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Efficacy and safety of inhaled extrafine beclomethasone dipropionate in adults with asthma: a randomized, parallel-group, dose-ranging study (BEAM)

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ABSTRACT

Introduction: This manuscript describes a Phase II, dose-ranging, randomized, double-blind, placebo- and active-controlled, parallel-group study conducted to identify the appropriate dose of beclomethasone dipropionate (BDP) to be used in a single-inhaler extrafine formulation triple combination of BDP, formoterol fumarate and glycopyrronium.

Methods: Patients aged 18–75 years with poorly-controlled asthma, receiving low/medium-dose inhaled corticosteroid (ICS), and who had forced expiratory volume in the 1st second (FEV₁) 50–85% predicted, were randomized to inhale BDP 50, 200 or 400 µg twice daily (BID); total daily doses of 100, 400 and 800 µg), placebo, or the active comparator QVAR® 160 µg BID, all via pressurized metered-dose inhalers for 8 weeks. The primary objective was to evaluate superiority of BDP over placebo for change from baseline in pre-dose morning FEV₁ at Week 8. ClinicalTrials.gov: NCT03084718.

Results: Of 610 patients randomized, 559 (91.6%) completed the study. For pre-dose morning FEV₁ at Week 8, BDP 200 µg BID was superior to placebo, with a statistically significant difference of 113 ml (95% CI 18, 209); differences vs placebo for BDP 50 and 400 µg BID were not significant (44 [–52, 140] and 93 [–3, 188] ml, respectively). Secondary efficacy endpoint results supported the primary endpoint in identifying BDP 200 µg BID as the appropriate dose. Adverse events were experienced by 23.5, 25.0 and 30.6% patients with BDP 50, 200 and 400 µg BID, 34.7% with placebo, and 30.6% with the active comparator.

Conclusion: In this dose-ranging study, BDP 200 µg BID offered the optimal balance of efficacy and safety in patients with asthma poorly controlled on low/medium-dose ICS.

Abbreviations: ACQ-7: Asthma Control Questionnaire-7; BDP: beclomethasone dipropionate; BID: twice daily; CI: confidence interval; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FEV₁: forced expiratory volume in the 1st second; FF: formoterol fumarate; FVC: forced vital capacity; G: glycopyrronium; ICS: inhaled corticosteroid; ITT: intention-to-treat; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; MMRM: mixed model for repeated measurements; PEF: peak expiratory flow; pMDI: pressurized metered dose inhaler; PP: per protocol; UFC: urinary free cortisol

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Introduction

A number of single-inhaler triple combinations of an inhaled corticosteroid (ICS), a long-acting β₂-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) are available or in development for the management of asthma and chronic obstructive pulmonary disease (COPD). One of these is the extrafine formulation (i.e. with mass median aerodynamic diameter <2 µm (1)) combination of beclomethasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium (G). Such

extrafine particles are more able to consistently reach small airways than non-extrafine particles (2–4), with resulting enhanced drug delivery to these areas, and lower deposition in the oropharynx (5). This is potentially important, since the pathophysiological involvement of small airways in both asthma and COPD has been well documented (6). Further, the extent of inflammation in the small airways correlates with asthma symptoms and control (7,8), and the level of resistance in the small airways of patients with asthma correlates with worsening

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 Supplemental data for this article can be accessed at [publisher's website](#).

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health status (9), dyspnea (9), and asthma exacerbations (10).

This manuscript reports the results of a dose-ranging study that was conducted as part of the US development program of extrafine BDP/FF/G delivered via pressurized metered dose inhaler (pMDI). The aim of the study was to identify the appropriate dose of BDP for use in this combination. No previous dose-finding study has been conducted for this extrafine formulation of BDP. The BDP dose that has been approved in Europe for the management of COPD within the triple therapy BDP/FF/G is 200 µg twice daily (BID).

Materials and methods

Trial design

This was a Phase II, multi-center, randomized, double-blind, placebo- and active-controlled, parallel group, dose-ranging study. After an initial screening visit, prior to which asthma maintenance medication was discontinued, patients entered a two-week run-in period, when they received the ICS QVAR® (Teva Respiratory, LLC, Parsippany, NJ, USA; which contains extrafine BDP and is approved in the US for the management of asthma) at an equivalent dose to their prior ICS. Patients were then randomized equally to one of five treatment groups, to inhale extrafine BDP 50, 200 or 400 µg BID (doses expressed ex-valve; Chiesi Farmaceutici SpA, Parma, Italy; total daily doses 100, 400 or 800 µg), placebo, or QVAR 160 µg BID (dose expressed ex-mouthpiece [200 µg ex-valve]; total daily dose 320 µg [400 µg ex-valve]; described as 'active comparator' henceforth to avoid confusion), all via hydrofluoroalkane pMDI. This dose of QVAR was selected as the active comparator on the basis of in-vitro data demonstrating comparable BDP delivered doses from pMDIs containing 50 µg per actuation (ex-valve) of the Chiesi and Teva formulations, and also comparable delivered doses from pMDIs containing 100 µg per actuation (Chiesi data on file). Over the eight-week treatment period, patients attended visits at Weeks 4 and 8. Albuterol (via pMDI) was permitted as rescue medication after screening and throughout the study, but not within 6 h prior to the start of a visit. ICSs (other than study medication), LABAs, LAMAs, short-acting β_2 -agonists (other than rescue medication), short-acting muscarinic antagonists, xanthine derivatives, and any other asthma treatment were not permitted for the duration of the study. Caffeine intake was not permitted in the 6 h prior to spirometry.

At each visit during the treatment period, spirometry was performed pre-dose (with forced expiratory volume in 1 s [FEV₁] and forced vital capacity [FVC] recorded), along with the Asthma Control Questionnaire-7 (ACQ-7). Patients recorded their peak expiratory flow (PEF), symptoms and rescue medication use daily in an electronic diary. Adverse events were captured throughout the study, with vital signs recorded at each visit. Hematology and blood chemistry, 12-lead electrocardiogram (ECG), and 24-h urinary free cortisol (UFC) and creatinine were recorded at baseline and Week 8.

All patients provided written informed consent prior to any study-related procedure. The study was approved by independent ethics committees for each institution and was performed in accordance with the principles of the Declaration of Helsinki, and the International Conference on Harmonization notes for guidance on Good Clinical Practice (ICH/CPMP/135/95). The study was registered at ClinicalTrials.gov (NCT03084718). The protocol was amended three times. Most changes were to clarify instructions to the investigators; the range of allowable FEV₁ was expanded, from 60–80% to 50–85% of predicted normal, and upper body mass index limit was increased from 30 to 35 kg/m², in order to facilitate patient recruitment.

Participants

The study recruited male or female patients between the ages of 18 and 75 years, who had been diagnosed with asthma at least a year prior to entry, evidence of poorly controlled disease (ACQ-7 ≥ 1.5), pre-bronchodilator FEV₁ 50–85% of predicted normal, a change in FEV₁ $\geq 12\%$ and ≥ 200 ml within 30 min after inhaling albuterol 360 µg, and a basal morning serum cortisol level 5–28 µg/dl. Eligible patients were receiving low- or medium-dose ICS (total daily dose 80–320 µg QVAR, or equivalent) with or without LABA for at least three months, with a stable dose for at least four weeks prior to entry. Among reasons for exclusion were COPD or asthma–COPD overlap; current or ex-smokers with smoking history >10 pack-years; an asthma exacerbation within three months or hospitalization within six months; or oral candidiasis on study entry. Full inclusion and exclusion criteria are listed in the [supplement](#).

Randomization and masking

Patients were allocated by the interactive response technology provider to treatment arms according to a central randomization list (generated by an

independent third party), stratified by region. Patients, investigators, site staff and sponsor personnel were blinded to BDP and matching placebo (but not the active comparator) for the duration of the study, with all patients inhaling once from each of four inhalers BID. BDP 50 µg was administered as one inhalation from a pMDI delivering 50 µg per actuation (ex-valve), whereas BDP 200 and 400 µg were administered from pMDIs delivering BDP 100 µg per actuation (ex-valve). QVAR was administered open-label as two inhalations from a pMDI delivering BDP 80 µg per actuation (ex-mouthpiece; 100 µg ex-valve).

Outcomes

The primary objective was to evaluate the superiority of BDP over placebo in terms of change from baseline in pre-dose morning FEV₁ at Week 8. All spirometry readings were centralized and performed according to the recommendation of the European Respiratory Society and American Thoracic Society. Secondary efficacy endpoints were change from baseline in: pre-dose morning FEV₁ at Week 4; pre-dose morning FVC and ACQ-7 at Weeks 4 and 8; and morning and evening pre-dose PEF, average use of rescue medication, percentage of rescue medication-free days, daily asthma symptoms scores, and the percentage of asthma symptom-free days and of asthma control days, all evaluated during the inter-visit periods and over the entire treatment period. Safety and tolerability were assessed in terms of adverse events, vital signs, 12-lead ECG parameters, blood chemistry and hematology, and creatinine and 24-h UFC (measured by liquid chromatography-tandem mass spectrometry).

Sample size and statistical methods

The sample size was calculated to evaluate the superiority of BDP over placebo in terms of change from baseline in pre-dose morning FEV₁ at Week 8. A total of 495 evaluable patients (99 per group) would provide 80% power to detect a mean difference of 200 ml between each BDP dose and placebo at a two-sided significance level of 0.0167 (0.05/3, since three BDP dose levels were tested), assuming a SD of 430 ml. Considering a non-evaluable rate of 15%, 585 patients (117 per group) were to be randomized.

The primary endpoint was analyzed using a linear mixed model for repeated measurements (MMRM), including treatment, visit, treatment by visit interaction, ICS dose before study (low/medium daily dose) and region as fixed effects, and the baseline value and baseline by visit interaction as covariates. The confidence

intervals (CIs) and *p* values of the comparisons between each BDP dose and placebo for the primary efficacy endpoint at Week 8 were adjusted for multiplicity, based on the parametric simulation method of Edwards and Berry (11). The same model was used to compare the active comparator with placebo, although with no adjustment for multiplicity. The secondary efficacy endpoints were analyzed using the same MMRM as the primary endpoint with no adjustment for multiplicity. For the diary data endpoints (rescue medication, symptoms and PEF), the inter-visit period was considered instead of visit in the model, with comparisons between treatments over the entire treatment period also derived from this model. The study was neither designed nor powered to compare BDP and the active comparator statistically.

The intention-to-treat (ITT) population, used for the efficacy analyses, was all randomized patients who received at least one dose of study treatment and with at least one available post-baseline efficacy evaluation (primary or secondary efficacy variables). The safety population was all randomized patients who received at least one dose of study treatment. The analyses of pre-dose morning FEV₁ at Weeks 4 and 8 were also performed in the per-protocol population, which was all patients in the ITT population without any major protocol deviations (i.e. excluding those whose data might significantly alter study results or data integrity).

Results

Participants

The study was conducted between July 2017 and December 2018 at 132 sites in the US. Of 1912 patients screened, 610 were randomized, with 608 receiving at least one dose of study medication and 559 (91.6%) completing the study (Figure 1). Eight patients were excluded from the ITT population, two who did not receive any study medication (and who were also excluded from the safety population), and six who provided no post-baseline efficacy data. The demographics and disease characteristics at screening were similar across the five groups (Table 1). The majority of recruited patients were female, white, and nonsmokers, with a mean ACQ-7 score of 2.4 (indicating poor asthma control).

Outcomes

Lung function

For the primary efficacy variable (pre-dose morning FEV₁ at Week 8 in the ITT population), BDP 200 µg BID was superior to placebo after adjustment for multiplicity, with

Table 1. Demographics and disease characteristics at screening (ITT population).

	BDP			Placebo (N = 124)	Active comparator (N = 124)
	50 µg BID (N = 118)	200 µg BID (N = 116)	400 µg BID (N = 120)		
Age, years, mean (SD)	50.2 (13.6)	48.1 (14.4)	48.2 (13.8)	45.4 (16.2)	48.8 (14.2)
Sex, male, n (%)	44 (37.3)	39 (33.6)	44 (36.7)	52 (41.9)	47 (37.9)
BMI, kg/m ² , mean (SD)	28.9 (4.0)	27.4 (4.3)	28.2 (4.3)	27.8 (4.6)	27.9 (4.0)
Race, n (%)					
Black or African American	27 (22.9)	23 (19.8)	28 (23.3)	21 (16.9)	24 (19.4)
White	78 (66.1)	82 (70.7)	84 (70.0)	93 (75.0)	93 (75.0)
Unknown or not reported	11 (9.3)	9 (7.8)	7 (5.8)	9 (7.3)	5 (4.0)
Other ^a	2 (1.7)	2 (1.7)	1 (0.8)	1 (0.8)	2 (1.6)
Smoking habits, n (%)					
Ex-smoker	13 (11.0)	18 (15.5)	18 (15.0)	21 (16.9)	23 (18.5)
Non-smoker	105 (89.0)	98 (84.5)	102 (85.0)	103 (83.1)	101 (81.5)
Pre-bronchodilator FEV ₁ , % predicted, mean (SD)	66.9 (9.5)	67.9 (8.4)	67.3 (8.6)	67.8 (8.8)	67.0 (9.7)
FEV ₁ reversibility, %, mean (SD) ^b	26.1 (13.9)	24.3 (12.7)	26.8 (15.5)	27.8 (14.2)	25.1 (14.2)
ACQ-7, mean (SD)	2.36 (0.55)	2.36 (0.46)	2.41 (0.61)	2.41 (0.57)	2.39 (0.55)
Prior asthma medication, n (%)					
LTRA	24 (20.3)	7 (6.0)	17 (14.2)	18 (14.5)	17 (13.7)
ICS alone	23 (19.5)	26 (22.4)	34 (28.3)	36 (29.0)	28 (22.6)
ICS/LABA	93 (78.8)	88 (75.9)	86 (71.7)	88 (71.0)	94 (75.8)
ICS/LABA/LAMA	2 (1.7)	2 (1.7)	0	0	1 (0.8)
ICS dose prior to study, n (%) ^c					
Low	50 (42.4)	50 (43.1)	48 (40.0)	54 (43.5)	51 (41.1)
Medium	68 (57.6)	66 (56.9)	72 (60.0)	70 (56.5)	73 (58.9)

^aAmerican Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander.

^bIncludes all patients (historical reversibility and reversibility measured at screening are combined).

^cLow dose was defined as 80–160 µg daily of QVAR or equivalent; medium dose was >160–320 µg. The active comparator was QVAR 160 µg (ex-mouthpiece); 200 µg ex-valve) BID. ITT, intention-to-treat; BDP, beclomethasone dipropionate; BID, twice daily; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; ACQ, Asthma Control Questionnaire; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist.

a statistically significant difference of 113 ml ($p=0.015$); the differences vs placebo for the other two doses were not significant (Figure 2A). In the Week 4 evaluation, BDP 200 µg BID was superior to both placebo (a difference of 118 ml) and BDP 50 µg BID, with the treatment–placebo differences for the other two BDP doses not significant (Figure 2A). The results in the per-protocol population were consistent with those in the ITT population, although at Week 8 the difference vs placebo for both BDP 200 and 400 µg BID reached significance (149 ml [$p=0.002$] and 122 ml [$p=0.013$], respectively, without adjustment for multiplicity; Figure 2B). The active comparator–placebo difference was statistically significant at Week 8 in both populations and was numerically similar to BDP 200 µg BID at Week 8, although was smaller than with BDP 200 µg BID at Week 4.

For pre-dose morning FVC, BDP 200 µg BID was superior to placebo at Week 8 (difference 105 ml; Figure 3). None of the other treatment–placebo differences were statistically significant (including the active comparator), and there were no significant differences between BDP doses. Changes from baseline in PEF were small in all groups, with no significant treatment–placebo differences (Supplemental Table 1).

Asthma control, rescue medication use and symptoms

Mean ACQ-7 improved from baseline in all groups (including placebo), with the improvements similar

for the two higher BDP doses and the active comparator (Figure 4). The 200 µg BID dose was the lowest BDP dose to exceed the 0.5 minimum clinically important decrease from baseline for ACQ-7 on both visits, with a statistically significant improvement vs placebo in the Week 4 assessment (although not at Week 8).

Baseline rescue medication use was low, and similar in all five groups (Supplemental Table 2). Improvements from baseline with the four active treatments were small; despite this, active–placebo differences reached statistical significance for BDP 200 µg BID in all analyses (the two inter-visit periods and overall), both for the average use of rescue medication and the percentage of rescue-free days. The other active treatments showed improvements over placebo, although none consistently reached statistical significance.

As with rescue medication use, baseline daily asthma symptom scores were low (mean of 0.5, on a scale of 0 to 3), with only small improvements from baseline (Supplemental Table 3). Despite these small differences, there was a significant improvement versus placebo with all active treatments. The baseline percentages of asthma symptom-free days and asthma control days were higher for the placebo group than any of the active treatments, and lowest for the active comparator group (Supplemental Table 3). Although the percentages improved versus placebo for all BDP

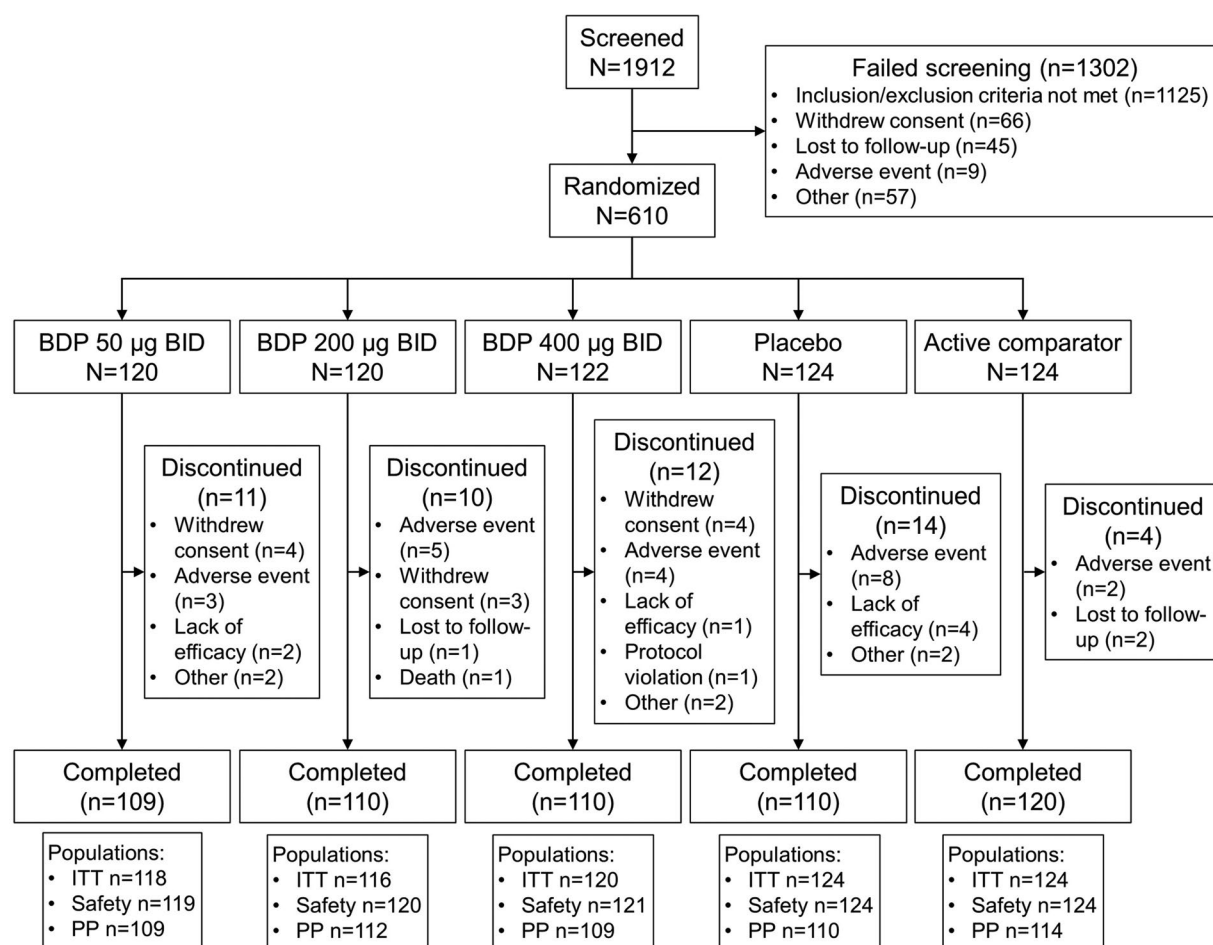


Figure 1. Patient flow through the study. The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. BDP, beclomethasone dipropionate; BID, twice daily; ITT, intention-to-treat.

groups in all evaluations, the differences did not reach statistical significance (with the exception of the overall analysis of asthma control days for BDP 400 µg BID; $p=0.048$).

Safety

The overall percentage of patients experiencing treatment-emergent adverse events was similar in the five treatment groups (Table 2). Although there was a trend to increasing adverse event occurrence with increasing BDP dose, the percentage of patients with an event was lower in all three BDP groups than with placebo, and the majority of events were mild or moderate in severity and not considered related to treatment. The most common related adverse event was oral candidiasis (although the overall incidence was low); no patients experienced this adverse event with BDP 200 µg BID or placebo, and only one patient did in the BDP 50 µg BID group. None of the severe adverse events were assessed as related to study treatment, and no serious adverse event preferred terms

were reported in more than one patient. One patient died during the study from alcohol poisoning, which was not considered to be study related.

The occurrence of clinically significant changes from baseline in blood chemistry was low, with no evidence of a relationship to BDP dose, and there were no clinically significant changes from baseline in vital signs, hematology or ECG parameters. For 24h UFC, there was a similar median decrease from baseline at Week 8 in all four active treatment groups, with no relationship to BDP dose (Table 3). Creatinine levels did not change notably from baseline to Week 8.

Discussion

Across the totality of the evidence from this study, 200 µg BID was the most effective BDP dose, and there were no substantial safety signals to impact the dose selection. Although oral candidiasis was more common with the highest BDP dose (400 µg BID) the incidence was low. BDP 200 µg BID was

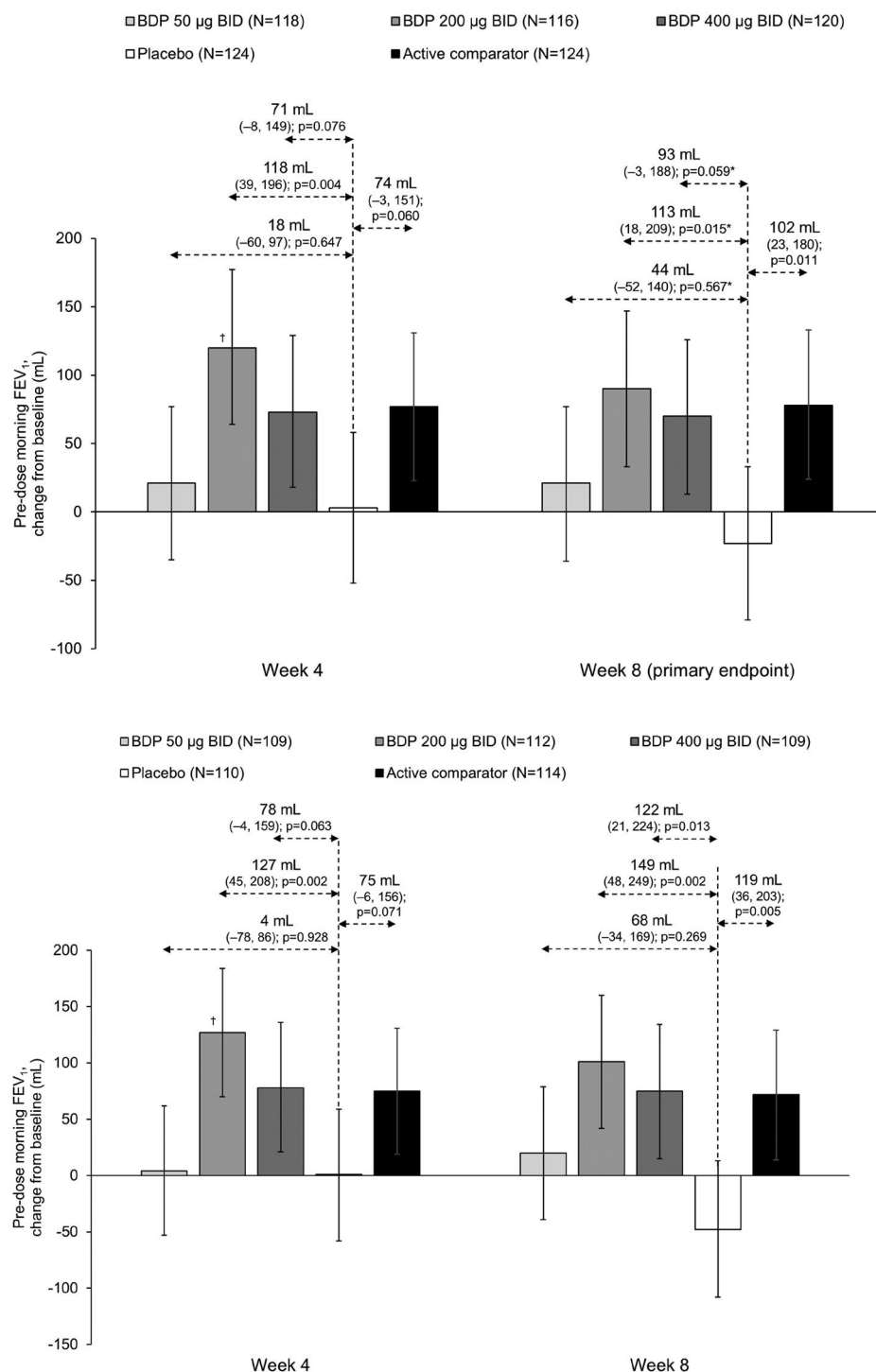


Figure 2. Pre-dose morning FEV_1 : (A) At Weeks 4 and 8 in the ITT population; (B) At Weeks 4 and 8 in the PP population. Bars are adjusted mean changes from baseline, with 95% confidence intervals (*95% CI and p values adjusted for multiplicity). Values are adjusted mean treatment–placebo differences, 95% confidence intervals and p values. † $p < 0.05$ vs BDP 50 µg BID. The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID; active comparator–BDP differences were not analyzed. ITT, intention-to-treat; PP, per protocol; BDP, beclomethasone dipropionate; BID, twice daily; FEV_1 , forced expiratory volume in 1 second.

the only dose to differ significantly from placebo for pre-dose morning trough FEV_1 at both Weeks 4 and 8, and for pre-dose morning FVC at Week 8. In addition, this was the lowest BDP dose to provide

a clinically relevant improvement from baseline in ACQ-7 and was the only active treatment to consistently demonstrate reductions in rescue medication use.

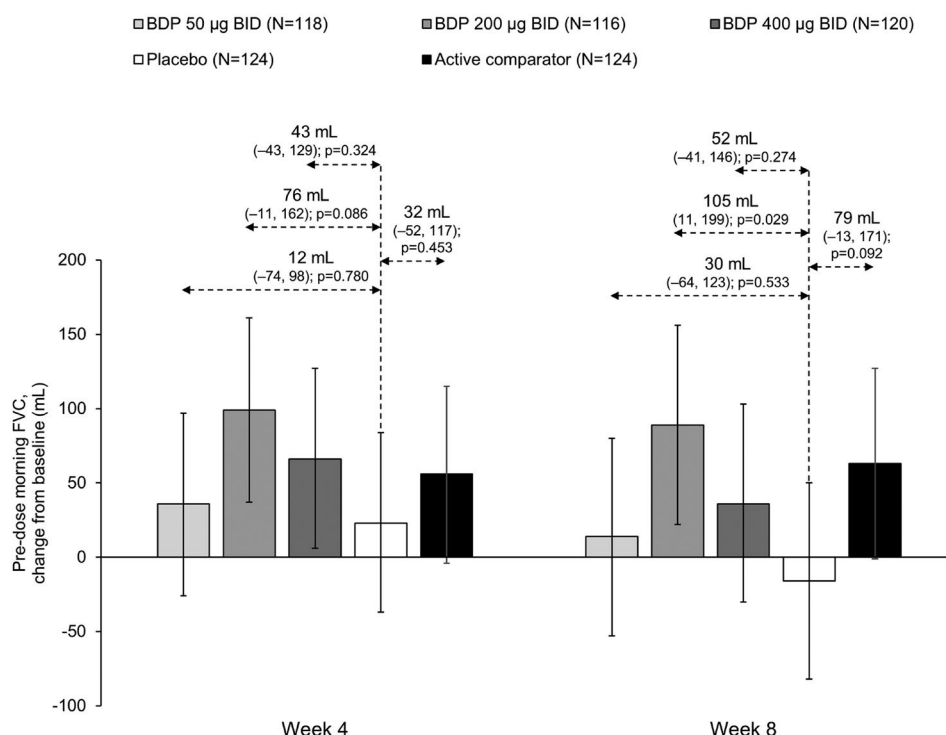


Figure 3. Pre-dose morning FVC at Weeks 4 and 8 (ITT population). Bars are adjusted mean changes from baseline, with 95% confidence intervals. Values are adjusted mean treatment–placebo differences, 95% confidence intervals and *p* values. There were no significant differences between BDP doses. The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID; active comparator–BDP differences were not analyzed. ITT, intention-to-treat; BDP, beclomethasone dipropionate; BID, twice daily; FVC, forced vital capacity.

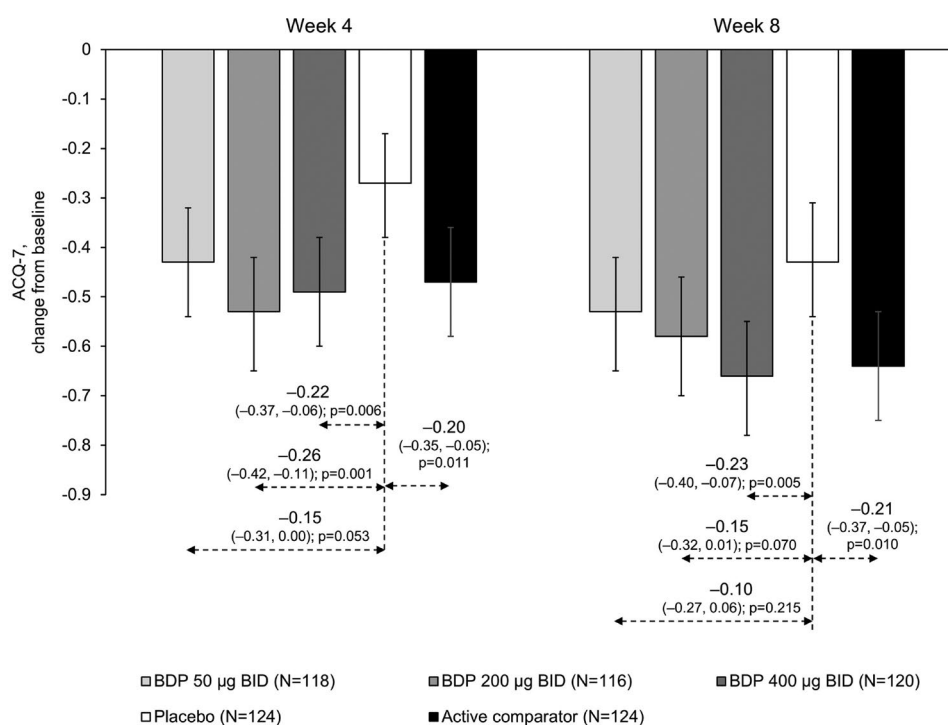


Figure 4. ACQ-7 at Weeks 4 and 8 (ITT population). Bars are adjusted mean changes from baseline, with 95% confidence intervals. Values are adjusted mean treatment–placebo differences, 95% confidence intervals and *p* values. There were no significant differences between BDP doses. The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID; active comparator–BDP differences were not analyzed. ITT, intention-to-treat; BDP, beclomethasone dipropionate; BID, twice daily; ACQ, Asthma Control Questionnaire.

Table 2. Adverse events, overall and most common preferred terms ($\geq 2\%$ patients in any group; safety population).

	BDP			Placebo (N = 124)	Active comparator (N = 124)
	50 µg BID (N = 119)	200 µg BID (N = 120)	400 µg BID (N = 121)		
Adverse events	28 (23.5)	30 (25.0)	37 (30.6)	43 (34.7)	38 (30.6)
Asthma	4 (3.4)	3 (2.5)	5 (4.1)	11 (8.9)	5 (4.0)
Viral upper respiratory tract infection	6 (5.0)	1 (0.8)	7 (5.8)	6 (4.8)	3 (2.4)
Upper respiratory tract infection	6 (5.0)	2 (1.7)	3 (2.5)	3 (2.4)	7 (5.6)
Oral candidiasis	1 (0.8)	0	6 (5.0)	0	4 (3.2)
Cough	0	2 (1.7)	2 (1.7)	4 (3.2)	1 (0.8)
Dyspnea	1 (0.8)	0	2 (1.7)	4 (3.2)	1 (0.8)
Headache	3 (2.5)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Gastroenteritis viral	1 (0.8)	1 (0.8)	3 (2.5)	0	0
Related adverse events	3 (2.5)	3 (2.5)	7 (5.8)	1 (0.8)	0
Oral candidiasis	1 (0.8)	0	6 (5.0)	0	4 (3.2)
Severe adverse events	2 (1.7)	3 (2.5)	6 (5.0)	6 (4.8)	6 (4.8)
Asthma	2 (1.7)	1 (0.8)	3 (2.5)	5 (4.0)	4 (3.2)
Serious adverse events	1 (0.8)	2 (1.7)	2 (1.7)	1 (0.8)	0
Related serious adverse events	0	0	0	0	0
Adverse events leading to study treatment discontinuation	4 (3.4)	6 (5.0)	4 (3.3)	11 (8.9)	2 (1.6)
Asthma	3 (2.5)	1 (0.8)	3 (2.5)	9 (7.3)	2 (1.6)
Adverse events leading to death	0	1 (0.8)	0	0	0

The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. BDP, beclomethasone dipropionate; BID, twice daily.

Table 3. Change from baseline in 24-h UFC at Week 8 (safety population).

	BDP			Placebo (N = 124)	Active comparator (N = 124)
	50 µg BID (N = 119)	200 µg BID (N = 120)	400 µg BID (N = 121)		
Baseline	45.2 (5.0, 436.9)	54.0 (2.2, 300.6)	37.4 (4.7, 583.2)	41.4 (5.8, 1458.7)	46.1 (3.0, 723.9)
Week 8	42.2 (1.1, 6516.4)	46.3 (4.1, 320.2)	30.2 (2.8, 511.2)	44.0 (6.3, 498.7)	37.4 (2.2, 210.0)
Change from baseline	-3.6 (-175.8, 6492.9)	-5.4 (-249.5, 299.5)	-4.1 (-285.1, 430.3)	1.4 (-1319.9, 459.2)	-3.5 (-692.2, 145.5)

Data are median (minimum, maximum); units are nmol/day. The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. UFC, urinary free cortisol; BDP, beclomethasone dipropionate; BID, twice daily.

We observed a plateau in dose-response in this study, with BDP 200 and 400 µg BID numerically similar for many of the endpoints, especially at Week 8. While BDP 400 µg BID did not reach statistical significance vs placebo for pre-dose morning trough FEV_1 at Week 8 in the ITT population, the difference was significant in the per-protocol population. Furthermore, the efficacy profiles of BDP 200 µg and 400 µg BID were broadly comparable to that of the active comparator, although BDP and the active comparator were not formally statistically compared. This plateau in efficacy is consistent with an analysis suggesting that 80–90% of the maximum clinical effect of an ICS is achievable at what is currently classified as a low dose (12). It is possible that a study enrolling patients with more severe asthma (i.e. uncontrolled on medium- or high-dose ICS), especially if a higher number was recruited, could discriminate between medium- and high-dose ICS, especially if we used a more ICS-sensitive clinical parameter (e.g. exacerbations) or biomarkers of Type 2 inflammation (e.g. blood eosinophils or fractional exhaled nitric oxide).

Asthma management guidelines recommend titration to the lowest ICS dose that maintains asthma control (13). The decision to step-up the ICS dose should always be balanced with the risk of clinically important systemic side effects. In the current study, there were no such side effects to impact dose selection, and although there was a trend to increasing adverse event occurrence with increasing BDP dose (including oral candidiasis), the percentage of patients with an adverse event was lower in all three BDP groups than with placebo (especially for the preferred term 'asthma', which includes asthma worsening and exacerbations), and the majority of events were mild or moderate in severity. Further, there was no clear dose-ranging trend in the safety parameters, including UFC, with the degree of cortisol suppression compared with baseline at Week 8 small, and similar across active treatments. This is an important observation, since a dose-related decrease in 24-h UFC has been previously reported in steroid-naïve patients with asthma after 14 days treatment with a different formulation of BDP (14). Similarly, 24-h UFC levels

decreased following treatment with the ICS fluticasone furoate for 8 weeks in patients with persistent moderate-to-severe asthma, who were symptomatic on medium-dose ICS therapy (15). In general the adverse event profile of BDP 200 µg BID in this study was slightly better than the active comparator (and the profile of BDP 400 µg BID was similar to the active comparator). Of course, care should be taken with such comparisons since the active comparator was administered open-label, whereas BDP (and the placebo comparator) were double-blind.

Given this study was conducted to support dose selection of BDP for use in an inhaled triple ICS/LABA/LAMA formulation, one limitation is that use of concomitant LABAs and LAMAs was not permitted. However, if patients had been permitted other bronchodilators as concomitant therapy, this would have blunted the FEV₁ dose-response to BDP, making interpretation of the results challenging. In addition, although the results of the study are being used to inform dose selection in patients with COPD or asthma, the study only recruited patients with asthma. This was to increase dose-sensitivity, since patients with asthma are more steroid-sensitive than those with COPD and is consistent with US Food and Drug Administration guidance (16). Moreover, we did not evaluate the inspiratory flow of the recruited patients and so cannot comment on their ability to inhale the full dose. However, inspiratory flow is usually more of a limiting factor with breath-actuated pMDIs and DPIs than hand-actuated pMDIs, and all randomized patients had to demonstrate correct pMDI use at both screening and randomization. Further, although considered the gold standard for assessing bronchodilation, standard spirometry has limited sensitivity in detecting small airway disease and assessing the response to extrafine aerosol therapy. Novel techniques such as functional respiratory imaging and impulse oscillometry may be more suitable for such an objective, and have been able to show improvement in small airway indices following treatment with extrafine BDP/FF pMDI and extrafine ciclesonide pMDI in patients with asthma (17,18). Strengths of the study include that rescue short-acting bronchodilator use (albuterol) was not permitted from 6 h prior to each visit, with the quality of the lung function data optimized using standardized equipment and centralized interpretation, and with 24-h UFC assessed at a central laboratory, using a validated assay.

In conclusion, this dose-ranging study, in patients with moderate persistent asthma that was poorly controlled by low- or medium-dose ICS, demonstrated a plateau of efficacy with BDP 200 µg BID. Considering

all the data, BDP 200 µg BID appears to offer the optimal balance of efficacy and safety in this population.

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Declaration of interest

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References

1. Hillyer EV, Price DB, Chrystyn H, Martin RJ, Israel E, van Aalderen WMC, Papi A, Usmani OS, Roche N, on behalf of the Respiratory Effectiveness Group, Small Airways Study Group. Harmonizing the nomenclature for therapeutic aerosol particle size: a proposal. *J Aerosol Med Pulm Drug Deliv.* 2018;31(2):111–113. doi:10.1089/jamp.2017.1396.
2. Braido F, Scichilone N, Lavorini F, Usmani OS, Dubuske L, Boulet LP, Mosges R, Nunes C, Sanchez-Borges M, Ansotegui IJ, et al. Manifesto on small airway involvement and management in asthma and chronic obstructive pulmonary disease: an Interasma (Global Asthma Association - GAA) and World Allergy Organization (WAO) document. *World Allergy Organ J.* 2016;9:1–6.
3. Lavorini F, Pedersen S, Usmani OS, Barnes PJ, Corbetta L, Corrigan CJ, Chawes BL, Dekhuijzen PNR, Hausen T, Lavorini F, et al. Dilemmas, confusion, and misconceptions related to small airways directed therapy. *Chest.* 2017;151(6):1345–1355. doi:10.1016/j.chest.2016.07.035.
4. Usmani OS, Barnes PJ. Assessing and treating small airways disease in asthma and chronic obstructive pulmonary disease. *Ann Med.* 2012;44(2):146–156. doi:10.3109/07853890.2011.585656.
5. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. *Am J Respir Crit Care Med.* 2005;172(12):1497–1504. doi:10.1164/rccm.200410-1414OC.

6. Bonini M, Usmani OS. The role of the small airways in the pathophysiology of asthma and chronic obstructive pulmonary disease. *Ther Adv Respir Dis.* 2015;9(6):281–293. doi:[10.1177/1753465815588064](https://doi.org/10.1177/1753465815588064).
7. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med.* 1996;154(5):1505–1510. doi:[10.1164/ajrccm.154.5.8912772](https://doi.org/10.1164/ajrccm.154.5.8912772).
8. Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V. Alveolar nitric oxide and asthma control in mild untreated asthma. *J Allergy Clin Immunol.* 2013;131(6):1513–1517. doi:[10.1016/j.jaci.2013.03.009](https://doi.org/10.1016/j.jaci.2013.03.009).
9. Takeda T, Oga T, Niimi A, Matsumoto H, Ito I, Yamaguchi M, Matsuoka H, Jinnai M, Otsuka K, Oguma T, et al. Relationship between small airway function and health status, dyspnea and disease control in asthma. *Respiration.* 2010;80(2):120–126. doi:[10.1159/000242113](https://doi.org/10.1159/000242113).
10. Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med.* 2000;161(6):1902–1906. doi:[10.1164/ajrccm.161.6.9906075](https://doi.org/10.1164/ajrccm.161.6.9906075).
11. Edwards D, Berry JJ. The efficiency of simulation-based multiple comparisons. *Biometrics.* 1987;43(4):913–928. doi:[10.2307/2531545](https://doi.org/10.2307/2531545).
12. Beasley R, Harper J, Bird G, Majers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma time for a new therapeutic dose terminology. *Am J Respir Crit Care Med.* 2019;199(12):1471–1477. doi:[10.1164/rccm.201810-1868CI](https://doi.org/10.1164/rccm.201810-1868CI).
13. Global Initiative For Asthma. Global strategy for asthma management and prevention [Internet]; 2020. [accessed 2020 Sep 8]. <https://ginasthma.org/gina-reports/>.
14. Harrison LI, Colice GL, Donnell D, Soria I, Dockhorn R. Adrenal effects and pharmacokinetics of CFC-free beclomethasone dipropionate: a 14-day dose-response study. *J Pharm Pharmacol.* 1999;51(3):263–269. doi:[10.1211/0022357991772439](https://doi.org/10.1211/0022357991772439).
15. Busse WW, Bleecker ER, Bateman ED, Lötvall J, Forth R, Davis AM, Jacques L, Haumann B, Woodcock A. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax.* 2012;67(1):35–41. doi:[10.1136/thoraxjnl-2011-200308](https://doi.org/10.1136/thoraxjnl-2011-200308).
16. US Food and Drug Administration. Draft guidance on beclomethasone dipropionate [Internet]. 2020. [accessed 2021 Mar 25]. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020911.pdf.
17. Vos W, De Backer J, Poli G, De Volder A, Ghys L, Van Holsbeke C, Vinchurkar S, De Backer L, De Backer W. Novel functional imaging of changes in small airways of patients treated with extrafine beclomethasone/formoterol. *Respiration.* 2013;86(5):393–401. doi:[10.1159/000347120](https://doi.org/10.1159/000347120).
18. Hoshino M. Comparison of effectiveness in ciclesonide and fluticasone propionate on small airway function in mild asthma. *Allergol Int.* 2010;59(1):59–66. doi:[10.2332/allergolint.09-OA-0122](https://doi.org/10.2332/allergolint.09-OA-0122).

Efficacy and safety of inhaled extrafine beclomethasone dipropionate in adults with asthma: A randomized, parallel-group, dose-ranging study (BEAM)

Supplement

Methods

Inclusion criteria

Patients had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male or female patients aged ≥ 18 and ≤ 75 years who had signed an informed consent form prior to initiation of any study-related procedure;
2. A diagnosis of asthma as defined in the Global Initiative for Asthma (GINA) Report, 2016, documented for at least 1 year prior to screening (V1, Week -2);
3. Poorly controlled or uncontrolled asthma evidenced by a score ≥ 1.5 on the ACQ-7 (this criterion had to be met at the screening [V1, Week -2] and randomization [V2, Week 0] visits);
4. A pre-bronchodilator $FEV_1 \geq 50\%$ and $< 85\%$ of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits;
5. A documented positive response to a reversibility test (pre-/post-bronchodilator) within 1 year prior to, or at screening, defined as change in $FEV_1 \geq 12\%$ and ≥ 200 mL over baseline within 30 minutes after inhaling four puffs of albuterol hydrofluoroalkane 90 μ g/actuation;
Note: in case the reversibility threshold was not met at screening, the test could be performed once before randomization;
6. Use of ICS (low/medium dose according to GINA Report, 2016), with or without a long-acting bronchodilator for three months (stable dose in the last four weeks) before the screening visit;
7. A cooperative attitude and ability to demonstrate correct use of the eDiary, peak flow meter, and the pMDI inhalers;
8. A basal morning (7:00 to 10:00 a.m.) serum cortisol level between 5–28 μ g/dL at screening;
9. BMI: $18.5 \leq \text{BMI} < 35$ kg/m².

If the inclusion criterion #5 (reversibility) was not met at screening and the patient returned to repeat the procedure once before randomization, inclusion criteria #3 and #4 also had to be repeated and met on the same day, before the reversibility test was conducted.

At randomization (V2, Week 0), inclusion criteria #3, #4 and #7 were also rechecked.

Exclusion criteria

If a patient met any of the following criteria, he/she was not enrolled into the study:

1. Pregnant (as evident by a positive urine hCG or serum β -hCG test) or lactating women and all women physiologically capable of becoming pregnant (i.e. WOCBP) unless they were willing to use a highly effective birth control method such as:
 - a. Placement of an intrauterine device or intrauterine releasing system;
 - b. Oral, intravaginal, transdermal combined estrogen and progesterone containing hormonal contraception or oral, injectable, implantable progesterone only hormonal contraception;
 - c. Bilateral tubal occlusion ligation;
 - d. Partner vasectomy (provided that partner was the sole sexual partner of the WOCBP study participant and that the vasectomized partner had received medical assessment of the surgical success);
 - e. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments;

Pregnancy testing was carried out during the course of the study in all WOCBP: serum pregnancy test was performed at screening (V1, Week -2), V4 (Week 8) and the early termination visit, urinary pregnancy test was performed at screening, V2 (Week 0) and V3 (Week 4). Women of non-childbearing potential, defined as physiologically incapable of becoming pregnant (i.e. post-menopausal [defined as no menses for 12 months without an alternative medical cause] or permanently sterile [hysterectomy, bilateral salpingectomy and bilateral oophorectomy]), were eligible. If indicated, as per Investigator's request, post-menopausal status was confirmed by follicle stimulating hormone levels (according to local laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy;

2. Patients who suffered from COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease Report, 2017, or who were suspected of having asthma COPD overlap syndrome as described in the GINA Report, 2016;
3. Inability to carry out pulmonary function testing, to comply with study procedures or with study treatment intake;
4. Current smokers or ex-smokers (tobacco, vapor cigarettes, marijuana) with a smoking history of >10 pack-years or having stopped smoking ≤ 1 year prior to screening visit.
5. History of life-threatening asthma, clinically significant uncontrolled disease or respiratory infection;
6. An asthma exacerbation requiring oral corticosteroids within three months or hospitalization within six months prior to screening;
7. Patients with unresolved bacterial or viral respiratory tract, sinus, or middle ear infection affecting asthma status within two weeks prior to screening;
8. Patients who received a vaccination within two weeks prior to screening or during the run-in;
9. Patients with oral candidiasis at screening or at randomization;
10. Patients with any clinically significant, uncontrolled condition e.g. fever, hyperthyroidism, diabetes mellitus or other endocrine disease; gastrointestinal disease (e.g. active peptic ulcer); neurological disease; hematological disease; autoimmune disorders, or other conditions which may have impacted the feasibility or the results of the study according to the Investigator's judgment;
11. Patients who had a clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, New York Heart Association Class III/IV heart failure, acute ischemic heart disease within 1 year prior to study entry, known history of atrial fibrillation or history of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to screening, not controlled with a rate control strategy;
12. Patients who had a clinically significant abnormal 12-lead ECG that resulted in an active medical problem which may have impacted the safety of the patient according to the Investigator's judgment;

13. Patients whose 12-lead ECG showed Fridericia-corrected QT interval (QTcF) > 450 msec for males or QTcF > 470 msec for females at screening or randomization visits;
14. Patients with known intolerance/hypersensitivity or contra-indication to treatment with inhaled β_2 -adrenergic receptor agonists, corticosteroids or propellant gases/excipients;
15. Patients with concomitant immunosuppressive therapy, use of oral or injected corticosteroids, anti-immunoglobulin E (IgE), anti-interleukin 5 (IL5) or other monoclonal antibodies (MAbs) or polyclonal antibodies within 12 weeks prior to screening;
16. Use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening;
17. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening;
18. Patients who had received an investigational drug within 1 month or five half-lives (whichever was greater) prior to screening visit, or had been previously randomized in this study, or were participating in another clinical trial;
19. Patients who were mentally or legally incapacitated, or patients accommodated in an establishment as a result of an official or judicial order;
20. Patients who had undergone major surgery in the 3 months prior to screening visit or had a planned surgery during the study.

Exclusion criteria #1, #3, #8, #9, #12 and #13 were rechecked at the randomization visit (V2, Week 0).

Results

Supplemental Table 1. Pre-dose PEF (ITT population).

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Morning (L/min)					
Baseline, mean (SD)	351 (108)	337 (97)	346 (93)	348 (118)	341 (113)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	−2 (−7.1, 3.7)	−3 (−8.1, 2.73)	−4 (−9.3, 1.5)	−6 (−11.3, −0.8)	0 (−5.0, 5.6)
Active–placebo difference, adjusted mean (95% CI); p value	4 (−3.2, 11.9); 0.260	3 (−4.2, 10.9); 0.387	2 (−5.4, 9.7); 0.574	—	6 (−1.1, 13.8); 0.097
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	−4 (−10.9, 2.3)	3 (−3.3, 10.0)	−5 (−11.7, 1.6)	−4 (−10.3, 2.8)	2 (−4.2, 8.8)
Active–placebo difference, adjusted mean (95% CI); p value	−1 (−9.9, 8.8); 0.908	7 (−2.2, 16.5); 0.135	−1 (−10.7, 8.1); 0.786	—	6 (−3.2, 15.3); 0.202
Overall					
Change from baseline, adjusted mean (95% CI)	−3 (−8.6, 2.6)	0.3 (−5.3, 6.0)	−4 (−10.0, 1.1)	−5 (−10.4, 0.6)	1 (−4.2, 6.8)
Active–placebo difference, adjusted mean (95% CI); p value	2 (−5.9, 9.7); 0.635	5 (−2.6, 13.1); 0.191	0.4 (−7.4, 8.3); 0.914	—	6 (−1.6, 13.9); 0.118

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Evening (L/min)					
Baseline, mean (SD)	366 (109)	348 (98)	353 (93)	367 (116)	358 (112)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	−6 (−11.4, −0.6)	−4 (−9.4, 1.6)	−6 (−11.8, −0.9)	−11 (−15.9, −5.2)	−5 (−10.5, 0.2)
Active–placebo difference, adjusted mean (95% CI); p value	5 (−3.1, 12.1); 0.240	7 (−1.0, 14.3); 0.089	4 (−3.4, 11.8); 0.280	—	5 (−2.1, 12.9); 0.158
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	−10 (−16.7, −3.3)	0 (−6.3, 7.2)	−9 (−15.6, −2.0)	−10 (−16.9, −3.5)	−3 (−9.6, 3.5)
Active–placebo difference, adjusted mean (95% CI); p value	0 (−9.3, 9.7); 0.965	11 (1.1, 20.2); 0.028	1 (−8.1, 11.0); 0.773	—	7 (−2.2, 16.6); 0.132
Overall					
Change from baseline, adjusted mean (95% CI)	−8 (−13.6, −2.4)	−2 (−7.4, 4.0)	−8 (−13.2, −1.9)	−10 (−15.9, −4.9)	−4 (−9.6, 1.4)
Active–placebo difference, adjusted mean (95% CI); p value	2 (−5.5, 10.3); 0.553	9 (0.7, 16.6); 0.032	3 (−5.1, 10.7); 0.487	—	6 (−1.5, 14.1); 0.113

The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. PEF, peak expiratory flow; BDP, beclomethasone dipropionate; BID, twice daily; ITT, intention-to-treat.

Supplemental Table 2. Use of rescue medication (ITT population).

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Average use of rescue medication (puffs/day)					
Baseline, mean (SD)	1.03 (1.09)	1.02 (1.06)	0.93 (1.10)	0.94 (1.13)	0.95 (1.05)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	-0.11 (-0.25, 0.03)	-0.27 (-0.41, -0.12)	-0.14 (-0.28, 0.00)	0.07 (-0.07, 0.21)	-0.13 (-0.26, 0.01)
Active-placebo difference, adjusted mean (95% CI); p value	-0.18 (-0.38, 0.01); 0.067	-0.34 (-0.53, -0.14); <0.001	-0.21 (-0.40, -0.01); 0.038	—	-0.20 (-0.39, -0.01); 0.044
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	-0.12 (-0.29, 0.05)	-0.35 (-0.52, -0.18)	-0.25 (-0.42, -0.08)	0.01 (-0.15, 0.18)	-0.18 (-0.34, -0.01)
Active-placebo difference, adjusted mean (95% CI); p value	-0.13 (-0.37, 0.11); 0.283	-0.37 (-0.60, -0.13); 0.003	-0.27 (-0.50, -0.03); 0.027	—	-0.19 (-0.42, 0.04); 0.111
Overall					
Change from baseline, adjusted mean (95% CI)	-0.11 (-0.26, 0.03)	-0.31 (-0.46, -0.16)	-0.20 (-0.34, -0.05)	0.04 (-0.10, 0.19)	-0.15 (-0.29, -0.01)
Active-placebo difference, adjusted mean (95% CI); p value	-0.16 (-0.36, 0.05); 0.135	-0.35 (-0.56, -0.14); <0.001	-0.24 (-0.44, -0.03); 0.024	—	-0.19 (-0.40, 0.01); 0.060

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Percentage of rescue-free days					
Baseline, mean (SD)	57.0 (33.9)	56.9 (34.4)	62.5 (36.5)	62.3 (35.1)	60.0 (34.2)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	5.9 (1.9, 9.9)	9.0 (5.0, 13.0)	6.1 (2.1, 10.1)	1.5 (−2.4, 5.3)	7.7 (3.9, 11.6)
Active–placebo difference, adjusted mean (95% CI); p value	4.4 (−1.1, 10.0); 0.115	7.6 (2.0, 13.1); 0.008	4.7 (−0.9, 10.2); 0.099	—	6.3 (0.8, 11.7); 0.024
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	8.9 (4.5, 13.3)	13.1 (8.7, 17.6)	10.0 (5.6, 14.4)	4.1 (−0.2, 8.4)	11.2 (7.0, 15.5)
Active–placebo difference, adjusted mean (95% CI); p value	4.8 (−1.4, 11.0); 0.129	9.0 (2.8, 15.2); 0.004	5.9 (−0.3, 12.1); 0.061	—	7.1 (1.0, 13.2); 0.022
Overall					
Change from baseline, adjusted mean (95% CI)	7.4 (3.4, 11.3)	11.1 (7.1, 15.1)	8.1 (4.1, 12.0)	2.8 (−1.1, 6.6)	9.5 (5.6, 13.3)
Active–placebo difference, adjusted mean (95% CI); p value	4.6 (−0.9, 10.1); 0.101	8.3 (2.8, 13.9); 0.003	5.3 (−0.2, 10.8); 0.061	—	6.7 (1.3, 12.1); 0.016

The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. BDP, beclomethasone dipropionate; BID, twice daily; ITT, intention-to-treat.

Supplemental Table 3. Asthma symptoms and control (ITT population).

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Overall daily asthma symptom scores (morning and evening)					
Baseline, mean (SD)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	-0.1 (-0.1, -0.0)	-0.1 (-0.1, -0.0)	-0.1 (-0.1, -0.0)	0.0 (-0.0, 0.1)	-0.1 (-0.2, -0.1)
Active-placebo difference, adjusted mean (95% CI); p value	-0.1 (-0.2, -0.1); <0.001	-0.1 (-0.2, -0.1); <0.001	-0.1 (-0.2, -0.1); <0.001	—	-0.1 (-0.2, -0.1); <0.001
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	-0.1 (-0.2, -0.1)	-0.1 (-0.2, -0.1)	-0.1 (-0.2, -0.1)	-0.0 (-0.1, 0.0)	-0.1 (-0.2, -0.1)
Active-placebo difference, adjusted mean (95% CI); p value	-0.1 (-0.2, -0.0); 0.010	-0.1 (-0.2, -0.0); 0.011	-0.1 (-0.2, -0.0); 0.002	—	-0.1 (-0.2, -0.1); <0.001
Overall					
Change from baseline, adjusted mean (95% CI)	-0.1 (-0.1, -0.1)	-0.1 (-0.1, -0.1)	-0.1 (-0.2, -0.1)	0.0 (-0.0, 0.1)	-0.1 (-0.2, -0.1)
Active-placebo difference, adjusted mean (95% CI); p value	-0.1 (-0.2, -0.0); 0.002	-0.1 (-0.2, -0.0); 0.001	-0.1 (-0.2, -0.1); <0.001	—	-0.1 (-0.2, -0.1); <0.001

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Percentage of asthma symptom-free days					
Baseline, mean (SD)	21.1 (30.6)	21.0 (31.9)	25.1 (32.0)	27.5 (34.2)	18.6 (27.2)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	8.6 (4.5, 12.7)	10.5 (6.4, 14.7)	10.1 (6.0, 14.2)	5.7 (1.6, 9.7)	12.8 (8.8, 16.8)
Active–placebo difference, adjusted mean (95% CI); p value	2.9 (−2.8, 8.7); 0.316	4.9 (−0.9, 10.7); 0.097	4.4 (−1.3, 10.2); 0.128	—	7.2 (1.5, 12.9); 0.013
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	16.4 (11.1, 21.7)	17.0 (11.6, 22.4)	17.2 (11.8, 22.51)	11.7 (6.5, 16.9)	21.2 (16.1, 26.4)
Active–placebo difference, adjusted mean (95% CI); p value	4.7 (−2.8, 12.2); 0.219	5.3 (−2.2, 12.8); 0.166	5.5 (−2.0, 12.9); 0.151	—	9.5 (2.1, 16.9); 0.012
Overall					
Change from baseline, adjusted mean (95% CI)	12.5 (8.0, 17.0)	13.8 (9.3, 18.3)	13.6 (9.2, 18.1)	8.7 (4.3, 13.1)	17.0 (12.7, 21.4)
Active–placebo difference, adjusted mean (95% CI); p value	3.8 (−2.5, 10.1); 0.233	5.1 (−1.2, 11.4); 0.113	5.0 (−1.3, 11.2); 0.120	—	8.3 (2.2, 14.5); 0.008

	BDP			Placebo (N=124)	Active comparator (N=124)
	50 µg BID (N=118)	200 µg BID (N=116)	400 µg BID (N=120)		
Percentage of asthma control days					
Baseline, mean (SD)	19.8 (29.6)	19.5 (31.5)	24.2 (31.8)	26.6 (33.8)	18.1 (26.7)
Baseline to Week 4					
Change from baseline, adjusted mean (95% CI)	7.3 (3.3, 11.3)	10.6 (6.5, 14.6)	10.4 (6.4, 14.5)	5.0 (1.1, 9.0)	12.8 (8.8, 16.7)
Active–placebo difference, adjusted mean (95% CI); p value	2.3 (−3.4, 7.9); 0.426	5.6 (−0.1, 11.2); 0.055	5.4 (−0.2, 11.1); 0.059	—	7.8 (2.2, 13.3); 0.007
Week 5 to Week 8					
Change from baseline, adjusted mean (95% CI)	14.3 (9.1, 19.5)	16.3 (11.0, 21.5)	17.5 (12.2, 22.7)	10.5 (5.3, 15.6)	20.6 (15.6, 25.7)
Active–placebo difference, adjusted mean (95% CI); p value	3.8 (−3.5, 11.2); 0.308	5.8 (−1.6, 13.2); 0.124	7.0 (−0.4, 14.3); 0.063	—	10.2 (2.9, 17.4); 0.006
Overall					
Change from baseline, adjusted mean (95% CI)	10.8 (6.4, 15.2)	13.4 (9.0, 17.9)	13.9 (9.5, 18.3)	7.7 (3.4, 12.1)	16.7 (12.4, 21.0)
Active–placebo difference, adjusted mean (95% CI); p value	3.1 (−3.1, 9.2); 0.331	5.7 (−0.5, 11.9); 0.073	6.2 (0.1, 12.4); 0.048	—	9.0 (2.9, 15.0); 0.004

The active comparator was QVAR 160 µg (ex-mouthpiece; 200 µg ex-valve) BID. BDP, beclomethasone dipropionate; BID, twice daily; ITT, intention-to-treat.