High-dose beclometasone dipropionate/ formoterol fumarate in fixed-dose combination for the treatment of asthma

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***Abstract*:** The high-strength formulation of extrafine beclometasone dipropionate/formoterol fumarate (BDP/Form) 200/6 µg has been developed to step up inhaled corticosteroid treatment, without increasing the dose of the bronchodilator, in patients who are not controlled with previous therapies. Two clinical studies have evaluated efficacy of high-strength BDP/Form as compared with another high-dose fixed combination and BDP monotherapy. Overall, data show that BDP/Form 200/6 µg improves lung function and has beneficial effects on symptoms, use of rescue medication and asthma control, with an acceptable safety profile comparable with that of high-dose fluticasone propionate/salmeterol. Therefore, BDP/Form 200/6 µg could be considered as an effective and safe treatment for patients with asthma who are not adequately controlled with high doses of inhaled corticosteroid monotherapy or medium doses of inhaled corticosteroid/long-acting β_2-agonist combinations.

Keywords: asthma, beclometasone dipropionate/formoterol fumarate, high-dose fixed combination, inhaled corticosteroid, long-acting β_2-agonist

Introduction

The Global Initiative for Asthma (GINA) guidelines recommend adjustment of asthma treatment based on the extent of day and night symptoms, limitations of physical activity, need for rescue medicine, and lung function impairment [Reddel and Levy, 2015]. GINA recommendations suggest a five-step approach with modifications of treatment based on the patient's current level of asthma control and pharmacologic treatment: short-term reliever therapy with an inhaled short-acting β_2-adrenoceptor agonist (SABA) for mild intermittent asthma (step 1), regular preventer therapy with low-dose inhaled corticosteroid (ICS) (step 2), then adding a long acting β_2-adrenoceptor agonist (LABA) therapy to the low dose of ICS (step 3), further increasing ICS dose (to medium–high dose) associated with LABA (step 4) and, finally, escalating to a series of add-on treatments (step 5). Treatment should be started at the step most appropriate to the initial severity of the disease, and then stepped up to improve disease control or stepped down to find and maintain the lowest controlling step [Reddel and Levy, 2015].

The beneficial effects of ICS in combination with bronchodilators in asthma treatment are well documented. A possible explanation may reside in reversing the β_2-receptor desensitization through the upregulation of the β_2-receptor gene expression. Furthermore, the combination of a LABA with an ICS has been shown to facilitate the translocation of the glucocorticoid receptor from the cytosol to the site of action (i.e. the cell nucleus). This phenomenon is likely to explain the clinical efficacy seen with combination therapy [Kuna and Kupryś–Lipińska, 2008].

The combination of an ICS and a LABA is therefore the appropriate treatment when asthma control cannot be achieved with ICS monotherapy, and availability of more than one strength of ICS in fixed combination with a LABA is crucial for a flexible adjustment of treatment.

Fixed-dose ICS/LABA combinations available for asthma (fluticasone propionate/salmeterol [FP/Salm], fluticasone propionate/formoterol [FP/form], fluticasone furoate/vilanterol [FF/Vil] and budesonide/ formoterol [BUD/Form]) have a

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range of doses which allow increasing the dose of ICS with or without increasing the dose of LABA.

The extrafine fixed combination of 100 µg of beclometasone dipropionate (BDP) and 6 µg of formoterol fumarate (Form), in both a pressurized metered dose inhaler (pMDI) and a dry power inhaler (DPI), is approved for asthma treatment with a posology of one or two inhalations twice daily and, according to GINA grading, provides a medium daily dose of ICS. The efficacy and safety of this combination was proved in clinical studies [Huchon *et al.* 2009; Papi *et al.* 2007a, 2007b] and its effectiveness was confirmed in real life conditions [Kuna *et al.* 2015; Müller *et al.* 2011; Allegra *et al.* 2012; Terzano *et al.* 2012].

The high-strength BDP/Form 200/6 µg formulation, delivered by both pMDI and DPI as two inhalations twice daily, has been developed in an effort to provide caregivers with a wider therapeutic option to adapt treatments to specific patient conditions. The higher strength of BDP in fixed combination with Form has the main purpose to step up ICS treatment in patients who are not controlled with previous therapies (high dose of ICS in monotherapy or medium dose of ICS + LABA), without increasing the dose of the bronchodilator.

Similarly to BDP/Form 100/6 µg, the high-strength BDP/Form has been developed as an extrafine formulation (i.e. with a median mass aerodynamic diameter [MMAD] <2.0 µm for both active components). In particular, MMAD is 1.5 for both components of BDP/Form 200/6 µg pMDI, and 1.4/1.7 for BDP and Form, respectively, in BDP/Form 200/6 µg NEXThaler. The extrafine formulation was shown to provide high and homogenous lung deposition in both large and small airways independently from pathophysiological conditions [De Backer *et al.* 2010; Scichilone *et al.* 2014].

This review describes findings from two phase III pivotal clinical studies, summarized in Table 1 (studies CCD-0604-PR-0018 [CT01] and NCT01577082 [FORCE]), which were undertaken to investigate safety and efficacy of extrafine BDP/Form 200/6 µg compared with high-dose BDP monotherapy (nonextrafine BDP 2000 µg or extrafine BDP 800 µg) and with high-dose FP/Salm (500/50 µg). These studies were aimed at assessing superiority of BDP/Form *versus* BDP in terms of lung function (predose forced expiratory volume [FEV_1] in study CT01 and predose morning peak expiratory flow [PEF] in the FORCE study) and symptoms (percentage of complete days without symptoms in CT01), and non-inferiority of BDP/Form *versus* FP/Salm in terms of lung function (predose FEV_1) in CT01.

Description of studies

CT01. This randomized, active and placebo-controlled trial was conducted to demonstrate superiority of extrafine BDP/Form 200/6 µg, two puffs twice daily, at a total daily dose 800/24 µg, *versus* a high dose of nonextrafine BDP (2000 µg/day) and non-inferiority *versus* FP/Salm DPI 500/50 µg (1000/100 µg/day), in terms of pulmonary function (change from baseline to end of treatment in predose morning FEV_1) and asthma control (change from baseline in percentage of complete days without asthma symptoms at end of treatment). The study was carried out in patients with severe, persistent uncontrolled asthma over a 24-week treatment period. The definition of severe asthma was in line with GINA guidelines in force at the time of the study [National Institutes of Health, 2006].

A screening visit was performed to select patients with persistent uncontrolled asthma (based on GINA parameters) in need of a step-up therapy. After a 2-week run-in period during which patients received BDP pMDI 250 µg, two inhalations twice daily, only patients who were still not controlled entered the randomization period and started a 6-month treatment period with assessments at 2, 6, 12, 18 and 24 weeks.

The sample size was calculated to demonstrate superiority of BDP/Form over BDP in the primary efficacy variable if the lower limit of the two-sided 95% CI for the treatment difference at the last visit was larger than -0.201. In addition, this sample size was set to provide 90% power for the superiority testing of BDP/Form *versus* BDP monotherapy on the change in percentage of complete days without asthma symptoms, assuming an estimated difference between treatments equal to 10% and a standard deviation (SD) of 30%, with a two-sided significance level fixed at 5%.

Secondary objectives of the study included additional lung function parameters, clinical outcome measures, and safety and tolerability (e.g. hypothalamic-pituitary-adrenal axis suppression).

Table 1. Overview of BDP/Form 200/6 µg pivotal clinical studies.

	Clinical studies	
	CT01	*FORCE*
Study objective	Non-inferiority of BDP/Form 200/6 µg *versus* FP/Salm 500/50 µg on FEV_1; Superiority of BDP/Form 200/6 µg *versus* nonextrafine BDP 250 µg on FEV_1 and asthma control	Superiority of BDP/Form 200/6 µg *versus* extrafine BDP 100 µg
Study design	Randomized, double-blind, triple-dummy, three-arm groups	Randomized, double-blind, double-dummy, two-arm groups
Study duration	24 weeks	12 weeks
Total daily doses	BDP/Form 800/24 µg FP/Salm 1000/100 µg BDP 2000 µg	BDP/Form 800/24 µg BDP 800 µg
Population	721 patients with severe, persistent uncontrolled asthma	378 patients with persistent asthma not optimally controlled on high doses of ICS or medium/high dose of ICS + LABA
Primary measurements	Predose FEV_1 and percentage of complete days without symptoms	Predose morning PEF
Secondary measurements	Additional lung function parameters and safety	Additional lung function parameters and safety

BDP/Form, beclometasone dipropionate/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; FP/Salm, fluticasone propionate/salmeterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PEF, peak expiratory flow.

BDP monotherapy used as a comparator consisted of the marketed nonextrafine BDP 250 µg pMDI. The selected dosage of BDP 2000 µg/day was chosen based on the equivalence between 100 µg of extrafine BDP and 250 µg of nonextrafine BDP [Acerbi *et al.* 2007]. FP/Salm DPI was used since, at the time of the study, it was not possible to blind the pMDI formulation.

FORCE. This was a phase III, multinational, multicentre, randomized, double-blind, double-dummy, active-control, two-arm parallel-group study with a 2-week run-in period (open-label), during which patients received extrafine BDP (800 µg/day), followed by a treatment period of 12 weeks.

Adult asthmatic patients who, despite previous treatment with high-dose ICS monotherapy or medium-dose ICS/LABA combinations, had a FEV_1 <80% predicted and were not fully controlled (based on GINA asthma control parameters and asthma control questionnaire [ACQ]) were included in the study.

The primary objective was to show superiority of BDP/Form 200/6 µg (800/24 µg daily dose) over extrafine BDP 100 µg pMDI (800 µg daily dose) in terms of change from baseline to the entire treatment period in predose morning PEF. The sample size was calculated to demonstrate the superiority of BDP/Form over BDP in the primary efficacy variable, assuming a mean difference of 15 l/min between treatments and a standard deviation of 40 l/min [Aubier *et al.* 1999].

Efficacy and safety results

Demographic and clinical characteristics of patients in studies CT01 and FORCE are reported in Table 2.

CT01: efficacy results. In the intention to treat (ITT) population, the adjusted mean change from baseline to the end of treatment in predose FEV_1 was 0.20, 0.16 and 0.22 l in BDP/Form, BDP and FP/Salm groups, respectively. The estimated treatment difference between BDP/Form and FP/Salm was -0.03 l (95% CI: -0.10, 0.05) in the ITT population and -0.02 l (95% CI: -0.10, 0.05) in the per protocol (PP) population, thus excluding any significant difference between the two high-dose ICS/LABA combinations. The difference between BDP/Form and BDP monotherapy was in favour of BDP/Form (0.04 l; 95% CI: -0.04, 0.11) but did not reach statistical significance. It is notable however, that FP/Salm did

Table 2. Demographic and other baseline characteristics of patients enrolled in BDP/Form 200/6 µg pivotal clinical studies.

	CT01			*FORCE*	
	BDP/Form 200/6 µg *n* = 237	BDP 250 µg *n* = 242	FP/Salm 500/50 µg *n* = 242	BDP/Form 200/6 µg *n* = 184	BDP 100 µg *n* = 175
Males, *n* (%)	106 (45.3)	102 (42.3)	100 (41.5)	84 (45.7)	63 (36.0)
Age, years, mean (SD)	48.8 (11.6)	47.4 (13.4)	49.7 (12.3)	49.5 (13.7)	49.1 (14.1)
BMI, kg/m², mean (SD)	27.7 (5.1)	27.4 (5.5)	27.4 (5.0)	28.9 (4.6)	27.1 (5.3)
Current smokers, *n* (%)	3 (1.3)	6 (2.5)	5 (2.1)	0 (0.0)	0 (0.0)
Exsmokers, *n* (%)	35 (15.0)	31 (12.9)	32 (13.3)	33 (17.9)	28 (16.0)
Nonsmoker, *n* (%)	196 (83.8)	204 (84.6)	204 (84.6)	151 (82.1)	147 (84.0)
Asthma therapy: ICS + LABA, *n* (%)	166 (70.9)	173 (71.8)	186 (77.2)	168 (91.3)	160 (91.4)
Asthma therapy: ICS, *n* (%)	68 (29.1)	68 (28.2)	55 (22.8)	16 (8.7)	15 (8.6)
ICS dosage (µg): mean (SD)	1332 (444)	1391 (570)	1376 (515)	985 (265)	952 (261)
FEV_1, % of predicted normal value, mean (SD)	65.64 (12.13)	65.22 (11.49)	65.65 (13.21)	64.7 (8.5)	65.2 (10.7)
PEF (l/min), mean (SD)	336.00 (100.59)	322.27 (102.26)	321.98 (107.20)	310.39 (107.65)	312.63 (102.58)
Reversibility test					
FEV_1 % change, mean (SD)	27.5 (17.0)	29.4 (17.4)	26.0 (15.1)	27.7 (15.7)	30.2 (19.3)
FEV_1 (l), mean (SD)	2.02 (0.62)	2.02 (0.63)	1.99 (0.63)	2.02 (0.60)	1.96 (0.55)

BDP/Form, beclometasone dipropionate/formoterol fumarate; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FP/Salm, fluticasone propionate/salmeterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PEF, peak expiratory flow; SD, standard deviation.

not show a statistically significant difference over BDP monotherapy either.

At the end of treatment, the percentage of complete days without symptoms was increased by 25%, 22% and 27% in the BDP/Form, BDP and FP/Salm group, respectively. Figure 1 shows the percentage of complete days without asthma symptoms at each timepoint, suggesting better and more rapid control of symptoms with BDP/Form compared with BDP monotherapy over the 6-month treatment period. However, no statistically significant difference between treatments was observed in any pairwise comparison. The adjusted mean difference between BDP/Form and BDP was 2.69 (95% CI: -5.22, 10.60), which was not statistically significant. Statistical significant difference was not observed even between FP/Salm and BDP (4.62, 95% CI -3.16, 12.39, $p = 0.244$). Similar results were obtained in a *post-hoc* analysis considering change from baseline in the percentage of complete days without asthma symptoms to the entire treatment period, defined as the average of any post treatment available value of days without asthma symptoms.

Clinically relevant differences between BDP/Form and BDP were observed in a number of secondary endpoints related to both lung function and asthma control. In particular, BDP/Form showed a statistically significant greater change from baseline in morning PEF than BDP throughout the whole study period with an adjusted mean change from baseline of 21.34 l/min (95% CI: 8.43, 34.25; $p = 0.001$) at the end of treatment. Similar results were obtained for evening PEF: at the end of treatment, the adjusted mean difference between BDP/Form and BDP was 23.44 l/min (95% CI: 10.44, 36.44; $p = 0.001$). Statistically significant differences favouring BDP/Form over BDP monotherapy were found in the percentage of days without the use of rescue medication (both during daytime and during the night-time), percentage of nights without symptoms and percentage of asthma control days (Figure 2a). No statistically significant difference was found for any of these parameters between BDP/Form and FP/Salm indicating comparable efficacy of the two high-strength combinations on lung function parameters and control of symptoms (Figure 2b).

The percentage of patients reporting asthma exacerbation was similar between the treatment groups: 66/721 (9.2%) patients overall, with 21/239 (8.8%) patients in the BDP/Form group;

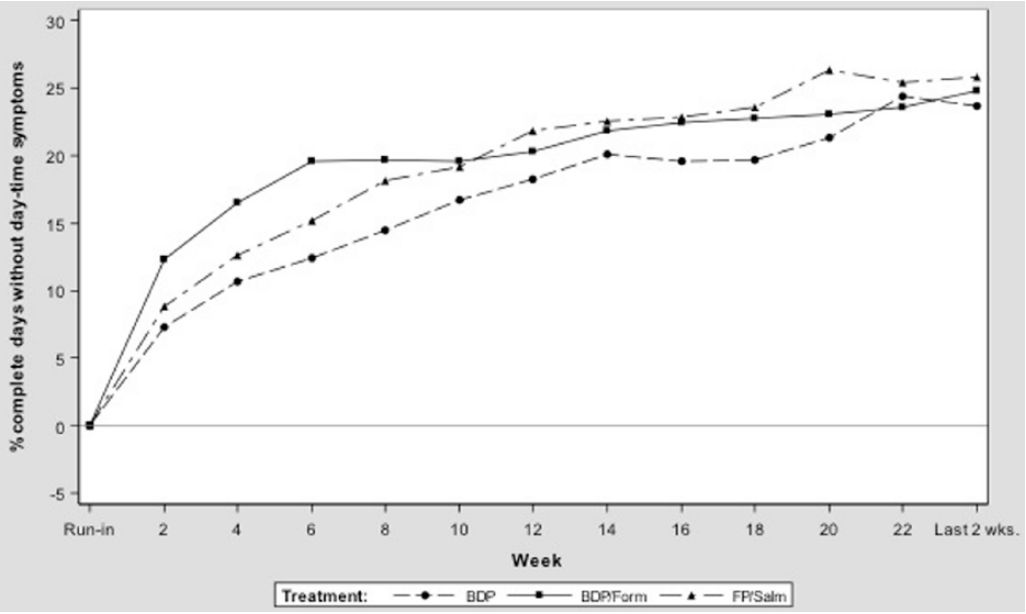

Figure 1. Change from baseline in percentage of complete days without asthma symptoms in study CT01.
*$p < 0.05$.
BDP, beclometasone dipropionate; BDP/Form, beclometasone dipropionate/formoterol fumarate; FP/Salm, fluticasone propionate/salmeterol.

24/244 (9.8%) patients in the BDP monotherapy group and 21/242 (8.7%) patients in the FP/Salm group.

CT01: safety results. Safety analyses were conducted on the safety population, which included 239 patients in the BDP/Form group, 244 patients in the BDP group and 242 in the FP/Salm group. The percentage of patients experiencing treatment-emergent adverse events (TEAEs) during the randomized treatment period was similar among the treatment groups (37.2% with BDP/Form, 38.1% with BDP monotherapy, and 37.2% with FP/Salm), as well as the percentage of patients experiencing adverse drug reactions (ADRs) during the randomized treatment period (8.8% with BDP/Form, 7.8% with BDP monotherapy, and 8.3% with FP/Salm). The incidence of dysphonia was significantly greater in the FP/Salm group (2.9%) than BDP monotherapy group (0.4%). There were no other significant differences between treatment groups for all other ADRs reported; however a higher incidence of oral candidiasis was reported in the BDP group (five cases *versus* one case in each ICS/LABA combination group).

Patients receiving BDP showed significantly lower morning serum cortisol levels at the end of the study compared with the BDP/Form and FP/S groups ($p < 0.001$ and $p = 0.007$, respectively). No statistically significant differences were observed between BDP/Form and FP/Salm.

The effect of the prolonged exposure to BDP/Form and specifically to the maximal dose of BDP given every day for 6 months was assessed in this study through adrenocorticotropic hormone (ACTH) stimulation test carried out in a subgroup of patients. BDP/Form showed a normal response to ACTH at baseline (visit 2) and after 6 months of treatment (visit 7), with mean serum cortisol values above the accepted threshold of 0.5 nmol/l (18 µg/dl) [Neary and Nieman, 2010].

The mean values of serum potassium and serum glucose stayed within narrow limits and were similar in all treatment groups pre- and post-dose at all timepoints. The mean values and changes in vital signs and physical examinations were not clinically relevant and were comparable in all treatment groups.

The mean changes from baseline and between pre- and 30 minutes post-doses for ventricular rate, PR interval, QRS interval, QTc Bazett interval and QTc Fridericia interval were small and similar between treatment groups at all timepoints.

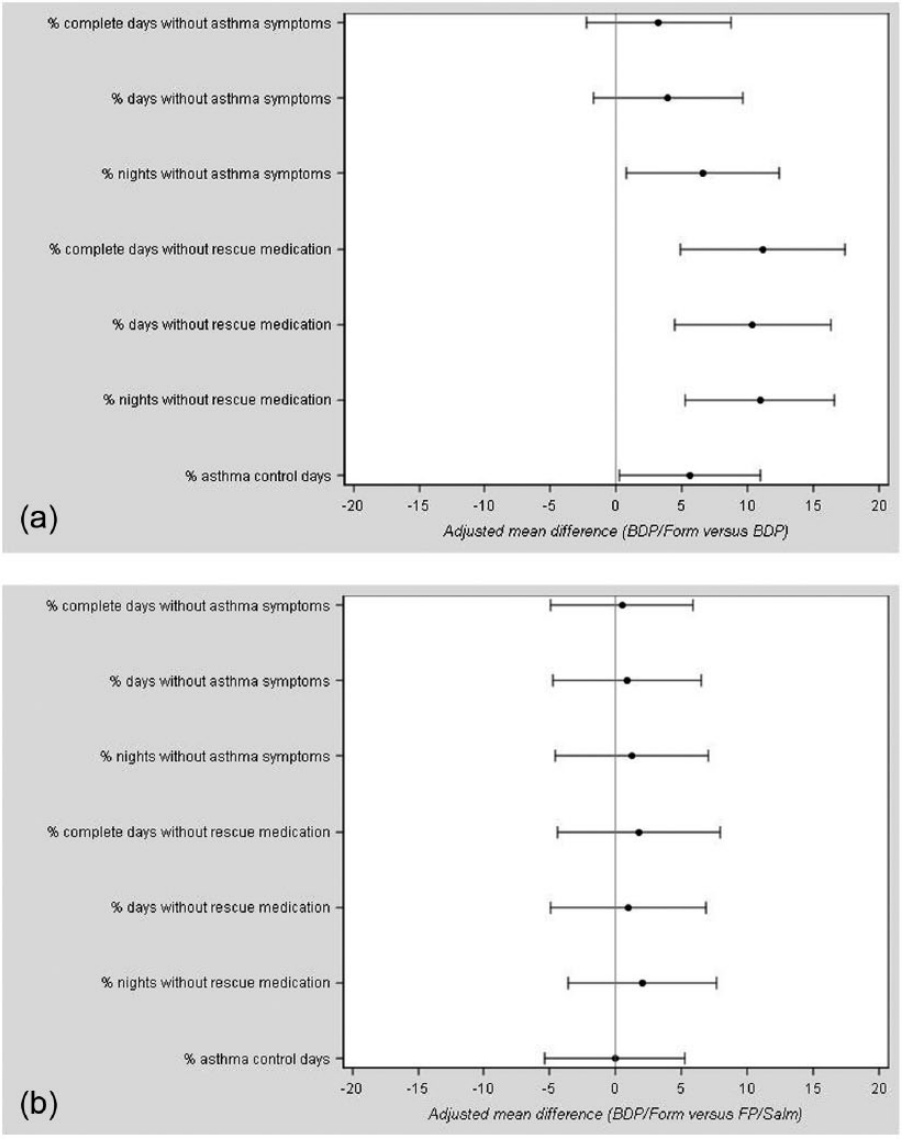

Figure 2a and b. Change from baseline in asthma control-related parameters in study CT01.
Bars represent 95% confidence interval.
BDP, beclometasone dipropionate; BDP/Form, beclometasone dipropionate/formoterol fumarate.

FORCE: efficacy results. After 12 weeks of treatment, morning PEF increased in the BDP/Form group while a slight decrease was observed in the BDP group (18 l/min and -1 l/min, respectively). In the ITT population, the difference in the adjusted mean change from baseline between the two treatment groups was significantly in favour of the BDP/Form group (18.53 l/min, 95% CI: 10.33, 26.73, $p < 0.001$), indicating superiority of BDP/Form *versus* BDP (Figure 3a). Results were similar in the PP population where the difference in the adjusted mean change from baseline between the two treatment groups was statistically significant in favour of the BDP/Form group (18.48 L/min, 95% CI: 9.88, 27.08, $p < 0.001$), confirming the superiority of BDP/Form treatment *versus* BDP.

A series of secondary efficacy analyses confirmed the greater benefit of BDP/Form as compared with BDP monotherapy. Specifically, BDP/Form resulted in a statistically significantly greater improvement of predose evening PEF, daily PEF variability, and predose FEV_1.

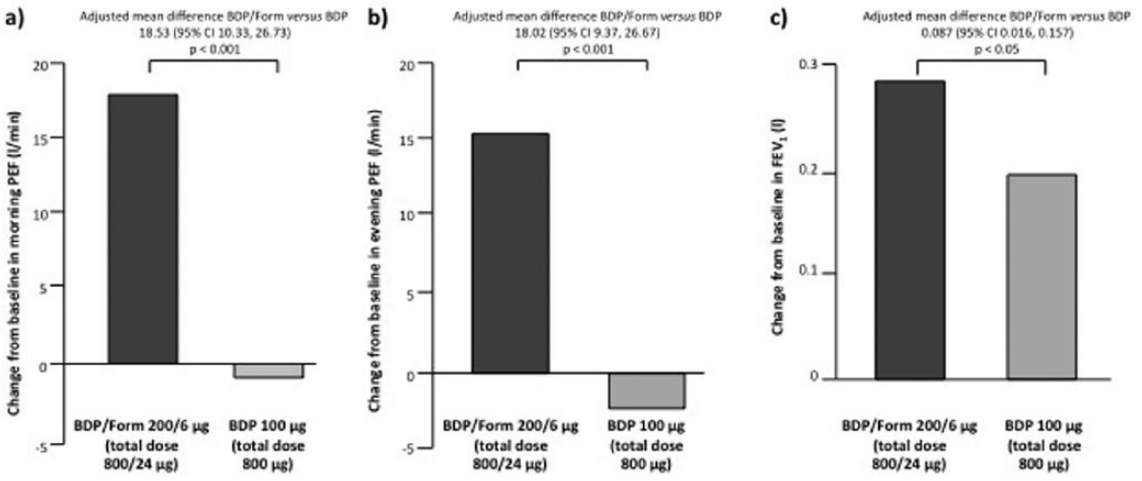

Figure 3. Change from baseline in lung function parameters in the FORCE study. (a) morning PEF; (b) evening PEF; (c) FEV_1 (*post-hoc* analysis taking into account the results of the reversibility test at screening). Data are reported as mean ± standard deviation.
BDP, beclometasone dipropionate; FEV_1, forced expiratory volume in 1 second; Form, formoterol fumarate; PEF, peak expiratory flow.

The difference in the change from baseline to each inter-visit period in evening PEF was statistically significant in favour of the BDP/Form group during the whole study duration. At the end of the treatment the adjusted mean difference between BDP/Form and BDP was 17.18 l/min (95% CI: 4.81, 29.54; $p = 0.007$). The analysis considering the entire treatment period showed a highly statistically significant difference between BDP/Form and BDP of 18.02 l/min (95% CI: 9.37, 26.67; $p < 0.001$) (Figure 3b). The difference in adjusted mean changes between treatment groups was statistically significant in favour of BDP/Form at week 1–2 ($p = 0.038$), week 3–4 ($p = 0.018$), week 7–8 (p = 0.005) and over the entire treatment period ($p = 0.010$).

A *post-hoc* analysis on predose FEV_1, which included the reversibility at screening as a covariate, showed a greater improvement of FEV_1 from baseline to each visit and to the entire treatment period with BDP/Form as compared with BDP treatment. The adjusted mean difference between BDP/Form and BDP in the change from baseline to the overall treatment period was 0.087 l (95% CI: 0.016, 0.157, $p = 0.023$) (Figure 3c).

Treatment with BDP/Form resulted in a significant reduction of rescue medication use as well as significant improvement of rescue-free days, symptom-free days, and asthma control (Table 3). No statistically significant difference was observed *versus* BDP monotherapy on these parameters.

FORCE: safety results. Safety analyses were conducted on the safety population, which included 189 patients in the BDP/Form group and 180 patients in the BDP group. Treatment-emergent ADRs were reported slightly less frequently in the BDP/Form group than in the BDP group: three events in two (1.1%) patients *versus* five events in five (2.8%) patients, respectively. Overall, the number of treatment-emergent ADRs was low in both treatment groups and with slightly lower frequency in the BDP/Form group (three events in two patients [1.1%]) than in the BDP group [five events in five (2.8%) patients].

All patients exhibited normal or not clinically significant abnormal haematology and blood chemistry parameters both at screening and at the end of the study.

Serum cortisol was measured by a central laboratory in approximately 15% of patients participating in the study. The difference from baseline in serum cortisol Area under the curve ($AUC_{0\text{-}24h}$) and minimum blood plasma concentration (C_{min}) was stable in the BDP/Form group and decreased in the BDP group with a statistically significant difference in favour of BDP/Form.

Table 3. Improvement of asthma control-related parameters observed with BDP/Form in the FORCE study.

	Baseline *mean (SD)*	**Entire treatment period** *mean (SD)*	**Change from baseline**	***p*-value** *versus* **baseline**
Use of rescue medication (puffs/day)	2.67 (2.72)	1.39 (1.60)	−48%	<0.001
Rescue use-free days	32.95 (37.36)	54.46 (39.74)	+65%	<0.001
Percentage of asthma symptom-free days	5.18 (16.08)	15.31 (27.97)	3 times more	<0.001
Percentage of asthma control days	4.64 (14.93)	14.98 (27.62)	3 times more	<0.001
ACQ score	2.12 (0.63)	1.49 (0.74)	−0.69 points (MCID = 0.5 points)	<0.001

ACQ, asthma control questionnaire; BDP/Form, beclometasone dipropionate/formoterol fumarate; MCID, minimal clinically important difference; SD, standard deviation.

There were no significant changes in vital signs and ECGs from baseline to each visit and to the end of the treatment period.

Discussion

Therapy for asthma is prescribed with a stepwise approach to individualize and adjust treatment according to the level of asthma control: therapy is stepped up if asthma is not adequately controlled and stepped down if asthma control is maintained for a sufficient time interval. Current international guidelines recommend high-dose ICS plus LABA for patients whose asthma is poorly controlled with a moderate dose of ICS plus LABA, or high-dose ICS in monotherapy. Here we described the characteristics of the fixed-dose ICS/LABA combination containing a high dose of BDP (200 µg/actuation) and the same dose of Form (6 µg/actuation).

The clinical efficacy and safety of extrafine BDP/Form 200/6 µg has been evaluated in two phase III pivotal studies in asthmatic patients with not fully controlled disease (according to GINA guidelines) despite the regular use of medium-dose ICS + LABA or high-dose ICS. In both pivotal studies, BDP/Form 200/6 µg showed a significant improvement in some lung function and clinical parameters compared with high dose ICS monotherapy, thus demonstrating the additive bronchodilating effect of LABA on top of high-dose ICS.

Study CCD0604PR0018 did not show superiority of BDP/Form 200/6 µg *versus* BDP alone on the two co-primary endpoints: change in predose FEV_1 and percentage of complete days without asthma symptoms. However, BDP/Form 200/6 µg showed superiority over BDP on a number of important clinical and functional outcomes (predose morning and evening PEF, asthma symptoms, use of rescue medication, asthma control), indicating overall a better and often faster control of the disease, which is now recognized by regulatory and scientific guidelines as the main therapeutic target of treatments for asthma. Furthermore, the results of study CT01 showed that BDP/Form 200/6 µg is non-inferior to high-dose FP/Salm (500/50 µg) in terms of lung function (predose PEF), symptoms and asthma control, with a similar safety profile.

The superiority of BDP/Form 200/6 µg *versus* BDP in lung function was not achieved probably because of different concomitant reasons: (i) The improvement in predose FEV_1 mainly reflects the effect of the ICS component: the review of Li and colleagues [Li *et al.* 2007] and the Cochrane analysis by Ducharme and colleagues [Ducharme *et al.* 2010] show that significant difference in predose FEV_1 between ICS and ICS/LABA is difficult to achieve and, when the difference is present (0.09 and 0.11 l), it is smaller than the minimum clinical important difference (MCID) of 0.23 l as reported by Santanello and colleagues [Santanello *et al.* 1999]. (ii) The study design might have blunted possible differences: during the 2-week run-in period, patients were treated with 1000 µg of BDP daily in order to 'standardise' the baseline treatment and then patients were stepped up to BDP/Form (800/24 µg total daily dose), FP/Salm (1000/100 µg total daily dose) or BDP 2000 µg daily. Doubling the dose of BDP (2000 µg daily) or using optimal doses of the two ICS/LABA combinations led to lung function improvement in all treatment arms. (iii) While the fair comparator for the corticosteroid monotherapy arm would

have been extrafine BDP HFA, it was not possible to prepare a double dummy for extrafine BDP at the time of study planning.

The results of CT01 are in line with a study [Aubier *et al.* 1999] comparing high-dose FP/Salm fixed combination (500/50 µg twice daily) *versus* FP + Salm in separate inhalers (500 + 50 µg twice daily) *versus* FP monotherapy (500 µg) in a randomized, double-blind, parallel-group trial of 28 weeks duration. All patients entering the study were on high-dose ICS for at least 4 weeks and still symptomatic after 2 weeks of run-in with the same ICS dosage. Mean morning PEF after 12 weeks of treatment, which was the primary endpoint, was significantly improved in the combination groups compared with fluticasone monotherapy. Other measures of asthma control, including FEV_1 and symptom scores, night-time awakenings, and salbutamol use, were more improved in the ICS/LABA group than in the two other groups; however, these differences were generally not statistically significant.

The prolonged exposure to 800/24 µg/day of BDP/Form for 6 months showed no clinically relevant effect on the hypothalamic-pituitary adrenal axis. This was confirmed by a lack of clinically relevant changes in 12-hour overnight urinary cortisol/creatinine ratio, morning serum cortisol, and serum cortisol ratios pre- and post-ACTH stimulation, while BDP was found to reduce slightly the levels of serum cortisol at the end of the treatment period. The safety profile of the BDP/Form 200/6 was comparable to that of BDP in terms of adverse events (AEs) and ADRs. In addition, ECG parameters were comparable among treatment groups with no clinically relevant changes in BDP/Form 200/6 or the BDP group.

In the FORCE study, the primary efficacy analysis showed that BDP/Form 200/6 was superior to BDP in improving predose morning PEF. The mean difference *versus* BDP was 19 l/min, which is in line with the mean difference between ICS/LBA and ICS monotherapy reported in the review by Li and colleagues (17.86 l/min) [Li *et al.* 2007] and in a Cochrane review (19.64 l/min) [Ducharme *et al.* 2010]. Of note, the average MCID for morning PEF reported by Santanello and colleagues [Santanello *et al.* 1999] in a comparable asthma population was 18.79 l/min. The observed difference in morning PEF between BDP/Form 200/6 and BDP is slightly less than that observed in clinical studies comparing high-dose FP/Salm *versus* high-dose fluticasone monotherapy as observed by Aubier and colleagues [Aubier *et al.* 1999], Boyd [Boyd, 1995], and van Noord and colleagues [van Noord *et al.* 1996]: at 22, 21 and 23 l/min, respectively.

A number of secondary efficacy analyses of the FORCE study supported superiority of BDP/Form 200/6 *versus* BDP. Overall, BDP/Form resulted in a greater and statistically significant improvement of predose morning PEF, predose evening PEF, and daily PEF variability. Treatment with BDP/Form 200/6 also resulted in a greater improvement of FEV_1 although the difference was statistically significant only at week 4. The increase in FEV_1 at the end of the study period was more than 200 ml which is the cut off to define the clinically relevant airway reversibility in asthma [Reddel *et al.* 2009]. The observed difference in predose FEV_1 between BDP/Form and BDP in the FORCE study was very close to statistical significance ($p = 0.058$) and confirms the poor sensitivity of this lung function parameter to show the additive effect of a LABA on top of high-dose ICS. However, when adding FEV_1 reversibility to salbutamol as a covariate in the statistical model, the observed difference in FEV_1 of ~0.09 l becomes statistically significant.

The number of patients with asthma exacerbations and the corresponding number of moderate/severe asthma exacerbations were slightly lower with BDP/Form 200/6 than BDP.

Overall, the FORCE study showed that BDP/Form 200/6 provides significant improvement of symptom-based parameters, use of rescue medication and asthma control. The difference *versus* BDP monotherapy was not significant, similar to what was previously reported in a study comparing FP/Salm to fluticasone alone [Aubier *et al.* 1999].

BDP/Form 200/6 and BDP showed a similar safety profile, with no issues of clinical concern observed with either treatment. Overall, TEAEs and treatment-emergent ADRs were reported with low frequency in both treatment groups and no serious TEAEs, serious treatment-emergent ADRs or TEAEs leading to death were reported during the study. While BDP/Form 200/6 showed no effect on the hypothalamus-pituitary-adrenal axis, BDP was found to slightly reduce the levels of serum cortisol.

Conclusion

The higher strength of extrafine BDP/Form has the main purpose to step up ICS treatment without increasing the dose of the bronchodilator. The clinical findings from the pivotal studies demonstrate that BDP/Form 200/6 µg improves lung function in not-fully-controlled asthmatic patients and has a beneficial effects on symptoms, use of rescue medication and asthma control, with an acceptable safety profile comparable to that of an approved high-dose fixed dose combination (FP/Salm 500/50 µg). BDP/Form 200/6 µg could therefore be considered as an effective and well tolerated treatment for patients with asthma not adequately controlled with high doses of ICS monotherapy or medium doses of ICS/LABA combinations.

Conflict of interest statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Massimo Corradi has during the last 3 years received honoraria for lectures from Chiesi Farmaceutici, Italy. Piotr Kuna has during the last 3 years received honoraria for participating in advisory board meetings or giving lectures for the following companies: Adamed, Allergopharma, Almirall, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Celon Pharma, Chiesi, FAES, GSK, HAL, Meda, MSD, Novartis, Pfizer, Polpharmex, Polpharma, Stallergen, Teva. Monica Spinola and Stefano Petruzzelli are full time Chiesi Farmaceutici employees.

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