Review Article

Small Airways, Big Problem: Extrafine beclomethasone/formoterol in asthma and chronic obstructive pulmonary disease

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic respiratory diseases characterized by an inflammatory process that extends from the central to peripheral airways. Conventional pressurized metered-dose inhalers and most dry-powder inhalers emit drug particles too large to target the small airways effectively. Advancements in drug formulation have given rise to a new generation of inhalers that can generate aerosols with extrafine drug particles that leads to more effective aerosol penetration into the lung periphery. An extrafine formulation of inhaled beclomethasone/formoterol (BDP-FF) with enhanced lung deposition is now available. This document reviews the various real-world and controlled studies that have evaluated the efficacy of extrafine BDP-FF in asthma and COPD.

KEY WORDS: Asthma, chronic obstructive pulmonary disease, extrafine beclomethasone/formoterol, extrafine formulation, repitition beclomethasone/formoterol, novel formulations, small airways disease

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INTRODUCTION

Both asthma and chronic obstructive pulmonary disease (COPD) are obstructive inflammatory disorders of the entire bronchial tree, including the peripheral airways. The term small airways refers to airways <2 mm in diameter (8th generation onward).[1] Small airways account for 98.8% (or ~4500 ml) of the lungs. The small airways have been called "the quiet zone" of the lungs, because of several important reasons. As the bronchioles divide, airways undergo a reduction in the length and diameter, as a result of which the cross-sectional area increases exponentially from ~2.5 cm^2 at the level of the trachea to ~180 cm^2 at the level of the terminal bronchioles and to nearly 300 cm^2 at the level of the acinar airways.[2] Owing to this expansion of the cumulative cross-sectional area, the velocity of airflow falls by an order of ~100 becoming laminar (and therefore literally "silent") and independent of gas density.[3] Second, the underlying disease in a large cross-sectional area can progress "silently" to a significant degree before becoming detectable. As much as 75% of the

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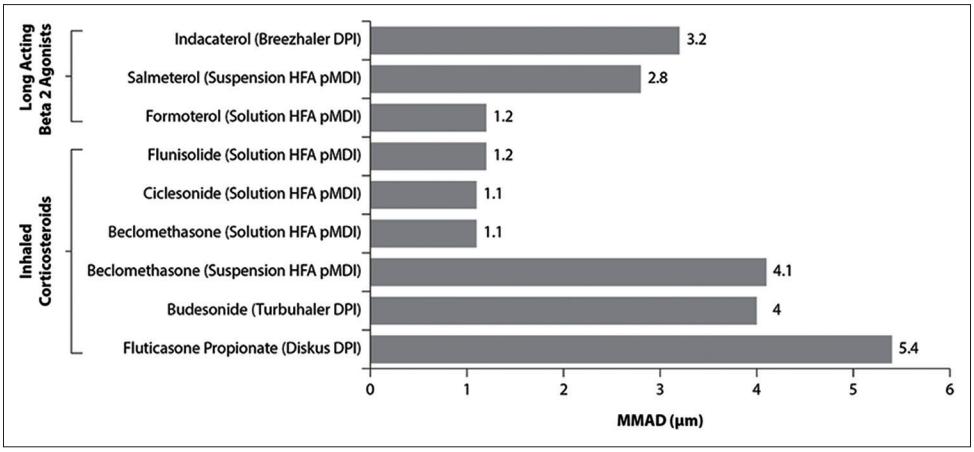

Figure 1: Particle size of various inhaled corticosteroids and long acting beta 2 agonists

small airway cross-sectional area needs to be obliterated for airflow limitation to be detected by spirometry.[4] Thus, the disease is almost invariably established before symptoms point to a potential problem. Incipient disease within the small airways, such as in emphysema, almost always precedes the larger airway obstruction, presenting a unique opportunity to identify and treat a specific condition before it advances to the rest of the tracheobronchial tree.[5]

In asthma, there is increasing evidence that small airways dysfunction correlates with symptoms, disease severity, increased number of exacerbations, and bronchial hyperresponsiveness and contributes to poor asthma control even in patients with milder disease.[6,7] The prevalence of small airways disease in asthma across all severities has been found to be 50%–60%.[8]

In COPD, small airways disease has been recognized for many years as a central feature. Early studies reported a 4–40-fold increase in small airways resistance in patients with emphysema.[9] The available pathophysiologic evidence for small-airway dysfunction and the clinical emergence of a small-airway phenotype makes it imperative to keep the small airways under sharp focus while evaluation and treatment of COPD.[10]

Inhalation therapy is currently the gold standard for addressing obstructive airways dysfunction. For inhalation therapy to be clinically effective, the drug delivery system must ensure the generation of an aerosol cloud containing particles that are able to penetrate and deposit along the respiratory tract.[11] The distribution of the delivered medication within the tracheobronchial tree is influenced by the size of the inhaled particle, measured in mass median aerodynamic diameter (MMAD). The MMAD of an aerosol refers to a particle diameter that has 50% of the aerosol mass residing above and 50% of its mass below it. Various papers have defined "extrafine" particles as particles with an MMAD of <2 µ. Particles <1 µ are defined as "submicron" and those with >2 µ have been defined as "large" or "coarse" particles.[10] For the drug to penetrate the smaller airways, the MMAD of the drug needs to be in the range of 1–2 µ. *In vitro* studies carried out on extrafine formulations marketed by Cipla Ltd have reported percentage of fine particle dose which is <2 µ to be 62.6% for beclomethasone for the beclomethasone product and 28.5% and 20.8% for beclomethasone and formoterol, respectively, in the fixed dose combination of formoterol with beclomethasone and 40.2% and 35.3% for ciclesonide 80 µg and 160 µg, respectively.

The majority of the inhaled drug delivered by conventional pressurized metered-dose inhalers (pMDIs) consist of particles in the range of 2–5 µ. The relatively larger particle size could theoretically prevent optimal deposition within the peripheral airways. Aerosols with larger particle size can cause local side effects such as oral candidiasis and dysphonia by preferentially depositing in the oropharynx. The oropharyngeal deposition indirectly leads to systemic adverse effects when the drug is swallowed and passed on to the gastrointestinal tract. The MMAD of various drugs used for asthma and COPD is given in Figure 1.[10]

In view of the increasing recognition of the role of small airways in asthma and COPD, a novel fixed dose combination of extrafine beclomethasone/formoterol (BDP-FF) formulation delivered via a hydrofluoroalkane (HFA) pMDI (Niveoli Inhaler, Cipla Ltd) has been introduced for the first time in India. Each actuation of the medication delivers 100/6 mcg of BDP-FF with the required MMAD for deposition in the smaller airways. This review aims to appraise the evidence on the therapeutic efficacy of extrafine formulation of BDP-FF in the management of asthma and COPD.

DEPOSITION CHARACTERISTICS OF INHALED EXTRAFINE BECLOMETHASONE/FORMOTEROL FORMULATION

The substitution of chlorofluorocarbon (CFC) by HFA as per the Montreal Protocol resulted in the production of aerosols that differed significantly in particle size from

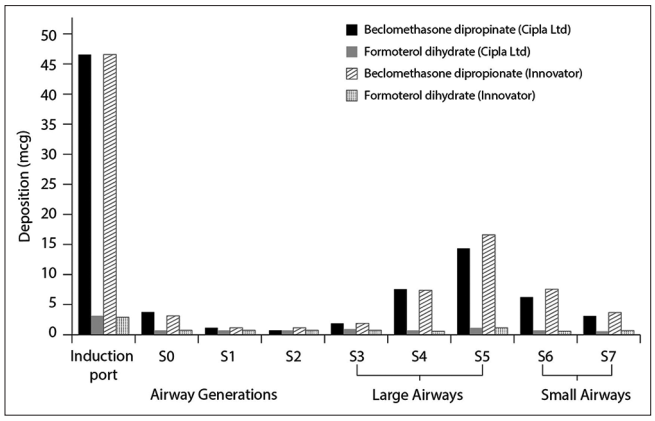

Figure 2: Particle size distribution in both large and small airways via Andersen Cascade Impaction (Niveoli Inhaler, Cipla Ltd) versus Innovator Product (Cheisi Ltd)

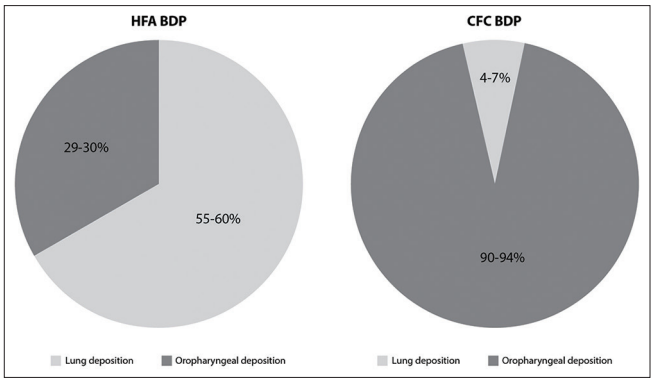

Figure 3: Lung and oropharyngeal deposition with HFA BDP and CFC BDP in healthy volunteers

the original CFCs and has had implications in terms of deposition of the drug particles in the airways.[12] In comparison to CFCs, the increased solubility of BDP in HFA facilitates a reduction of particle size, which has the potential of translating into increased drug delivery to the lungs (from 4%–7% to 55%–60%) compared to conventional formulations.

In vitro data

The *in vitro* characterization of aerosols is carried out using the Andersen Cascade Impactor**.** Within the impactor, the deposition characteristics of the Niveoli Inhaler (Cipla Ltd) were found to be similar to those of the innovator product (Foster, Cheisi Ltd) as shown in Figure 2.

In vivo data

The ability of extrafine BDP-FF to achieve central and peripheral lung deposition was investigated in an open-label, single-dose, parallel-group study involving healthy volunteers, 8 patients with persistent asthma, and 8 patients with stable COPD.[13] Patients inhaled four actuations of radiolabeled ^{99m}Tc BDP-FF; subsequent gamma camera imaging measured activity in the entire lung and extrathoracic region, as well as the amount of exhaled activity. Lung deposition was found to be remarkably consistent in the three groups: 34.08%, 30.86%, and 33.10% of the nominal dose in healthy volunteers, asthmatics, and COPD patients, respectively. BDP-FF also improved the forced expiratory volume in 1 s (FEV_1) in all groups [Table 1]. The study demonstrated that inhalation of BDP-FF HFA produces homogeneous deposition in both large and small airways regardless of the pathophysiological condition.

Small particle HFA-BDP has been shown to be as effective as 2–3 times the dose of CFC-BDP.[12] In a study conducted on healthy volunteers (n = 6), the authors found that 55%–60% of the HFA-BDP ex-actuator dose was deposited in the lungs and 29%–30% deposited in the oropharynx. In contrast, CFC-BDP deposition was 4%–7% in the lungs and 90%–94% in the oropharynx. Hence, extrafine formulation of BDP-FF contains 2.5-fold lower amount of BDP than that of the conventional beclomethasone CFC. Thus, 100 µg of extrafine particle BDP per actuation is equivalent to 250 µg of conventional BDP-CFC per actuation [Figure 3].

The pattern of deposition within the lungs for HFA-BDP was relatively uniform throughout the airways, whereas CFC-BDP was predominantly deposited within the central airways with little or no peripheral airway deposition.

A study by Wos *et al*. evaluated the effects of BDP-FF on physiological, imaging, and clinical parameters in 24 stable asthmatics.[14] Patients who were on other drugs (short-acting β 2-agonist, long-acting β2-agonist [LABA], or inhaled corticosteroid [ICS]/LABA fixed combinations) were switched to a fixed combination of extrafine HFA solution of BDP-FF (100/6 mcg b.i.d). Significant changes were documented in imaging parameters with airway volume (iVaw) increasing from 8.36 ± 4.71 to 9.64 ± 5.19 cm^3 (P = 0.0007) and CFD (computational fluid dynamics)-based airway resistance (iRaw) decreasing from 0.082 ± 0.084 to 0.050 ± 0.030 kPa s/l (P = 0.01), with a maximal increase in iVaw of 11.7% of the baseline value. Asthma control measured by the asthma control test (ACT) score improved from 19.79 ± 4.46 at baseline to 21.67 ± 4.55 at the end of treatment (P = 0.016). FEV_1 increased from 96.3 ± 15.72% of predicted normal values to 100.1 ± 16.8% (P = 0.044). This study documented that changes in imaging parameters correlated significantly with clinically relevant improvements.

CLINICAL EFFICACY OF EXTRAFINE BECLOMETHASONE/FORMOTEROL IN ASTHMA

Extrafine beclomethasone/formoterol versus conventional formulations of beclomethasone and formoterol given via separate inhalers

In a study involving 645 patients, with moderate-to-severe asthma, the fixed dose combination of extrafine BDP-FF was found to be noninferior to BDP and formoterol

Table 1: Deposition following administration of one single dose of four puffs of the beclomethasone/formoterol hydrofluoroalkane (100/6 μg) radiolabelled formulation in healthy subjects, asthmatic, and chronic obstructive pulmonary disease patients

	Healthy subjects (*n*=8)	Asthma patients (*n*=8)	COPD patients (*n*=8)
Lung deposition (percentage nominal dose)	34.08±9.30 (20.00-43.80)	30.86±8.89 (21.50-47.40)	33.10±8.90 (14.00-43.60)
C/P	1.42±0.32 (1.14-2.09)	1.96±0.43* (1.44-2.78)	1.94±0.69 (1.15-3.07)

*P=0.046 versus healthy subjects. C/P: Central/peripheral

conventional formulations administered via separate inhalers with respect to improvement in morning peak expiratory flow (PEF).[15] The fixed combination was found to be superior to BDP and formoterol (administered separately) and BDP monotherapy in relation to clinical measures of asthma control, i.e., percentage of symptom free days (day and night time symptoms) [Table 2]. In another 24-week study, extrafine BDP-FF delivered by an HFA pMDI (400/24 μg) was superior in improving asthma control and resulted in lesser number of exacerbations compared to the same drugs formulated as nonextrafine agents at equipotent doses given via separate inhalers.[16] In addition, the lung function of patients (forced vital capacity [FVC], FEV_1, and forced expiratory flow 25%–75% [$FEF_{25\%–75\%}$]) along with patient-related clinical outcomes (day and night time symptom scores and symptom free days) was better with the extrafine BDP-FF delivered by an HFA pMDI [Table 2].

Extrafine beclomethasone/formoterol versus other inhaled corticosteroid/long-acting β2-agonist formulations

Scichilone *et al*. conducted a 12-week, double-blind study in 30 asthmatics to assess small airways patency by single-breath nitrogen washout test ($SbN_{2)}$ and large airways patency by methacholine (Mch) challenge test.[17] Patients were randomized to BDP-FF 400/24 μg daily or fluticasone–salmeterol (FP-S) 500/100 μg daily. The predose FEV1 value in both BDP-FF and FP-S groups showed a significant increase ($P < 0.01$) compared to baseline (0.37 ± 0.13 l and 0.36 ± 0.12 l, respectively). The Mch provocative dose causing 20% reduction in FEV1 ($PD_{20}MchFEV_1$) improved significantly from 90.42 (±30.08) μg at baseline to 432.41 (±122.71) μg at week 12, in the BDP-FF group ($P = 0.01$) but not in the FP-S group ($P = 0.01$ versus baseline in the BDP-FF group). A trend toward improvement versus baseline was observed only for extrafine BDP-FF in closing capacity. Although both the treatments caused a decrease in the magnitude of airway hyperresponsiveness, this improvement was significant only in the extrafine BDP-FF group. No differences were recorded in the other sbN_2 test parameters. Thus, there was uniform distribution of extrafine BDP-FF throughout the bronchial tree both at the level of small airways and at the level of large airways.

Another 24-week crossover study assessed changes in the functional parameters relevant to small airway function in 10 moderate to persistent asthmatics.[18] The patients were randomized to either extrafine BDP-FF (12/200 mcg; b. i. d) or FP-S (50/250) mcg b. i. d. Extrafine BDP-FF significantly decreased closing volume and induced a near significant decrease in the small airway parameters such as slope of N_2 phase 3 and an increase of (heliox) midexpiratory flow ($MEF_{50\%}$) at isovolume.[18] However, FP-S given at equipotent doses did not show any improvement in these parameters. This suggests that extrafine BDP-FF not only reaches the peripheral airways but is also efficacious in reducing distal airways inflammation, thus improving small airways patency compared to the conventional formulation. In a 12-week, phase 3 study, 244 moderate-to-severe asthmatics with either partly controlled or uncontrolled symptoms were randomized to 400/6 mcg of BDP-FF and 500/100 μg of FP-S daily to assess improvement in lung function.[19] After 12 weeks' treatment, morning and evening PEF increased significantly by 38 ± 50.4 and 39 ± 51.3 L/min, respectively, in the BDP-FF group and 45 ± 56.9 and 40 ± 53.9 L/min, respectively, in the FP-S group; the difference was not significant between groups. However, at the end of treatment, FVC improved significantly by 0.06 L at 5 min after BDP-FF inhalation ($P = 0.0005$), while the change in FVC was not statistically significant until after 30 min of postinhalation of FP-S. The BDP-FF combination was comparable in efficacy and tolerability to FP-S combination with rapid onset of improvement of FVC, consistent with the faster improvement of pulmonary hyperinflation and air trapping with extrafine BDP-FF.

Barnes *et al*., in a 12-week study involving 416 patients, demonstrated that asthma control was maintained in patients who were previously controlled with FP-S (500/100 μg) and there was no deterioration in asthma symptoms and asthma control when the patients were switched to extrafine BDP-FF (400/24 μg).[20] When compared to baseline, both BDP-FF (from 3.10 [0.82] to 3.13 [0.82] L) and FP-S (from 3.15 [0.82] to 3.16 [0.79] L) groups showed nonsignificant change in morning predose FEV1 at the end of treatment. Similar results were observed with regard to the other pulmonary function parameters (FEV1% predicted, PEF, FVC, and $FEF_{25\%–75\%}$). Asthma control evaluated by Asthma Control Questionnaire-7 questionnaire did not show significant differences between extrafine BDP-FF and FP-S groups at the end of treatment. In the last 4-week treatment period, the mean percentage of complete days without asthma symptoms was 88.5% in the BDP-FF group and 88.8% in the FP-S group (P = nonsignificant [ns]). Two separate, 12-week, randomized phase 3 clinical trials were conducted, one comparing the efficacy of extrafine

BDP-FF versus budesonide/formoterol (BUD-F) and the other comparing the efficacy of extrafine BDP-FF versus FP-S.[21,22] The trials looked at similar efficacy parameters such as morning PEF in the last 2 weeks of treatment, symptom score, and use of rescue medications. In the study comparing BDP-FF (400/24 μg daily) versus BUD-F (800/24 μg daily), it was shown that the mean improvements in PEF in the final 2-week period were 27.50 ± 53.35 L/min and 27.43 ± 39.39 L/min in the BDP-FF and BUD-F groups, respectively.[22] The differences between the two groups were not significant. In the study comparing extrafine BDP-FF (400/24 μg daily) versus FP-S (500/100 μg daily), the values for morning predose PEF during the last 2 weeks of the treatment period with FP-S (333.0 l/min) and BDP-FF (329.6 l/min) demonstrated no significant difference between the two groups.[23] Similarly, in both the studies, significant increase versus baseline was shown in daily FEV1 measured by patients in both groups with no significant difference between groups at the end of treatment. It was shown that extrafine formulation of BDP-FF was noninferior to conventional formulation of FP-S and BUD-F with respect to efficacy and tolerability. However, faster bronchodilation was observed with BDP-FF combination versus conventional FP-S combination both at baseline and at the end visit as reported by the change in FEV1 from predose to 60 min after dosing that was significantly greater at all time points (from 5 to 60 min postdosing) in the BDP-FF group when compared to the FP-S group.

Many clinical trials undertaken in asthma are not necessarily representative of the heterogeneity in patient profiles that is evident in real-world clinical practice. The clinical efficacy of extrafine BDP-FF has been demonstrated in numerous real-world studies. In a 6-month multicenter, observational study, involving 16,844 asthmatics switching from conventional inhalers to extrafine BDP-FF, asthma control was shown to be increased in 74.2% of patients. At the end of 6 months, 60.1% of the patients met the criteria of controlled asthma; 31.4%, of partly controlled asthma; and 8.3%, of uncontrolled asthma [Figure 4].[23]

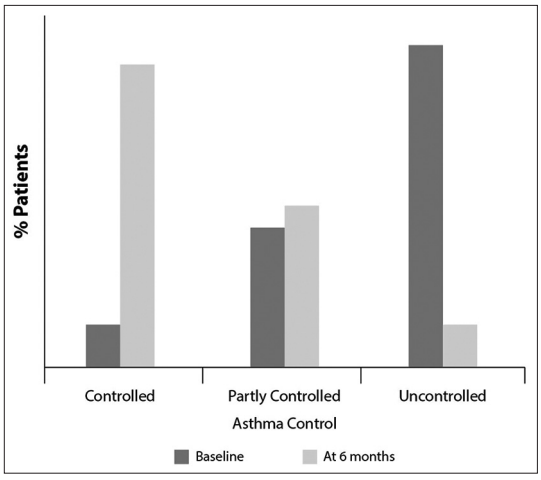

Figure 4: Asthma control assessed (according to the Global Initiative for Asthma) at baseline versus 6 months (end visit) ($P < 0.0001$)

In another real-life, observational study, 59 uncontrolled asthmatic patients were switched to extrafine BDP-FF from FP-S or BUD-F for a period of 8 weeks.[24] Before and after treatment, differences between forced vital capacity percent of predicted (FVC% pred) were calculated and subjects were ranked according to their therapeutic response as "top responders" and "poor responders." Significant improvement in the inflammatory markers (exhaled breath temperature, C reactive protein [CRP], and eosinophils) was noted in the top responders compared to the poor responders. The eosinophil count in blood reduced from 381.7 ± 91.2 to 244.2 ± 43.2 cells/μL, $P = 0.02$) in the top responders. Compared to poor responders, top responders had significant reduction in CRP values. Overall, significant improvement was seen in visual analog scale and quality of life scores (49.1 ± 2.4 vs. 73.1 ± 2.05 and 146.1 ± 2.7 vs. 176.7.1 ± 3.4, respectively, $P < 0.001$). Another real-world study evaluated the effect of extrafine BDP-FF in 111 moderate to severe persistent asthmatics. Day time symptom score, rescue medication use, and ACT score were evaluated. Asthma control was achieved by 45.9% of patients; 38.7% were partially controlled; and 15.3% were uncontrolled. In the extrafine BDF/F group, asthma control total score (5.8 ± 6.2 vs. 8.5 ± 6.8; $P = 0.0160$), daytime symptom score (1.4 ± 1.8 vs. 2.3 ± 2.1; $P = 0.012$), and rescue medication use score (1.8 ± 2.2 vs. 2.6 ± 2.2; $P = 0.025$) were significantly better than those using fixed combinations of FP-S and BUD-F. Improvement in clinical efficacy was achieved with a significantly lower ICS mean daily dose. The added advantage of reduction in the mean daily dose of ICS was also demonstrated in two trials by Allegra *et al*. and Terzano *et al*.[25,26] The mean daily dose of ICS in the three ICS/LABA fixed combinations was lower for extrafine BDP-FF (311.7 [109.5] μg) as compared to either BUD-F (590.1 [242.4] mcg) or FP-S (675.3 [342.9] mcg); $P < 0.0001$. Therefore, extrafine beclomethasone/formoterol was associated with significant benefit in terms of asthma control and quality of life when compared to conventional combinations. The results of these studies highlight the efficacy of extrafine BDP-FF compared to conventional formulations at equipotent or lesser doses in asthmatics in both controlled and real-world studies.

CLINICAL EFFICACY OF EXTRAFINE BECLOMETHASONE/FORMOTEROL IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Tzani *et al*. evaluated the effects of extrafine BDP-FF (200/12 mcg b. i. d) versus FP-S in 18 patients with COPD (FEV_1 <65%) for 12 weeks [Table 3].[27] Improvement in functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), RV/TLC, FRC/TLC, and transition dyspnea index (TDI) at 12 weeks versus baseline was observed in the extrafine BDP-FF group but not in the FP-S. There was

Table 2: Summary of clinical studies of beclomethasone/formoterol versus beclomethasone and formoterol given via separate inhalers

Study	Subjects	Treatment	Design, duration	Assesment	Results
Bonnet Gonod *et al*.[15]	645 moderate to severe asthma	BDP-FF 200/12 µg b.i.d.; BDP CFC 500 µg b.i.d.; BDP CFC 500 µg plus formoterol 12 µg b.i.d.	Randomised, double-blind, 3-arms parallel-group, 24 weeks	Primary: Morning PEF Secondary: PFTs, asthma exacerbations, symptoms, use of rescue medication, asthma control	Morning PEF: BDP-FF noninferior to BDP + F; BDP-FF > BDP monotherapy. Percentage symptom free days (day and night time symptoms): BDP-FF > BDP + F; BDP-FF > BDP monotherapy. Percentage patients with exacerbations needing oral corticosteroids: BDP-FF group: (6.0%), BDP + F group: (12.1%), BDP monotherapy group: (14.1%)
Huchon *et al*.[16]	645 moderate to severe asthmatics	Extrafine BDP-FF 400/24mcg 1000/24 mcg nonextrafine BDP-FF 1000 mcg nonextrafine BDP	Randomized, double-blind, double-dummy 24 weeks	Primary: Morning PEF Secondary: FEV_1, FVC, $FEF_{25\%-75\%}$, day and night symptom scores, symptom free days	Improvement in morning PEF: BDP-FF group: 339.64l/min; BDP+F group: 332.37l/min; BDP monotherapy group: 309.41l/min (ITT Population). (P<0.001 between combination groups vs. BDP monotherapy), nonsignificant between combination groups. Number of asthma exacerbations: BDP-FF group: 280; BDP+F group: 351; BDP monotherapy group: 428 Percentage of days with asthma control: BDP-FF > BDP + F (P<0.005); BDP-FF > BDP monotherapy (P<0.0001)

PEF: Peak expiratory flow, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, $FEF_{25\%-75\%}$: Mid expiratory flow, PFTs: Pulmonary function tests, ITT: Intention to treat population, BDP-FF: Beclomethasone/formoterol, CFC: Chlorofluorocarbon

significant reduction in residual volume (RV) in the BDP-FF group, indicating that the BDP-FF extrafine combination reduced air trapping and dyspnea. Another study used novel functional respiratory imaging consisting of multislice computed tomography (CT) scans and computational fluid dynamics (CFD) [Table 3] to evaluate the effects of extrafine BDP-FF formulation on airway geometry in 27 COPD patients (stage 2–4).[28] The administration of extrafine BDP-FF led to a significant improvement in airway geometry at 4–6 h; hyperinflation and dyspnea score also improved after 6 months of treatment versus baseline values. With a (−11%) change in extrathoracic deposition and (+1% to + 4%) change in lobar deposition with extrafine formulation, this CFD-based aerosol deposition analysis demonstrated that the extrafine formulation increased the effective lung dose and reached the peripheral areas in the lung compared to non-extrafine particle formulations.

Singh *et al*. evaluated extrafine BDP-FF versus FP-S in moderate-to-severe COPD patients [Table 3].[29] BDP-FF gave similar results to FP-S in terms of TDI score, but it was superior corresponding to change from predose in the first 30 mins in FEV_1 ($P < 0.001$). Importantly, an improvement that gave clinically relevant outcome (>4 units) in St. George Respiratory Questionnaire (SGRQ) was detected only in the BDP-FF group.

Another study, assessed the effects of 48 weeks of BDP-FF versus formoterol treatment in 1186 COPD patients [Table 3].[30] Compared to formoterol monotherapy, BDP-FF reduced the exacerbation rate, improved pre-dose morning FEV1, prolonged the time to first exacerbation, and improved the SGRQ total score.

In another study, 718 hospital outpatients with severe COPD were randomized to receive BDP-FF (200/12 μg), BUD-F (400/12 μg) or formoterol (12 μg) twice daily for 48 weeks.[31] BDP-FF treatment was shown to improve pulmonary function and reduce symptoms compared to formoterol monotherapy and was found to be safe and well tolerated in patients with severe stable COPD [Table 3]. Extrafine BDP-FF showed noninferiority when compared to BUD-F group with respect to improvement in pulmonary function and reduction in symptoms, but was more effective than formoterol monotherapy.

SAFETY AND TOLERABILITY

The safety and tolerability profile of BDP-FF in asthma has been found to be similar to the available formulations of FP-S and BUD-F.[22,23] In a comparative study versus BUD-F, adverse events (all non-serious) were reported in 15 (13.8%) patients in the BDP-FF group and in 18 (16.5%) in the BUD-F group (P = nonsignificant). Worsening of asthma and upper/lower respiratory tract infections were the most common events, which could be attributed to seasonal variations rather than to drug tolerability concerns as suggested by their similar frequency in the two groups. There were no clinically significant changes in heart rate, blood pressure, electrocardiogram (ECG), or QTc interval in either group. The rate of drug-related adverse events, effects on heart rate and ECG (QTc interval), and change from baseline of 12-h overnight cortisol/creatinine ratio did not differ between groups.

The safety of BDP-FF pMDI extrafine formulation on serum cortisol levels was evaluated in 12 healthy male subjects.[32] Lower systemic exposure to beclomethasone 17-monopropionate (B17MP), the active metabolite of beclomethasone, was observed with the fixed combination of BDP-FF (400/24 μg) than with the separate components (BDP CFC 1000 μg and formoterol 24 μg),

Table 3: Summary of studies demonstrating clinical efficacy with extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease

Study	Subjects	Treatment	Design, duration	Assessment	Results
Tzani *et al*.[27]	20 patients with COPD	BDP-FF 400/24 mcg FP-S 500/100 mcg	Double-blind, double dummy, randomized, parallel group 12 week	FRC, RV, TLC, FVC, FRC/TLC, RV/TLC, TDI	Improvement in postdose RV/TLC % versus baseline: BDP-FF (58.22±4.69) to (−4.76±2.35) > FP-S (64.00±2.29) to (0.65±2.35) Trend toward improvement only in BDP-FF Improvement in postdose RV versus baseline: BDP-FF (4.73±0.76) to (−0.77±0.29) > FP/S (4.82±0.28) to (0.14±0.29) (P<0.05) Improvement in TDI total score: Clinically relevant improvement versus baseline (1.144) seen only in BDP-FF group (P=0.026) not in FP-S group
Singh *et al*.[29]	419 patients; moderate/ severe COPD	BDP-FF 200/12 mcg FP-S 500/50 mcg bid	Multicentre, randomised, double-blind, double dummy 12 week	Primary: TDI score, change from predose FEV_1 in 30 min Secondary: PFT, symptom free days, reliever use, SGRQ, symptom score, COPD-6, exacerbations	Equivalence in TDI score: (44.1% patients) BDP-FF group and (43.0% patients) FP-S group had a≥1 improvement in TDI score (P=0.92) Improvement in postdose FEV_1 at 5, 15, 30 min: BDP-FF group>FP-S group at all time points (P<0.001) Improvement in SGRQ score: Clinically relevant improvement>4 units in BDP-FF group but not in FP-S group
De Backer *et al*.[28]	27 patients stage II to IV COPD	BDP-FF (100/6 mcg) 2 inhalations, bid	Prospective, open-label, 24 weeks	Primary: siVaw, siRaw, siRaw, FEV_1, FVC, PEF, MEF50, MEF25. VC, IVC, FRC, TLC, Raw, SGaw Secondary: MMRC SGRQ	Deposition (recorded by CFD): 11% lesser extrathoracic deposition versus nonextrafine formulation 4% increase in lobe deposition with extrafine BDP-FF Improvement in FEV_1% pred versus baseline: 4-6 h after administration 46±14% to 50±15% (P=0.0003) Hyperinflation: Reduction in FRC of 7±10% pred (P 0.002)
Forward study Wedzicha *et al*.[30]	1186 patients; severe COPD	BDP-FF 400/24 mcg, versus F 24 mcg	Randomised, double-blind, parallel-group; 48 weeks	Primary: Exacerbation rate, change in predose morning FEV_1 (L) from baseline (randomisation visit) to week 12 Secondary: Time to first COPD exacerbation, (SGRQ)	Percentage of patients with exacerbations: BDP-FF group: (44.4%) F group: (49.7%) Mean FEV_1 change at week 12: BDP-FF > F group (0.081 L versus 0.012 L, P<0.001)
Calverley *et al*.[31]	718 patients; severe but stable COPD	BDP-FF (200/12 mcg) BUD-F (400/12 mcg) F (12 mcg)	Double-blind, double-dummy, randomised, active-controlled, parallel-group 48 weeks	Primary: Change in predose morning FEV_1 from baseline to 48 weeks, mean rate of COPD exacerbations Secondary: Dyspnoea score, SGRQ score	Improvement in predose morning FEV1: 0.077 L, 0.080 L and 0.026 L for BDP-FF, BUD-F and F, respectively Exacerbation rate: 0.414 per patient per year in BDP-FF group; 0.423 in BUD-F group; 0.431 in the F group Reduction in dyspnoea score: BDP-FF (-0.19±0.74) versus baseline and BUD-F (-0.18±0.78) versus baseline; F (-0.07±0.76) versus baseline

siVaw: Airway volumes specific for the lung volume, siRaw: Specific airway resistance, iVlobes_FRC: Lobar volumes at FRC, iVlobes_TLC: Lobar volumes at total lung capacity, Raw: Airway resistance, SGaw: Specific airway conductance, SGRQ: St. George's Respiratory Questionnaire, TDI: Transition Dyspnoea Index, COPD: Chronic obstructive pulmonary disease, BDP-FF: Beclomethasone/formoterol, FRC: Functional residual capacity, RV: Residual volume, TLC: Total lung capacity, FVC: Forced vital capacity, TDI: Transition dyspnea index, FEV1: Forced expiratory volume in 1 s, PFT: Pulmonary function test, CFD: Computational fluid dynamics, BUD-F: Budesonide-formoterol, IVC: Inspiratory vital capacity

which is indicative of less cortisol suppression. Despite a lower total systemic exposure to B17MP with the fixed combination, B17MP plasma concentrations during the first 30 min after administration, indicative of pulmonary absorption, were 86% higher with BDP-FF than with the separate components. Extrafine BDP-FF demonstrated less serum cortisol suppression over a 24-h period as compared to BDP and formoterol administered separately. The treatments were well tolerated and no clinically relevant differences in serum potassium and cardiovascular or spirometric parameters were observed between the treatments. Table 4 summarizes the key results.

DOSAGE AND ADMINISTRATION

A fixed dose combination of BDP-FF (100/6 μg) extrafine formulation is now approved for the maintenance treatment of asthma in adults >18 years of age. The recommended dose is 1–2 inhalations, twice daily; it has been recommended that the dosage not exceed more than 8 inhalations per day.

Table 4: Changes in important pharmacodynamic parameters after treatment

	Serum cortisol C_{min} (ng/mL)	Urinary cortisol Ae/Ae_{creat}	Serum potassium C_{min} (mEq/L)	Cardiac parameter (QTc)
BDP-FF FDC	25.0±15.4	48.8±35.4	3.88±0.20	392±14
BDP+F given separately	17.2±10.2	46.4±16.5	3.89±0.18	392±11
Placebo	38.8±15.3	61.7±11.1	3.89±0.14	393±10
P	<0.001	0.017	0.981	0.946

C_{min}: Minimum plasma drug concentration, Ae/Ae_{creat}: Urinary cortisol excretion normalized for creatinine, QTc: QTc over 12 h (ms) corrected QT interval, BDP-FF: Beclomethasone/formoterol, FDC: Fixed dose combination

In studies, the use of a spacer was shown to optimize the lung delivery of beclomethasone and formoterol in subjects who find it difficult to synchronize aerosol actuation. Importantly, use of a spacer did not increase the total systemic exposure to 17-BMP and formoterol.[33]

Place in therapy

The novel extrafine formulation of BDP-FF might offer significant advantages in the treatment of asthma and COPD due to its mechanism of targeted drug delivery and relatively uniform lung deposition. Increased lung deposition with extrafine BDP-FF has resulted in the adjustment of ICS dosage to 2.5 times lesser dose than conventional beclomethasone CFC formulation. The nominal dose reduction of BDP resulted in lower systemic exposure and lower cortisol suppression, thereby showing a low potential for systemic side effects. The formulation of extrafine BDP-FF in an inhalation solution rather than a suspension form enables generation of a mist with a uniform particle size facilitating uniform codeposition throughout the bronchial tree.[34] Based on the available evidence and published literature, extrafine BDP-FF will potentially find its place in therapy in patients with severe asthma, treatment-resistant asthma, poorly controlled asthma (patients who are symptomatic despite being on high doses of ICS-LABA), frequent exacerbations, nocturnal asthma, and COPD. Randomized clinical trials and real-world studies carried out in patients with obstructive airways disease demonstrated superior or comparable efficacy profile between BDP-FF extrafine combination and other available conventional formulations of ICS/LABA, suggesting that extrafine formulation of BDP-FF could be a valuable therapeutic alternative for the management of obstructive airways diseases.

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Conflicts of interest

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