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Comparison of the effect of beclometasone/formoterol in asthma patients after methacholine-induced bronchoconstriction

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TITLE: Comparison of the effect of beclometasone/formoterol in asthma patients after methacholine-induced bronchoconstriction: a non-inferiority study using metered dose versus dry powder inhaler.

PIs: Dave Singh, Frans van den Berg, Brian Leaker and Brian Lipworth (PIs at each site). They had direct clinical responsibility for patients.

RUNNING TITLE: Beclometasone/formoterol DPI as reliever

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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 (MART) is effective and reduce the risk of exacerbations in uncontrolled asthmatics.
- There are only two dry powder inhalers (DPI) with indication for MART therapy.

WHAT THIS STUDY ADDS

- Extrafine Foster® NEXThaler® DPI is suitable for 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.

ABSTRACT

Aim

To demonstrate the non-inferiority of extrafine beclomethasone/formoterol Fumarate (BDP/FF) dry powder inhaler (DPI) vs extrafine BDP/FF pressurised 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 FEV₁ at 5 min post-dose. 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 post-dose.

Results

FEV₁ adjusted mean difference between BDP/FF DPI and BDP/FF pMDI at 5 min post-dose was 2 ml (95% CI: -0.060; 0.065). A similar result was observed at the other time points. Median time to 85% recovery in FEV₁ 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 (MART) approach also with NEXThaler®.

Trial registration number: ClinicalTrials.gov Identifier NCT03108534, EudraCT number 2016-003672-

1. 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 optimise ICS/LABA therapy in uncontrolled asthma (2). The effectiveness of this regime 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). In fact, 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 BDP/FF vs. SABA 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 represent 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 one-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 μ g of BDP and 6 μ g 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 (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, 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.

In order 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 the Foster® NEXThaler® with the pMDI using methacholine induced bronchoconstriction, which is a widely used and representative model of bronchoconstriction and a well-accepted bioassay for bronchodilator efficacy in asthma.

2. METHODS

2.1 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: non-smokers or ex-smokers, pre-bronchodilator FEV₁ of at least 65% of predicted value and at least 1.5 L, a positive response to methacholine challenge test (defined as a PD₂₀ FEV₁ ≤ 1 mg) and stable treatment with low-medium doses of ICS or ICS plus LABA combination as per current GINA 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.

Non-permitted concomitant medications included systemic corticosteroids, leukotriene modifiers, anti-IgE antibodies, antihistamines, anticholinergic drugs and beta-blockers. Patients could remain on their previous treatment with ICS or ICS plus LABA combination, provided that LABA was withheld in the 48 hours before each study visit. Salbutamol was also allowed as rescue medication, with a required washout of at least 8 hours 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 4 clinical sites in United Kingdom, 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 form was obtained from all study participants.

2.2 Study design

This was a randomised, double blind, double dummy, active treatment and placebo controlled, 3-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, in order 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 randomised and attended the clinical site for 3 treatment visits (V1 - V3), each separated by a 5 to 21 days washout period.

At each treatment visit, a baseline FEV₁ was measured followed by a methacholine challenge test. To minimise variability between treatment days, FEV₁ values before treatment visits had to be within \pm 15% of value at visit 1. During the challenge, performed using the "5-breath dosimetric method", increasing doubling doses of methacholine were administered to the patients until a decrease in FEV₁ between 30% and 45% of the baseline value was observed. In case the level of dyspnoea became too severe or the decrease in FEV₁ 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 minute from the end of the provocation test, according to the randomisation list. The following treatments were administered: 1 inhalation of extrafine formulation BDP/FF 100/6 μ g as DPI NEXThaler® (Foster® NEXThaler® 100/6 μ g) or 1 inhalation of extrafine formulation BDP/FF 100/6 μ g as pMDI (Foster® 100/6 μ g pMDI) or 1 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 first, the other half Foster® 100/6 pMDI.

FEV₁ and level of dyspnoea, assessed with the Borg scale, were measured before the methacholine challenge test (FEV₁ only), at the end of the challenge (PD30) and at 1, 3 (Borg scale only), 5, 10, 20 and 30 minutes after study drug intake.

2.3 Study procedures

FEV₁ 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 2 (during methacholine challenge test) or 3 (for post-dose time points) technically satisfactory attempts was recorded and used in the analysis. In order to avoid unnecessary discomfort for the patients due to the exhalation until the residual volume, each effort was terminated after 2 sec 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 pre-diluted vials of methacholine chloride solution was used by all clinical sites (Stockport Pharmaceuticals). Saline solution was inhaled first, followed by a post-saline FEV₁, 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. FEV₁ measurements after each dose of methacholine were obtained in duplicate.

2.4 Statistical Methods

The primary objective of the study was to demonstrate the non-inferiority of BDP/FF 100/6 DPI vs BDP/FF 100/6 pMDI on the onset of relief from methacholine-induced bronchospasm in terms of change in FEV₁ (L) from baseline to 5 minutes after study drug intake. The non-inferiority 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 FEV₁ (L) from baseline to all other time-points after study drug intake, time to recovery in FEV₁ (defined as the return to 85% of the baseline FEV₁ value), FEV₁ AUC_{0-10min} normalised 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 post-methacholine 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 non-inferiority testing of BDP/FF 100/6 DPI vs BDP/FF 100/6 pMDI, based on the change in FEV₁ (L) from baseline to 5 minutes after study drug intake, assuming a non-inferiority margin of -0.120 L between the two treatments, a within-subject standard deviation of 0.20 L and at a two-sided alpha error set at 0.05. Assuming a drop-out rate of 10%, approximately 60 subjects were to be randomized. All randomised subjects who completed at least one treatment period were included in the Intention To Treat (ITT)

Population.

Change in FEV₁ from baseline to 5 minutes after study drug intake was analysed using an analysis of covariance (ANCOVA) model including treatment, period and subject as fixed effects and FEV₁ baseline and FEV₁ 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 FEV₁ (L) from baseline to all other time-points and FEV₁ AUC_{0-10min} normalised 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 baseline 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 (IQR). For subjects who recovered within 30 minutes 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 minutes, the time to recovery was extrapolated by the trend observed in the first 30 minutes. In the event the extrapolated time to recovery was greater than 50 minutes, it was conventionally set at 50 minutes. Comparison between treatment groups and p-value were estimated by Cox model.

AEs, Serious AEs (SAEs) and AEs leading to discontinuations were presented descriptively.

All efficacy analyses were performed on the Intention to Treat (ITT) population, defined as all randomised 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 randomised subjects who received at least one dose of study treatment after randomisation.

Data were analysed using SAS Version 9.4 for Windows.

3. RESULTS

Patients' baseline characteristics are reported in Table 1. Sixty-five subjects were randomised to treatment. Five subjects did not complete the treatment periods for the following reasons (1 subject each): adverse event, baseline FEV₁ < 65% of predicted value, fall in FEV₁ of at least 30% not reached, excessive reaction to methacholine with fall in FEV₁ > 45% and lost to follow-up.

3.1 Methacholine challenge

Baseline FEV₁ measurements (P1) and measurements at the end of the challenge (P2) were similar between all the treatments (Table 2). The FEV₁ at the end of the provocation dropped to approximately 66% of P1.

3.2 FEV₁

Both BDP/FF formulations caused rapid FEV₁ increases; there was an FEV₁ improvement at 5 minutes post dose, 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 minutes post-dose, 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 FEV₁ AUC_{0-10min} normalised by time were 2.26 L, 2.25 L 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 actives being superior to placebo ($p < 0.001$).

The recovery with BDP/FF DPI was fast (median time of 8 minutes), similar to BDP/FF pMDI (median time of 7.5 minutes; $p = 0.554$), and much shorter than placebo (28 minutes; $p < 0.0001$) (Figure 3). At 5 minutes post-dose, the mean FEV₁ value was greater than 82% of baseline value after inhalation of the active treatments and lower with placebo (74%).

3.3 Borg dyspnoea scale

The mean Borg dyspnoea score was below 0.5 before the methacholine challenge test (Figure 4, P1) and increased (worsening) up to more than 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 minutes post-dose time point). Median time to recovery, expressed as the time needed for the Borg dyspnoea score to reach 50% of recovery, was 4.2 minutes with BDP/FF DPI, which was similar to BDP/FF pMDI (4.0 minutes, $p = 0.609$), and significantly shorter than placebo (10.0 minutes; $p = 0.042$).

3.4 Adverse events

No serious or severe adverse events (AEs) or adverse drug reactions (ADRs) were reported. The frequency of the reported AEs was comparable among treatments (4 patients reported AEs after intake of BDP/FF DPI and BDP/FF pMDI and 5 patients after intake of placebo). The most commonly reported AEs were nasopharyngitis (1 after BDP/FF DPI and 1 after BDP/FF pMDI) and cough (2 after BDP/FF DPI). Other AEs, occurring in no more than 1 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.

4. DISCUSSION

The results of the present study showed that BDP/FF extrafine formulation DPI was non-inferior to BDP/FF extrafine formulation pMDI in the reliever effect as measured by 5-minute post-dose FEV₁. The FEV₁ increase was 224 and 222 mL higher than placebo with BDP/FF DPI and pMDI, respectively, at 5 minutes 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.

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 DPI and BDP/FF 100/6 pMDI were again comparable, with times to recovery of 8 and 7.5 minutes, respectively, confirming rapid reliever effect.

The FEV₁ improvements exceed the threshold accepted for significant bronchodilator reversibility (14), and were observed rapidly (within 5 minutes). Furthermore, the FEV₁ improvements at 5 minutes 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 FEV₁ after the use of methacholine was greater than 30% from baseline values, with most patients demonstrating a post-methacholine FEV₁ lower than 2L, 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 FEV₁ recovery was <5 minutes for both treatments, while in the current study this was approximately 7-8 minutes 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 minutes versus 21.4 minutes). 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, then 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 FEV₁ % predicted than in the current study (92 % versus 80 % respectively). It is possible that a thickened mucosa and submucosa and altered airway secretions have affected the availability of the β₂-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 FEV₁ to return to 85% of

baseline was 7.2 minutes with formoterol DPI, 6.5 min with salbutamol and 34.7 minutes 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 (sGaw) as primary endpoint, as sGaw can be a more sensitive index of changes in airway calibre than FEV₁, 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 (BAM), that is activated at an average inspiratory flow rate of 35 L/min (9)(10), triggers the counting only of effective inhalations as compared to other available DPIs such as 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 to generate a drop of 4 kPa, that is lower than that of other device not used for MART posology like Ellipta® (74 L/min) (19).

In another published study (20), the *in vitro* characteristics of NEXThaler® were compared to Diskus® and Turbohaler® dry powder at flow rates between 30 L/min and 100 L/min, relevant to the target population for MART, showing 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 therefore all patients were able to activate and use the device effectively.

In summary, this study shows that the bronchodilator effect of Foster® 100/6 NEXThaler® extrafine formulation occurs rapidly and is non-inferior to Foster® 100/6 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 DPI

NEXThaler® for the MART approach.

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D.Singh, F. van den Berg, B. Leaker and B. Lipworth were the principal investigators of the 4 clinical sites where the clinical trial was performed. D. Singh also acted as coordinating investigator. S. Jabbal was the co-investigator at the Scottish Centre for Respiratory Research in Dundee. M. Corradi, S. Collarini, V. Mongelli, L. Santoro, A. Piccinno and B. Lipworth were involved in the study design and results interpretation. S. Biondaro and L. Santoro 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. Corradi, S. Collarini, L. Santoro and A. Piccinno and reviewed and approved by all the authors.

COMPETING INTERESTS:

D. Singh 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. van den Berg has no conflict of interests to declare.

B. Leaker 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. Corradi has received grants and honoraria for lectures from Chiesi.

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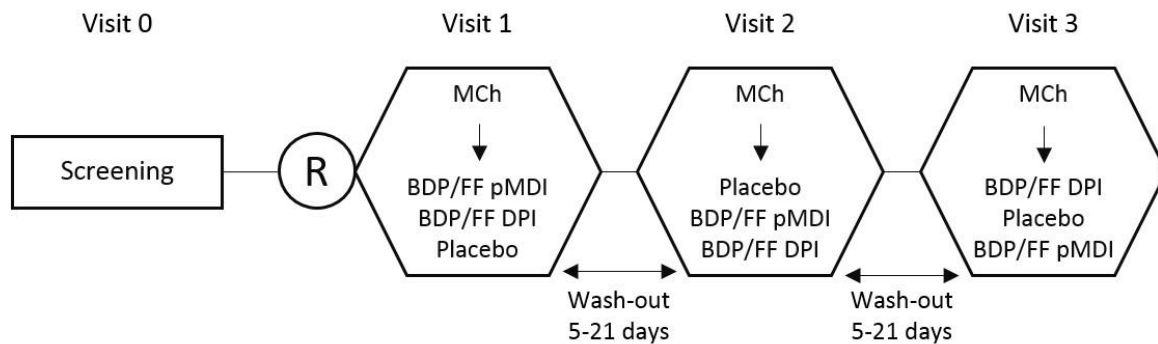


Figure 1: Study flow chart

R = randomisation, MCh = Methacholine challenge test, BDP/FF = Beclometasone dipropionate/formoterol fumarate

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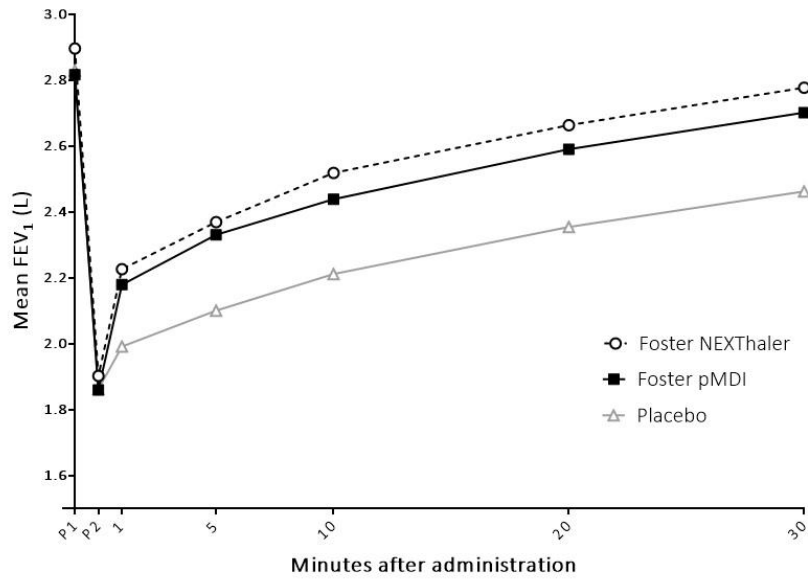


Figure 2: FEV₁ profiles

P1: baseline value; P2: value at the end of the methacholine challenge test

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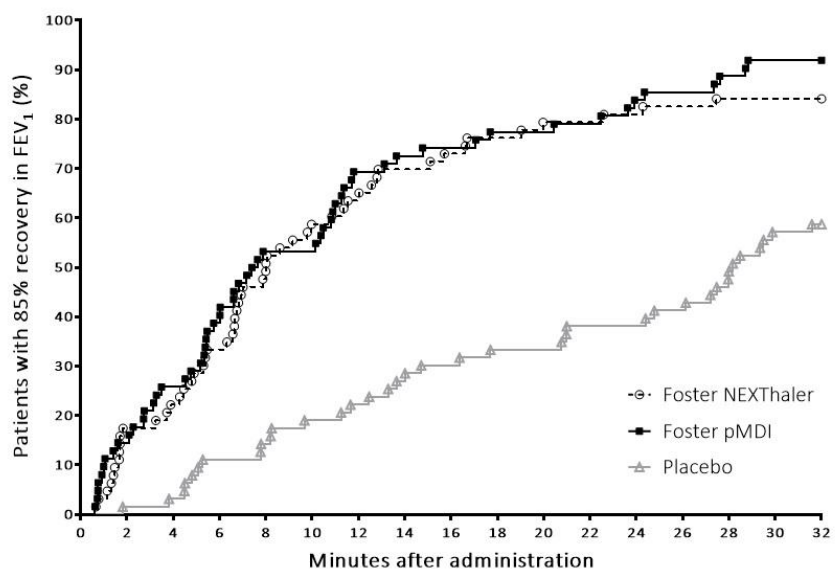


Figure 3: FEV₁ time to recovery from methacholine challenge

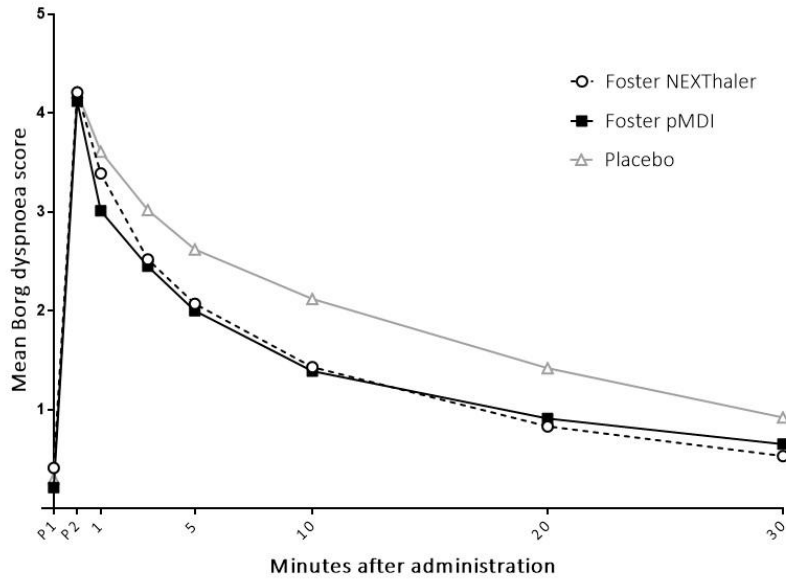


Figure 4: Borg dyspnoea score profiles

P1: value before the start of the methacholine challenge test; P2: value at the end of the methacholine challenge test (baseline)

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Table 1: Patient baseline demographics. ICS: inhaled corticosteroids, LABA: long-acting beta₂-agonist, SD: standard deviation

Characteristics	Patients (n = 65)
Male/female	40/25
Mean Age ± SD, yrs	41.3 ± 10.8
Non-smokers/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 alone	40
ICS/LABA combinations (free or fixed)	25

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Table 2: FEV₁ and Borg dyspnoea evaluation data (ITT population). L: liter; SD: Standard Deviation; SE: Standard Error; CI: Confidence Interval; IQR: InterQuartile Range. † Estimated by the Kaplan-Meier method. For FEV₁: 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. * p < 0.0001 for superiority testing

	BDP/FF DPI (N = 63)	BDP/FF pMDI (N = 62)	Placebo (N = 63)
FEV₁, 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 post-dose, 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) *
BDP/FF pMDI vs placebo		0.22 (0.16; 0.28) *	
Time to recovery, min: median (IQR) †	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 post-dose			
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) *
BDP/FF pMDI vs placebo		-0.62(-0.96; -0.29) *	
Time to recovery, min: median (IQR) †	4.25 (2.50; 10.00)	4 (1.00; 8.75)	10.00 (3.00; 20.00)