Fluticasone/formoterol: a new single-aerosol combination therapy for patients with asthma

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Summary
International asthma management guidelines recommend a long-acting \( \beta_2 \)-agonist (LABA) as add-on therapy in patients whose asthma is not controlled by low-dose inhaled corticosteroid (ICS) monotherapy. Treatment with a single inhaler containing an ICS/LABA combination is advocated because it may facilitate adherence to a regimen. When prescribing ICS/LABA combination therapy, the potency of the ICS and the speed of onset of the LABA are considered important factors; therefore, an inhaled therapy containing components with these properties may be valued by physicians. The ICS fluticasone propionate (fluticasone) has potent and sustained anti-inflammatory effects, and the LABA formoterol fumarate (formoterol) provides rapid bronchodilation; the efficacy and safety profiles of these agents have been well established in clinical practice. Fluticasone and formoterol have been combined, for the first time, in a single hydrofluoroalkane-based aerosol (flutiform\(^{\text{®}}\); fluticasone propionate/formoterol fumarate). Here, we review data from the published randomized, controlled, clinical trials that demonstrate the efficacy and tolerability of this product. It has been shown that fluticasone/formoterol is more efficacious than fluticasone or formoterol given alone, and provides similar improvements in lung function to fluticasone and formoterol administered concurrently via separate inhalers. Fluticasone/formoterol has similar efficacy and tolerability profiles to budesonide/formoterol and fluticasone/salmeterol, but with the additional benefit of more rapid bronchodilation than fluticasone/salmeterol.

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Introduction
International asthma management guidelines recommend that a long-acting \( \beta_2 \)-agonist (LABA) is prescribed as an add-on therapy for patients whose asthma is not controlled by low-dose inhaled corticosteroid (ICS) monotherapy. A substantial evidence base shows that co-administration of a LABA and an ICS results in better clinical effectiveness than that achieved with an ICS alone. It has also been shown that the addition of a LABA to existing low-dose ICS therapy is more effective at reducing the risk of a severe exacerbation or a poorly controlled asthma day than doubling the dose of ICS administered. Combining an ICS and a LABA in a single inhaler may encourage improved adherence to the treatment regimen and may be preferred by patients to the use of separate inhalers. Until recently, only three ICS/LABA fixed-dose combinations were available in Europe, and data from randomized, controlled, clinical trials have demonstrated that each of these products is highly efficacious. However, many patients do not achieve control of their asthma even when they are prescribed ICS/LABA therapy. There are several possible reasons for this: the effectiveness of any inhaled asthma therapy in everyday clinical practice is influenced by drug efficacy and delivery, and requires the correct inhalation technique, handling of the device and patient adherence to their treatment regimen.

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Incomplete control of asthma disrupts the lives of patients and has a large impact on their health and health-related quality of life. As a consequence, morbidity associated with uncontrolled asthma remains a significant worldwide health and economic problem. The development of alternative therapies is therefore required, especially for the treatment of patients whose asthma responds poorly to current therapies. A recent Delphi initiative (sponsored by Mundipharma International Limited) has shown that a panel of expert respiratory specialists considered the potency of the ICS and speed of onset of the LABA among the factors to be most important when prescribing an ICS/LABA combination therapy for asthma. A rapid onset of action is also important to patients; data show that patients want to feel their combination therapy working quickly, while providing lasting therapeutic benefits. Importantly, patients who were non-adherent to a regimen identified rapid bronchodilation (‘If I could feel it helping my asthma soon after taking it’) among the leading factors that would encourage adherence; indeed, a key reason given for poor adherence to asthma maintenance therapy is the lack of a rapid effect. Taken together, these data might suggest the combination of the ICS fluticasone propionate (fluticasone), which has potent anti-inflammatory effects, and the LABA formoterol fumarate (formoterol), which provides rapid bronchodilation, provides an additional treatment option for asthma that may be valued by both physicians and patients.

The efficacy and safety profile of fluticasone is well established; it is a widely prescribed, highly effective maintenance treatment for asthma, both as a single-inhaler therapy and as the ICS component of the fixed-dose combination fluticasone/salmeterol. Fluticasone exhibits potent anti-inflammatory activity in vitro and in vivo. Furthermore, it undergoes a high level of first-pass metabolism and has a significantly lower oral bioavailability than budesonide or beclomethasone dipropionate (-1% versus -11% and 13%, respectively) and the active metabolite beclometasone-17-monopropionate), which has no anti-inflammatory activity. Formoterol provides significantly more rapid bronchodilation than salmeterol - comparable to that of the short-acting β2-agonist salbutamol. Formoterol is the LABA component of the fixed-dose combinations of budesonide/formoterol and beclomethasone/formoterol. Fluticasone and formoterol have been combined for the first time in a single hydrofluoroalkane (HFA)-based pressurized metered-dose inhaler (pMDI; flutiform®). Fluticasone/formoterol is formulated as a suspension aerosol; other available ICS/LABA aerosol combinations are prepared in suspension (fluticasone/salmeterol; also available as a dry-powder inhaler) or solution (beclomethasone/formoterol) formulations. Across most of Europe, budesonide/formoterol is only available in a dry-powder inhaler. Fluticasone/formoterol has been approved in Europe for the regular treatment of asthma in adults and adolescents (12 years and above) with symptoms that are uncontrolled on an ICS alone, or controlled using an ICS in combination with a LABA. This review provides an overview of the published data from a comprehensive clinical trial programme that demonstrates the efficacy and tolerability profiles of fluticasone/formoterol.

**Efficacy of fluticasone/formoterol versus its components administered alone**

Data from four clinical trials have demonstrated that fluticasone/formoterol is superior to its components administered as monotherapies for improvement in measures of lung function and asthma control. Two of these studies have been published and are summarized here. Both studies compared fluticasone/formoterol with fluticasone or formoterol administered as monotherapies, and with a placebo over a 12-week period, and both were of double-blind, placebo- and active-controlled, parallel-group design. These studies assessed the contribution of the individual components to the efficacy of the ICS/LABA combination as co-primary endpoints. The contribution of the ICS component was assessed by comparing fluticasone/formoterol with formoterol alone for mean change in forced expiratory volume in 1 second (FEV1) from morning pre-dose at baseline to pre-dose at week 12. The contribution of the LABA component was assessed by comparing fluticasone/formoterol with fluticasone alone for mean change in FEV1 from morning pre-dose at baseline to 2 hours post-dose at week 12. The third co-primary endpoint, time to discontinuation due to lack of efficacy, was used to evaluate the efficacy of fluticasone/formoterol compared with placebo. Primary efficacy analyses were carried out using the full analysis set (all patients who received at least one dose of treatment and had measurements for pre-dose baseline FEV1, at least one post-baseline pre-dose FEV1 and at least one post-baseline post-dose FEV1).

The first study assessed the efficacy of low-dose fluticasone/formoterol in 475 adolescent and adult patients with asthma (60–85% predicted FEV1 at baseline), who were randomly assigned to receive fluticasone/formoterol (100/10 μg twice daily [b.i.d.], fluticasone alone (100 μg b.i.d.), formoterol alone (10 μg b.i.d.) or placebo, all administered via an HFA-based pMDI (EudraCT number: 2007-002866-36; US NCT number: NCT00393991). Fluticasone/formoterol was superior to formoterol administered alone for increase from baseline to week 12 in mean morning pre-dose FEV1 (least-squares [LS] mean between-treatment difference: 0.101 L; 95% confidence interval [CI]: 0.002: 0.199; p = 0.045), demonstrating the contribution of the fluticasone component of the combination treatment. In addition, fluticasone/formoterol provided significantly greater improvement in mean morning FEV1 than fluticasone monotherapy from pre-dose at baseline to 2 hours post-dose at week 12 (LS mean between-treatment difference: 0.200 L (95% CI: 0.109: 0.292; p < 0.001), which highlighted the contribution of formoterol to the combination. Fluticasone/formoterol was associated with a significantly longer time to discontinuation due to lack of efficacy (assessed as either an asthma exacerbation or a loss of asthma control; p = 0.015), compared with placebo. Furthermore, fewer patients in...
the fluticasone/formoterol treatment group discontinued therapy due to lack of efficacy (6.1%) compared with the fluticasone, formoterol or placebo groups (7.7%, 11.2% and 16.2%, respectively). Fluticasone/formoterol provided a significant reduction in rescue medication use compared with fluticasone alone (p = 0.008). Fluticasone/formoterol also provided greater improvement than fluticasone alone in several clinically meaningful secondary endpoints, such as decrease in symptom-free days (p = 0.027) and asthma control days (p = 0.017). Although these endpoints had a p value of \leq 0.05 versus fluticasone alone, they were not considered statistically significant per the sequential gatekeeper approach used in the study.43

In the second study, which assessed medium-dose fluticasone/formoterol versus its individual components administered alone, 557 adolescent and adult patients with asthma (40-80% predicted FEV1 at baseline) were randomly assigned to treatment with fluticasone/formoterol (medium dose, 250/10μg b.i.d. for the co-primary endpoints), fluticasone alone (250μg b.i.d.), formoterol alone (10μg b.i.d.) or placebo; patients were also assigned to a fluticasone/formoterol exploratory group (low dose, 100/10μg b.i.d.); all treatments were administered via an HFA-based pMDI (EudraCT number: 2006-005989-39; US NCT number: NCT00393952).42

Medium-dose fluticasone/formoterol was superior to formoterol administered alone for change in mean FEV1 from pre-dose at baseline to pre-dose at week 12 (LS mean between-treatment difference: 0.189 L; 95% CI: 0.042, 0.336; p = 0.001). Similarly, fluticasone/formoterol was superior to fluticasone monotherapy for change in mean FEV1 from pre-dose at baseline to 0 hours post-dose at week 12 (LS mean between-treatment difference: 0.146 L; 95% CI: 0.042, 0.250; p = 0.006). As described previously, these data are indicative of the relative contributions of the fluticasone and formoterol components to the improvements in lung function observed with fluticasone/formoterol. Medium-dose fluticasone/formoterol also demonstrated a significantly longer time to discontinuation due to lack of efficacy (assessed as either an asthma exacerbation or a loss of asthma control) than placebo (p < 0.001). Furthermore, fewer patients in the fluticasone/formoterol treatment group discontinued therapy due to lack of efficacy (10.2%) than in the fluticasone, formoterol or placebo groups (12.8%, 20.9% and 39.0%, respectively).42

Analysis of clinically meaningful secondary endpoints also supported the greater efficacy of fluticasone/formoterol compared with fluticasone monotherapy. Fewer patients in the fluticasone/formoterol group had an exacerbation of any severity (p = 0.030) than in the fluticasone-alone group. In addition, fluticasone/formoterol was associated with more rescue-medications-free days (p = 0.042) and more asthma control days (defined as days with an asthma symptom score indicating no symptoms; p = 0.027) than fluticasone alone. Although these endpoints had a p value of <0.05 versus fluticasone alone, they were not considered statistically significant per the sequential gatekeeper approach used in the study.42

In both studies described above, fluticasone/formoterol had a tolerability profile similar to that of its individual components. Adverse events (AEs) were mostly mild-to-moderate in severity, with a numerically smaller proportion of patients in the fluticasone/formoterol group reporting treatment-emergent AEs compared with those in the fluticasone, formoterol or placebo groups.42,43

Efficacy of fluticasone/formoterol compared with its components administered concurrently via separate inhalers

The efficacy of high-dose fluticasone/formoterol was compared with fluticasone + formoterol administered together via separate inhalers in a double-blind, double-dummy, randomized, parallel-group, 8-week study. In this study, 620 adults with persistent, reversible asthma (≥40% to ≤80% predicted FEV1 at baseline) were randomly assigned to 8 weeks of treatment with high-dose fluticasone/formoterol (500/20μg b.i.d.), fluticasone (500μg b.i.d.) plus formoterol (24μg b.i.d.), fluticasone alone (500μg b.i.d.) or low-dose fluticasone/formoterol (100/10μg b.i.d.; included as a secondary comparator); all treatments were administered via an HFA-based pMDI (EudraCT number: 2007-001633-34; US NCT number: NCT00734318). The primary analysis population for the non-inferiority comparison (high-dose fluticasone/formoterol versus fluticasone + formoterol) was the per-protocol population (PPP; defined as all patients who completed the study without major protocol violations affecting the primary endpoint), with confirmatory analyses performed in the intent-to-treat (ITT) population (all patients randomized who received at least one dose of study treatment and had at least one post-dose primary efficacy [FEV1] measurement). The co-primary endpoints were mean change in morning pre-dose FEV1 from baseline to week 8, and mean change in morning FEV1 from pre-dose at baseline to 2 hours post-dose at the end of week 8; non-inferiority for the co-primary efficacy endpoints was concluded if the lower limit of the 95% CI for the between-treatment difference was ≥−0.2 L.46

The fluticasone/formoterol combination (500/20μg b.i.d.) was non-inferior to its components administered concurrently (500μg + 24μg b.i.d.) for both co-primary efficacy endpoints. Fluticasone/formoterol and fluticasone + formoterol demonstrated similar mean increases in morning pre-dose FEV1 between baseline and week 8 (LS mean of the treatment difference: 0.060 L; 95% CI: −0.059, 0.180) (Fig. 1). For mean change in FEV1 from pre-dose at baseline to 2 hours post-dose at study end, the increase was similar in the fluticasone/formoterol (500/20μg b.i.d.) group and the fluticasone + formoterol group (LS mean of the treatment difference: 0.0181 L; 95% CI: −0.098, 0.135).46

Fluticasone/formoterol also provided similar improvements to fluticasone + formoterol for several clinically relevant measures of asthma control, including rescue medication use, sleep disturbance, asthma symptom and health status scores, as assessed in the ITT population.

Fluticasone/formoterol had a similar tolerability profile to fluticasone + formoterol; 19.5% of patients in the
Figure 1. Fluticasone/formoterol administered as a combination therapy via a single inhaler has an efficacy profile similar to that of its components administered concurrently (fluticasone + formoterol). Data show (a) the mean change in morning pre-dose forced expiratory volume in 1 second (FEV₁) from baseline to week 8, and (b) change in morning pre-dose FEV₁ from baseline to 2 hours post-dose at week 8, for the per-protocol population.46 b.i.d., twice daily. Figures adapted from Bodzenta-Lukszyk A, Pulka G, Dymek A, Bumbacea D, McIver T, Schwab B, Mansikka H, Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respiratory Medicine 2011;105(5):674-82. Copyright 2011, with permission from Elsevier.
Figure 2. Fluticasone/formoterol provides more rapid bronchodilation than fluticasone/salmeterol. Values are shown as percentage change in least-squares (LS) mean forced expiratory volume in 1 second (FEV$_1$) from morning pre-dose at baseline ± standard error. *p ≤ 0.05. Data from a post hoc analysis are shown for the full analysis set. Improvement in lung function was assessed by change in FEV$_1$ from morning pre-dose at 5, 10, 30, 60, 90 and 120 minutes post-dose, on (a) day 0 and (b) day 84.48 Figure reproduced with kind permission from Springer Science+Business Media B.V. from Figure 2 of Aalbers R, Brusselle G, Bodzenta-Lukaszyk A, Onset of bronchodilation with fluticasone/formoterol combination versus fluticasone/salmeterol in an open-label, randomized study. Advances in Therapy 2012; 29(11):958–69.

Efficacy of fluticasone/formoterol versus budesonide/formoterol

The efficacy and tolerability of fluticasone/formoterol (250/10 μg b.i.d.) compared with budesonide/formoterol (400/12 μg b.i.d.) was assessed in a double-blind, double-dummy, randomized, two-arm, parallel-group study in 279 adolescent and adult patients with persistent, reversible asthma (50–80% predicted FEV$_1$ at baseline; EudraCT number: 2009-017223-25; US NCT number: NCT01099722). For the primary study endpoint, fluticasone/formoterol and budesonide/formoterol provided similar changes in mean morning pre-dose FEV$_1$ from baseline to week 12 (LS mean treatment difference: −0.044 L; 95% CI: −0.130, 0.043). Non-inferiority was concluded because the lower limit of the 95% CI for treatment difference was greater than −0.2 L. Both treatments demonstrated similar efficacy for several measures of asthma control, including improvements in asthma symptom scores and sleep disturbance scores and in number of asthma control days, symptom-free days and awakening-free nights. The tolerability profiles were similar in both treatment groups.49

Long-term safety and efficacy of fluticasone/formoterol

The long-term safety and efficacy of fluticasone/formoterol (100/10 or 250/10 μg b.i.d.) was assessed in an open-label, multicentre study over 6 or 12 months in 472 adult and adolescent patients with asthma (40–85% predicted FEV$_1$ at baseline; EudraCT number: 2005-003518-14; US NCT...
number: NCT00394121). In total, 413 patients (87.5%) completed the study (of whom 175 participated for 12 months). Overall rates of AEs reported (36.9%) were consistent with those observed in a 1-year study of fluticasone/salmeterol (250/50 μg b.i.d.) and budesonide/formoterol (adjustable maintenance dosing). The majority of AEs were mild-to-moderate in severity. Asthma exacerbations were reported by 11.2% of patients (9.7% with mild-to-moderate exacerbations and 1.9% with severe exacerbations [defined as requiring additional therapy, hospitalization or a visit to an emergency department]). Significant improvements from pre-treatment baseline lung function (FEV₁, % predicted FEV₁, peak expiratory flow rate and forced vital capacity) were maintained over the 6- or 12-month treatment period.

Drug particle size and lung deposition: the importance of particle size and fine particle fraction

Both proximal and distal airways are implicated in the pathophysiology of asthma; inflammation extends from the large bronchi to the alveoli. Therefore, it is necessary for ICSs to be delivered to both proximal and distal airways; however, to date no clear clinical benefit of targeting ICSs to the latter has been demonstrated. In contrast, although β₂-receptors are located in all parts of the airways and are found in greatest density in the alveolar walls, the bronchodilatory effects of β₂-agonists are due to their actions on smooth muscle in the proximal airways. Thus, targeting of β₂-agonists to the proximal airways may be more important than deposition in distal airways for providing effective bronchodilation. It is therefore logical that the lung deposition profile of an ICS/LABA combination product should demonstrate a balance between targeting bronchoconstriction in the proximal airways and generalized inflammation throughout the lungs, in order to achieve optimal distribution of deposited drug.

The particle size of inhaled drugs has been identified as one of the critical determinants of both the total lung dose and their regional pulmonary deposition pattern. However, the extent of lung deposition of polydisperse aerosols is less dependent on the single particle size summary statistic (mass median aerodynamic diameter; MMAD) than it is on particle size distribution around the MMAD. The seminal publication by Heyder and colleagues exploring the relationship between particle size and regional lung deposition, demonstrated that particles in the range 2-6 μm are associated with both central and alveolar deposition (Fig. 3). Therefore, there is an apparent lower limit of 2 μm for an effective particle size; particles <2 μm are prone to deposit largely in the alveoli and those <1 μm are transported to the alveoli but can also be easily exhaled (and would thus not exert a therapeutic effect). In light of these data, it is instructive to note the stage-by-stage particle size distribution of the fluticasone/formoterol aerosol: in the eight-stage Andersen Cascade Impactor, operated under standard pharmacopoeial conditions, the largest individual

![Figure 3. Extent and site of lung deposition of inhaled drugs relative to their size (based on the International Commission Radiological Protection model). Copyrighted material reproduced with permission from Mary Ann Liebert, Inc. Publishers, from Pritchard JN, The influence of lung deposition on clinical response. J Aerosol Med 2001;14(Suppl 1):S19–26.](image-url)
formoterol aerosol are indicative of the potential for high drug deposition in the lung, an effective regional lung deposition pattern and a favourable oropharyngeal to pulmonary deposition ratio. The consistent delivery of a high fine particle fraction with fluticasone/formoterol may be a useful characteristic in an inhaled therapy, because patients often exhibit variability in inhalation flow rate in the day-to-day use of their inhaler.

Conclusions
Fluticasone/formoterol brings together a rapid-acting LABA with a potent ICS in a single-aerosol inhaler. A robust clinical data set demonstrates that fluticasone/formoterol is superior to either component administered as a monotherapy. Fluticasone/formoterol has similar efficacy and tolerability profiles to fluticasone and formoterol administered concurrently via separate inhalers. Similarly, fluticasone/formoterol has similar efficacy and tolerability profiles to budesonide/formoterol and fluticasone/salmeterol and, importantly, offers the additional benefit of more rapid bronchodilation than fluticasone/salmeterol. The fast onset of bronchodilation with formoterol, together with the sustained anti-inflammatory effects of fluticasone, are important treatment characteristics because patients want a maintenance treatment that they can feel working quickly and that provides lasting therapeutic benefits. These attributes may encourage patients to adhere to their treatment regimen, a factor that has been associated with real-world improvements in asthma control. The emitted aerosol consistently contains a high fine particle fraction between flow rates, an attribute that may be valuable given patient variability in inhalation manoeuvres. In summary, the fluticasone/formoterol combination aerosol described in this review represents an additional therapeutic option for the treatment of asthma in adults who require an ICS/LABA, with attributes that may be important for effectiveness in clinical practice.

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Conflict of interest statement
S.F., B.G. and S.D. are employees of Mundipharma Research Limited. K.K. is an employee of SkyePharma AG.

Prescribing information
Prescribing information can be obtained from: http://www.medicines.org.uk/emc/medicine/26954

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