations reduces the direct and indirect treatment costs compared with the administration of the same drugs given by separate inhalers [9]. Taking into consideration the evidence-based advantages offered by the combined administration of LABA/ICS, the new BDP/F combination is a valid alternative in the treatment of asthma. In view of the fact that BDP delivered *via* a pMDI is an established ICS used worldwide, the availability of a new BDP/F combination may also allow patients not

TABLE 4 Adverse events observed in >2% of patients, numbers and percentages in the population analysed for safety

Adverse event	BDP/F	BUD/F
Subjects n	109	109
Worsening of asthma	16 (14.7)	12 (11.0)
Respiratory tract infections	6 (5.5)	7 (6.4)
Bronchitis	7 (6.4)	5 (4.6)
Nasopharyngitis	2 (1.8)	5 (4.6)
Herpes simplex infection	3 (2.8)	1 (0.9)
Tremor	1 (0.9)	3 (2.8)

Data are presented as n (%), unless otherwise stated. BDP/F: beclomethasone/formoterol; BUD/F: budesonide/formoterol.

adequately controlled with ICS alone to continue using the same device with the same inhalation technique and the same molecule.

Although the daily nominal dose of BDP used in the present study was two-fold lower than the equipotent daily dose of BUD present in the BUD/F combination, it cannot be claimed that extrafine BDP was twice as potent as BUD, as the minimum dose required to achieve asthma control was not established.

Similarly, the difference in corticosteroids dose between the two treatment groups does not imply a difference in systemic exposure, as this depends not only on the nominal dose but also on the amount of drug reaching the lungs and on the pharmacokinetics properties of the two corticosteroids. Previous studies indicated that the fine particle dose of BUD, *i.e.* the amount of drug supposed to reach the lower airways after one inhalation of DPI combination 200/6 µg BUD/F, is 46.0 µg [30], whereas the fine particle dose of BDP, after one inhalation of extra-fine 100/6 µg BDP/F, is 34.5 µg [31].

In conclusion, the present study is the first to compare the efficacy and safety of a new pMDI containing the combination BDP/F with a standard combination of BUD/F in patients with moderate-to-severe asthma whose symptoms were not adequately controlled with ICS alone. The results have shown that the two tested combinations produced equivalent benefits in lung function and in clinical symptoms, and led to a significant decrease in the use of rescue medications. In addition, no significant differences were observed between groups in terms of rates of asthma exacerbation and/or the need of additional prevention therapy.

The present study shows that the new pressurised metered-dose inhaler containing the beclomethasone/formoterol combination is a valid alternative for the treatment of asthma.

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