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Relief of methacholine-induced bronchospasm with extrafine beclomethasone dipropionate/formoterol in comparison with salbutamol in asthma

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ABSTRACT

Background: Short-acting beta2-agonists like salbutamol and terbutaline are used as rescue medications for acute bronchoconstriction and relief of symptoms due to their rapid onset of action. The aim of this study was to assess whether inhaled beclomethasone dipropionate (BDP)/formoterol fumarate (FF) combination in extrafine formulation is non-inferior to salbutamol in the speed of reverting methacholine-induced bronchoconstriction and symptoms.

Methods: Fifty-six asthmatic patients were examined in a multicentre, randomised, double blind, double dummy, active treatment and placebo controlled three period cross-over study. On three different days, a single dose of BDP/FF 100/6 μg in pressurised metered-dose inhaler (pMDI) extrafine formulation or salbutamol 200 μg pMDI or placebo was inhaled after FEV_1 had dropped by 30–45% with methacholine challenge.

Results: The median time to recovery of FEV_1 to 85% of baseline was similar for BDP/FF and salbutamol (3.66 and 2.15 min, respectively), but significantly longer for placebo (21.1 min). The planned analysis on adjusted mean time to recovery showed that the difference from methacholine-induced bronchoconstriction between BDP/FF and salbutamol was 3.82 min (95% confidence interval: −0.85 to 8.5), therefore greater than 2 min supposed in the study design. The difference between BDP/FF and salbutamol was not clinically significant. The two active treatments were also comparable in terms of the relief of symptoms (as assessed by the Borg dyspnoea scale).

Conclusions: BDP/FF combination has a fast onset of action, similar to that of salbutamol, and may represent a good alternative as rescue medication in asthmatic patients.

1. Background

Short-acting beta2-agonists (SABA), like salbutamol and terbutaline, are used as rescue medications for acute bronchoconstriction and symptom relief due to their rapid onset of action [1]. Formoterol (FF), a long-acting beta2-agonist (LABA), also has a rapid onset of action comparable to that of salbutamol [2]. Clinical studies have shown that FF used as a rescue medication provides a similar quick relief of asthma symptoms as compared to salbutamol, and also leads to better asthma control due to the longer duration of action [3]. The rescue use of FF is not shared with other LABA such as salmeterol which has slower onset of action.

Persistent symptoms in patients with asthma are associated with increased airway inflammation. Regular maintenance therapy with inhaled corticosteroids (ICS) provides anti-inflammatory effects in such patients. Combination therapy using an ICS associated with a LABA in the same inhaler is now the first line maintenance treatment option in patients not adequately controlled by ICS alone [4]. Recently, studies have shown that a strategy using the budesonide/FF combination in a dry powder inhaler (DPI) as both maintenance and reliever therapy may lead to a reduction in the

Abbreviations: BDP, Beclomethasone dipropionate; CI, Confidence interval; CFC, Chlorofluorocarbon; DPI, Dry powder inhaler; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; FF, Formoterol fumarate; HFA, Hydrofluoroalkane; ICS, Inhaled corticosteroids; LABA, Long-acting inhaled beta2-agonist; LS, Least square; MEF50, Maximum expiratory flow rate at 50% of FVC; Mch, Methacholine challenge; pMDI, Pressurised metered-dose inhalers; PC, Provocative concentration; SABA, Short-acting beta2-agonist; sGaw, Specific airway conductance.

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Table 1
Main characteristics of the intention-to-treat population.

Patients	56
Male/female	25/31
Mean age, yrs	40.3 (±12.9)
Smoking habit: S/NS/EX	3/43/10
FEV_1, L (% pred)	2.95 ± 0.68 (92.2 ± 12.0)
FVC, L (% pred)	3.96 ± 0.90 (95.2 ± 11.6)
FEF_{25-75}, L/s	2.36 ± 0.81
Previous medication for asthma	
- ICS alone	15
- LABA/ICS combinations	41

S = Smoker, NS = Never smoked, EX = Ex smoker, ICS = inhaled corticosteroids, LABA = long-acting beta2-agonist. Means + SD are shown.

rate of severe asthma exacerbations compared to traditional strategies using fixed maintenance doses of ICS/LABA combination with the use of SABA as rescue medication [5]. The efficacy of this maintenance and reliever therapy is due to the rapid onset of action of FF, which is able to afford a quick relief of asthma symptoms and to the concomitant increase in the dose of ICS to provide increased anti-inflammatory effects at a time when the asthmatic condition is worsening [6,7].

The extra-fine beclomethasone/formoterol (BDP)/FF combination delivered through hydrofluoralkanes (HFA-pMDI), has demonstrated similar efficacy, in terms of improvement in pulmonary function and asthma control, compared to fluticasone/salmeterol and budesonide/FF combinations in asthma [8,9]. Furthermore, the onset of bronchodilation, evaluated as FEV_1 change after 5, 15, 30 and 60 min from the morning dose on the first and last day of a 12-week treatment period, was not different between the patients who received BDP/FF 200/12 μg b.i.d. compared with budesonide/FF 400/12 μg b.i.d. [10]. Theoretically, the BDP/FF combination can also be used as "maintenance and reliever therapy", although to date this has not been evaluated.

The budesonide/FF combination has a rapid onset of bronchodilation that is similar to salbutamol in a methacholine-induced bronchoconstriction model [7]. We wanted to study the BDP/FF combination in the same model to investigate whether this drug could also effectively provide rapid relief of methacholine induced bronchoconstriction, for this drug to be used instead of salbutamol as a reliever in clinical practice, it is necessary to ensure that the acute bronchodilator effects of BDP/FF and salbutamol are similar. Therefore, we determined whether BDP/FF was non-inferior to salbutamol for the relief of methacholine induced bronchoconstriction. We show data that supports further clinical studies to investigate the effects of BDP/FF combination as a maintenance and reliever therapy in asthma.

2. Methods

2.1. Patients

Asthmatic patients aged ≥18 yrs were recruited according to the following inclusion criteria: a diagnosis of asthma for at least 6 months; an increase in FEV_1 of 12% and >200 mL over baseline after administration of 400 μg salbutamol pMDI or a positive response to a methacholine challenge test (defined as a $PC_{20}FEV_1 < 8$ mg/mL or $PD_{20}FEV_1 < 1$ mg); previous treatment with low-medium doses of ICS or ICS with a LABA; $FEV_1 > 70\%$ of the predicted value and at least 1.5 L. Patient characteristics are reported in Table 1. The main exclusion criteria were a recent (in previous 6 weeks) asthma exacerbation requiring systemic corticosteroids and the presence of uncontrolled cardiovascular, respiratory or other clinically relevant diseases. Non-permitted medications during the study period included beta-blockers, leukotriene modifiers, antihistamines, cromoglycate and nedocromil, systemic corticosteroids, anti-IgE antibodies or cholinesterase inhibitors. Ten centres in two countries (Italy and UK) participated to the study, which was approved by the corresponding Ethic Committees. The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all applicable regulations. Written informed consent was obtained from each patient. The EudraCT number was 2008-000905-12.

2.2. Study design

This was a randomised, single dose administration, double blind, double dummy, active treatment and placebo controlled three period cross-over study. The study design is shown in Fig. 1. There was a screening visit (V1) to verify inclusion/exclusion criteria followed by a run-in period of 5–9 days during which patients continued ICS at doses of 200–1000 μg BDP-Chlorofluorocarbon (CFC) daily or equivalent. If patients used a fixed ICS/LABA combination at the screening, they were moved to the free combination of the same ICS and LABA dose via two separate inhalers. There were three treatment days (V2–V4) separated by a wash-out of 3–7 days. LABA treatment was stopped 48 h before and SABA 8 h before these visits.

At each study visit baseline FEV_1 was measured, and then the methacholine challenge test was performed if FEV_1 did not differ more than ±15% from the visit 1 baseline FEV_1 value (otherwise, the test was postponed and the patient was re-tested within 3 days). Methacholine was administered at increasing doses, until a decrease in FEV_1 between 30% and 45% from the baseline value was obtained [if dyspnoea became too severe during the provocation test, as judged by the subject or by the investigator, a "rescue" medication (salbutamol pMDI) was given and the visit was re-scheduled (3 days' window)]. After the target bronchoconstriction

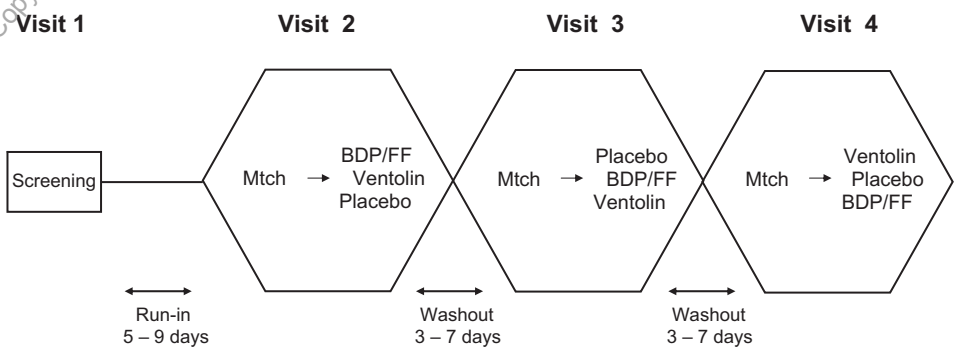

Fig. 1. Study design flow chart. Mtch = methacholine challenge. BDP/FF = beclomethasone/formoterol.

was obtained, the Borg scale of dyspnoea was assessed, and then study drugs and double-dummy placebo treatments were administered in accordance with the randomisation schedule: one inhalation of BDP/FF 100/6 μg in pMDI extra-fine formulation (Foster™ pMDI), or two inhalations of salbutamol 100 μg in pMDI (Ventolin™ pMDI), or placebo. All test medications were administered in the first minute after the measurement of FEV_1 achieving the target methacholine-induced bronchoconstriction. FEV_1 was then measured at 1, 3, 5, 10, 20 and 30 min after the inhalation of the test treatments. After 30 min, the patients were managed without any drug restriction according to the investigator's judgement.

2.3. Study procedures

Spirometry was performed in each centre according to the ATS/ERS recommendations [11]. Throughout the study, methacholine challenge, study treatment and pulmonary function tests started in the morning between 7:00 and 11:00 a.m. and at the same time of the day for each subject. At least two acceptable maximal expiratory flow–volume curves were obtained, with a difference between two highest FEV_1 and FVC of less than 200 mL. In addition to FEV_1, other measures were FVC, FEF_{25-75} and MEF_{50} (these last two measurements were obtained from the best test curve, i.e. greatest sum FEV_1 + FVC).

For the methacholine challenge test, saline solution was inhaled first, and the post-saline FEV_1 value was retained as the baseline value. Freshly prepared different concentrations of methacholine chloride were administered using a dosimetric technique, in order to obtain the following cumulative doses: 22.5, 45, 90, 180, 360, 720, 1440 and 2880 μg. Each dose was administered at 5 min intervals. After each dose, expiratory flow–volume curves were obtained in duplicate. After appropriate instruction, patients estimated the intensity of the breathlessness by selecting a modified 10 point Borg dyspnoea ranging from 0 to 10, with 0 indicating no breathlessness (nothing at all), 0.5 extremely weak, 1 to 5 from very light to hard, 7 very hard, and 10 indicating a maximal tolerable sensation (very very hard).

2.4. Statistical analysis

The primary outcome of the study was the time to recovery in FEV_1, as expressed by the time to return of FEV_1 to 85% of the pre-methacholine value (baseline value). The effect of BDP/FF was compared with that of salbutamol and placebo, using an ANCOVA model on untransformed data with subject as random effect, treatment and period as fixed effect and with baseline as a covariate. The hypothesis being tested was the non-inferiority of BDP/FF compared to salbutamol in the FEV_1 recovery after drug administration. The BDP/FF − salbutamol difference of adjusted treatment means of the model is presented as a two-sided 95% CI. Non-inferiority was decided *a priori* to be if the upper limit of this interval was lower than or equal to +3 min. The non-inferiority margin was less than one-third of the difference between active treatments and placebo observed in published papers [7,12–15].

A sample size of 42 was required to assure a power of 80% for the non-inferiority testing of BDP/FF vs. salbutamol, estimating a difference of 0 min between the two treatments, a standard deviation of the differences equal to 5 min and a two-sided significance level set at 5%. Time to recovery was illustrated graphically using the Kaplan–Meier method.

Secondary outcomes were time to recovery in Borg scale (50% decrease from post-methacholine value) and changes during recovery in FVC, FEF_{25-75} and MEF_{50} after methacholine-induced maximal bronchoconstriction. These outcomes were analysed with the same methods applied for the primary endpoint.

3. Results

Fifty-seven subjects were randomised and treated. Fifty-six were included in the intent to treat population (treated subjects with any post-baseline efficacy evaluation) and 50 performed all the three treatment periods. Six subjects did not complete the treatment period because of protocol violation, adverse event or consent withdrawal.

3.1. FEV_1

The mean FEV_1% predicted did not significantly change before the methacholine challenges at V2–V4. Fig. 2 shows the mean FEV_1 values measured before methacholine inhalation, at the maximum methacholine-induced bronchoconstriction, and at the different time points after inhalation of salbutamol, BDP/FF or placebo. Both active treatments induced a rapid reversal of methacholine-

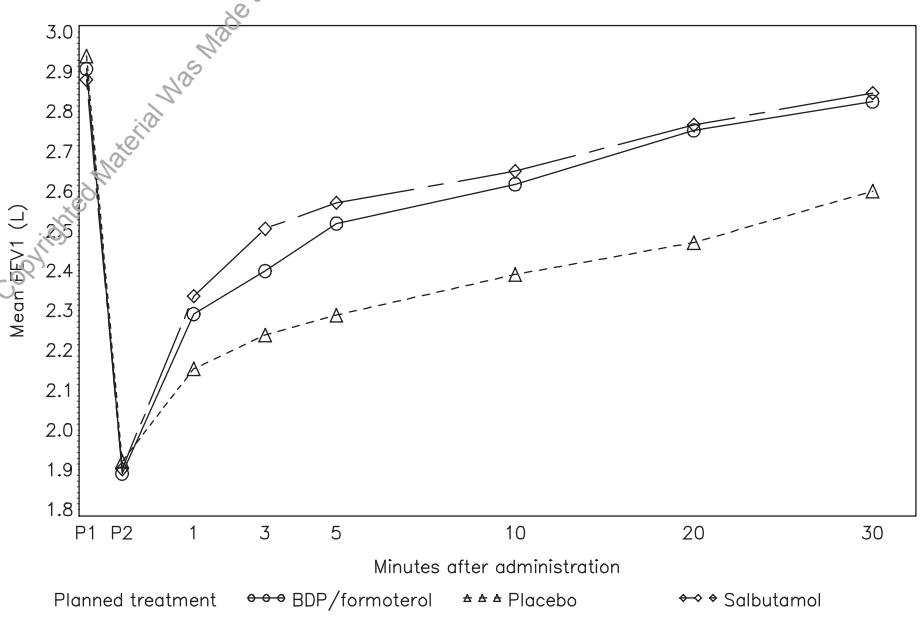

Fig. 2. FEV1 pre- and post-methacholine challenge. Points represent group mean values. P1 = pre-methacholine challenge P2 = immediately post-methacholine challenge.

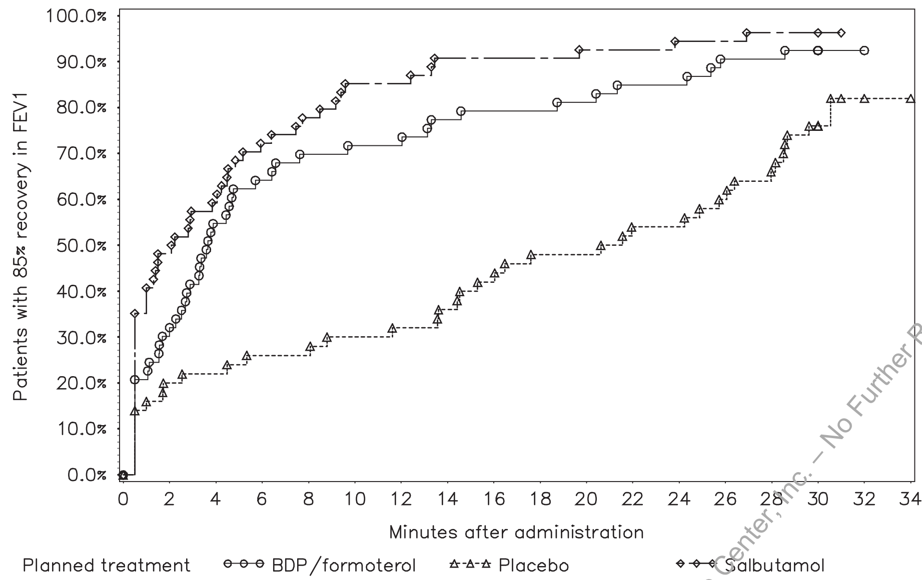

Fig. 3. Time to recovery from methacholine challenge; the percentage of patients with FEV1 > 85% of pre-methacholine challenge value are shown by treatment period. Points represent group mean values.

induced bronchoconstriction, and the difference between both active treatments and placebo was significant in all time points. At 1 min from the drug administration, FEV_1 improved by 0.23 L after salbutamol and by 0.17 L after BDP/FF in comparison with placebo; these increases were significant for both treatments in comparison with placebo, while there was no significant difference between the two active treatments.

Fig. 3 shows the probability of reaching an 85% recovery in FEV_1. A trend to a shorter recovery with salbutamol compared to BDP/FF was observed. The median time to recovery of FEV_1 to 85% of baseline was similar for BDP/FF and salbutamol (3.66 and 2.15 min, respectively), but significantly longer for placebo (21.4 min) (Table 2). The estimated probability of patients with recovery within 5 min (which is the accepted time for allowing the classification of inhaled drug as “fast-acting bronchodilators”) [16,17] were similar for BDP/FF and salbutamol group (Fig. 3 and Table 2).

The adjusted mean times to recovery in the three groups were 9.99, 6.17 and 22.50 min for BDP/FF, salbutamol and placebo respectively. The analysis of the primary endpoint showed that the difference in adjusted mean time to recovery from methacholine-induced bronchoconstriction between BDP/FF and salbutamol was 3.82 min [95% CI: −0.85 to 8.5]. Non-inferiority could not be declared because the right upper limit of the 95% CI was above the pre-specified non-inferiority margin of +3 min.

When changes in FVC, FEF_{27-75} or MEF_{50} during the reversal from methacholine-induced bronchoconstriction were considered, similar results were obtained: for all these spirometric indices, the recovery was shorter with salbutamol and BDP/FF than with placebo, without any difference between two active treatments. FVC data are shown in Fig. 4; At 30 min the FVC (L) was statistically significantly lower compared to pre-methacholine test values with all 3 treatments; mean difference = −0.19 L, 95% CI: −0.28 to −0.01 with BDP/FF, mean

Table 2
FEV_1 measurements and Borg score before methacholine challenge and at maximum methacholine-induced bronchoconstriction, and the times to FEV_1 or Borg recovery.

	Placebo (*N* = 50)	Salbutamol (*N* = 54)	BDP/FF (*N* = 53)
FEV_1, L (Mean ± SD)			
Baseline	2.94 ± 0.68	2.88 ± 0.71	2.91 ± 0.65
After methacholine	1.92 ± 0.43	1.90 ± 0.49	1.89 ± 0.43
Time of FEV_1 recovery (min)[a]			
Adjusted means[d]	22.50	6.17	9.99
Treatment comparison: difference (95% CI)			
Formoterol/BDP vs. Salbutamol or Placebo	−12.50 (−17.20; −7.71)[b]	3.82 (−0.85; 8.50)	
Salbutamol vs. Placebo	−16.30 (−21.10; −11.50)[b]		
Median time (95% CI)[c]	21.1 (14.4–26.4)	2.15 (1–4.2)	3.66 (2.7–5.7)
% of recovery within 5 min (95% CI)[c]	24% (14%–38%)	69% (56%–80%)	62% (49%–75%)
Borg score (Mean ± SD)			
After methacholine	4.52 ± 2.33	4.31 ± 2.45	4.02 ± 2.50
Time of Borg recovery[a]			
Median time (95% CI)[c]	8.25 (5–15)	3.5 (3–5.67)	5 (4–7.5)
% of recovery within 5 min (95% CI)[c]	40% (28%–55%)	61% (49%–74%)	56% (44%–70%)

SD = standard deviation.
[a] Calculated by linear interpolation as the difference between the time to return of FEV_1 to 85% of baseline or the time to return of Borg to 50% of baseline, and the time of the third medication intake.
[b] $p < 0.001$ [*p* value for superiority test].
[c] Estimated by the Kaplan and Meier method.
[d] Estimated by the ANCOVA model on untransformed data.

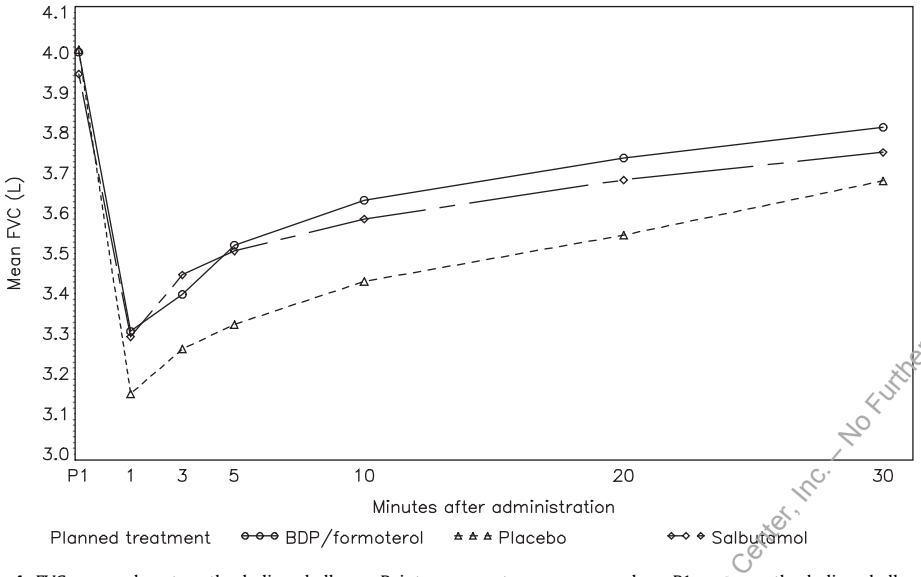

Fig. 4. FVC pre- and post-methacholine challenge. Points represent group mean values. P1 = pre-methacholine challenge.

difference = −0.20 L, 95% CI: −0.28 to −0.11 with salbutamol, and mean difference = −0.33 L, 95% CI: −0.44 to 0.21 with placebo. Similar patterns were observed at other time points, with no difference between the active treatments.

3.2. Borg dyspnoea scale

Fig. 5 shows the mean Borg dyspnoea scores measured at the maximum methacholine-induced bronchoconstriction and at the different time points after inhalation of salbutamol, BDP/FF or placebo. Methacholine-induced bronchoconstriction was associated with a high Borg score (4.02 4.31 and 4.52, before administration of BDP/FF, salbutamol placebo, and respectively). All treatments induced a significant decrease (improvement) in Borg dyspnoea scale from the maximum bronchoconstriction up to 30 min of recovery. The median time of recovery of the Borg dyspnoea scale (the time to achieve a 50% decrease from the post-methacholine value) for both active treatments was shorter compared to placebo, with no significant difference between the two active treatments (see Table 2). Similar results were obtained when the percentage of the patients who reached the pre-defined 50% recovery in Borg dyspnoea scale was plotted at the different time points (Fig. 6). At 5 min the mean Borg dyspnoea score for both BDP/FF and salbutamol was about 2, corresponding to a perception of dyspnoea as “fairly light”.

3.3. Adverse events

No serious or severe treatment emergent adverse events (AEs) or adverse drug reactions (ADRs) were reported. Between the treatment periods, one patient reported dysmenorrhoea 3 days after the treatment with salbutamol, one patient reported dyspnoea and tremor 7 days after the treatment with salbutamol and another patient reported nasopharyngitis 4 days after treatment with placebo. Moreover, one patient reported asthma exacerbation 6 days after the treatment with salbutamol and was withdrawn due to this AE.

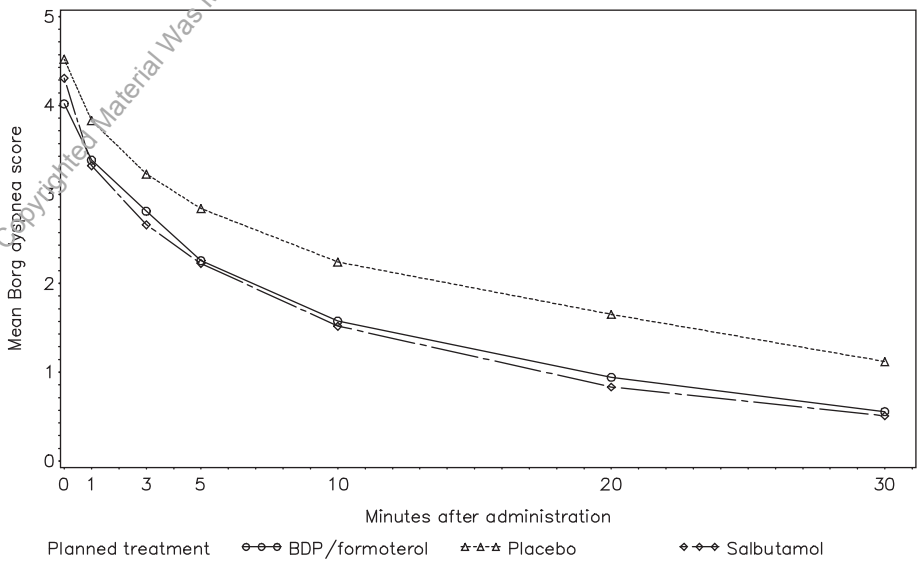

Fig. 5. Borg dyspnoea scores pre- and post-methacholine challenge. Points represent group mean values.

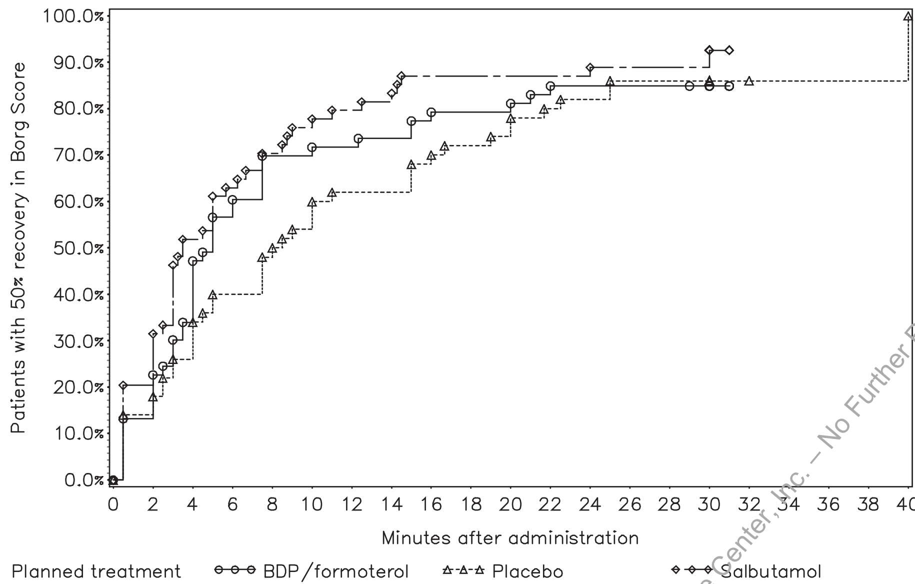

Fig. 6. Time to recovery from methacholine challenge; the percentage of patients with >50% recovery in Borg score are shown by treatment period. Points represent group mean values.

4. Discussion

The median time to recovery for both BDP/FF and salbutamol was less than 5 min, indicating that BDP/FF acted as a fast-acting bronchodilator in this methacholine challenge model (16, 17). The difference between the median times to recovery of FEV_1 between salbutamol and BDP/FF was minimal (1.5 min); this difference is unlikely to be clinically relevant. The primary endpoint analysis was not able to show that BDP/FF was non-inferior to salbutamol. However, these data show that the difference between these two drugs is small, and support the use of BDP/FF combination as a rescue medication in asthmatic patients. This is also confirmed by previous evidence showing that the onset of bronchodilation, was not different between the patients who received BDP/FF 200/12 μg b.i.d. compared with budesonide/FF 400/12 μg b.i.d. [10].

Previous studies have compared the onset of action of FF to that of salbutamol or salmeterol, using the same model of reversal from methacholine-induced bronchoconstriction. This model can be used to evaluate the speed of onset of bronchodilation induced by drugs that act by relaxation of bronchial smooth muscle. At least four studies have compared FF, in different formulations, with salbutamol, salmeterol and placebo, and have shown that FF has a very fast onset of action, similar to salbutamol and better than salmeterol, achieving pre-challenge values of airway conductances (SGaw) or FEV_1 within 3–5 min (12–15). Beach et al. [18] showed that the mean FEV_1 recovery time with FF 24 μg (5.7 min) was similar to salbutamol 400 μg (6.4 min), but that FF 12 μg had a longer recovery time (10.2 min). This suggests that the relative potency of FF and salbutamol in this model is 6 μg–100 μg respectively. This ratio has been confirmed by Benhamou et al. [19] using the same methacholine-induced bronchoconstriction model. The current study compared BDP/FF 100/6 μg with salbutamol 200 μg, so it is perhaps not surprising that the strict statistical non-inferiority between the two treatments could not be achieved.

Two studies have evaluated the onset of action of the budesonide/FF combination, with the aim to support its use as rescue medication [7,15]. It is notable that in both these studies no statistical hypothesis for non-inferiority was declared. The time to recovery of FEV_1 to 85% of the baseline value (the same primary outcome used in the present study) with a similar nominal dose of FF 6 or 12 μg ranged from 2.8 to 3.7 min (median time) (with an upper C.I. of 7.6 min), which is similar to the current study for BDP/FF.

Jonkers et al. [7] showed that the median recovery time with salbutamol 200 μg was 3.2 min, compared to 3.7 and 22 min for BUD/FF and placebo respectively. The small difference in recovery time between active treatments was also associated with a significantly shorter mean Borg recovery time for salbutamol (mean change: −0.41, $p = 0.024$). However, Jonkers et al. concluded that these differences between active treatments (0.5 min difference in recovery times) were not clinically relevant [7].

Derom et al. [20] used the sensitive measurement of airway resistance as endpoint in this methacholine model, and showed that FF even when used at higher than recommended doses has as slower onset of action compared to salbutamol. This suggests that salbutamol has an extremely rapid onset of action on airway calibre that cannot be matched by FF. The important question is whether these differences in airway calibre translate into clinically meaningful differences.

We speculate that any small immediate measurable benefits in terms of relief of bronchoconstriction in favour of salbutamol should be balanced against the longer duration of formoterol that can have clinical benefits. Furthermore, the delivery of the ICS component of the combination therapy also has benefits when used as reliever medication by reducing progression to a severe exacerbation.

In comparison with previous studies, the present study has several important differences: a) the number of patients enrolled in the present protocol was much greater than in other studies, and this number was obtained by computing the exact number of patients to be examined according to the power of the study; b) the primary outcome was to demonstrate the non-inferiority of BDP/FF vs. salbutamol based on lung function (FEV_1); c) several centres participated to the study, and this may increase the strength of the results obtained; d) all patients were ICS or ICS/LABA combination users before screening, which represents the target population of the maintenance and reliever approach; e) our study employed an extrafine pMDI, which has a relative case of use in case of shortness of breath as compared to a passive DPI requiring the patients inspiratory effort to aerosolize and deliver the formoterol dose to the lung.

In the current study, patients who were on ICS/LABA combinations discontinued the LABA for 48 h before methacholine challenge. This was done to minimise beta agonist tolerance caused by regular LABA treatment; this ensured that the reliever properties of salbutamol and BDP/FF were fully observed rather than attenuated by the development of beta agonist tolerance. However, one could argue that BDP/FF would be used in real-life as a reliever only by patients who were taking this inhaled treatment as a maintenance therapy as well. A reasonable alternative to the current study design would have been to place all patients on BDP/FF as a maintenance therapy, and continue this up to methacholine challenge. This would evaluate the effect of the reliever under conditions where beta agonist tolerance may have developed. This is study design that is worthy of consideration in the future. Nevertheless, the current study does still provide a robust comparison of the drugs in the methacholine challenge model.

These data support the use of BDP/FF combination as rescue medication in asthma management, like for budesonide/FF in the context of the maintenance and reliever strategy. Because the “maintenance and reliever strategy” using an ICS and a fast-acting beta2-agonist in the same combination has been demonstrated to be effective in preventing exacerbations and maintaining a good asthma control [4], the demonstration of BDP/FF combination as a quick reliever of bronchoconstriction may suggest that it can be used both as maintenance and as rescue medication in asthmatic patients not adequately controlled by ICS alone. This hypothesis must be demonstrated by appropriately designed controlled clinical trials.

5. Conclusions

In conclusion, BDP/FF combination has a fast onset of action, similar to that of salbutamol, and may represent a good alternative as rescue medication in asthmatic patients.

Competing interests

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Authors’ contributions

D Singh, M Corradi, PL Paggiaro, E Bindi, R. Baronio S Petruzzelli were involved in the design of the study, data collection, analysis and interpretation and the drafting of the paper. All authors had complete access to the study report, made final decisions on all aspects of the article and hence are in agreement with, and approve, the final version of the submitted article.

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