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Stepping-across controlled asthmatic patients to extrafine beclometasone/formoterol combination

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ABSTRACT

Background: Asthma management focuses on achieving and maintaining asthma control. Few studies have assessed whether complete and sustained asthma control is maintained in clinical practice after stepping-across ICS/LABA fixed combinations. Aim of this double-blind, double-dummy, randomized, parallel group, controlled study was to demonstrate clinical equivalence between equipotent doses of extrafine beclometasone/formoterol (BDP/F) pMDI and fluticasone/salmeterol (FP/S) Diskus® in maintaining lung function and asthma control.

Methods: A total of 416 asthmatic patients already controlled with FP/S 500/100 μg/day (Diskus®, pMDI or separate inhalers) were randomized to a 12-week treatment with extrafine BDP/F 400/24 μg/day pMDI or FP/S 500/100 μg/day Diskus®. Pre-dose 1-s forced expiratory volume (FEV_1) was the primary efficacy variable; secondary variables included asthma control questionnaire (ACQ-7) and $FEV_1$0-1 h area under the curve (FEV_1AUC_{0-1h}). Safety was assessed through adverse events monitoring and vital signs.

Results: After 12 weeks of treatment, pre-dose FEV_1 did not differ between treatments (difference between means 0.01 L; 95% CI −0.03–0.06 L) with no significant changes from baseline in both groups ($p = 0.726$ and $p = 0.783$ in BDF/F arm and FP/S, respectively). ACQ-7 score showed that control was maintained after stepping-across to extrafine BDP/F. FEV_1AUC_{0-1h} was significantly higher in BDP/F arm at the beginning ($p = 0.004$) and at the end of the 12-week treatment period ($p = 0.019$). No safety issues were reported in both groups.

Conclusions: Patients previously controlled with FP/S in any device formulation can effectively step-across to extrafine BDP/F pMDI, maintaining lung function and asthma control with a 5-min onset of action.

1. Introduction

Asthma represents a global public health issue due to high prevalence rates in the general population (ranging from 1% to 18% of the population in different countries) and several studies now indicate that the impact on public health is even more severe due to the difficulty in achieving full disease control with available therapies [1,2]. Indeed, achieving and maintaining asthma control are the focus of current asthma treatment guidelines [3–5].

To date, there are many definitions for "asthma control", and criteria used in its assessment varied widely from study to study [6].

One definition of "asthma control" is the extent to which the various features of the disease such as symptoms, airway obstruction, airway hyperresponsiveness and inflammation, are reduced or removed by treatment. There is increasing recognition of the importance of asthma control over time beyond patient's recent clinical status (e.g. symptoms, night-time awakenings, reliever use, and lung function).

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The concept of representing control as a numeric score is attractive and has been adopted by several research groups. Several numerical measures have been proposed such as the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT) [7–10]. Comparisons between such composite scores are difficult because each uses a different "gold standard" for defining optimal asthma control, and they have been directly compared only in a few studies [11–13].

To date, one of the most widely used tools for assessing asthma control in clinical trials is the ACQ, which has been validated in separate studies [7,14,15] and for which the minimal important difference has been established. The optimal cut-point for "Well-Controlled" disease using the ACQ has been set to less than or equal to 0.75, while a value equal to 1.50 or greater confirms "not Well-Controlled" asthma [16].

Several studies have shown that in moderate and severe asthma, the combination of an inhaled corticosteroid (ICS) and a long acting β2-agonist (LABA) provides superior asthma control, better lung function, and fewer exacerbations than doubling the ICS dose [17,18]. Different ICS/LABA fixed combination therapies have therefore been developed or are under development. In particular, beclometasone/formoterol (BDP/F) combination delivers extrafine particles of BDP (100 μg) and F (6 μg) per actuation, which are approximately half the size compared to other available fixed combinations, allowing uniform distribution throughout the entire bronchial tree [19,20]. There is increasing evidence of a correlation between small airways impairment and poor asthma control [21]. Therefore, small airways are a key target region for pharmacological treatments in asthma [22].

While different studies have demonstrated the effectiveness of ICS/LABA fixed combination in achieving asthma control, a literature search using Medline, Pre-Medline, Embase, and Cochrane Library databases between 1991 and January 2011 identified no studies that assessed whether asthma control is maintained after stepping-across (equivalent ICS dose) to another ICS/LABA fixed combination in clinical practice.

The extrafine beclometasone/formoterol (BDP/F) pressurized metered dose inhaler (pMDI) formulation assessed in this study is a solution using a chlorine-free hydrofluoroalkane HFA-134a propellant and developed to provide stable and uniform dose delivery, thanks to the non-volatile content of this solution formula, the actuator orifice geometry, metered volume and vapour pressure of the propellant which allows a quite small fraction of the cloud with fine particle dose <5 μm [23,24]. This pMDI formulation produces a slow moving particle cloud over a relatively long period of time, which may make co-ordination of inspiration with drug delivery easier for the patient and may improve lung deposition and reduce oropharyngeal deposition [23,24]. In particular, BDP/F combination delivers extrafine particles of BDP (100 μg) and F (6 μg) per actuation, which are approximately half the size compared to other available fixed combinations, allowing uniform distribution throughout the entire bronchial tree and high lung deposition (31% of the emitted dose in asthmatic patients) (19).

The risk of losing asthma control from changing the pharmacotherapy of controlled asthmatic patients has been previously reported [25,26], but no randomized, controlled clinical trials are available. Therefore, it may be important to providing reassurance in terms of device, molecule, strength and dosing schedule for an evidence-based decision regarding specific pharmacotherapy change.

This study was designed to demonstrate the clinical equivalence between equipotent doses of extrafine BDP/F pMDI (FOSTER®, Chiesi Farmaceutici, Italy) and fluticasone/salmeterol (FP/S) dry powder for inhalation (DPI) (Seretide® Diskus®, GSK, UK) in maintaining asthma control in terms of lung function, clinical symptoms and use of rescue medication in patients already controlled with fluticasone plus salmeterol 500/100 μg daily delivered either via DPI or pMDI.

2. Patients and methods

This was a multinational, multicentre, double-blind, double-dummy, randomized, parallel group, controlled clinical study carried out in 41 centres in France, Germany, The Netherlands, and Spain (ClinicalTrials.gov Identifier NCT00901368).

A total of five clinic visits were performed during the study: a screening visit (Visit 1), followed by a 4-week run-in period, and four study visits (Visits 2, 3, 4, and 5) every four weeks (Fig. 1).

2.1. Patients

Adult patients aged 18–65 years, with controlled asthma in the previous week before study entry, were eligible for the study. All patients were treated with fluticasone propionate 500μg + salmeterol 100 μg daily, delivered either via a dry powder inhaler (DPI), or pressurized metered dose inhaler (pMDI), or separate inhalers for ≥4 weeks before the screening visit and had features of controlled asthma according to GINA guidelines [27] defined as: forced expiratory volume in 1 s (FEV_1) > 80% of predicted normal values or personal best, no nocturnal symptoms or awakenings, no exacerbations, no limitations of activities, and daytime symptoms and use of rescue medication ≤2 days per week in the last 4 weeks. These findings were to be confirmed at the end of the 4-week run-in period.

Patients satisfying any of the following criteria were excluded from the study: diagnosis of Chronic Obstructive Pulmonary Disease (COPD) as defined by Chronic Obstructive Lung Disease (GOLD) guidelines; history of near fatal asthma; evidence of severe asthma exacerbation or symptomatic infection of the lower airways in the previous six months; three or more courses of oral corticosteroids or hospitalization due to asthma during the previous 6 months; patients treated with leukotriene antagonists during the previous 4 weeks; current smokers or recent (less than one year) ex-smokers defined as smoking at least 15 packs/year; patients with asthma exacerbations during the run-in period will also be excluded from the study.

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.

2.2. Assessments

2.2.1. Efficacy

The primary efficacy variable was pre-dose morning FEV_1 (L) at the end of the 12-week treatment period. Secondary efficacy variables were PEF, FVC, $FEF_{25-75\%}$, FEV_1% predicted normal and Area Under the Curve in the first hour post-dose (FEV_1AUC_{0-1h}), ACQ-7 score, use of rescue medication.

Percentages of patients with controlled, partly controlled or uncontrolled asthma (according to GINA guidelines), days without asthma symptoms (%), days without use of rescue medication (%) and daily asthma symptoms' score were also monitored and assessed from diary cards.

2.2.2. Safety

Safety was assessed throughout the study period by monitoring adverse events (AEs), adverse drug reactions (ADRs), vital signs (heart rate and blood pressure), centralized ECG and clinical laboratory assessments.

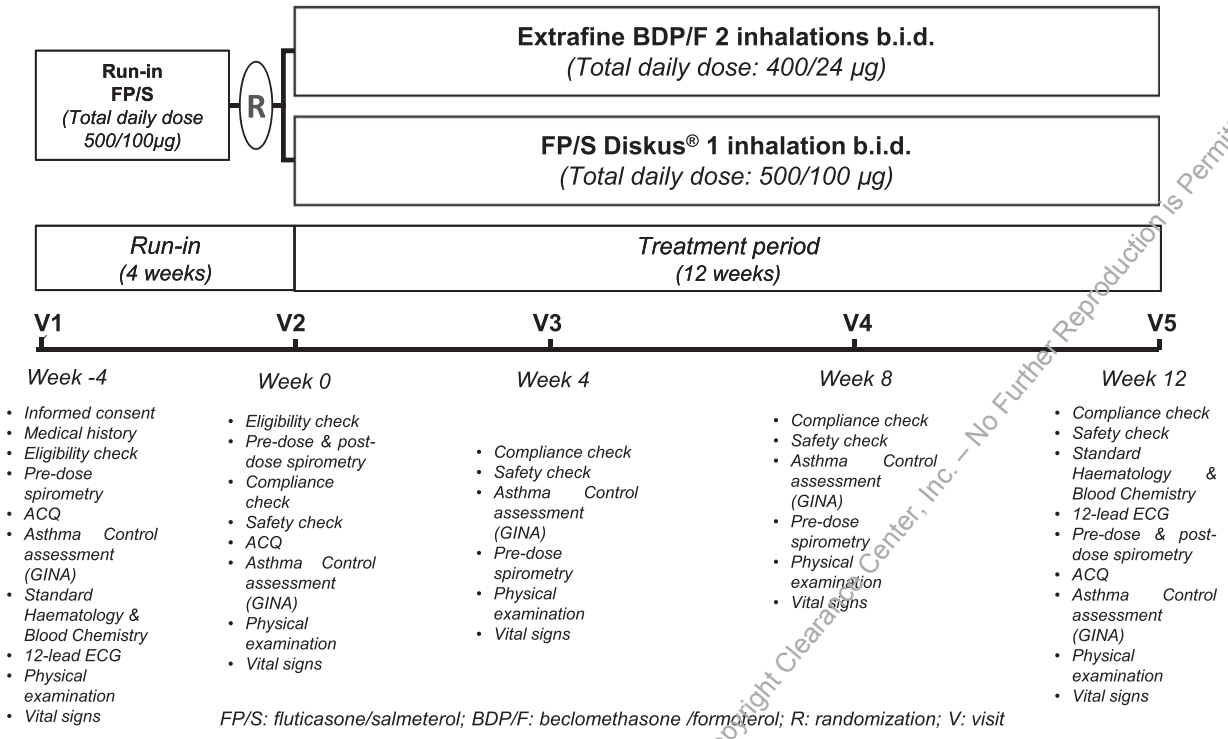

Fig. 1. Study flow-chart.

2.3. Statistics

Descriptive statistics were presented for all the efficacy and safety variables, in the Intention-To-Treat (ITT) and in the safety populations, respectively.

The primary analysis of pre-dose morning FEV_1 used a Mixed Model for Repeated Measures (MMRM) with treatment, visit, treatment by visit interaction, country, age, sex, and height as fixed effects, baseline value and baseline by visit as covariates, and unstructured covariance matrix for each patient. The Kenward–Roger adjustment was used for the degrees of freedom. Equivalence between extrafine BDP/F and FP/S Diskus® was evaluated by calculating the two-sided 95% confidence interval (CI) for the difference in Least Square (LS) means between the test and the reference treatment group. Extrafine BDP/F was to be declared equivalent to FP/S Diskus® if the two-sided 95% CI was within the pre-specified margins of ±0.15 L.

The primary efficacy analysis for pre-dose morning FEV_1 was performed in the ITT population using Last Observation Carried Forward (LOCF) technique as imputation method and on the PP population as sensitivity analysis to assess the impact of missing data.

The other spirometry measures (FEV_1% predicted normal, FVC, PEF and $FEF_{25-75\%}$, as absolute values and % predicted normal), asthma symptoms score, and use of rescue medications (number of puffs) were analysed using the same model as the pre-dose FEV_1 and comparison between treatment group was made evaluating the 95% confidence interval for differences. The number and the percentage of patients with controlled or partly controlled asthma were compared by treatment group using Chi-square test.

3. Results

Patient flow and baseline characteristics are shown in Fig. 2 and Table 1. A total of 491 patients were screened of which 431 were randomized to the study treatments: 215 to the extrafine BDP/F arm and 216 to the FP/S arm. 17 patients (7.9%) in the BDP/F group and 21 patients (9.7%) in the FP/S group were withdrawn from the study, and 198 patients in the BDP/F group and 195 in the FP/S group completed the 12-week treatment period. Overall, 393 patients (91.2%) completed the study (Fig. 2).

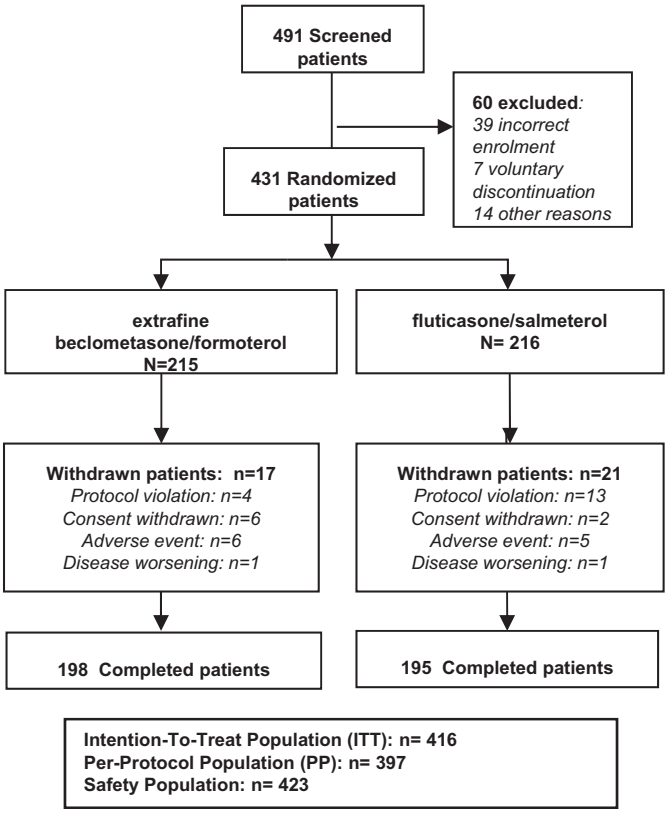

Fig. 2. Patients disposition.

Table 1
Baseline characteristics.

	Extrafine BDP/F	FP/S
Gender (F/M)	118/89	117/92
Age (years) (SD)	44.1 (14.4)	44.0 (13.8)
BMI (SD)	26.7 (5.0)	26.6 (5.0)
Non smokers (%)	167 (80.7)	168 (80.4)
Former smokers (%)	40 (19.3)	41 (19.6)
Packs/year(SD)	6.2 (3.9)	6.5 (3.6)
FEV_1 L (SD)	3.10 (0.82)	3.15 (0.82)
FEV_1% predicted (SD)	97.0 (13.3)	97.4 (13.9)
FVC L (SD)	3.99 (0.98)	3.96 (1.00)
FVC % predicted (SD)	104.1 (12.1)	102.3 (13.4)
ACQ score (SD)	0.33 (0.4)	0.34 (0.4)
Seasonal Allergy (%)	16 (7.7)	15 (7.2)
House Dust Allergy (%)	11 (5.3)	14 (6.7)
Hypersensitivity (%)	17 (8.2)	6 (2.9)
Allergy to animal (%)	9 (4.3)	6 (2.9)
Allergy to plants (%)	3 (1.4)	4 (1.9)

Data are presented as *n* and means (SD). BMI: body mass index; BDP/F: beclometasone/formoterol; FP/S: fluticasone/salmeterol; ICS: inhaled corticosteroids; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. The p = values were considered non-significant between groups for all comparisons.

3.1. Efficacy

3.1.1. Lung function

For the morning pre-dose FEV_1 (L) at the end of 12-week treatment period, the difference between adjusted means (LSMs) of the BDP/F group (3.15 L) and the FP/S group (3.14 L) was 0.01 L (95% CI −0.03, 0.06 L). The two-sided 95% CI of the difference was within the pre-specified margins of ±0.15 L and, therefore, BDP/F was considered to be equivalent to FP/S. When compared with the baseline, both groups showed non-significant change in morning pre-dose FEV_1 at the end of treatment [BDP/F: from 3.10 (0.82) L to 3.13 (0.82) L; FP/S: from 3.15 (0.82) L to 3.16 (0.79) L]. Similar results were observed as regards to the other pulmonary function parameters (FEV_1% predicted, PEF, FVC, $FEF_{25-75\%}$) (Table 2).

The change in post-dose FEV_1 at 5, 15, 30 and 60 min after dosing, at day 1 and after 12-week treatment, is shown in Fig. 3. Changes in FEV_1AUC_{0-1h} were greater in the BDP/F group than in the FP/S group; a significant difference between treatments was shown both at the baseline visit [0.04 (0.01); 95% CI: 0.01, 0.07; $p = 0.004$] and at the end of treatment [0.06 (0.02); 95% CI: 0.01, 0.10; $p = 0.019$] (Table 3).

3.1.2. Asthma control

At the end of treatment, the mean ACQ-7 score did not show statistically significant differences between treatment groups and changed marginally compare to baseline, both in the BDP/F and FP/S groups [BDP/F: 0.03 (0.44) versus FP/S: 0.02 (0.40)] (Fig. 4).

Table 2
Secondary pulmonary function parameters.

	Extrafine BDP/F		FP/S	
	Baseline	Final	Baseline	Final
FEV_1% pred.	97.0 (13.3)	97.4 (13.8)	97.4 (13.9)	97.4 (13.3)
FVC (L)	3.99 (0.98)	4.00 (1.00)	3.96 (1.00)	3.98 (0.96)
FVC% pred.	104.1 (12.1)	104.1 (13.1)	102.3 (13.4)	102.4 (13.1)
PEF (L/min)	463 (123)	464 (126)	478 (131)	483 (128)
$FEF_{25-75\%}$ (L/s)	2.86 (1.24)	2.88 (1.18)	3.08 (1.35)	3.09 (1.34)
$FEF_{25-75\%}$ %pred.	75.1 (27.3)	76.0 (25.6)	80.8 (30.7)	81.0 (31.0)

Data are presented as pre-dose mean (SD). BDP/F: beclometasone/formoterol; FP/S: fluticasone/salmeterol; FEV_1: Forced Expiratory Volume in 1 s; pred.: predicted; FVC: Forced Vital Capacity; PEF: Peak Expiratory Flow; FEF_{25-75}%: Forced Expiratory Flow between 25% and 75% of forced vital capacity.

At all visits the majority of patients, in both treatment groups, were judged as controlled, according to GINA guidelines and this was similar between groups. At the end of treatment, the proportion of controlled patients was 80.8% in the BDP/F group and 79.0% in the FP/S group ($p = ns$ between groups).

3.1.3. Asthma symptoms

In the last 4-week treatment period, the mean daytime symptoms score was 0.16 (0.03) in the BDP/F group and 0.13 (0.03) in the FP/S group (p = ns). Similarly, the mean night-time symptoms score in the two treatment groups was not significantly different (0.11 (0.02) and 0.08 (0.02) in the BDP/F and FP/S group, respectively).

In the last 4-week treatment period, the mean percentage of complete days without asthma symptoms was 88.5% in BDP/F group and 88.8% in FP/S group (p = ns).

In the same way, also for the percentage of days without rescue medication treatment effect was not significant (95.9% and 98.0% in the BDP/F and FP/S groups, respectively).

3.2. Safety

The most common AEs were nasopharyngitis, dysphonia and bronchitis, with a similar incidence between the treatment groups. A total of 11 (2.6%) patients were withdrawn due to an AE (BDP/F: six patients, 2.8%; FP/S five patients, 2.3%). Three patients (1.4%) in the BDP/F group and four patients (1.9%) in the FP/S group experienced asthma exacerbation, with two of them that discontinued the study due to it, one in BDP/F group (0.5%) and one in FP/S group (0.5%).

Severe treatment emergent AEs were reported in one patient (0.5%) after treatment with BDP/F and three patients (1.3%) after treatment with FP/S. During the study, two patients in each treatment group reported serious AEs.

ADRs were reported in nine patients (4.3%) treated with BDP/F and six patients (2.8%) treated with FP/S.

Overall, both treatments were well tolerated and no notable differences in laboratory parameters, vital signs or ECG were detected between the two treatment groups.

4. Discussion

In the present trial, we demonstrated that extrafine BDP/F 400/24 μg daily is as effective as FP/S in maintaining lung function in patients previously controlled with an equipotent dose of fluticasone plus salmeterol 500/100 μg daily, delivered in any device formulation of either pMDI or DPI.

Moreover, extrafine BDP/F demonstrated comparable efficacy versus FP/S 500/100 μg Diskus® in maintaining asthma control as measured via the validated questionnaire, ACQ-7. After 12-week treatment, the ACQ-7 remained well below the threshold indicative of asthma control (score <0.75), thus demonstrating that transferring patients to extrafine BDP/F did not result in any deterioration of patient conditions.

A recently published real-life study demonstrated the value of BDP/F extrafine particles in achieving asthma control [2]. Similar results were confirmed in another real-life study showing improvement in quality of life, measured via Euroqol scale [28].

To our knowledge, there are no studies that assessed whether asthma control is maintained after stepping-across to another ICS/LABA fixed combination with equivalent ICS dose in clinical practice. The risk of losing asthma control from changing the pharmacotherapy of controlled asthmatic patients has been previously reported [25,26], but no randomized, controlled clinical trials are available. Therefore, it may be important to provide reassurance in terms of device, molecule, strength and dosing schedule for an

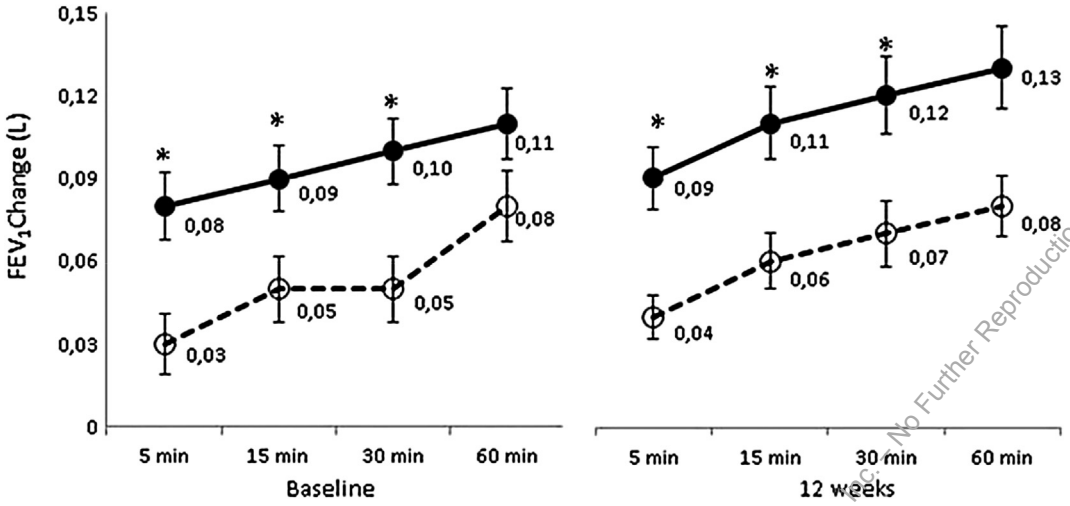

Fig. 3. Change (L) from morning pre-dose FEV_1 (SE) at baseline and at the end of treatment after 5, 15, 30, and 60 min post-dose. ● Extrafine beclometasone/formoterol; ○ fluticasone/salmeterol. *$p < 0.05$ between treatments. Mean changes from morning pre-dose ± SE.

evidence-based decision regarding specific pharmacotherapy change in case this is needed in clinical practice.

The design of this study was primarily aimed at demonstrating equivalence between the two test therapies in maintaining lung function and asthma control in patients with already controlled and stable asthma. Therefore, a significant difference versus baseline was not expected. This was demonstrated in a previous study comparing extrafine BDP/F and FP/S in moderate to severe partly controlled and uncontrolled asthmatic patients, in which a significant improvement in lung function parameters versus baseline in both treatment groups was observed [29].

Additionally and as shown by the change in FEV_1 from pre-dose to 60 min after dosing, a more rapid onset of bronchodilation at the beginning and also at the end of treatment period has been noticed with extrafine BDP/F compared to FP/S even in the controlled asthmatic patients enrolled in this study. This was mainly due to the pharmacodynamic properties of formoterol and confirmed the observations from the above mentioned previous study in partly controlled and uncontrolled asthmatics [29].

In terms of safety, both treatments were well tolerated and no relevant differences in the monitored parameters were detected between the two treatment groups.

The results of this study on the step-across from FP/S to extrafine BDP/F should not be extended to other fixed combination therapies or to generic formulations ICS/LABA, formulated with devices different from the originator, since a number of variables (i.e. different devices, molecules, strengths, and dosing schedules) could be introduced.

A limitation in this study is the lack of the relation between control level and future risk of exacerbation, mainly due to the duration of the treatment period. Further studies need to address this point.

Table 3
FEV_1AUC_{0-1h} (L).

	Extrafine BDP/F	FP/S	Difference
Baseline	3.22 (3.20 ± 3.24)	3.18 (3.16–3.20)	0.04[a] (0.01–0.07)
End of treatment	3.30 (3.26–3.34)	3.24 (3.21–3.26)	0.06[b] (0.01–0.10)

[a] $p = 0.004$ between treatments.
[b] $p = 0.019$ between treatments.
Data are presented as Least Square (LS) Means (95%CI).

Although spirometry is the most widely employed measure of pulmonary function, the FEV_1 does not properly reflect small airways abnormalities. Notably, a number of studies published in previous years suggested that specific formulations of ICS or ICS/LABA can modify biomarkers/parameters related to small airways. Extrafine BDP/F is the only fixed combination ICS/LABA able to reach both large and small airways and is formulated with extrafine particles which are half the size of other fixed combinations [20]. A scintigraphic study confirmed high lung deposition [19] and also showed that drug distribution was uniform throughout the entire bronchial tree including the small airways which are an important site of disease inflammation in asthma [30,31].

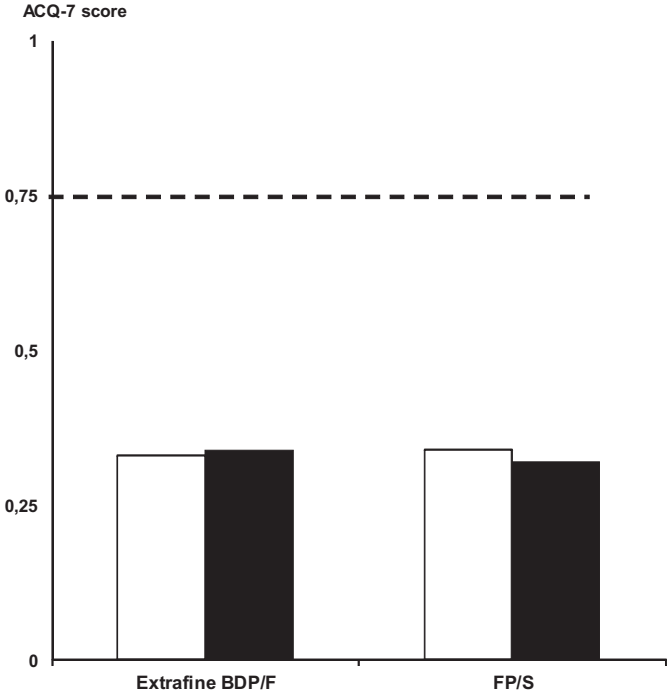

Fig. 4. Mean ACQ-7 score at baseline (□) and at the end of treatment (■) in the two groups.

In a recently completed retrospective study, it was shown that there is a significant unmet need in terms of persistent small airways dysfunction despite treatment [32]. This study also showed that extrafine ICS reduced small airways resistance compared to larger particles ICS. It has been postulated that asthma control may be improved by targeting small airways [33–37]. The demonstration that extrafine BDP/F is as effective as a higher dose of fluticasone and salmeterol would potentially allow this hypothesis to be investigated more thoroughly.

Potentially promising techniques to assess small airways function include impulse oscillometry, the nitrogen washout test, sputum induction and alveolar nitric oxide derived by measurements of nitric oxide at multiple expiratory flows [30,31]. However, considering that this study involved many General Practitioners or private Pulmonologists, the standardization of these assessments would have been very difficult from a clinical practice point of view and this has, therefore, limited the use of recent methods or valuable parameters to mirror asthma inflammation or dysfunctions occurring in the distal airways, such as NO and IOS.

In conclusion, the present study demonstrated that patients already controlled with FP/S in any device formulation can effectively step-across to extrafine BDP/F pMDI, maintaining lung function and asthma control with a 5-min onset of action.

Disclosure statement

N. Barnes has lectured or done ad hoc consultancy for Chiesi, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Teva, Nycomed Takeda and Sandoz. He has had research funded by AstraZeneca, GlaxoSmithKline, Novartis and Nycomed Takeda. J.A. Van Noord, L. Lindemann, M. Perpiña and P. Chanez received clinical research funds from Chiesi Farmaceutici S.p.A. as site investigators for this study. C. Brindicci, G. Varoli, D. Guastalla D. Casula and S. Patel are employees of Chiesi Farmaceutici S.p.A., sponsor of the study.

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