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ORIGINAL ARTICLE

Comparison of the effect of beclometasone/formoterol in asthma patients after methacholine-induced bronchoconstriction: A noninferiority study using metered dose *vs.* dry powder inhaler

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Keywords asthma, inhalation, Clinical Trials

AIMS

To demonstrate the noninferiority of extrafine beclomethasone/formoterol fumarate (BDP/FF) dry powder inhaler (DPI) *vs.* extrafine BDP/FF pressurized metered dose inhaler (pMDI; Foster® 100/6 μg NEXThaler and pMDI, respectively) in the onset of reliever effect after methacholine induced bronchospasm in asthmatic patients, evaluated in terms of forced expiratory volume in 1 s (FEV_1) at 5 min postdose. The DPI provides an alternative device option for patients who cannot use a pMDI properly during an acute asthma attack.

METHODS

Sixty-five patients received one inhalation of BDP/FF DPI, BDP/FF pMDI or placebo after methacholine challenge, according to a double-blind, double-dummy, cross-over design. Lung function and Borg dyspnoea score were assessed up to 30 min postdose.

RESULTS

FEV_1 adjusted mean difference between BDP/FF DPI and BDP/FF pMDI at 5 min postdose was 2 ml (95% confidence interval: –0.060; 0.065). A similar result was observed at the other time points. Median time to 85% recovery in FEV_1 was 8 min for BDP/FF DPI, 7.5 min for BDP/FF pMDI and 28 min for placebo ($P = 0.554$ DPI *vs.* pMDI). The Borg score improved after treatment with both BDP/FF DPI and pMDI and the effect was greater than after placebo. Median time to reach 50% recovery was 4.2 min for BDP/FF DPI, 4.0 min for BDP/FF pMDI and 10.0 min for placebo ($P = 0.609$ DPI *vs.* pMDI).

CONCLUSIONS

Extrafine Foster® NEXThaler, a flow-independent DPI, is comparable to extrafine Foster® pMDI when administered as reliever therapy after methacholine challenge, thus supporting the maintenance and reliever therapy approach also with Foster® NEXThaler.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of budesonide/formoterol or extrafine beclometasone/formoterol in a single inhaler as maintenance and reliever therapy is effective and reduces the risk of exacerbations in uncontrolled asthmatics.
- There are only two dry powder inhalers (DPIs) with indication for maintenance and reliever therapy.

WHAT THIS STUDY ADDS

- Extrafine Foster® NEXThaler DPI is suitable for Maintenance and Relief Therapy (MART) approach, providing a valuable choice for asthmatic patients preferring DPIs instead of pMDIs. The reliever effect of Foster® NEXThaler DPI is comparable to that of extrafine Foster® pMDI.

Introduction

Despite effective pharmacological treatments currently available for asthma, many patients are still poorly controlled [1]. The use of a combination inhaler containing inhaled corticosteroid (ICS), such as budesonide or beclometasone dipropionate, and the long-acting β-agonist (LABA) formoterol as both maintenance and relief therapy (MART) has been recommended to optimize ICS/LABA therapy in uncontrolled asthma [2]. The effectiveness of this regimen is thought to be the result of early intervention with rapid increases in ICS dose at the first symptoms, together with rapid symptom relief by virtue of the fast onset of action of formoterol [3]. It has been shown that if a fast onset ICS/LABA is administered as *maintenance and reliever* at the first evidence of asthma worsening, it is possible to taper the inflammation as soon as it starts, thus preventing the development of the asthma exacerbation [4]. Moreover, the effect on symptoms of a MART approach may significantly postpone the occurrence of exacerbations, thus reducing the yearly rate, as shown in a randomized clinical trial comparing the MART use of a low dose of extrafine formulation BDF/FF *vs.* short-acting β-agonist as rescue medication plus regular ICS/LABA intake [5]. Prevention of asthma exacerbations is recognized in all current asthma guidelines as an important component of treatment because it results in a substantial reduction in work productivity and school or university attendance and represents the greatest cost for health-care systems. Finally, MART posology effectively enforces ICS adherence by linking use to reliever therapy with formoterol and is intuitive for patients to use on a flexible basis.

The fixed combination of extrafine formulation beclometasone dipropionate and formoterol fumarate (BDP/FF; Foster®, Chiesi, Parma, Italy) was the first registered pMDI for the MART approach in asthma. A single dose of BDP/FF pMDI showed a fast onset of action, similar to that of salbutamol, in the methacholine-induced bronchospasm model [6]. Furthermore, a 1-year study investigating the MART regime with BDP/FF pMDI demonstrated a prolonged time to first severe exacerbation and reduced rate of severe exacerbations in uncontrolled asthma patients along with a lower need to receive courses of systemic corticosteroids [5].

To provide an additional delivery device option, a DPI, the NEXThaler, containing the same extrafine formulation active ingredients of Foster® pMDI (100 μg of BDP and 6 μg of FF) has been developed [7]. It is well established that some asthma patients cannot properly operate pMDI devices, or prefer to use a DPI [8]. For these patients, Foster® NEXThaler provides an alternative option in clinical practice, but its effectiveness in the MART approach has not been established. The NEXThaler is a multidose breath-actuated DPI, which is activated at an average inspiratory flow of 35 l min^{-1} [9, 10]. Flow independency in the drug delivery from NEXThaler has been demonstrated for both BDP and FF at different inspiratory flows ranging from 30 to 90 l min^{-1}, supporting the utility and effectiveness of the inhaler in patients with different degrees of lung function impairment and disease control. Considering the inspiratory flow independency for the DPI activation and that both pMDI and DPI contain the same active components, we hypothesized that there would be no differences between the two devices in terms of bronchodilation capacity to reverse acute bronchoconstriction, for example induced by methacholine.

To validate the potential use of Foster® NEXThaler for the MART approach, it is necessary to evaluate whether its administration provides a quick onset of efficacy during acute severe bronchospasm. Therefore, we have compared the onset of bronchodilator action of Foster® NEXThaler with Foster® pMDI using methacholine induced bronchoconstriction, which is a widely used and representative model of bronchoconstriction and a well-accepted method for bronchodilator efficacy in asthma.

Methods

Patients

Patients aged between 18 and 60 years inclusive with a diagnosis of persistent asthma for at least 6 months were recruited in the trial and were required to fulfil the following criteria at study entry: nonsmokers or ex-smokers, prebronchodilator forced expiratory volume in 1 s (FEV_1) of at least 65% of predicted value and at least 1.5 l, a positive response to methacholine challenge test (defined as a $PD_{20} \leq 1$ mg) and stable treatment with low-medium doses of ICS or ICS plus LABA combination as per current Global Initiative for Asthma guidelines [2].

Patients were excluded from the study if they had experienced an asthma exacerbation in the previous 4 weeks or if they had any clinically relevant and uncontrolled concomitant disease. Pregnant or breastfeeding women were also excluded from the study participation.

Nonpermitted concomitant medications included systemic corticosteroids, leucotriene modifiers, anti-IgE antibodies, antihistamines, anticholinergic drugs and β-blockers. Patients could remain on their previous treatment with ICS or ICS plus LABA combination, provided that LABA was withheld in the 48 h before each study visit. Salbutamol was also

allowed as rescue medication, with a required washout of at least 8 h before any spirometric measurements.

Patients were carefully trained with placebo inhalers to the use of both pMDI and DPI devices.

The study was conducted in four clinical sites in UK after approval from an independent Ethics Committee (North West – Liverpool Central Research Ethics Committee). The study was performed in accordance with Good Clinical Practice, the Declaration of Helsinki and all applicable regulations. Written informed consent was obtained from all study participants.

Study design

This was a randomized, double-blind, double-dummy, active treatment and placebo controlled, three-way crossover study. The study design is shown in Figure 1. A screening visit (V0) was performed to verify inclusion and exclusion criteria. During this visit, patients taking ICS/LABA fixed combinations were switched to the free combination of the same ICS and LABA, administered as separate inhalers to allow the required washout from LABA prior to each visit. Treatment with ICS was maintained for the overall duration of the run-in and washout periods. Eligible patients were randomized and attended the clinical site for three treatment visits, each separated by a 5–21-day washout period.

At each treatment visit, a pre-challenge FEV_1 was measured followed by a methacholine challenge test. To minimize variability between treatment days, FEV_1 values pre-challenge had to be within ±15% of value at visit 1. During the challenge, performed using the *five-breath dosimetric method*, increasing doubling doses of methacholine were administered to the patients until a decrease in FEV_1 between 30% and 45% of the baseline value was observed. In case the level of dyspnoea became too severe or the decrease in FEV_1 exceeded the 45% of baseline value, patients were immediately treated with salbutamol as reliever medication and discontinued from the study. Patients who reached the target-induced bronchoconstriction were treated with the study drug within 1 min from the end of the provocation test, according to the randomization list. The following treatments were administered: one inhalation of extrafine formulation BDP/FF 100/6 μg as DPI NEXThaler (Foster® NEXThaler 100/6 μg) or one inhalation of extrafine formulation BDP/FF 100/6 μg as pMDI (Foster® 100/6 μg pMDI) or one inhalation with placebo, all appropriately blinded with another inhalation of placebo, in a double-dummy fashion. The two active drugs contained exactly the same combination of ICS (BDP) and LABA (FF), but were administered with a different formulation and device (i.e. dry powder via DPI NEXThaler and solution via pMDI).

The double-dummy technique was used to ensure blinding, so all patients inhaled from both types of inhaler devices. Half of the patients took Foster® NEXThaler 100/6 μg first, the other half Foster® 100/6 μg pMDI.

FEV_1 and level of dyspnoea, assessed with the Borg scale, were measured before the methacholine challenge test (FEV_1 only), at the end of the challenge (PD_{30}) and at 1, 3 (Borg scale only), 5, 10, 20 and 30 min after study drug intake.

Study procedures

FEV_1 was measured with Pneumotrac 6800 (Vitalograph Ltd, Bucks, UK) according to the ATS/ERS recommendations [11] and the spirometry curves were centrally analysed. The highest value taken from two (during methacholine challenge test) or three (for postdose time points) technically satisfactory attempts was recorded and used in the analysis. To avoid unnecessary discomfort for the patients due to the exhalation until the residual volume, each effort was terminated after 2 s of exhalation [12].

The 10-point Borg scale was used to provide a measure of the patient's perception of dyspnoea [13], with 0 indicating no appreciable breathlessness and 10 indicating the maximal tolerable sensation. The value at the end of the bronchoprovocation test was considered as the baseline value for dyspnoea assessments.

Methacholine challenge test was performed with Marcos Mefar MB3 dosimeter and MB2 nebuliser (Air Liquide Medical Systems, Italy) according to the ATS recommendations [12]; the same source of prediluted vials of methacholine chloride solution was used by all clinical sites (Stockport Pharmaceuticals). Saline solution was inhaled first, followed by a postsaline FEV_1, which was used as baseline value for lung functions assessments. Methacholine was administered at increasing concentrations in order to obtain the cumulative doses ranging from 0.0028 to 2.8772 mg. FEV_1 measurements after each dose of methacholine were obtained in duplicate.

Statistical methods

The primary objective of the study was to demonstrate the noninferiority of BDP/FF 100/6 μg DPI *vs*. BDP/FF 100/6 μg pMDI on the onset of relief from methacholine-induced bronchospasm in terms of change in FEV_1 from baseline to

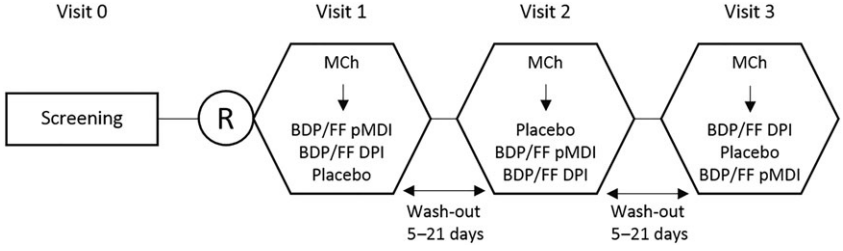

Figure 1

Study flow chart. R = randomization, MCh = methacholine challenge test, BDP/FF = beclometasone dipropionate/formoterol fumarate

5 min after study drug intake. The noninferiority rather than the equivalence approach was chosen in order to demonstrate that BDP/FF DPI has a reliever effect that is at least good as compared to BDP/FF pMDI, which is already approved in clinical practice for the MART indication.

Secondary endpoints included: change in FEV_1 from baseline to all other time-points after study drug intake, time to recovery in FEV_1 (defined as the return to 85% of the baseline FEV_1 value), FEV_1 $AUC_{0–10min}$ normalized by time, change in the Borg scale from the end of methacholine challenge test to all time-points after drug intake and time to recovery in the Borg scale (defined as 50% decrease from the postmethacholine value).

Safety and tolerability were assessed by analysis of adverse events (AEs) and vital signs.

A sample size of 54 evaluable subjects provided 86% power for noninferiority testing of BDP/FF 100/6 μg DPI *vs.* BDP/FF 100/6 μg pMDI, based on the change in FEV_1 from baseline to 5 min after study drug intake, assuming a noninferiority margin of −0.120 L between the two treatments, a within-subject standard deviation of 0.20 l and at a two-sided α error set at 0.05. Assuming a drop-out rate of 10%, approximately 60 subjects were to be randomized. All randomized subjects who completed at least one treatment period were included in the intention to treat (ITT) population.

Change in FEV_1 from baseline to 5 min after study drug intake was analysed using an analysis of covariance (ANCOVA) model including treatment, period and subject as fixed effects and FEV_1 baseline and FEV_1 at the end of challenge as covariates. The adjusted means in each treatment group and the adjusted mean differences between treatments were estimated by the model with their 95% confidence intervals (CIs).

Change in FEV_1 from baseline to all other time-points and FEV_1 $AUC_{0–10min}$ normalized by time were analysed using the same ANCOVA model as for the primary endpoint.

Change in the Borg scale from the end of methacholine challenge test to all time-points after drug intake was analysed using an ANCOVA model including treatment, period and subject as fixed effects, Borg scale pre-challenge and Borg scale at the end of challenge as covariates.

Time to recovery variables were analysed by using the Kaplan–Meier method. This provided plots and estimates of median times to recovery and pertinent 95% interquartile range. For subjects who recovered within 30 min from study drug intake the exact time to recovery was estimated by a linear interpolation between the last time point before recovery and the first time point showing recovery. For subjects who did not recover within 30 min, the time to recovery was extrapolated by the trend observed in the first 30 min. In the event that the extrapolated time to recovery was >50 min, it was conventionally set at 50 min. Comparison between treatment groups and *P*-value were estimated by Cox model.

AEs, serious AEs and AEs leading to discontinuations were presented descriptively.

All efficacy analyses were performed on the ITT population, defined as all randomized patients who received at least one dose of study treatment and with at least one available evaluation of efficacy after the baseline. Analysis on primary endpoint was also repeated on the per protocol population (ITT population without any major protocol violation). Safety analyses were performed on the Safety population consisting of all randomized subjects who received at least one dose of study treatment after randomization.

Data were analysed using SAS Version 9.4 for Windows.

Results

Patients' baseline characteristics are reported in Table 1. Sixty-five subjects were randomized to treatment. Five subjects did not complete the treatment periods for the following reasons (one subject each): adverse event, baseline FEV_1 < 65% of predicted value, fall in FEV_1 of at least 30% not reached, excessive reaction to methacholine with fall in FEV_1 > 45% and lost to follow-up.

Methacholine challenge

Baseline FEV_1 measurements (P1) and measurements at the end of the challenge (P2) were similar between all the treatments (Table 2). The FEV_1 at the end of the provocation dropped to approximately 66% of P1.

FEV_1

Both BDP/FF formulations caused rapid FEV_1 increases; there was an FEV_1 improvement at 5 min postdose, which was 224 ml and 222 ml higher than placebo with BDP/FF DPI and BDP/FF pMDI respectively, demonstrating a rapid relief of bronchoconstriction with both formulations (Figure 2). Significant differences were observed between active treatments and placebo at all time points. At 5 min postdose, the adjusted mean difference between BDP/FF DPI and BDP/FF pMDI was 2 ml (95% CI: -0.060; 0.065), with similarity between the effects of these BDP/FF formulations also observed at other time points.

The adjusted mean FEV_1 $AUC_{0–10min}$ normalized by time were 2.26, 2.25 and 2.07 l for BDP/FF DPI, BDP/FF pMDI and placebo, respectively, with no differences between BDP/FF DPI and BDP/FF pMDI; both activities were superior to placebo ($P < 0.001$).

Table 1

Patient baseline demographics. FEV1: forced expiratory volume in 1 s; ICS: inhaled corticosteroids, LABA: long-acting β_2-agonist, SD: standard deviation

Characteristics	Patients (n = 65)
Male/female	40/25
Mean age ± SD, years	41.3 ± 10.8
Nonsmokers/ex-smokers	50/15
Mean FEV_1 ± SD, l [% pred]	2.95 ± 0.64 [80.7 ± 11.0]
Mean FVC ± SD, l [% pred]	4.37 ± 0.86 [97.1 ± 10.2]
Previous asthma medication	
ICS monotherapy	40
ICS/LABA combinations (free or fixed)	25

Table 2

Forced expiratory volume in 1 s (FEV_1) and Borg dyspnoea evaluation data (intention to treat population). BDP/FF: beclomethasone/formoterol fumarate; DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler; SD: standard deviation; SE: standard error; CI: confidence interval; IQR: interquartile range

	BDP/FF DPI (*n* = 63)	BDP/FF pMDI (*n* = 62)	Placebo (*n* = 63)
FEV_1, l			
Baseline, l: mean ± SD	2.90 ± 0.62	2.82 ± 0.60	2.83 ± 0.60
After methacholine: mean ± SD	1.90 ± 0.44	1.86 ± 0.42	1.86 ± 0.40
Change *vs.* baseline at 5 min postdose, l			
Adjusted means ± SE	−0.51 ± 0.02	−0.51 ± 0.02	−0.73 ± 0.02
Comparison: difference (95% CI)			
BDP/FF DPI *vs.* BDP/FF pMDI or placebo		0.002 (−0.06; 0.07)	0.22 (0.16; 0.29)[b]
BDP/FF pMDI *vs.* placebo		0.22 (0.16; 0.28)[b]	
Time to recovery, min: median (IQR)[a]	8.0 (4.5; 16.7)	7.5 (3.50; 17.1)	28.2 (13.3; 38.4)
Borg dyspnoea score			
Baseline: mean ± SD	0.41 ± 0.80	0.21 ± 0.53	0.30 ± 0.78
After methacholine: mean ± SD	4.21 ± 1.91	4.12 ± 2.09	4.21 ± 1.94
Change *vs.* baseline at 5 min postdose			
Adjusted means ± SE	−2.14 ± 0.12	−2.17 ± 0.12	−1.55 ± 0.12
Comparison: difference (95% CI)			
BDP/FF DPI *vs.* BDP/FF pMDI or placebo		0.02 (−0.32; 0.36)	−0.599 (−0.94; −0.26)[b]
BDP/FF pMDI *vs.* placebo		−0.62(−0.96; −0.29)[b]	
Time to recovery, min: median (IQR)[a]	4.25 (2.50; 10.00)	4 (1.00; 8.75)	10.00 (3.00; 20.00)

[a]Estimated by the Kaplan–Meier method. For FEV_1: comparison BDP/FF DPI *vs.* pMDI, $P = 0.554$; comparison BPP/FF DPI *vs.* placebo, $P < 0.0001$. For Borg score: comparison BDP/FF DPI *vs.* pMDI, $P = 0.609$; comparison BPP/FF DPI *vs.* placebo, $P = 0.042$
[b]$P < 0.0001$ for superiority testing

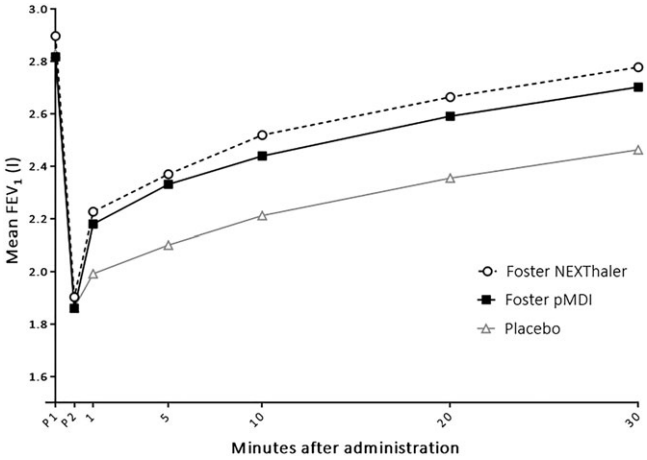

Figure 2

Forced expiratory volume in 1 s (FEV_1) profiles. P1: baseline value (post-saline); P2: value at the end of the methacholine challenge test

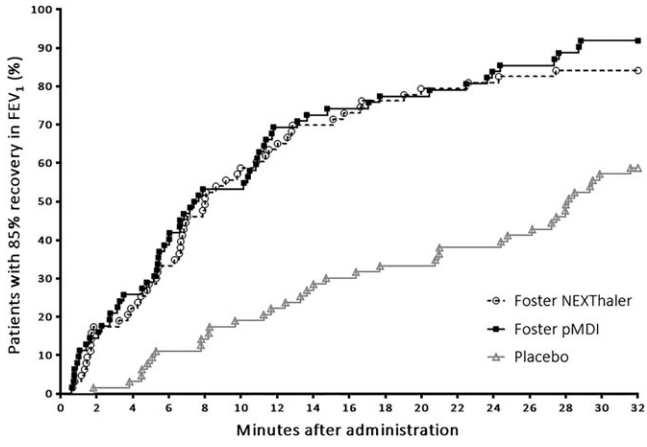

Figure 3

Forced expiratory volume in 1 s (FEV_1) time to recovery from methacholine challenge

The recovery with BDP/FF DPI was fast (median time of 8 min), similar to BDP/FF pMDI (median time of 7.5 min; $P = 0.554$), and much shorter than placebo (28 min; $P < 0.0001$; Figure 3). At 5 min postdose, the mean FEV_1 value was >82% of baseline value after inhalation of the active treatments and lower with placebo (74%).

Borg dyspnoea scale

The mean Borg dyspnoea score was <0.5 before the methacholine challenge test (Figure 4, P1) and increased (worsening) up to >4 at the maximum methacholine-induced bronchoconstriction in all treatment periods (Figure 4, P2). After dosing, an improvement in the mean Borg dyspnoea score occurred after administration of all treatments, with a greater effect observed with the two active drugs as compared to placebo (47.3% improvement with BDP/FF DPI, 44.1% with BDP/FF pMDI and 34.2% with placebo at the 5 min postdose time point). Median time to recovery, expressed as the time needed for the Borg dyspnoea score to reach 50% of recovery, was 4.2 min with BDP/FF DPI, which was similar to BDP/FF pMDI (4.0 min, $P = 0.609$), and significantly shorter than placebo (10.0 min; $P = 0.042$).

AEs

No serious or severe AEs or adverse drug reactions were reported. The frequency of the reported AEs was comparable among treatments (four patients reported AEs after intake of BDP/FF DPI and BDP/FF pMDI and five patients after intake of placebo). The most commonly reported AEs were nasopharyngitis (one after BDP/FF DPI and one after BDP/FF pMDI) and cough (two after BDP/FF DPI). Other AEs, occurring in no more than one patient, were: urinary tract infection after BDP/FF DPI; seasonal allergy; chest pain and headache after BDP/FF pMDI; lower respiratory tract infection; arthropod bite; limb injury; dizziness; oropharyngeal pain; and urticaria after placebo. Only one AE was considered as possibly related to the study drug (oropharyngeal pain), while another AE lead to the permanent discontinuation of the study drug (lower respiratory tract infection). Both AEs occurred after administration of placebo.

Discussion

The results of the present study showed that BDP/FF extrafine formulation DPI was noninferior to BDP/FF extrafine formulation pMDI in the reliever effect as measured by 5-min postdose FEV_1. The FEV_1 increase was 224 and 222 ml higher than placebo with BDP/FF DPI and pMDI, respectively, at 5 min post dose. Other lung function measures and the Borg dyspnoea score as secondary endpoints showed similar results with the two formulations, confirming that DPI and pMDI are similar when used as a reliever therapy.

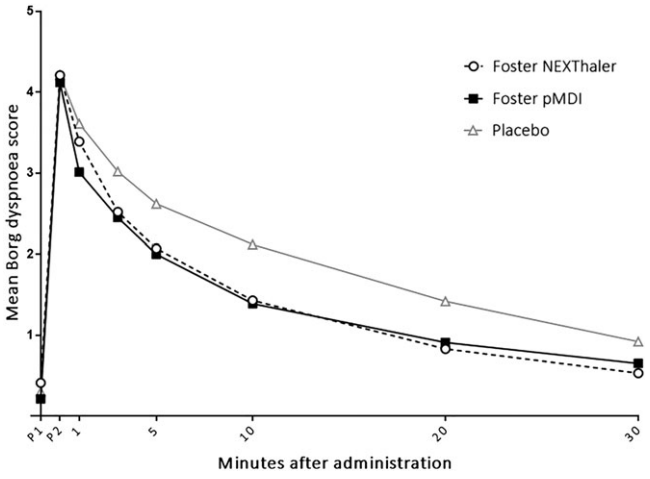

Figure 4

Borg dyspnoea score profiles. P1: value before the start of the methacholine challenge test; P2: value at the end of the methacholine challenge test (baseline)

In terms of time to recovery of lung function, expressed as the median time to return to 85% of the baseline value, BDP/FF 100/6 μg DPI and BDP/FF 100/6 μg pMDI were again comparable, with times to recovery of 8 and 7.5 min, respectively, confirming rapid reliever effect.

The FEV_1 improvements exceed the threshold accepted for significant bronchodilator reversibility [14], and were observed rapidly (within 5 min). Furthermore, the FEV_1 improvements at 5 min were associated with greater improvements in the Borg dyspnoea rating, indicating that the bronchodilation was also perceived by patients. Early patient withdrawals induced a slight imbalance in the number of patients per sequence. The only effect of this imbalance was a small loss of efficiency in statistical testing. However, the potential *sequence effect* was already accounted for by the *subject effect* included in all statistical models. Moreover, a wash-out period between treatments of appropriate duration (minimum 5 days and maximum 21 days) excluded by design any carry-over effect.

Overall, the results demonstrate that in asthmatic patients subjected to methacholine-induced bronchoconstriction to mimic an asthma attack, the degree of bronchodilation achieved with BDP/FF NEXThaler was practically identical to that achieved with BDP/FF pMDI, both in terms of magnitude and onset of action.

In this study, the mean drop in FEV_1 after the use of methacholine was >30% from baseline values, with most patients demonstrating a postmethacholine FEV_1 < 2 l, representing clinically relevant bronchoconstriction as might occur in acute asthma. This model has previously been used to demonstrate the similarity of BDP/FF extrafine formulation pMDI compared to salbutamol. In this previous study (hereafter mentioned as MART1 trial) [6], it was observed that the median time to FEV_1 recovery was <5 min for both treatments, while in the current study this was approximately 7–8 min for BDP/FF administered by pMDI or DPI. A relatively slower time to recover was observed for BDP/FF pMDI in the current study but also the median time to recovery with placebo was also slower in the current study (28.2 min *vs*. 21.4 min). The overall magnitude of bronchoconstriction achieved (P2 time point in Figure 2) was similar in both studies (approximately 65% of P1 measurement, Figure 2). Considering that the same bronchial challenge protocol was used in both studies, with similar effects at P2, it appears that the current study involved subjects with a naturally longer time to recovery, highlighted in the comparison of BDP/FF pMDI and placebo results between studies. It should be noted that the asthma population previously studied in the MART1 trial was less severe in terms of FEV_1% predicted than in the current study (92% *vs*. 80% respectively). It is possible that a thickened mucosa and submucosa and altered airway secretions have affected the availability of the β_2-agonists to their related receptors, delaying the bronchodilator response [15]. Furthermore, in the current study, only 38% (*vs*. 73% in the

previous study) of asthma patients were in previous treatment with ICS plus LABA, potentially suggesting a lower level of control on the airway tone by the LABA component in the enrolled population. While caution should be exercised when comparing across studies, differences in the study population characteristics may have contributed to the differences observed.

An indirect comparison between formoterol in the DPI formulation in the present study and salbutamol in MART1 study is difficult to perform. However, the results of the present study are in agreement with other studies that have evaluated the acute effects of bronchodilators using this model [16, 17]. Politiek *et al*. [17] found that the geometric mean time for FEV_1 to return to 85% of baseline was 7.2 min with formoterol DPI, 6.5 min with salbutamol and 34.7 min with placebo. Beach *et al*. [16], when comparing the speed of action of single doses of formoterol and salbutamol in DPI formulation in reversing methacholine induced bronchoconstriction, reported that both salbutamol and formoterol produced bronchodilator effects within 2 min after inhalation and reached a maximum after 10 min. Another study [18] with the same model but with specific airway conductance as primary endpoint, as this can be a more sensitive index of changes in airway calibre than FEV_1, concluded that both salbutamol and formoterol have very rapid onset of action with salbutamol slightly faster. In terms of perception of the relief of dyspnoea assessed by the Borg scale, in the present study, the median time to 50% recovery was 4.25 min in agreement with the obtained value of 5 min for BDP/FF pMDI and 3.5 min for salbutamol in the MART1 study. This indicates that the administration of BDP/FF pMDI, BDP/FF DPI and salbutamol had comparable effects in terms of dyspnoea relief after induced bronchoconstriction.

BDP/FF NEXThaler is the only extrafine formulation DPI designed to provide physicians and patients with an alternative easy to use delivery system, especially for those patients preferring DPIs or experiencing poor coordination with pMDIs. The breath actuated mechanism that is activated at an average inspiratory flow rate of 35 l min^{-1} [9, 10], triggers the counting only of effective inhalations as compared to other available DPIs such us Turbohaler and Ellipta devices.

The NEXThaler is a medium resistance device and is comparable in that respect to the marketed Turbohaler device, already approved as Symbicort Turbohaler for MART posology and it requires an inspiratory flow rate of 54 l min^{-1} to generate a drop of 4 kPa, which is lower than that of other devices not used for MART posology such as Ellipta® (74 l min^{-1}) [19].

In another study [20], the *in vitro* characteristics of NEXThaler were compared to Diskus and Turbohaler dry powder at flow rates between 30 l min^{-1} and 100 l min^{-1}, relevant to the target population for MART, shown to deliver consistent delivery performance across different flow rates and regardless the applied inspiratory flow.

Other data [10] evaluated the inspiratory profile of the NEXThaler device in adult asthma patients with different level of asthma control and all patients were able to activate and use the device effectively.

In summary, this study shows that the bronchodilator effect of Foster® 100/6 µg NEXThaler extrafine formulation occurs rapidly and is noninferior to Foster® 100/6 µg extrafine formulation pMDI in reversing methacholine-induced severe bronchoconstriction as a model of acute severe bronchospasm. The results support the suitability of extrafine formulation BDP/FF 100/6 µg DPI NEXThaler for the MART approach.

Competing Interests

D.S. has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Apellis, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Johnson and Johnson, Mundipharma, Novartis, Peptinnovate Pfizer, Pulmatrix, Skypharma, Teva, Therevance and Verona. F.v.d.B. has no competing interests to declare. B.L. has received investigator fees from Chiesi for this and other studies; similar investigator fees were also received from Regeneron Pharmaceuticals, Astra Zeneca, Afimmune, Verona, Moerae Matrix and Hemay Pharmaceutical Pty. Ltd in the last 12 months. M.C. has received grants and honoraria for lectures from Chiesi. S.J. has received personal fees and nonfinancial support from Chiesi, personal fees and nonfinancial support from Pfizer, nonfinancial support and other from Napp, personal fees and nonfinancial support from AstraZeneca, nonfinancial support from Teva, nonfinancial support from Meda, personal fees from Boehringer Ingelheim, outside the submitted work. S.C., V.M., L.S., A.P. and S.B. are full-time employees at Chiesi Farmaceutici S.p.A.. B.L. and the Scottish Centre for Respiratory Research have received funding in the form of consultancy, advisory boards, research, travel grants, equipment or giving talks from Chiesi Farmaceutici S.p.A., Boerhinger Ingelheim, Teva, Meda Pharma, Mylan, AstraZeneca, Dr Reddys, Cipla, Lupin, Genentech, Sanofi, Jansen, GSK, Novartis, Vectura, Glenmark.

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D.S., F.v.d.B., B.L. and B.L. were the principal investigators of the four clinical sites where the clinical trial was performed. D.S. also acted as coordinating investigator. S.J. was the co-investigator at the Scottish Centre for Respiratory Research in Dundee. M.C., S.C., V.M., L.S., A.P. and B.L. were involved in the study design and results interpretation. S.B. and L.S. were involved in data collection and analysis and are responsible for the integrity of the data and accuracy of the data analysis. SGS Belgium NV (Antwerp, Belgium) was responsible for monitoring, data management, statistics, pharmacovigilance and medical writing during the trial. Biomedical Systems (Brussels, Belgium) was responsible for central collection and over-reading of the lung function data. The manuscript was written by M.C., S.C., L.S. and A.P. and reviewed and approved by all the authors.

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