



Lupin Healthcare (UK) Limited

Product Name: beclometasone dipropionate/formoterol fumarate dihydrate
pressurised inhalation solution; 100/6 mcg

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4. OVERVIEW OF EFFICACY

4.1. Asthma

Currently available drugs for asthma treatment, including short- and long-acting bronchodilators alone or in combination and corticosteroids alone or in combination with bronchodilators, are all effective and reasonably safe (Nicolini et al., 2008). The goal of asthma treatment, as defined in the recent guidelines update (GINA 2019; SIGN158, 2019) is to reach and maintain asthma control, defined as minimal symptoms, no exacerbations, and no limitation of activities, together with normal lung function.

Inhaled corticosteroids (ICSs) are the mainstay of daily controller treatment for persistent and uncontrolled asthma. However, many clinicians are wary of ICSs because of safety concerns. Clinicians need to know the underlying efficacy data that support the use of ICSs to weigh efficacy against safety. Pivotal efficacy trials of ICS in asthma have revealed that ICSs are effective in reducing the risk of exacerbations in both children and adults. ICSs also reduce the risk of hospitalization and asthma-related death, improve asthma symptoms, and improve quality of life. Intermittent therapy may not be as effective as daily therapy, and clinicians should weigh reduced efficacy against reduced risk of adverse effects (Covar, 2016).

A post hoc analysis of data from the START study (Pauwels et al., 2003) found that low-dose ICS leads to substantial risk reduction in mild asthma, both for exacerbations and for decline in lung function, in patients with infrequent baseline symptoms who would not previously have been considered for ICS treatment (Reddel et al., 2017). This analysis supported the potential benefit of using ICS based on population risk reduction rather than only on symptom frequency (Antoniou, 2003).

There is considerable literature available on BDP, covering all relevant outcomes in asthma treatment in both adults and children. In the only available study showing that inhaled corticosteroids (ICS) reduce asthma mortality (Suissa et al., 2000), 93% of the prescribed canisters contained low-dose BDP. Formoterol is the only fast, long-acting bronchodilator with dose-dependent effects (McGavin et al., 2001) and well-documented efficacy and safety in obstructive diseases (Prenner, 2007); it can also be used as a reliever medication in asthma, provided the patient is receiving regular ICS treatment (GINA 2019).

Luforbec 100/6 micrograms per actuation pressurised inhalation solution formulations, contain beclometasone dipropionate (BDP) and formoterol fumarate dihydrate (FFD) combination is an extrafine solution formulation in which the BDP dose is lower than the conventional BDP CFC product. The reduction in BDP nominal dose, together with the extrafine particle size, allows a similar dose of the drug to reach the lower airways and less drug to be deposited in the upper airways, potentially improving the efficacy/safety ratio. The formoterol component in BDP/F is not associated with nominal dose reduction (Dhillon and Keating, 2006).



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The rationale for developing an extrafine formulation lies in the fact that asthma is characterized by airway inflammation and remodeling in all parts of the airways, including small airways (Tulic et al., 2001). Therefore, the optimized drug deposition that results from reduced particle size may lead to improved clinical benefits.

Most of ICS benefits are achieved in adults in relatively low doses. However, there is marked variability partly due to heterogeneity of airway inflammation. To achieve good asthma control, add-on therapy with another class of controller such as LABA is preferred over increasing dose of ICS (Bateman et al., 2004).

The Gaining Optimal Asthma control (GOAL) study was a 1-year, randomized, stratified, double-blind, parallel-group study and included 3,421 patients with uncontrolled asthma and compared fluticasone propionate and salmeterol/fluticasone. The patients received stepwise increments in treatment until their asthma was totally controlled or they were receiving the maximum ICS dose of 500 mg b.i.d. Patients were divided into three strata: previously corticosteroid-free, low-dose corticosteroid users, and moderate-dose corticosteroid users. Significantly more patients in each stratum achieved asthma control with ICS/LABA than with ICS alone. Across all strata after dose escalation, a higher proportion of patients treated with ICS/LABA than those treated with ICS exhibited total control (31% vs. 19%, respectively; $p < 0.001$). The corresponding figures at 1 year were 41% and 28%. Across all strata, 68% of patients treated with ICS/LABA and 76% of those treated with ICS ultimately received the highest corticosteroid dose. The GOAL study provides further evidence that ICS/ LABA therapy is more effective than ICS alone for the treatment of asthma (Bateman et al., 2004). Although considering a different ICS/LABA combination, the study confirmed the utility of the principle of this approach to combination therapy.

Controlled studies have shown that delivering ICS and LABA in combination inhaler is as effective as giving each drug separately (Main et al., 2008). Fixed combination inhalers are more convenient for patients, may increase adherence compared with separate inhalers and ensure that LABA is always accompanied by ICS (Stoloff et al., 2004).

The significant synergistic effects of ICS and LABA in one device are well evidenced. A fixed dose combination therapy reduces the daily dosage of ICS and asthma exacerbation. It is safe to use regularly as controller. The efficacy of each individual combination on asthma treatment is generally similar. Clinical experience, ease of use, cost and side effects of medication would guide the clinician's preferences (Chantaphakul and Ruxrungham, 2016).

An observational study was conducted in 5789 asthmatic patients from Poland in patients treated with ICS/LABA inhalers and to identify factors related to optimal asthma control. Throughout the study period, the rate of patient-reported control of asthma increased from 24.8% to 67.7%, while physician-reported control increased from 22.6% to 66.4%. The incidence of exacerbations decreased from 23.4% to 1.9%. Less than 0.1% of the patients reported adverse drug reactions.



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The results confirmed the efficacy and safety of combined ICS/LABA inhalers in a real-life clinical setting ([Rogala et al., 2017](#)).

The extrafine fixed combination of 100 µg of BDP and 6 µg of FFD in a pressurized metered dose inhaler (pMDI) provides a medium daily dose of ICS. The efficacy and safety of this combination was proved in clinical studies ([Huchon et al., 2009](#)) and its effectiveness was confirmed in real life conditions ([Kuna et al., 2015](#)).

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4.2. COPD

Recognition that chronic inflammation is also present in COPD provided a rationale for use of inhaled corticosteroids in COPD. Symptoms (dyspnoea and exercise limitation) and exacerbations are still the focus of treatment, and there are separate algorithms for each of these treatable traits ([Barnes et al., 2003](#)).

The disease encompasses multiple structural and functional components of which inflammation is at the core of the disease, affecting the lungs and other organs. Pharmacotherapy with bronchodilating agents, including the β_2 -agonists, anticholinergics and methylxanthines, is central to the symptomatic management of all stages of COPD ([Hanania, 2008](#)).

Several large-scale studies in patients with moderate-to-severe COPD have demonstrated that treatment with LABA/ICS leads to significantly greater improvements in lung function, exacerbations, health status and breathlessness, compared with placebo or monotherapy with the component drugs ([Hanania, 2008](#)).

A Cochrane review of fourteen RCTs comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD, showed that combined inhalers reduced the frequency of exacerbations compared with their LABA component alone ([Nannini et.al., 2012](#)).



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Combination therapy with an inhaled corticosteroid (ICS) and a long-acting β -agonist (LABA) is considered an important approach for treating patients with severe COPD who have frequent exacerbations ([Cazzola and Matera, 2017](#)).

Although to date none of the currently available interventions have been shown to halt or slow down the decline in lung function in COPD patients, the results of the TORCH (Towards a Revolution in COPD Health) trial, a prospective, multicenter, randomized, double-blind, parallel-group study in 6112 COPD patients, suggest that LABA [SFC (50/500 mg)] has a beneficial effect on lung function in the medium term.

According to TORCH study, regular treatment with LABA narrowly missed demonstrating a statistically significant benefit on the reduction in all-cause mortality over 3 years (17.5% reduction in risk, $P = 0.052$), further emphasizing the clinical usefulness of LABA+ICS therapy in COPD. In view of this increasing evidence for the additional effectiveness of LABA+ICS combinations compared with the individual components, and the potential benefits of LABA+ICS on lung function, disease progression and potentially on all-cause mortality, initiation of LABA+ICS combination treatment early in the COPD disease process may be warranted ([Calverley et al., 2007](#)).

The fixed dose combinations of Luforbec 100/6 micrograms per actuation pressurised inhalation solution formulations, are characterised by an extrafine (i.e., mean mass aerodynamic diameter (MMAD) $< 2.0 \mu\text{m}$) formulation of both active components. Small airway inflammation and remodeling are cardinal features of COPD; therefore, the ability of this extrafine formulation to reach the small, as well as the large, airways is likely to be therapeutically important by enabling treatment of inflammatory processes in the whole bronchial tree. The clinical development of extrafine BDP/FFD has demonstrated significant benefits over extrafine FFD in terms of lung function improvement and reduction of the exacerbation rate, thus supporting the beneficial effect of an ICS combined to a LABA in COPD patients ([Singh et al., 2016](#)).

The extrafine formulation enables drug delivery to both the large and small airways and allows the clinical benefits to be achieved with a lower ICS dose compared with larger-particle ICS/LABA combinations. The clinical studies performed show a benefit of extrafine BDP/FFD over FFD in terms of lung function and the risk of exacerbations that is comparable to the effect sizes observed for other ICS/LABA combinations.

A study investigating the lung deposition profile of a fixed combination ICS+LABA, and correlating this pattern to the lung function at baseline of patients with different obstructive diseases, indicate that BDP+formoterol (100+6 mcg) extrafine formulation is efficiently delivered to the lung, produces high lung deposition, low variability, and homogeneous distribution of BDP and formoterol throughout the airways, regardless of pathophysiological condition and independent of lung function ([De Backer et al., 2010](#)).



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The FORWARD study was conducted to compare extra fine BDP/FFD 100/6 µg with extra fine FF 6 µg with two co-primary efficacy end points: COPD exacerbation rate over 1 year and change in pre-dose morning FEV1 from baseline (randomisation visit) to Week 12. Use of tiotropium as a concomitant medication was permitted, except for a 72-h wash-out period before each clinic visit. Making this study more relevant in ‘real-life’ setting with a severe COPD population, as a large proportion (50–70%) of severe COPD patients in Western Europe use tiotropium. Outcome of FORWARD study, a 28% reduction of moderate-to-severe exacerbations with extrafine BDP/FFD compared with FFD & the change in pre-dose morning FEV1 from baseline to Week 12 validates superiority of Extrafine BDP/FFD over FFD alone ([Wedzicha et al., 2014](#)).

A phase 3, double-blind, double-dummy, randomised, active-controlled, 3-arm parallel-group multicentre study was conducted in 76 centres in 8 countries across Europe ([Calverley et al., 2010](#)). Over 48 weeks, beclometasone/formoterol, budesonide/formoterol and formoterol alone improved pre-dose morning FEV1 (the first primary outcome) by 0.077 L, 0.080 L and 0.026 L respectively in 718 people with severe COPD (FEV1 between 30% and 50% of predicted). In the intention-to-treat analysis, beclometasone/formoterol was shown to be non-inferior to budesonide/formoterol (the lower limit of the 97.5% CI was –0.052 L, which is within the pre-specified non-inferiority margin of –0.100 L) and statistically significantly better than formoterol alone (p=0.046).

In this study, the mean rate of COPD exacerbations/patient per year (the second primary outcome) was not statistically significantly different between the treatments (beclometasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol alone 0.431). The number of patients with exacerbations leading to hospitalisation was statistically significantly higher in the beclometasone/formoterol group compared with the budesonide/formoterol and formoterol alone groups (13 [5.6%] compared with 7 [2.9%, p<0.001] and 8 [3.4%, p=0.008] respectively). However, the numbers of exacerbations were lower than expected and these analyses may have been underpowered. Quality of life and COPD symptoms improved in all groups and use of rescue medication decreased.

A 12-week multicentre, randomised, double-blind, double dummy study, the FUTURE study, in 419 patients with moderate/severe COPD randomised to BDP/FFD 200/12 µg or FP/S 500/50 µg twice daily was conducted ([Singh et al., 2014](#)). The study evaluated the efficacy of beclomethasone dipropionate/formoterol fumarate (BDP/FFD) extrafine combination versus fluticasone propionate/salmeterol (FP/S) combination in COPD patients. The primary objective was to demonstrate the equivalence between treatments in terms of Transition Dyspnoea Index (TDI) score and the superiority of BDP/FFD in terms of change from pre-dose in the first 30 minutes in forced expiratory volume in the first second (FEV1). Secondary endpoints included lung function, symptom scores, symptom-free days and use of rescue medication, St. George’s Respiratory Questionnaire, six-minute walking test and COPD exacerbations.



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The study found that beclometasone/formoterol and fluticasone/salmeterol statistically significantly improved Transition Dyspnoea Index scores (a measure of breathlessness; the first primary outcome) by 1.32 units respectively and 1.15 units over 12 weeks in 419 people with moderate-to-severe COPD. The full NICE guideline on COPD considers an improvement of 1 unit to be clinically important. The combination treatments were found to be equivalent in the intention-to-treat analysis (the 95% CI for the difference [-0.39 to 0.72] was entirely within the pre-specified ± 1 equivalence margins).

As assessed by the change in FEV1 from pre-dose in the first 30 minutes after drug inhalation (the secondary primary outcome), in this study beclometasone/formoterol had a statistically significantly faster onset of action than fluticasone/salmeterol (AUC_{0-30min} adjusted means at 12 weeks 0.18 L compared with 0.11 L respectively, $p < 0.001$). It is unclear whether this difference is clinically important.

Overall, the clinical development of extrafine BDP/FFD demonstrates that this extrafine formulation achieves the type of health benefits expected from such a targeted ICS/LABA combination.

Early randomised controlled trials (RCTs) did not show an effect of ICS monotherapy on exacerbations of COPD (ECOPD) rate/severity; although, since they investigated the potential effects of ICS on lung function decline, they were not enriched with patients at increased risk of ECOPD.

Later RCTs of ICS/long-acting β_2 -agonist (LABA) combinations generally recruited patients with ≥ 1 ECOPD in the previous year and showed that ICS/LABA combinations reduce ECOPD rates by approximately 25–35% compared with LABA monotherapy.

In RCTs of ICS/long-acting β_2 -agonist (LABA) combinations whereby patients with ≥ 1 ECOPD in the previous year were recruited, it was shown that ICS/LABA combinations reduce ECOPD rates by approximately 25–35% ([Calverley et al., 2003](#)).

Likewise, despite not specifically focusing on patients at increased ECOPD risk, TORCH and SUMMIT were large enough to demonstrate ICS efficacy on ECOPD ([Calverley et al., 2007](#); [Vestbo et al., 2016](#)).

In summary, for asthma and chronic obstructive pulmonary disease (COPD), an important step in simplifying management and improving adherence with prescribed therapy is to reduce the dose frequency to the minimum necessary to maintain disease control. Fixed-dose combination therapy is thought to enhance compliance by decreasing the number of medications and/or the number of daily doses ([Marceau et al., 2006](#)). Furthermore, they have the potential for enhancing, sensitizing, and prolonging the effects of mono components ([Cazzola et al., 2012](#)).

It seems reasonable to postulate that targeting bronchoconstriction through two distinct mechanisms should maximize the bronchodilator response and help to overcome inter- and



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inpatient variability in bronchomotor tone associated with airway obstruction ([Bellia et al., 2006](#)).



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5. OVERVIEW OF SAFETY

As Luforbec contains beclometasone dipropionate and formoterol fumarate dihydrate, certain adverse reactions of varying type and frequency associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Beclometasone

Glucocorticosteroids have been widely used for asthma management for a long time. Inhaled corticosteroids offer advantage of delivery of drug to the airways in doses that are effective with a much lower risk of systemic side effects. Systemic effects of inhaled corticosteroids (e.g., Beclometasone dipropionate) may occur particularly when administered at high doses or prescribed for prolonged periods ([Fostair[®] SPC](#); [Pandya et al., 2014](#)).

The most common local AEs of ICS are hoarseness and weakness of the voice (dysphonia) due to atrophy of the vocal cords following laryngeal deposition of steroid. Oropharyngeal is observed in ~5% of the patients. The systemic AEs associated with ICS include adrenal suppression and insufficiency, growth suppression, bruising, osteoporosis, cataracts, glaucoma, metabolic abnormalities (glucose, insulin, triglycerides), psychiatric disturbances (euphoria, depression) and pneumonia, the main ones being Adrenal suppression and Growth suppression ([Goodman and Gilman, 12th Edition, 2011](#)).

Clinical experience over the past 20 years suggests that the occurrence of adrenal axis suppression with the use of ICS alone is very low. Most of the reported cases generally reflect an excess of dosing or the residual effect of prior oral corticosteroid treatment. Thus, children receiving low to moderate doses of ICS do not require routine monitoring of adrenal axis function unless there is evidence of growth suppression ([Colucci et al., 2007](#)).

In a crossover study of asthmatic children not controlled on other medications were commenced on beclomethasone dipropionate (BDP) or budesonide (BUD), both administered at the dose of 200 micrograms twice per day for 2 weeks each in randomized order. Monitoring included twice daily symptom scores recording at home, peak expiratory flow readings, and the use of additional antiasthma medications. Before and after each treatment period the patients were admitted for overnight blood sampling for cortisol, ACTH, and growth hormone, 24-h urine collections for cortisol, and detailed lung function tests. A total of 12 children completed the study. The nocturnal serum cortisol production was significantly reduced by 27 and 35% after 2 and 4 weeks of treatment ($p = 0.005$, $p = 0.004$; Wilcoxon test), and the urinary free cortisol showed a similar reduction of 33 and 48% ($p = 0.023$, $p = 0.005$). Such suppression could be shown on both drugs, BDP and BUD, and there was no significant difference between them. The ACTH and growth hormone values were not significantly changed on any treatment. Lung function tests showed an impressive improvement in FVC, FEV1, FEF50, and FEF25 after 2 weeks of treatment regardless of the medication. Differences in lung function improvements between the two drugs were very small and not of clinical relevance. The observations indicate



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that even low-dose inhaled corticosteroids in the form of BDP or BUD have a systemic effect, which emphasizes the importance of using the minimum dose compatible with good control of asthma (Nicolaizik et al., 1994).

Although most respiratory specialists believe that these drugs may induce growth suppression, many have rarely or never observed such an AE in children using ICS. The risk of growth suppression can be influenced by several factors, including total dose, drug delivery device, genetic predisposition, age, and asthma severity (Brand, 2001).

Patients transferring from oral to inhaled corticosteroids may remain at risk of impaired adrenal reserve for a considerable time. Because recovery from impaired adrenocortical function caused by prolonged systemic steroid therapy is usually slow, special care is necessary for the first 9 to 12 months after the transfer, until the HPA axis has sufficiently recovered to enable the patient to cope with any emergencies such as trauma, surgery, severe infections, or an acute attack of asthma (Brogden et al., 1975).

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

The risk of pneumonia in COPD patients using ICS is higher in those with older age, lower body mass index (BMI), greater overall fragility, receiving higher ICS doses and those with blood eosinophils $<100 \text{ cells} \cdot \mu\text{L}^{-1}$. All these factors must be carefully considered and balanced in any individual COPD patient before adding ICS to her/his maintenance bronchodilator treatment (Agusti et al., 2018).

Formoterol

The use of a regular LABA is now established in asthma guidelines as the preferred option for second-line controller therapy in addition to inhaled corticosteroids.

Tolerance of human airway smooth muscle to β_2 agonists *in vitro* has been demonstrated, although the concentration of agonist necessary is high and the degree of desensitization is variable (Goodman and Gilman, 12th Edition, 2011).

A review was conducted to assess tolerability of short-term use (4–48 hours) of high doses of formoterol (up to 228 μg) in healthy volunteers and patients with stable asthma. In patients with asthma, formoterol had a tolerability profile comparable to that of equivalent doses of albuterol. Potential adverse effects of formoterol on cardiovascular and metabolic parameters, including plasma potassium concentrations, resolved relatively rapidly (within 24 hours), whereas the bronchodilating effects of therapy persisted for 12 hours. Of the studies describing the effects of high-dose formoterol on the QTc interval, the QTc interval returned to baseline within 24 hours in the 2 studies in healthy adults, and the change was similar in magnitude to that with albuterol



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but less than that with fenoterol. In one of the studies in adult patients with asthma, the QTc interval was not significantly affected by administration of formoterol doses of 12 to 48 µg. Overall, the range and incidence of adverse effects observed with formoterol did not appear to be significantly different from that of other β₂-agonists ([Ostrom, 2003](#)).

Excessive doses of formoterol may lead to effects that are typical of β₂-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia ([British National Formulary 2020](#)).

Epidemiological evidence has suggested a link between use of β₂-agonists and increased asthma mortality. Much debate has surrounded possible causal links for this association, and whether regular (daily) long-acting β₂-agonists (LABAs) are safe, particularly when used in combination with inhaled corticosteroids (ICSs). The Cochrane Review included data from two large trials including 11,679 adults and 6208 children and author did not find a difference in the risk of death or serious adverse events in either adults or children. The possible risks still have to be weighed against the benefits experienced by people who take combination treatment ([Cates et al., 2018](#)).

β₂-agonists should be used with caution with patients with diabetes because of the risk of ketoacidosis. β₂-AR stimulation in the liver induces glycogenolysis and therefore raises blood sugar levels ([Philipson, 2002](#)). β₂-agonists stimulate the Na⁺, K⁺-ATPase driven pump coupled to β₂-ARs in skeletal muscle, thus facilitating the release of Na⁺ out of the cell and the intracellular accumulation of K⁺, thereby lowering K⁺ plasma levels and causing hypokalaemia ([Matera et al., 2016](#)).

BDP/FF combination

Clinical experience with BDP and FFD is extensive and the adverse effects of the respective components of the drug combination are manageable. As Luforbec contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Inhaled doses of BDP/FFD for up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed ([Fostair® SPC](#)).

There have been reports of Takotsubo cardiomyopathy, a transient cardiac dysfunction with a ballooning shape, following medical interventions with ICS/LABA in status asthmaticus ([Saito et al., 2016](#)). The pathogenic mechanism of this disease is still unclear but sympathetic



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hyperactivity, as well as coronary vasospasm, microcirculatory disorder, and estrogen deficiency, have been considered as one of the most likely pathogenic mechanism ([Yoshikawa, 2015](#)).

[Calverley et al. \(2010\)](#) found that the incidence of adverse events did not differ significantly between beclometasone/formoterol, budesonide/formoterol and formoterol alone. The most commonly reported adverse event was exacerbation or worsening of COPD, which occurred in 27–28% of participants. Pneumonia was reported by 5 people (2.1%) in the beclometasone/formoterol group, 7 people (2.9%) in the budesonide/formoterol group and 1 person (0.4%) in the formoterol group (statistical significance of differences not reported).

In [Singh et al. \(2014\)](#), serious adverse events occurred statistically significantly more often in the fluticasone/salmeterol group than the beclometasone/formoterol group (13 people [6.3%] compared with 4 people [1.9%], $p=0.024$). Pneumonia was reported in 3 people (1.4%) treated with fluticasone/salmeterol and none treated with beclometasone/formoterol.

Safety analyses from Phase 3 study (CT01) conducted on the safety population 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) ([Corradi et al., 2016](#)).

Safety analysis from another Phase 3 study (FORCE), 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. ([Corradi et al., 2016](#))

Safety of excipients

Lupin is developing a beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FFD) pressurized inhalation solution using a proprietary actuator. Lupin's BDP/FFD formulations contain approximately [REDACTED] of an organic acid – maleic acid, in the presence of [REDACTED] water. Once maleic acid is in contact with the water in the formulation or body fluids, such as airway surface liquid, the acid donates its proton and is converted to maleate. This process happens almost instantaneously. The amount of maleic acid delivered to patients through inhalation is small.

Maleic acid, a dicarboxylic acid, can be conjugated to free base compounds/drugs to improve physiochemical properties, including stability, solubility, and dissolution rate. Therefore, maleate