

EXPERT
REVIEWSFluticasone propionate/
formoterol fumarate in
fixed-dose combination for
the treatment of asthma*Expert Rev. Respir. Med.* 8(3), 275–291 (2014)David Price*^{1,2} and
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A new combination inhaler containing fluticasone, a potent inhaled corticosteroid (ICS), and formoterol, a long-acting β -agonist (LABA) with rapid onset and sustained bronchodilator effect, has been approved for treatment of persistent asthma in patients ≥ 12 years of age requiring combination ICS-LABA therapy. The fluticasone/formoterol combination, delivered via pressurized metered-dose inhaler and available in three dose strengths, has demonstrated a good safety and tolerability profile in trials of up to 1 year. The efficacy of fluticasone/formoterol is greater than that of fluticasone or formoterol alone and noninferior to that of fluticasone/salmeterol and budesonide/formoterol in tightly controlled 8–12-week clinical trials. Advantages of the fluticasone/formoterol combination aerosol include rapid onset of bronchodilation, an attribute preferred by patients, and emission of a high fine-particle fraction that is consistent at different flow rates, which may aid consistency of delivery (given patient variability in inhalation maneuvers) and provide real-life benefits.

KEYWORDS: anti-inflammatory • asthma • bronchodilator • fluticasone propionate • formoterol fumarate • inhaled corticosteroid • long-acting β -agonist

As estimated by the Global INitiative for Asthma (GINA), 1 in 10 adults in the Western world will develop asthma at some point during their lifetimes [1]. The cardinal symptoms of asthma are wheezing, breathlessness, chest tightness and cough. These symptoms arise from reversible airway obstruction caused by the chronic airway inflammation and airway hyper-responsiveness that characterize asthma. On a microscopic level, changes seen in the lungs of patients with persistent asthma include thickening of bronchial walls due to edema, smooth muscle hyperplasia and inflammatory cell infiltration by eosinophils, activated T helper lymphocytes, mast cells and sometimes neutrophils [2]. Airway inflammation and dysfunction can affect both large and small airways; and small airways dysfunction is associated with worse asthma control [3].

The control of asthma comprises two components: current symptomatic control and reduction in future risk, particularly of exacerbations [4]. Current symptom control is defined as minimal daytime and nocturnal symptoms, no

limitation on activities, no need for reliever bronchodilator therapy and normal lung function [5]. Despite substantial progress in our understanding of asthma pathophysiology and optimal treatment strategies, the results of recent surveys in Europe and the USA indicate that many patients have poorly controlled asthma, and the burden of uncontrolled asthma remains substantial [6–9]. Indeed, according to one assessment, the societal burden associated with asthma in Europe is of the same magnitude as that associated with diabetes [6].

Asthma therapies are categorized according to function and include fast-acting reliever therapies (bronchodilators) and long-term controller (or maintenance) therapies, most delivered by oral inhalation directly to the lungs [2]. The most commonly prescribed reliever therapies are the short-acting β_2 -adrenergic agonists (short-acting β -agonists (SABAs)), such as albuterol (also known as salbutamol), levalbuterol and terbutaline. Controller therapies include anti-inflammatory agents, namely, inhaled corticosteroids (ICS) and leukotriene receptor

antagonists (LTRAs) and long-acting bronchodilators, such as the long-acting β -agonists (LABAs).

Therapy for asthma is prescribed in stepwise fashion, individualized and adjusted according to 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, typically several weeks. While the recommendations of expert consensus national and international asthma guidelines vary in some details, the general progression of stepwise therapy is the same, with provision of reliever therapy for use as-needed at all steps [5,10–12]. Patients with mild persistent asthma are prescribed an anti-inflammatory controller agent, such as an ICS or LTRA. For patients whose asthma is not well controlled with ICS, the next recommended step up in therapy is typically the addition of a LABA, such as salmeterol, formoterol, or vilanterol [5,10,11,13].

Overview of the market

The efficacy of inhaled medications is dependent on their delivery to the lungs, which in turn depends on several factors, including drug properties (particle size and pharmacodynamic characteristics), inhaler device type and patients' ability to perform the correct inhalation maneuver for the relevant inhaler device. The safety and tolerability of inhaled medications depend on pharmacokinetic properties such as oral bioavailability, retention in the lung and systemic clearance [14].

In real-life clinical practice, the effectiveness of therapy for persistent asthma, as for all chronic conditions, requires patient education to promote adherence and persistence with prescribed regimens. Training in inhaler device handling and proper inhalation technique, with repeated reassessments, is an integral component of patient education about their asthma therapy. Different device types require different inhalation maneuvers, as described in detail in prior publications [15,16]. In brief, proper use of dry powder inhalers (DPIs) requires a rapid onset, forcible inhalation to release the dose, while pressurized metered dose inhalers (pMDIs) and breath-actuated MDIs (BAIs) require slow and deep inhalations. Improved adherence and outcomes may result from aligning patient preferences and abilities with choice of inhaler device and from using the same device types for reliever and controller medications [17–19]. In addition, the use of a spacer device with an inhaler can reduce oropharyngeal deposition and increase lung deposition. Patients who are prone to developing oral candidiasis and young children or others who have problems with coordinating device actuation with inhalation, may have better outcomes if using a spacer to maximize the dose delivered to the lungs.

Fixed-dose combination inhalers of ICS and LABA have been developed to facilitate the concomitant administration of these two agents, thus potentially improving patient adherence to therapy [20–22]. In addition, the provision of ICS/LABA in combination precludes the use of LABA as monotherapy, which is strongly discouraged for patients with asthma because of safety concerns about LABA use without ICS because of asthma-related deaths that occurred in patients receiving

salmeterol in a placebo-controlled trial without mandated ICS prescribed alongside [5,10,11,23,24]. As a result, all LABA inhalers as well as ICS/LABA combination products carry a so-called “black box warning” in the US. The increase in asthma-related deaths is currently considered a potential class effect of all LABA and the US FDA has required manufacturers of LABA products to conduct large-scale randomized controlled trials to further investigate whether adding ICS mitigates or eliminates the risk associated with LABA [23,24]. Others, however, have argued that the signal found is principally related to lack of mandated co-prescribing of ICS [25].

Here we describe the characteristics of the fixed-dose ICS/LABA combination inhaler of fluticasone propionate and formoterol fumarate (hereinafter called fluticasone/formoterol; flutiform[®], SkyePharma PLC, London, UK), a hydrofluoroalkane (HFA)-driven pMDI, approved by the European Commission in July 2012 for treating persistent asthma in adults and adolescents 12 years and older [26]. This report supplements and updates the information included in prior reviews [27,28].

Other fixed-dose combination inhaler products available in most of the European Union (EU) include budesonide/formoterol via DPI; fluticasone/salmeterol via DPI and pMDI; beclomethasone/formoterol in solution via pMDI, mometasone furoate/formoterol via pMDI, and the recently approved combination of fluticasone furoate/vilanterol via DPI.

Introduction to the drugs

Fluticasone is a topically active ICS administered by oral inhalation for asthma as monotherapy or in an ICS/LABA combination. In Europe, fluticasone is the most commonly prescribed ICS in fixed-dose combination with a LABA [29–31].

Formoterol is a LABA distinguished by rapid onset together with long duration of bronchodilating effect, lasting at least 12 h after oral inhalation [32,33].

Chemistry

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid; the chemical formula is $C_{25}H_{31}F_3O_5S$ (FIGURE 1). Formoterol fumarate is a long-acting, selective β_2 -adrenergic receptor agonist; the chemical formula of formoterol is $C_{19}H_{24}N_2O_4$ (FIGURE 2).

Pharmacodynamics

ICS attenuate the chronic airway inflammation of asthma, which helps to control and prevent asthma symptoms. Fluticasone has relatively high binding affinity for the glucocorticoid receptor and is considered a potent ICS, recommended for administration at half the dose of budesonide and regular-size-particle beclomethasone [10,14,34,35].

Formoterol is a full, selective β_2 -adrenergic receptor agonist [33,36]. The onset of bronchodilation (1–3 min) with formoterol is similar to that with albuterol, a SABA, and more rapid than that with salmeterol, a LABA [33,37]. Moreover, the onset of bronchodilation with a combination inhaler of fluticasone/formoterol is significantly more rapid than that with fluticasone/salmeterol, and this difference is maintained after

12 weeks of treatment for adults with mild to moderate-severe persistent asthma (see below for details) [38]. With regard to the relative potencies of the two LABAs, a dose of salmeterol 50 µg is estimated to correspond to a dose of formoterol of 9 µg (95% CI: 3–19 µg) [33].

The effects of low and high doses of fluticasone/formoterol (100/10 µg and 500/20 µg twice daily for 4 weeks) on airway responsiveness to inhaled adenosine 5'-monophosphate (AMP) challenge have been evaluated post hoc in a placebo-controlled, crossover study of 62 adult patients with asthma [39]. A significant dose-response for reduction in airway responsiveness to AMP was found for the 15 patients who received both high and low doses: the change in AMP PD₂₀ FEV₁ was greater with the high dose (least-squares [LS] means for high dose = 11 mg; 95% CI: 4.3–27.9 vs low dose = 4.6 mg, 95% CI: 1.8–11.8), with a statistically significant 2.4-fold difference in AMP PD₂₀ FEV₁ (1.2 doubling doses) between doses (LS mean, 2.4; 95% CI: 1.3–4.5; *p* = 0.012).

The effects of fluticasone/formoterol on the hypothalamic–pituitary–adrenal (HPA) axis, assessed as changes in urinary and serum cortisol levels, have been assessed in three 4- to 12-week trials enrolling healthy subjects and patients with mild asthma [40,41]. These studies found that twice daily doses of fluticasone/formoterol of 100/10 µg and 250/10 µg produced no significant changes, as compared with placebo, in urinary or serum cortisol levels from baseline to study end. Suppression of the HPA axis with the highest dose of 500/20 µg twice daily for 4 weeks was evident but less than that with the individual components delivered concurrently: healthy subjects receiving fluticasone/formoterol (*n* = 24) had a decrease in mean 24-h urinary-free cortisol levels (corrected for creatinine) at the end of study (from 13 to 7 nmol/24 h) and serum cortisol levels of 399, 272 and 412 nmol/L on day 1, day 29 and poststudy. For those receiving the individual components (*n* = 24), fluticasone 500 µg + formoterol 24 µg, urinary cortisol levels fell from 14 to 4 nmol/24 h, and serum cortisol levels were 430, 154 and 390 nmol/L on day 1, day 29 and poststudy [41]. The bioavailability of fluticasone from the fluticasone/formoterol combination inhaler was 67% of that from the individual component at steady state. The effects of fluticasone/formoterol on bone markers and bone mineral density have not been evaluated.

Upon inspiration from an inhaler, drug particles enter the lungs or alternatively are deposited in the oropharynx and swallowed; additionally, some may be exhaled. The delivery path and lung deposition of inhaled medications is determined by many factors, including inhaler device type, drug and aerosol characteristics, and the patient's anatomy and inhalation maneuver [16,42]. Theoretically, targeting the proximal airways for β₂-agonist delivery makes the most sense as this is where β₂-agonists act on receptors in smooth muscle to produce bronchodilation [43]. Instead, a more diffuse and widespread lung delivery of ICS may be desirable because of the generalized location of asthmatic airway inflammation, often extending into the small airways [3,16].

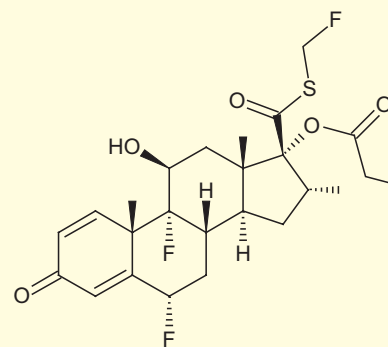


Figure 1. Fluticasone propionate.

Drug particle size is an important determinant of the location and extent of lung deposition of inhaled medications [16,42]. A range in particle size of 2–6 microns has been proposed as ideal because of deposition in both central and alveolar locations [27,42,44]. Very small particles (0.1–1 microns) are more prone to be exhaled than larger particles, particularly if the patient's breath-hold is not long enough; however, measured exhaled amounts are small (mean, 2% of nominal dose) and counter-balanced by improved pulmonary deposition of extra-fine particles [16,45,46].

Johal and coworkers [45] used an Anderson Cascade Impactor to determine particle size distribution of fluticasone/formoterol compared with three other ICS/LABA products: fluticasone/salmeterol by DPI, budesonide/formoterol by DPI, and beclomethasone/formoterol by HFA-driven pMDI. Five inhalers were tested for each product at two different inhalation flow rates to determine the fine-particle dose (mass of dose comprising particles <5 microns) and the fine-particle fraction as a percentage of the labeled dose. The median mass aerodynamic diameters (geometric SD) for fluticasone/formoterol were 3.52 (1.59) and 3.15 (1.77) microns at flow rates of 28.3 and 60.0 L/min, respectively. TABLE 1 summarizes the particle sizes

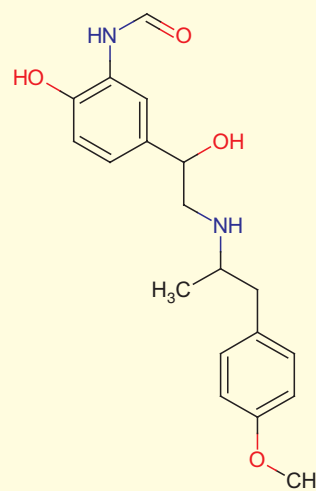


Figure 2. Formoterol.

Table 1. Drug particle size and fine-particle fraction determined using eight-stage Andersen Cascade Impactor at two flow rates in the DIFFUSE study.

ICS/LABA	MMAD (GSD)		Fine-particle fraction (%) [†]	
	Flow rate 28.3 L/min	Flow rate 60 L/min	Flow rate 28.3 L/min	Flow rate 60 L/min
ICS component				
FP/formoterol 125/5 µg	3.52 (1.59)	3.15 (1.77)	41.2	43.7
FP/salmeterol [†] 250/50 µg	4.65 (1.66)	3.72 (1.83)	12.5	17.8
Bud/formoterol [‡] 200/6 µg	3.77 (1.94)	2.49 (1.91)	8.2	35.0
BDP/formoterol [§] 100/6 µg	1.21 (2.77)	0.50 (4.46)	28.5	43.0
LABA component				
FP/formoterol 125/5 µg	3.52 (1.56)	3.17 (1.71)	39.1	42.1
FP/salmeterol [†] 250/50 µg	4.89 (1.86)	3.97 (1.96)	11.3	14.8
Bud/formoterol [‡] 200/6 µg	3.77 (1.92)	2.53 (1.89)	6.5	30.0
BDP/formoterol [§] 100/6 µg	1.24 (2.87)	0.49 (5.33)	26.1	39.6

[†]Seretide® Accuhaler® (Glaxo Operations UK).

[‡]Symbicort® Turbohaler® (AstraZeneca).

[§]Foster® (Chiesi).

[†]The fine-particle fraction was defined as the mass of dose <5.0 µm.

BDP: Beclomethasone dipropionate; Bud: Budesonide; FP: Fluticasone propionate; GSD: Geometric standard deviation; ICS: Inhaled corticosteroid; LABA: Long-acting β-agonist; MMAD: Median mass aerodynamic diameter.

Data taken from [45].

and fine-particle fractions of fluticasone/formoterol and the comparators [45].

The fluticasone/formoterol inhaler produced a fine-particle fraction that was consistent at both flow rates. At a flow rate of 28.3 L/min, the fine-particle fractions of the fluticasone/formoterol components (41 and 39%, respectively) were greater than those of fluticasone/salmeterol DPI, budesonide/formoterol DPI and beclomethasone/formoterol pMDI, while at 60.0 L/min, the fine-particle fractions of fluticasone/formoterol (44 and 42%) were also greater than those of fluticasone/salmeterol and budesonide/formoterol and were similar to those of beclomethasone/formoterol (43 and 40%) (TABLE 1) [45]. The fine-particle fraction from DPIs is usually dependent on inhalation flow rate because the dry powder formulations are disaggregated with inspiration into respirable particles [16].

Pharmacokinetics & metabolism

The pharmacokinetic properties of inhaled fluticasone and formoterol have been reviewed [47–49]. After inhalation, systemic absorption of fluticasone occurs mainly via the lungs; the half-life after inhalation is 14.4 h [14,26,47]. If swallowed, fluticasone has low oral bioavailability (<1%) as it is incompletely absorbed in the gastrointestinal tract and undergoes extensive first-pass metabolic inactivation in the liver, by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping, before entering the circulation [34]. Excretion is mainly via the feces.

Formoterol is rapidly absorbed from the lungs after inhalation, reaching maximum plasma drug concentrations within 5 min of inhalation of a single dose by healthy volunteers [26]. The plasma protein binding of formoterol is 61–64%, and

there is no saturation of binding sites at therapeutic doses. Elimination of formoterol is primarily by metabolism, chiefly by direct glucuronidation and secondarily by O-demethylation followed by further glucuronidation. In patients with asthma or chronic obstructive pulmonary disease (COPD) who received 12–24 µg formoterol twice daily, from 7 to 10% of the dose was recovered unchanged in the urine [26].

Information below about the pharmacokinetic properties of the fluticasone/formoterol combination derives from that provided by the manufacturer's prescribing information [26]. While there is considerable variability within and among pharmacokinetic studies, the general trend reported is for lower systemic exposure of fluticasone and formoterol from the fixed combination than from the separate components [26].

In a study of healthy volunteers administered a single dose of fluticasone/formoterol 250/10 µg, fluticasone reached a mean maximum plasma concentration (C_{max}) of 32.8 pg/ml within 45 min of inhalation. After inhalation of double that dose (500/20 µg), formoterol reached a C_{max} of 9.9 pg/ml within 6 min. Use of an AeroChamber Plus (Trudell Medical International) spacer device by healthy volunteers, as compared with pMDI only, increased mean systemic bioavailability of fluticasone by 35% because of increased pulmonary absorption, while decreasing mean systemic bioavailability of formoterol by 25%, likely because of a decrease in gastrointestinal tract delivery [26]. After inhalation of fluticasone/formoterol 500/20 µg, the terminal elimination half-life of fluticasone was approximately 14 h and that of formoterol was approximately 6.5 h [26].

No formal drug interaction studies have been performed with the fluticasone/formoterol combination inhaler. Nonetheless, as

fluticasone is a substrate of CYP3A4, long-term treatment and coadministration with strong CYP3A4 inhibitors should be avoided when possible [26].

Clinical efficacy

Phase III studies: overview

The eight Phase III clinical trials that have been published to date are summarized in TABLE 2. These multicenter trials evaluated the efficacy of fluticasone/formoterol over 8–12 weeks for adult and adolescent patients with asthma as compared with the individual components administered as monotherapy [50–53], the individual components administered concurrently using separate inhalers [54,55], and combination inhalers of fluticasone/salmeterol [56] and budesonide/formoterol [57]. A recent paper reports a pooled analysis of the efficacy and safety of fluticasone/formoterol combination therapy compared with fluticasone monotherapy [58] for patients enrolled in earlier studies who were receiving ICS therapy at the time of enrollment [50–54]. In addition, the long-term efficacy and safety of fluticasone/formoterol for adults and adolescent patients with asthma has been assessed in an open-label study for up to 12 months [59].

The doses investigated in clinical trials included low, medium and high doses of fluticasone/formoterol, defined as 100/10, 250/10 and 500/20 µg, respectively, administered twice daily. Asthma severity was defined as mild to moderate with a baseline prebronchodilator forced expiratory volume in 1 sec (FEV₁) of 60–85% of the predicted normal value (FEV₁ %predicted) and mild to moderate-severe with baseline FEV₁ of 40–80/85 %predicted. Trial medications were administered by HFA-driven pMDI, with the exception of the formoterol comparator in one trial [55] and budesonide/formoterol in another trial [57], which were administered by DPI. Spacer use was standardized for each study (all or none; see TABLE 2). All double-blind studies used a double-dummy design to ensure blinding, and patients were provided with reliever medication for as-needed use to control symptoms.

Patient eligibility requirements were similar across trials (TABLE 2). Patients were required to show FEV₁ reversibility after bronchodilator inhalation either at study start or at some point during the prior year, depending on the study. In addition, each double-blind trial included a run-in period of 2–4 weeks to confirm that all patients had symptoms of active asthma by their use of at least two inhalations per day of reliever medication (SABA) on 3 days of a 7-day period, in addition to experiencing daytime asthma symptoms on at least 3 days or sleep disturbance because of asthma on at least one night. During run-in, patients were supplied with SABA to use as-needed and, for those already receiving ICS, open-label fluticasone 50–250 µg twice daily depending on the study and determined according to their prestudy dose. Key exclusion criteria were a ≥10 pack-year or recent within 1 year history of smoking; a history of life-threatening asthma within 12 months; or receipt of systemic corticosteroids within 1–3 months, omalizumab within 6 months, or leukotriene antagonist within 1 week of screening.

Two trials enrolled only adults (≥18 years old) [54,56], while most trials enrolled both adults and adolescents (≥12 years old), the latter who comprised from 7 to 20% of the overall patient populations studied in those trials. Mean patient age was 39–49 years, and mean duration of asthma, where stated, 10–21 years. Women were in the majority in all studies, ranging from 54 to 68% of patients [50–57].

Lung function parameters, typically mean changes in or comparisons of FEV₁ at study end, were the designated primary efficacy end point(s) in all studies and were based on the full analysis set [50–53], or for noninferiority trials [54–57], on the per-protocol set, with supportive analyses using the full analysis set. The full analysis set comprised all patients who received at least one dose of study medication, had a baseline FEV₁ measurement, and had at least one postbaseline predose and 2-h postdose FEV₁ measurement; the per-protocol set comprised all patients with no major protocol violations affecting the primary end point(s). Additional efficacy measures studied included discontinuations due to lack of efficacy, rescue medication use, morning and evening peak expiratory flow rate (PEFR) from patient diaries, asthma symptom scores, sleep disturbance scores and asthma exacerbations.

Fluticasone/formoterol versus fluticasone or formoterol as monotherapy

The efficacy of fluticasone/formoterol for patients with asthma as compared with each of its two components was assessed in four randomized controlled clinical trials, all double-blind, parallel-group and 12 weeks in duration (TABLE 2) [50–53]. These trials used co-primary efficacy end points to detect differences between the combination product and each of the comparators: (1) the improvement in predose (trough) morning FEV₁ from baseline to week 12 versus formoterol monotherapy highlighted the contribution of fluticasone in the combination product; (2) change in trough FEV₁ at baseline to 2-h postdose FEV₁ at 12 weeks versus fluticasone monotherapy highlighted the contribution of formoterol in the combination product; and (3) in the two placebo-controlled trials [50,51], the time to discontinuation of therapy as a result of asthma exacerbation or loss of asthma control was compared versus placebo.

In the two low-dose comparisons enrolling patients with mild to moderate asthma (FEV₁ 60–85% predicted) [50,52], eligible patients had to either be off ICS for ≥12 weeks or be receiving an ICS for ≥4 weeks with daily dose equivalent to ≤500 µg fluticasone before the trial; randomization in both trials was stratified according to prior ICS use, as well as age (12–18 years vs >18 years) and study site. Patients who were on prior ICS received fluticasone 50 µg twice daily during a 14-day run-in period. In the medium-dose comparisons of Corren *et al.* [51] and Pertseva *et al.* [53], eligible patients had to be on current ICS therapy for ≥4 weeks at an ICS daily dose equivalent to ≤500 µg inhaled fluticasone; randomization was stratified according to baseline FEV₁ %predicted (40–60% vs >60–80%) [53], or both FEV₁ %predicted as well as age (12–18 years vs >18 years) and study site [51].

Table 2. Phase III clinical trials of fluticasone/formoterol: efficacy and safety.

Study design	Key inclusion criteria	Treatment arms (n)	Key outcomes and results [†]	Ref.
<i>Fluticasone/formoterol vs each individual component as monotherapy</i>				
DB parallel-group plc-controlled RCT/12 weeks	- Age ≥12 years - Asthma for ≥12 months - Baseline FEV₁ 60–85%pred - FEV₁ reversibility ≥14.5% - Active symptoms during run-in (see text)	By HFA pMDI, no spacer: – FP/form 100/10 µg b.i.d. (115) – FP 100 µg b.i.d. (117) – form 10 µg b.i.d. (116) – plc b.i.d. (111)	• Change in trough FEV₁ → FP/form > form • Change in trough to postdose FEV₁ → FP/form > FP • Discont d/t lack of efficacy → FP/form > plc • Safety → no clinically relevant differences	[50]
DB parallel-group plc-controlled RCT/12 weeks	- Age ≥12 years - Asthma for ≥12 months - Baseline FEV₁ 40–80%pred - FEV₁ reversibility ≥14.5% - Active symptoms during run-in (see text)	By HFA pMDI, no spacer: – FP/form 250/10 µg b.i.d. (110) – FP/form 100/10 µg b.i.d. (113) – FP 250 µg b.i.d. (113) – form 10 µg b.i.d. (111) – plc b.i.d. (109)	• Change in trough FEV₁ → both doses FP/form > form • Change in trough to post-dose FEV₁ → both doses FP/form > FP • Discont d/t lack of efficacy → FP/form 250/10µg > plc • Safety → no clinically relevant differences	[51]
DB parallel-group RCT/12 weeks	- Age ≥12 years - Asthma for ≥12 months - Baseline FEV₁ 60–85%pred - FEV₁ reversibility ≥14.5% - Active symptoms during run-in (see text)	By HFA pMDI: – FP/form 100/10 µg b.i.d. (119) – FP 100 µg b.i.d. (119) – form 10 µg b.i.d. (119)	• Change in trough FEV₁ → FP/form > form • Change in trough to postdose FEV₁ → FP/form > FP • Safety → no clinically relevant differences	[52]
DB parallel-group RCT/12 weeks	- Age ≥12 years - Asthma for ≥12 months - Baseline FEV₁ 40–80%pred - FEV₁ reversibility ≥15% - Active symptoms during run-in (see text)	By HFA pMDI: – FP/form 250/10 µg b.i.d. (146) – FP 250 µg b.i.d. (146) – FP 250 µg b.i.d. (146)	• Change in trough to postdose FEV₁ → FP/form > each of FP formulations • Safety → no clinically relevant differences	[53]
<i>Fluticasone/formoterol vs fluticasone + formoterol via separate inhalers</i>				
DB parallel-group noninferiority RCT/8 weeks	- Age ≥18 years - Asthma for ≥6 months - Baseline FEV₁ 40–80%pred - FEV₁ reversibility ≥15% - Active symptoms during run-in (see text)	By pMDI with a spacer: – FP/form 500/20 µg b.i.d. (154) – FP/form 100/10 µg b.i.d. (155) – FP 500 µg + form 24 µg b.i.d. (156) – FP 500 µg b.i.d. (155)	• Change in trough FEV₁ → FP/form 500/20 µg noninferior to FP + form • Change in trough to postdose FEV₁ → FP/form 500/20 µg noninferior to FP + form • Safety → no differences among Rx groups	[54]
OL parallel-group noninferiority RCT/12 weeks	- Age ≥12 years - Asthma for ≥6 months - Baseline FEV₁ 40–85%pred - FEV₁ reversibility ≥15% - No run-in period	By pMDI with a spacer except form by DPI, no spacer: – FP/form 100/10 µg b.i.d. or FP/form 250/10 µg b.i.d. (105) – FP 100 µg + form 12 µg b.i.d. or FP 250 µg + form 12 µg b.i.d. (105)	• 30–60 min postdose FEV₁ on day 84 → FP/form noninferior to FP + form • Safety → no differences between Rx groups	[55]

[†]Trough FEV₁ was measured in the morning before the first dose of medication; postdose FEV₁ was measured 2 h after the dose.

> denotes significantly (p < 0.05) better outcome.

b.i.d.: Twice daily; bud: Budesonide; DB: Double-blind; DPI: Dry powder inhaler; d/t: Due to; FEV₁: Forced expiratory volume in 1 s; form: Formoterol; FP: Fluticasone propionate; HFA: Hydrofluoroalkane; OL: Open-label; plc: Placebo; pMDI: Pressurized metered-dose inhaler; RCT: Randomized controlled trial; sal: Salmeterol.

Table 2. Phase III clinical trials of fluticasone/formoterol: efficacy and safety (cont.).

Study design	Key inclusion criteria	Treatment arms (n)	Key outcomes and results [†]	Ref.
<i>Fluticasone/formoterol vs other combination inhaler products (fluticasone/salmeterol and budesonide/formoterol)</i>				
OL parallel-group noninferiority RCT/12 weeks	• Age ≥18 years • Asthma for ≥6 months • Baseline FEV₁ 40–85%pred • FEV₁ reversibility ≥15%	By HFA-pMDI with a spacer: – FP/form 100/10 µg b.i.d. or FP/form 250/10 µg b.i.d. (101) – FP/sal 100/50 µg b.i.d. or FP/sal 250/50 µg b.i.d. (101)	• Trough FEV₁ at week 12 → FP/form noninferior to FP/sal • Onset of bronchodilation significantly faster with FP/form • Safety → no differences between Rx groups	[56]
DB parallel-group RCT/12 weeks	• Age ≥12 years • Asthma for ≥6 months • Baseline FEV₁ 50–80% pred • FEV₁ reversibility ≥15% • Active symptoms during run-in (see text)	– FP/form 250/10 µg b.i.d. by HFA-pMDI (140) – bud/form 400/12 µg b.i.d. by DPI (139)	• Change in trough FEV₁ → FP/form noninferior to bud/form • Change in trough to postdose FEV₁ → FP/form noninferior to bud/form • Safety → no differences between Rx groups	[57]

[†]Trough FEV₁ was measured in the morning before the first dose of medication; postdose FEV₁ was measured 2 h after the dose.

> denotes significantly (p < 0.05) better outcome.

b.i.d: Twice daily; bud: Budesonide; DB: Double-blind; DPI: Dry powder inhaler; d/t: Due to; FEV₁: Forced expiratory volume in 1 s; form: Formoterol; FP: Fluticasone propionate; HFA: Hydrofluoroalkane; OL: Open-label; plc: Placebo; pMDI: Pressurized metered-dose inhaler; RCT: Randomized controlled trial; sal: Salmeterol.

The first study by Nathan and coworkers [50] assessed the efficacy of low-dose fluticasone/formoterol for 475 patients with mild to moderate asthma. Results for the three co-primary end points all significantly favored the fluticasone/formoterol combination (FIGURE 3; TABLE 2) [50]. Moreover, for patients receiving fluticasone/formoterol, the improvements from trough FEV₁ at baseline to trough FEV₁ and 2-h postdose FEV₁ at 12 weeks were clinically relevant (LS means of 0.20 and 0.39 L, respectively). Results of the second low-dose study comparing fluticasone/formoterol with its individual components as monotherapy supported the prior findings, with improvements in the co-primary end points that were significantly greater for the fluticasone/formoterol treatment group than for fluticasone or formoterol alone (TABLE 2) [52]. In the third study investigating efficacy of the medium dose for patients with moderate to severe asthma, efficacy results at week 12 for the fluticasone/formoterol 250/10 µg twice daily combination were significantly superior for the three co-primary end points (TABLE 2). The time to discontinuation of therapy due to lack of efficacy as compared with placebo is depicted in FIGURE 4 [51]. Moreover, for adolescents and adults with moderate to severe asthma, the medium dose of fluticasone/formoterol provided significantly greater improvement in lung function at 12 weeks as compared with each of the two different formulations of fluticasone propionate (SkyePharma fluticasone and Flovent®, GlaxoSmithKline) administered at 250 µg twice daily [53].

A recent analysis by Papi *et al.* [58] has examined data pooled from five randomized 8- to 12-week studies enrolling 1055 adults and adolescent patients with asthma who received fluticasone/formoterol (100/10, 250/10, or 500/20 µg twice daily; n = 528) or fluticasone alone (100, 250 or 500 µg twice daily; n = 527). They found that fluticasone/formoterol provided significantly greater increases than fluticasone alone in mean

morning trough FEV₁ from baseline to study end (LS mean treatment difference, 0.048 L; p = 0.043) and in the improvement from baseline trough FEV₁ to the final FEV₁ at study end 2 h postdose (LS mean difference, 0.146 L; p < 0.001). Moreover, fluticasone/formoterol provided greater increases than fluticasone alone in the percentage of asthma control days (no symptoms, no rescue medication use and no sleep disturbance due to asthma) from baseline to study end (LS mean difference, 8.6%; p < 0.001), and was associated with fewer exacerbations (annualized rate ratio, 0.71; 95% CI: 0.54–0.94) [58].

Comparison with fluticasone & formoterol administered concurrently via separate inhalers

The coadministration of ICS and LABA via one inhaler is more convenient for patients and potentially could improve adherence to therapy [20–22]. The efficacy and safety profile of the fluticasone/formoterol combination has been compared with that of fluticasone and formoterol administered concurrently but via separate inhalers in two noninferiority trials [54,55]. The first of these investigated the high-dose combination for adults with severe persistent asthma [54], and the second, the low- and medium-dose combinations for adults and adolescents with mild to moderate-severe asthma (TABLE 2) [55].

The co-primary efficacy end points in the double-blind trial of severe asthma were (1) the mean change in predose (trough) morning FEV₁ from baseline to the end of treatment and (2) change in trough FEV₁ at baseline to 2-h postdose FEV₁ at the end of treatment. In the open-label trial, the primary efficacy end point was FEV₁ value at 30–60 min postdose on day 84. The noninferiority cut-point in both trials was a lower limit of -0.2 L for the 95% CI of the difference between treatment groups, determined for the per-protocol population with a supportive analysis carried out for the full analysis set.

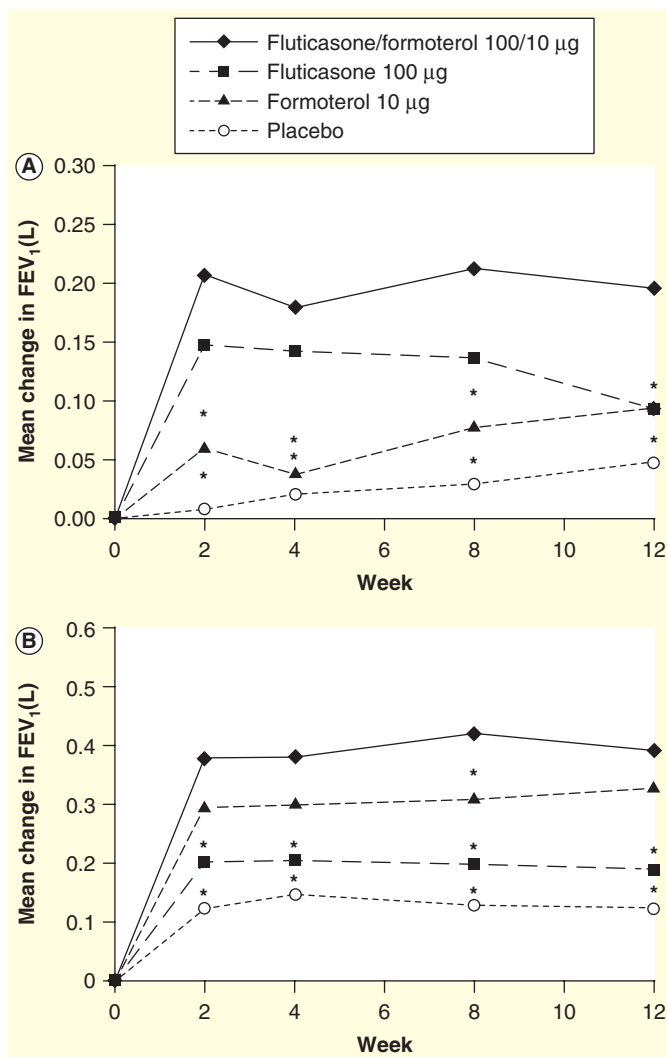


Figure 3. Mean change in FEV₁ (L). (A) Mean change from baseline to predose at weeks 2, 4, 8, and 12, full analysis set (LOCF). Baseline means were 2.416 L, 2.425 L, 2.459 L, and 2.352 L for the fluticasone/formoterol, fluticasone, formoterol, and placebo treatment groups, respectively, for all patients in the full analysis set. (B) Mean change from baseline to 2 h postdose at weeks 2, 4, 8, and 12, full analysis set (LOCF). Baseline means were 2.416 L, 2.425 L, 2.459 L, and 2.352 L for the fluticasone/formoterol, fluticasone, formoterol, and placebo treatment groups, respectively, for all patients in the full analysis set. * $p \leq 0.05$ versus fluticasone/formoterol 100/10 µg b.i.d. combination therapy treatment group. b.i.d.: Twice daily; FEV₁: Forced expiratory volume in 1 s; LOCF: Last observation carried forward. Reproduced with permission from [50] under the terms of the BioMed Central Open Access license agreement.

Overall, 620 adult patients with severe persistent asthma (prestudy ICS dose ≥ 500 µg fluticasone or equivalent) were randomly assigned to one of four treatment groups in the double-blind trial (see TABLE 2) [54]. The increase in mean trough FEV₁ from baseline to week 8 was similar for the fluticasone/formoterol 500/20 µg group and the fluticasone 500 µg + formoterol 24 µg group, with LS mean difference of 0.060 (95%

CI: -0.059 to 0.180; $p < 0.001$ denoting noninferiority). Similarly, fluticasone/formoterol was noninferior to the combination in separate inhalers for change from baseline mean trough FEV₁ to FEV₁ at 2 h postdose at 8 weeks. The efficacy of fluticasone/formoterol was significantly greater compared with fluticasone alone for one co-primary end point (change in trough FEV₁) but not the other (change from trough FEV₁ to 2 h postdose FEV₁), and the efficacy was dose-dependent for several secondary efficacy parameters, including discontinuations due to lack of efficacy (3.9% vs 11.6% of patients in the low-dose group; TABLE 2) [54].

In the open-label study [55], a total of 210 adult and adolescent patients were randomized to receive fluticasone/formoterol in combination inhaler or via separates. The starting doses depended on patients' asthma history or prior medication, and both dose groups were combined for fluticasone/formoterol versus fluticasone + formoterol separates (TABLE 2). Noninferiority of the fluticasone/formoterol combination was demonstrated with an LS mean treatment difference of -0.033 L (95% CI: -0.148 to 0.081) in FEV₁ value at 30–60 min postdose on day 84, supported by similar results for the full analysis set.

Comparison with fluticasone/salmeterol & budesonide/formoterol

The efficacy, safety and onset of action of fluticasone/formoterol were compared with those of fluticasone/salmeterol in a 12-week open-label, randomized noninferiority trial that enrolled adult patients ≥ 18 years old ($n = 202$) with persistent mild to moderate-severe asthma (TABLE 2) [56]. The primary efficacy end point was the mean predose (trough) FEV₁ at week 12; other efficacy end points included additional lung function parameters, time to onset of action and asthma symptoms. At 12 weeks, trough FEV₁ values for patients in the fluticasone/formoterol treatment group were comparable with those for patients in the fluticasone/salmeterol group (LS mean difference -0.061 L; 95% CI: -0.161 to 0.040; $p = 0.007$ for noninferiority). Other outcomes, including asthma symptom scores and rescue medication use, were also comparable. However, the time to onset of action of fluticasone/formoterol was significantly faster than that of fluticasone/salmeterol, which the authors attributed to the faster bronchodilatory effects of formoterol as compared with salmeterol [56].

A post hoc analysis was conducted to further characterize the onset of bronchodilation (defined as the time point of the first postdose FEV₁ $\geq 12\%$ higher than the predose FEV₁) and responder rates (patients achieving bronchodilation) in the latter study [38]. FIGURE 5 depicts the onset of bronchodilation on days 0 and 84 for the full analysis set. On days 0 and 84, the odds of a patient achieving bronchodilation within 5 min of treatment were significantly greater with fluticasone/formoterol (day 0 odds ratio [OR] 3.97; 95% CI: 1.96–8.03; and day 84 OR, 9.58; 95% CI: 2.14–42.90); at 120 min on day 84, the odds were nearly two times greater (OR, 1.93; 95% CI: 1.08–3.43).

A second noninferiority study, this one randomized double-blind, compared the efficacy and safety of fluticasone/formoterol versus budesonide/formoterol (TABLE 2) [57]. At 12 weeks, fluticasone/formoterol was noninferior to budesonide/formoterol for the primary end point: the change in mean trough FEV₁ from baseline to week 12 was comparable for the two treatment groups, with LS means difference of -0.044 L (95% CI: -0.130 to 0.043) and thus lower limit of the 95% CI of greater than -0.2 L ($p < 0.001$ for noninferiority). Results for the secondary end points were comparable for the two treatment groups [57].

There are currently no published comparative trials of fluticasone/formoterol versus mometasone/formoterol.

Safety & tolerability

Both fluticasone and formoterol are well-established therapies for persistent asthma and have well-defined safety and tolerability profiles in adolescent and adult patients [29,30,60]. Reported adverse effects associated with fluticasone monotherapy comprise events related to oropharyngeal deposition, including sore throat, hoarseness and candidiasis, particularly at higher doses (800–1000 µg/day) [29,30]. At very high doses (2000 µg/day fluticasone), patients with severe asthma receiving oral steroids may be able to reduce the oral steroid dose [29]. With regard to formoterol, a recent review found no evidence of increased risk of asthma-related hospitalization or asthma-related deaths among patients receiving formoterol, 93% of whom were also receiving ICS, as compared with those not receiving a LABA [61]. Moreover, no significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone was found in a prior Cochrane review [62].

The safety and tolerability profile of the fluticasone/formoterol combination was assessed in all of the 8- to 12-week trials described here [50–57]. In each individual trial, the fluticasone/formoterol combination had a tolerability profile similar to the trial comparator(s). This was the case also for the pooled analysis, as the incidence and types of adverse events were similar with fluticasone/formoterol as with fluticasone alone [58].

The long-term safety of fluticasone/formoterol was further investigated in a 12-month open-label trial in which 472 adults and adolescents (≥ 12 years old) with mild to moderate-severe asthma received therapy with fluticasone/formoterol 100/10 or 250/10 µg twice daily for up to 12 months [59]. To be eligible, patients had to have documented use of ICS for ≥ 4 weeks before screening at a dose equivalent to ≤ 500 µg/

day fluticasone. Patients who entered the study were assigned to the fluticasone/formoterol dose group dependent on their corticosteroid dose before screening (100–249 vs 250–500 µg/day fluticasone-equivalent). Visits were scheduled at 2 and 4 weeks after initiating treatment and then monthly thereafter. Safety assessments included vital sign assessments and 12-lead electrocardiograms before pulmonary function testing at each visit and clinical laboratory testing at screening, weeks 0 and 4, and months 3, 6 and 12, or at the final visit for premature discontinuation.

The safety population included all 472 patients who entered the study; and 413 (88%) patients completed their assigned 6- or 12-month treatment period. Overall, 174 (37%) patients reported adverse events. Most adverse events were mild to moderate in severity; those occurring with an incidence of $>1\%$ are presented in TABLE 3. In total, 18 (4%) patients reported adverse events possibly or probably related to study medication, including asthma ($n = 2$) and dysphonia ($n = 5$). Five patients in each treatment group experienced a total of 12 serious adverse events, none of which were considered to be related to study therapy [59]. Fifty-three (11%) patients experienced asthma exacerbations, including 46 exacerbations assessed as mild to moderate and 9 severe. No abnormal trends or dose-related changes were noted on laboratory test or vital signs results. Efficacy assessments were the secondary end points, and significant improvements were recorded in spirometry tests throughout the study.

Regulatory affairs

The fixed-dose combination inhaler of fluticasone/formoterol was approved by the European Commission in July 2012 for

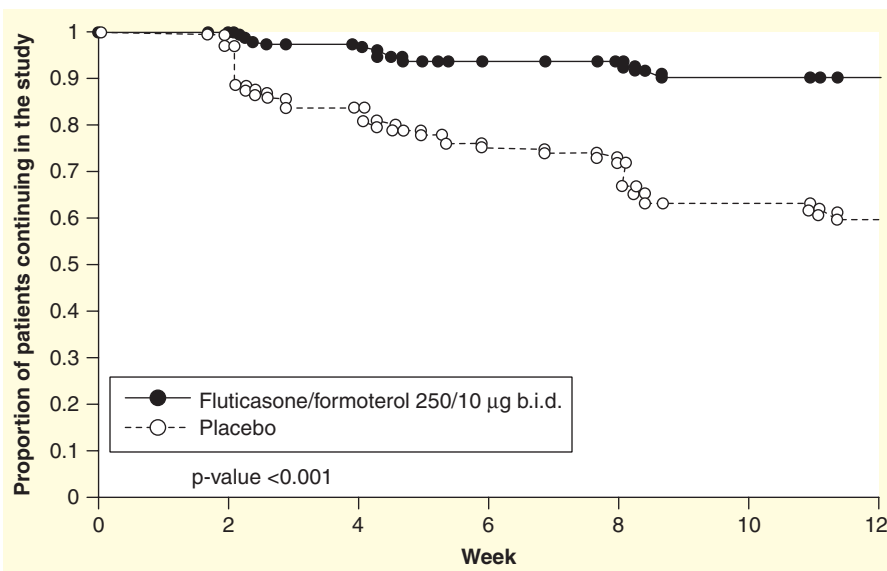


Figure 4. Time to discontinuation due to lack of efficacy (asthma exacerbation or loss of asthma control).

p-value based on stratified log-rank test adjusting for baseline FEV₁ %predicted categories.

b.i.d.: Twice daily.

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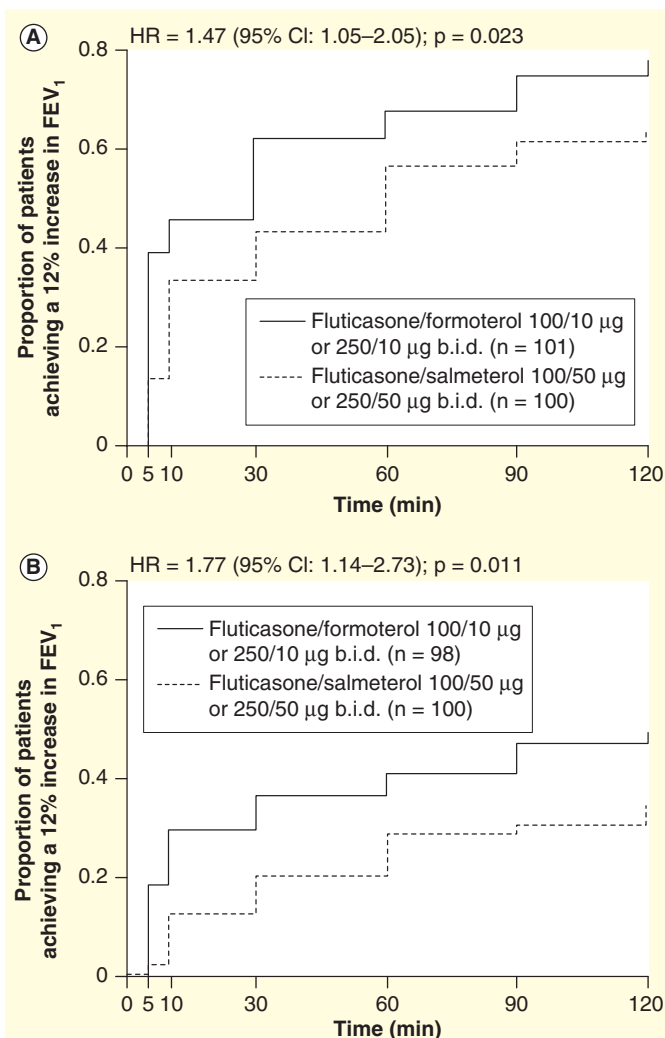


Figure 5. Kaplan–Meier plots showing the onset of bronchodilation. (A) day 0 and (B) day 84 (intention-to-treat population). HRs are from post hoc analyses. Onset of bronchodilation was defined as the first time point postdose when FEV₁ was $\geq 12\%$ greater than the predose value. b.i.d.: Twice daily; CI: Confidence interval; FEV₁: Forced expiratory volume in 1 s; HR: Hazard ratio. This figure is modified from [56] and reproduced with permission from [38].

regular treatment of asthma for adults and adolescents when the use of a combination product (an ICS and LABA) is appropriate, including for patients not adequately controlled with ICS and ‘as required’ inhaled SABA and for patients already adequately controlled on both an ICS and a LABA [26]. Fluticasone/formoterol is now approved in 21 European countries, as well as in Australia, Hong Kong and, in September 2013, in Japan for the treatment of asthma. The Japanese approval is for the regular treatment of asthma in patients aged 16 years and over when concomitant use of an ICS and LABA is required. The fluticasone/formoterol combination is not currently licensed for use as single maintenance and reliever therapy (SMART).

In Europe, fluticasone/formoterol suspension is delivered via press-and-breathe, HFA-driven pMDIs containing at least 120 actuations (60 doses) and available in three dose strengths: (ex-valve) doses of 50/5, 125/5 and 250/10 µg per actuation (equivalent to ex-actuator doses of 46/4.5, 115/4.5 and 230/9 µg per actuation). The fluticasone/formoterol 50/5 and 125/5 µg inhalers are indicated for adults and adolescents 12 years and older, and the 250/10 µg inhaler is indicated for adults only [26]. In Japan, the two lower dose strengths are available as inhalers containing 56 or 120 actuations.

Each 120-actuation pMDI has a dose indicator showing how many actuations are left in the inhaler, using color coding ranging from green (45–120 actuations), to yellow (25–45) and then red (<25 actuations remaining).

Conclusion

The fluticasone/formoterol combination pMDI has demonstrated a good tolerability profile for patients with mild to moderate-severe asthma over 12 months of administration and as compared over 8–12 weeks with its individual components and the fluticasone/salmeterol and budesonide/formoterol combinations. The efficacy of fluticasone/formoterol over 8–12 weeks is greater than that of fluticasone or formoterol alone and noninferior to that of fluticasone/salmeterol and budesonide/formoterol. An advantage of the fluticasone/formoterol combination is a more rapid onset of bronchodilation than with fluticasone/salmeterol, an effect that is maintained over 12 weeks of administration. In addition, the fluticasone/formoterol combination aerosol emits a high fine-particle fraction that is consistent at different flow rates, which may aid consistency of delivery given patient variability in inhalation maneuvers.

Expert commentary

Results of the Phase III clinical trial program support the tolerability and the efficacy of the fluticasone/formoterol combination inhaler, particularly with regard to pulmonary function. The real-life efficacy, known as *effectiveness*, of fluticasone/formoterol has not yet been assessed in a community setting, outside of randomized clinical trials. Patients enrolled in the clinical trials were selected to have $\geq 14.5\%$ reversibility, an indication that they were responders to β -agonists. Moreover, the clinical trial population was more homogeneous than the varied patient population seen in clinical practice, as eligible patients had to have a prespecified decrement in pulmonary function, active asthma symptoms and limited or no smoking history. Patients may respond differently to the alternative step-up strategies for asthma therapy (e.g., increased ICS dose or add-on LTRA), and to date, fluticasone/formoterol therapy has not been compared with the alternatives. Moreover, responsiveness may be influenced by genotype, such as polymorphism at codon 16 of the β_2 -adrenergic receptor gene, another area for future study [63].

Table 3. Treatment-emergent adverse events reported for >1% of patients in either dose group or overall, safety population.

	Number (%) of patients		
	<i>Fluticasone/formoterol</i> 100/10 µg b.i.d. (n = 224)	<i>Fluticasone/formoterol</i> 250/10 µg b.i.d. (n = 248)	<i>Overall</i> (n = 472)
Any event	67 (29.9)	107 (43.1)	174 (36.9)
<i>Infections and infestations</i>			
Nasopharyngitis	17 (7.6)	28 (11.3)	45 (9.5)
Pharyngitis	6 (2.7)	7 (2.8)	13 (2.8)
Lower respiratory tract infection	5 (2.2)	7 (2.8)	12 (2.5)
Upper respiratory tract infection	6 (2.7)	6 (2.4)	12 (2.5)
Bronchitis	4 (1.8)	5 (2.0)	9 (1.9)
Bronchitis acute	6 (2.7)	3 (1.2)	9 (1.9)
Rhinitis	2 (0.9)	7 (2.8)	9 (1.9)
Acute sinusitis	1 (0.4)	5 (2.0)	6 (1.3)
Sinusitis	1 (0.4)	3 (1.2)	4 (0.8)
Abscess	0	3 (1.2)	3 (0.6)
Respiratory tract infection	3 (1.3)	0	3 (0.6)
Urinary tract infection	0	3 (1.2)	3 (0.6)
<i>Respiratory, thoracic and mediastinal disorders</i>			
Dyspnea	5 (2.2)	19 (7.7)	24 (5.1)
Asthma [†]	3 (1.3)	9 (3.6)	12 (2.5)
Cough	2 (0.9)	8 (3.2)	10 (2.1)
Dysphonia	1 (0.4)	6 (2.4)	7 (1.5)
Pharyngeal pain	5 (2.2)	1 (0.4)	6 (1.3)
Rhinitis allergic	0	4 (1.6)	4 (0.8)
<i>Nervous system disorders</i>			
Headache	7 (3.1)	6 (2.4)	13 (2.8)
<i>Gastrointestinal disorders</i>			
Abdominal pain	3 (1.3)	0	3 (0.6)
<i>Musculoskeletal and connective tissue disorders</i>			
Pain in extremity	1 (0.4)	3 (1.2)	4 (0.8)
Arthralgia	0	3 (1.2)	3 (0.6)
<i>Eye disorders</i>			
Conjunctivitis	2 (0.9)	3 (1.2)	5 (1.1)
<i>Immune system disorders</i>			
Seasonal allergy	3 (1.3)	1 (0.4)	4 (0.8)

[†]An asthma exacerbation was considered an adverse event if it did not resolve with the study drug treatments (including albuterol) and additional medication was required (e.g., systemic corticosteroids).
b.i.d.: Twice daily.

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In making the transition to prescribing in real-life clinical practice, several additional factors come into play that can influence the effectiveness of inhaled therapies for asthma. These factors include inhaler characteristics and associated ease of use by the varied patient population in community practice [16,17]. In addition, patient adherence and persistence with therapy are important factors, often shaped by preferences and level of satisfaction with inhaler device and patient-centered outcomes of therapy [18,22,63].

Several studies have assessed patient and/or physician preferences with regard to ICS/LABA combination inhalers [22,64–67]. In two small randomized controlled trials, Leidy and coworkers [65] tested whether adult patients can feel an inhaler therapy working right away. They found that patients who perceived their inhaler working right away characterized this perception as easier breathing and, in turn, further characterized this perception as beneficial to their self-care. In a follow-up study using a Delphi process evaluation, the consensus of community-based healthcare workers was that patient perceptions of rapid inhaler effects were clinically meaningful and could promote improved patient adherence to therapy [64]. Other studies have corroborated the importance to patients of rapid onset of effect of ICS-LABA combination inhalers, with associated satisfaction and potentially beneficial effects on adherence [22,66]. Bousquet and coworkers [67] surveyed primary and secondary care asthma specialists for the attributes they considered important for selecting an ICS-LABA combination therapy. The key attributes identified ($\geq 69\%$ agreement) were the availability of a range of doses, the efficacy of the combination, the safety and tolerability of the therapy, the potency of the ICS, and the speed of onset of the LABA.

The fluticasone/formoterol combination inhaler thus has several attributes corresponding to those identified as important to patients (rapid onset of effect) as well as healthcare providers (range of doses, efficacy and tolerability, ICS potency and LABA speed of onset). In addition, the fact that the inhaler is a pMDI may also be an advantage. Results of a real-life study indicate better asthma outcomes when patients are prescribed the same inhaler device for controller and reliever medication [19], and patients are often prescribed a pMDI for their reliever medication. In a study of patients with asthma in UK primary care, those who were prescribed fluticasone/salmeterol combination therapy by pMDI, as compared with a DPI, had significantly greater odds over 1 year of achieving asthma control (defined as no recorded hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory infection), as well as significantly greater odds of treatment success (defined as no asthma exacerbation or change in therapy) [68]. Only 19% of patients in the pMDI cohort were prescribed mixed devices (i.e., different device types for combination controller and reliever) versus 78% in the DPI cohort, suggesting that device mixing should perhaps be avoided.

Another factor that contributes to the effectiveness of inhaled therapies is inhaler device technique, which includes the

handling and preparation of the device as well as the correctness of the inhalation maneuver [16]. The fact that the fine-particle fraction from the fluticasone/formoterol inhaler was high and remained consistent in the laboratory at two different flow rates suggests that dose delivery may remain consistent also *in vivo*, which could eliminate the adverse effect on dose delivery of natural variability in patient inhalation flow rates [45]. Moreover, the high fine-particle fraction may confer a clinical advantage. Extrafine beclomethasone and extrafine beclomethasone/formoterol have greater and more uniform lung deposition than larger-particle formulations [46,69–71]. The results of functional studies suggest clinically relevant improvements in small airway obstruction [72], while those of real-life studies suggest that asthma-related outcomes are similar or better at lower prescribed doses with extrafine as compared with larger-particle ICS [73,74].

Finally, the inclusion of an easy-to-read, color-coded dose counter on the fluticasone/formoterol inhaler is likely to be beneficial. Integrated pMDI dose counters could reduce the risk of subtherapeutic dosing and of inhaler depletion by giving patients ample warning before a new inhaler is needed. Results of a large retrospective cohort study, published to date only in abstract form [75], indicate that, in the real-life setting, albuterol inhalers with dose counters, versus those without dose counters, are associated with a significantly reduced rate of respiratory-related visits to the emergency department (adjusted rate ratio, 0.55; 95% CI: 0.47–0.64).

Five-year view

Topics that are currently front and center in respiratory research include the need to better individualize therapy, to reduce future risk of exacerbations, to improve inhaler device choice and handling, and to understand the efficacy and safety of therapies in real life [4,17,76–78]. Individualized, or personalized, medicine is particularly relevant for asthma, a heterogeneous condition encompassing different phenotypes and, in older individuals, often overlapping with COPD [79,80].

Ongoing studies of fluticasone/formoterol are summarized in TABLE 4 [81]. These studies include a recent crossover trial assessing patient handling technique for the fluticasone/formoterol pMDI device and for a novel breath-actuated pMDI known as the K-Haler® (Mundipharma Research Ltd.). This inhaler may address the needs of patients who have trouble with the press-and-breath pMDI in coordinating actuation with inhalation. Other current clinical trials are designed to assess the efficacy and safety of fluticasone/formoterol for children with mild-moderate or moderate-severe asthma and for patients with COPD, the latter over a 1-year period.

The tightly controlled noninferiority studies conducted for licensing purposes have demonstrated that the fluticasone/formoterol combination inhaler has short-term efficacy noninferior to that of the combination inhalers containing fluticasone/salmeterol and budesonide/formoterol. However, healthcare policymakers and providers are placing increased emphasis on the need to demonstrate real-life efficacy – known as

Table 4. Ongoing or still-to-be-published clinical trials of fluticasone/formoterol [81].

Study design	Clinicaltrials.gov number	Key inclusion criteria	Treatment arms (n)	Key outcomes and results
Fluticasone/formoterol for children				
OL parallel-group noninferiority RCT/12 weeks	NCT00475813	• Age 4–12 years • Asthma for ≥6 months • baseline FEV₁ 60–100% pred • FEV₁ reversibility ≥15%	By HFA-pMDI with a spacer: – FP/form 100/10 µg b.i.d. (106) – FP/sal 100/50 µg b.i.d. (105)	• Change in trough FEV₁ → FP/form noninferior to FP/sal • Change in trough to postdose FEV₁ → FP/form noninferior to FP/sal • Discont d/t lack of efficacy → no discontinuations • Safety → no differences between Rx groups
OL extension long-term safety study/6 months		Continuation of above	By HFA-pMDI with a spacer: – FP/form 100/10 µg b.i.d. (208)	• Safety → safe and well-tolerated – 2 episodes of treatment-related oral candidiasis
DB parallel-group noninferiority RCT/12 weeks	NCT01511367	• Age 5 to <12 years • asthma for ≥6 months • baseline FEV₁ 60–90% pred • FEV₁ reversibility ≥15% • Stable ICS dose for ≥4 weeks	By HFA-pMDI with a spacer: – FP/form 100/10 µg b.i.d. – FP/sal 100/50 µg b.i.d. – FP 100 µg b.i.d.	• Change in trough to postdose FEV₁: vs FP • Change in trough to postdose FEV₁: noninferiority vs FP/sal Study is ongoing, no results yet
Fluticasone/formoterol inhaler device handling				
Prospective observational cross-over/58 days	NCT01739387	• Age ≥12 years • Asthma or COPD • On current Rx for asthma or COPD	Inhaler handling comparison: – pMDI placebo vs – BAI placebo	Inhaler device training, then 1–3 weeks later: • Assessment of inhaler device use No results yet
Fluticasone/formoterol in COPD				
DB parallel-group RCT/52 weeks	NCT01946620	• Age ≥40 years • smoking hx ≥10 packs/year • Moderate to severe COPD exac in prior year • No asthma diagnosis	HFA pMDI: – FP/form 500/20 µg b.i.d. – FP/form 100/10 µg b.i.d. – form 12 µg b.i.d.	• Annual rate of moderate and severe COPD exacerbations Not recruiting yet

BAI: Breath-actuated inhaler; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; DB: Double-blind; exac: Exacerbation; FEV₁: Forced expiratory volume in 1 sec; form: Formoterol; FP: Fluticasone propionate; HFA: Hydrofluoroalkane; hx: History; ICS: Inhaled corticosteroid; OL: Open-label; plc: placebo; pMDI: Pressurized metered-dose inhaler; RCT: Randomized controlled trial; Rx: Therapy; sal: Salmeterol.

effectiveness – in everyday practice where most patients receive their medical care (rather than in the idealized conditions of clinical trials) [76,82–84]. Thus, while characteristics of the inhaler and formulation suggest potential benefits in practice, the real-life effectiveness of fluticasone/formoterol will need to be assessed going forward as the combination inhaler comes into wider use.

Several broad-based initiatives are working towards the goal of better understanding and standardizing end points for defining asthma control and exacerbations. These include an American Thoracic Society/European Respiratory Society Task Force established in 2004 [4]; the Asthma Outcomes Workshop, convened

in 2010 by the US National Institutes of Health (NIH)/Agency for Healthcare Research and Quality [85]; and the Respiratory Effectiveness Group (REG), established in 2012 as an international collaborative effort to develop and promote quality standards for evaluating real-life data [82]. Results of these initiatives will be important for evaluating real-life effects of respiratory therapies and improving patient care in respiratory medicine.

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Key issues

- A fixed-dose combination of fluticasone/formoterol is now available via pressurized metered-dose inhaler (pMDI) for regular treatment of asthma for adults and adolescents when the use of a combination product (an inhaled corticosteroid and long-acting β -agonist) is appropriate.
- Clinical trial results indicate that the efficacy of the fluticasone/formoterol combination over 8–12 weeks is greater than that of fluticasone or formoterol alone and noninferior to that of combination products containing fluticasone/salmeterol and budesonide/formoterol.
- The safety and tolerability of fluticasone/formoterol was demonstrated for the 250/10 μ g and 100/10 μ g doses administered twice daily for up to 1 year.
- Advantages of the fluticasone/formoterol combination aerosol include rapid onset of bronchodilation and a high fine-particle fraction that is consistent at different flow rates in laboratory testing.
- The fluticasone/formoterol combination is an efficacious option for patients requiring an inhaled corticosteroid and long-acting β -agonist in combination for their asthma, particularly for those already accustomed to a pMDI and using reliever therapy via pMDI.

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• of interest

•• of considerable interest

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