

The combination of fluticasone furoate and vilanterol trifenate in the management of asthma: clinical trial evidence and experience

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Abstract: The treatment of persistent asthma has been aided by the recent approval of new medications. The combined inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) powder inhaler fluticasone furoate (FF)/vilanterol trifenate (VI) is one of these new agents, which was recently approved as a maintenance therapy for persistent asthma. This once-daily ICS/LABA inhaler has previously been approved and used in chronic obstructive pulmonary disease as a maintenance therapy. Both FF and VI individually have been shown to have efficacy in the treatment of persistent asthma; the combination of FF/VI at the dose of 100/25 μg daily improves trough peak expiratory flows and forced expiratory volume in 1 s. It also reduces the frequency of asthma exacerbations in patients with persistent asthma. The once-daily dosing is well tolerated, with limited clinically significant adverse events; the once-daily inhaled dosing regimen should also improve medication adherence. The data supporting the use of the FF/VI inhaler in persistent asthma are reviewed. The dry powder inhaler of FF/VI (100/25 μg) is an effective and well tolerated once-daily maintenance treatment for patients with persistent asthma.

Keywords: combined inhaler, fluticasone furoate/vilanterol trifenate, inhaled corticosteroid, long-acting β_2 agonist, persistent asthma, powder inhaler

Background

The syndrome of asthma is a variable clinical disorder associated with chronic airway inflammation, recurrent symptoms including wheezing, coughing, chest tightness, dyspnea and airway hyperresponsiveness (AHR). Asthma differs from the syndrome of chronic obstructive pulmonary disease (COPD) based on age of onset, tobacco/biomass exposure, variable presence of chronic bronchitis symptoms and the potential presence of emphysema with nonreversible or partially reversible airway obstruction. The asthma–COPD overlap syndrome (ACOS) recognizes a phenotype of patients with obstructive airway disease that overlaps the syndromes of asthma and COPD [Louie *et al.* 2013; GINA, 2015; GOLD, 2015]. The wide variety of asthma syndrome phenotypes has provided treatment challenges. Despite many drug categories available for the treatment of asthma, it often remains difficult for

both the clinician and patient, and expensive, with an incremental direct cost of \$3259 (in 2009 US dollars) per person per year [Barnett and Nurmagambetov, 2011]. The 2015 updated Global Initiative for Asthma (GINA) provides a comprehensive guideline for the recognition and treatment of the various phenotypes of asthma [GINA, 2015]. This paper reviews the literature supporting the use of the once-daily, combined dry powder inhaler fluticasone furoate (FF) and vilanterol trifenate (VI) in the maintenance treatment of asthma.

Medication adherence in chronic diseases

Medication ‘adherence’ has been defined as the extent to which a patient follows medical plans, including taking medications and lifestyle modifications [Shams and Fineman, 2014]. This implies a mutual consent between patient and provider as

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Table 1. Factors contributing to nonadherence of asthma medications.

Previous medication exposure
Dosing frequency and regimen complexity (including polypharmacy)
Route of medication (poor inhaler technique)
Reduced medical knowledge or disease understanding
Reduced general intelligence
Preference for natural or nonpharmacological treatments
Psychopathology
Patient perception
Travel inconvenience (distance to specialist)
Long waiting times at clinic/pharmacy
Psychological outlook of patient regarding their disease
Medication side effects (cost-benefits analysis)
Medication cost/lack of insurance coverage
Improper technique
Caregiver-related factors
Relationship to patient (lack of trust)
Patient with lack of sense of control
Cultural, social, and economic barriers
Patients with difficulty understanding written directives
Lack of well written and understandable treatment plans

Based on Bender *et al.* [1997]; Kelloway *et al.* [1994]; Coutts *et al.* [1992]; Ingersoll and Cohen [2008]; Kang *et al.* [2013]; Zeiger *et al.* [2015]; McFadden [1995].

opposed to medication ‘compliance’ which is more about the patient following the physician’s ‘instructions, prescriptions and proscriptions’ [Shams and Fineman, 2014]. There are many reasons for medication nonadherence and these are summarized in Table 1.

Rates of medication nonadherence have ranged from 30% to 70% among patients with asthma, and nonadherence has been associated with poor health outcomes [Lindsay and Heaney, 2013a]. A dosing frequency and medication adherence study in patients with chronic diseases (excluding human immunodeficiency virus, psychiatric illness, cancer and organ transplant) showed that the percentage of adherence rates for all regimens dosed more frequently than once daily were significantly lower compared with once-daily regimens [Coleman *et al.* 2012]. Compared with once-daily medication adherence, the rates for twice daily, three times daily and four times daily for actual taking of the drug were reduced respectively by -6.7%, -13.5% and -19.2%, and for regimen adherence were reduced respectively by -13.1%, -24.9% and -23.1% [Coleman *et al.* 2012]. A review of the literature evaluating medication adherence in chronic diseases also found that dose frequency and regimen complexity

emerged as important predictors of medication adherence [Ingersoll and Cohen, 2008]. In two studies of patients with asthma, oral montelukast once daily demonstrated better overall medication adherence than twice-daily inhaled corticosteroids (ICS). In the first trial ICS were used less than prescribed on 49.5% of the days in the double-blind (DB) phase and 57.5% less during the open-label (OL) phase compared with 22.5% less during the DB phase and 28.6% less during the OL phase for once-daily oral montelukast ($p < 0.0001$) [Rand *et al.* 2007]. The second trial compared twice-daily ICS with once-daily oral montelukast in economically disadvantaged African American youths with asthma [McNally *et al.* 2009]. Medication adherence was, on average, higher ($p < 0.01$) with oral once-daily montelukast (40.9%) compared with twice-daily fluticasone propionate (FP) (33.9%). However, after a year of study, significantly low medication adherence rates were seen with both drugs, with only 31% adherence to prescribed doses of once-daily oral montelukast and 23% adherence to twice-daily ICS FP being found [McNally *et al.* 2009]. Nonadherence to asthma treatment is associated with poor baseline asthma control, increased frequency of exacerbations and asthma-related hospitalizations [Lindsay and Heaney, 2013]. When

frequencies of ICS dosing are directly compared in patients with asthma, the use of once-daily mometasone furoate dry powder inhaler measured by an automatic dose counter was significantly better ($p < 0.001$) than the same drug given twice daily (93.3% *versus* 89.5%) in a 12-week OL trial in 1233 patients with asthma [Price *et al.* 2010]. Higher rates of medication adherence were self reported, and health-related quality of life improved by 20% in patients receiving once-daily ICS compared with a 14% improvement in those receiving twice-daily ICS [Price *et al.* 2010]. Frequency of dosing appears to be an important variable in determining asthma medication adherence. Asthma medication adherence is greater with ICS combined with a long-acting β_2 agonist (LABA) than it is with ICS alone [Feehan *et al.* 2015].

The use of LABAs for asthma

Controversy surrounding the use of LABAs for asthma has existed for some time now. It centers on the role of the use of inhaled LABAs in the treatment of patients with asthma. As early as 1989, the results of a case controlled trial from New Zealand suggested an increase in mortality when the short-acting β_2 agonist (SABA) fenoterol was used in patients with asthma [Crane *et al.* 1989; Spitzer *et al.*, 1992]. Other large studies failed to find increased mortality in patients with asthma over 16 weeks with the LABA salmeterol (SAL) or SABA salbutamol [Castle *et al.* 1993]. Tolerance and lack of toxicity to the LABA SAL was reported in a small study of patients with mild asthma [Cheung *et al.* 1992]. In contrast, the SMART Trial (the Salmeterol Multicenter Asthma Research Trial) evaluated the use of the LABA SAL metered-dose inhaler (MDI) twice daily *versus* placebo MDI in 26,355 patients with asthma [Nelson *et al.* 2006]. Combined asthma-related deaths or life-threatening experiences showed a small but significant increase in total numbers, 37 with SAL *versus* 22 with placebo, giving a relative risk (RR) of 1.71 [95% confidence interval (CI) 1.01–2.89] for SAL *versus* placebo. The majority of the imbalance or negative effect was mostly associated with the African-American subjects compared with the white subjects [Nelson *et al.* 2006]. This and other study results have generated a ‘black-box’ warning for the use of all LABA agents in the treatment of patients with asthma by the US Food and Drug Administration (FDA). Despite this small increased risk, the use of LABA agents in

combination with ICS is included in the current international GINA guidelines for the treatment of adults with persistent asthma symptoms [GINA, 2015]. The concomitant use of an inhaled LABA with an ICS may mitigate the increased risk of LABA use in patients with asthma. It is unclear whether this finding applies to all subpopulations with asthma [Weatherall *et al.* 2010]. A review of the addition of inhaled LABA to ICS as first-line therapy for persistent asthma in steroid-naïve adults and children did not find that combination therapy (LABA/ICS) reduced the risk of asthma exacerbations requiring oral corticosteroids over that with just ICS [Ni Chroinin *et al.* 2009]. However, the combination of LABA/ICS significantly improved lung function and reduced symptoms and the need for rescue SABA use compared with ICS alone [Ni Chroinin *et al.* 2009]. A recent large study of up to 78 weeks in 2019 patients with asthma aged 12 years or over who had had at least one asthma exacerbation in the previous year showed a reduced risk of exacerbations and improved lung function with a combined ICS/LABA compared with just an ICS [Bateman *et al.* 2013]. There were only two deaths in the ICS alone group (pneumonia and cancer) and one in the ICS/LABA combination inhaler group (automobile accident). Patient-tailored, guideline-informed use of LABAs in asthma can significantly improve outcomes when combined with ICS use.

Inhaled FF in the treatment of asthma

Inhaled FF was shown to have longer lung retention time than FP [Allen *et al.* 2013a]. The efficacy of once-daily inhaled FF in asthma has been demonstrated in several randomized and placebo-controlled trials (Table 2). The threshold of effect for inhaled FF appears to be around 50 μg once daily when given in the evening [O’Byrne *et al.* 2014b]. Doses of inhaled once-daily FF at 800 μg appear to be associated with an increase in frequency of adverse events [Busse *et al.* 2014]. In addition to pairing FF with a LABA, which will be discussed further later, FF combined with the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC) has been studied in asthma. In a dose-ranging study, FF (100 μg) combined with UMEC (31.25, 62.5 and 250 μg) once daily improved trough forced expiratory volume in 1 s (FEV_1) compared with FF (100 μg) alone given once daily in adults with asthma [Lee *et al.* 2015]. A separate study by the same group suggested that a combined once-daily inhaler of FF (100 μg)/UMEC (250 μg)

Table 2. Major clinical trials using inhaled fluticasone furoate in asthma.

Type of study	Number of patients	Design	Outcomes	Conclusions	Reference
1. R, DB, MC, PC	598	FF (20, 50, 100 or 200 µg) daily <i>versus</i> P daily × 8 weeks	FF 50–200 µg improved FEV ₁ from baseline	FF 50–200 µg demonstrated dose–response improvement with 100–200 µg being the optimal doses	[Bateman <i>et al.</i> 2012]
2. R, DB, MC, PC	646	FF (200 or 400 µg) once each morning, FF (200 or 400 µg) once each evening or FF (200 µg) twice daily <i>versus</i> P × 8 weeks	All doses of FF significantly improved trough FEV ₁ compared with P; FF 400 µg once each evening and FF 200 µg twice daily had similar efficacy	Excellent tolerability without significant AEs. Both FF (200 or 400 µg) were more effective than P in improving trough FEV ₁ ; FF 200 µg twice daily = FF 400 µg	[Woodcock <i>et al.</i> 2011a]
3. R, DB, X, MC, PC	190	FF (100 µg) twice daily, FF (200 µg) daily, FP (100 µg) twice daily, FP (200 µg) daily or P, × 3–28 day periods with crossover design	FF (200 µg) daily was noninferior to FF (100 µg) twice daily in improving trough FEV ₁ . All FF and FP doses were superior to P in improving trough FEV ₁	No significant AEs; FF (200 µg) daily was more effective than P and not inferior to the same twice daily dose	[Woodcock <i>et al.</i> 2011b]
4. R, DB, MC, PC	627	FF (200, 400 600 or 800 µg) once each evening or FP (500 µg) twice daily <i>versus</i> P once each evening, × 8 weeks	All doses of once-daily FF and twice-daily FP were significantly superior to P in improving trough FEV ₁ . Oral candidiasis was higher with FF (800 µg) than P	FF doses < 800 µg have a favorable therapeutic index. Doses of 200 µg daily appear appropriate	[Busse <i>et al.</i> 2012]
5. R, DB, DD, PG, MC, PC	575	FF (100 µg) once each morning or FF (100–250 µg) once each evening or P once each morning or once each evening, × 4 weeks	All doses and times of FF statistically improved the PEF compared with P. No study drug AEs seen	FF 100 µg once each morning or once each evening appeared to give comparable improvement in PEF compared with P given once each morning or once each evening	[Medley <i>et al.</i> 2012]
6. R, DB, DD, MC, PC	343	FF (100 µg) once each evening, FP (250 µg) twice daily or P twice daily	Both once daily FF and twice daily FP significantly improved predose FEV ₁ at 24 weeks compared with P. On treatment asthma exacerbations were FF (3%), FP (2%) and both were lower than P (7%)	FF (100 µg) once each evening resulted in improved FEV ₁ comparable to that seen with FP (250 µg) twice daily with a similar safety profile	[Lotvall <i>et al.</i> 2014b]
7. R, DB, MC, PG	239	FF (100 µg) once each evening, FF (200 µg) once each evening, × 24 weeks	Both FF doses resulted in significant increases in trough FEV ₁ from baseline	Both doses of FF resulted in improved trough FEV ₁ compared with baseline	[Woodcock <i>et al.</i> 2014]
8. R, DB, DD, PG, MC, PC	351	FF (50 µg) once each evening, FP (100 µg) BID or P BID, × 24 weeks	No significant improvement in trough FEV ₁ with FF (50 µg) once each evening was seen but the improvement was significant with FP (100 µg) twice daily	FP (100 µg) twice daily but not FF (50 µg) once each evening improved through FEV ₁	[Busse <i>et al.</i> 2014]
9. R, DB, PG, MC, PC	248	FF (50 µg) once each evening or P once each evening, × 12 weeks	A significant increase in trough FEV ₁ was seen after FF (50 µg) once each evening compared with P once each evening. Significant reduction in rescue inhaler use was seen with FF compared with P. AEs <1% (FF) and 3% (P)	FP (50 µg) once each evening improved trough FEV ₁ and reduced rescue inhaler use compared with P	[O'Byrne <i>et al.</i> 2014b]

AE, adverse event; DB, double blind; DD, double dummy; FEV₁, forced expiratory volume 1 s; FF, fluticasone furoate; FP, fluticasone propionate; MC, multicenter; P, placebo; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; R, randomized; X, crossover.

was associated with a 10% increase in trough FEV₁ compared with FF (100 µg) alone [Yang *et al.* 2015]. Once-daily use of inhaled FF (≥ 100 µg) alone or in combination with a LAMA appears to provide effective treatment for patients with asthma. Preliminary trials exploring a triple inhaler with FF, UMEC combined with VI have recently been published [Brealey *et al.* 2015]. The use of once-daily FF has been shown to have efficacy in the maintenance of patients with persistent asthma.

Inhaled VI in the treatment of asthma

The use of the inhaled LABA VI has been shown to have a bronchodilator effect in patients with asthma that lasts at least 24 h, allowing once-daily dosing (Table 3). Most trials in patients with asthma with inhaled VI have been done with patients on stable doses of ICS before the addition of VI, probably because of previously discussed safety concerns regarding LABAs in the treatment of asthma [Lotvall *et al.* 2012, 2014a; Sterling *et al.* 2012]. The GINA guidelines recommend the use of LABA only with an ICS usually as a fixed dose combination product [GINA, 2015]. Two of the three major outcome trials in patients on ICS medications demonstrated significant improvement in trough FEV₁ after inhaled once-daily VI was added [Lotvall *et al.* 2012; Sterling *et al.* 2012] but one trial failed to show an improvement in trough FEV₁ after adding inhaled VI to stable ICS treatment in patients with persistent asthma [Lotvall *et al.* 2014a]. Doses greater than or equal to 12.5 µg of inhaled VI daily appeared to be needed to achieve a bronchodilator effect in patients with asthma [Lotvall *et al.* 2012]. The pharmacokinetics of VI 25 µg daily was consistent in children aged 5–11 years regardless of age or sex [Oliver *et al.* 2014b]. No significant safety issues were uncovered with inhaled VI in these trials.

Inhaled FF/VI combination in treatment of asthma

Inhaled FF/VI was FDA approved at the dose of 100/25 µg in May 2013 for the treatment of COPD based on several studies demonstrating efficacy and was not significantly different than inhaled twice daily 500/50 µg or 250/50 µg FP/SAL [Agusti *et al.* 2014; Dransfield *et al.* 2014]. In April 2015 the FDA approved powdered inhaled FF/VI (100/25 µg) for the once-daily maintenance treatment of asthma in patients 18 years of age and older [FDA, 2015].

A summary of published clinical trials of FF/VI in the treatment of asthma can be found in Table 4. Twenty-seven patients with asthma were randomized to once-daily FF (100 µg), VI (25 µg), FF/VI (100/25 µg) or placebo for 21 days and then were allergen challenged [Oliver *et al.* 2013]. The late and early asthmatic response (LAR and EAR) after allergen challenges were evaluated using weighted mean (wm) FEV₁. The combination therapy provided significant protection against EAR after allergen challenge compared with placebo or the individual components of VI or FF alone [Oliver *et al.* 2013]. Similar findings were found with LAR, except the improvement with combined FF/VI was statistically significant only when compared with placebo and with VI alone. A similar larger study (52 patients with mild asthma) compared FF/VI (100/25 µg) with placebo or FF (100 µg). In this study, all drugs were given once daily in the evening for 28 days. EAR was evaluated after inhaled allergen challenge using the wm FEV₁ as the outcome measure [Oliver *et al.* 2012]. Both FF alone and the combination of FF/VI significantly protected against EAR as measured by change in FEV₁ after allergen challenge compared with placebo at 23 h after the last dose. Similarly, LAR was significantly modified by FF/VI compared with placebo or FF alone. FF/VI has been shown in small studies to protect against inhaled allergen challenge.

In a randomized, DB repeated-dose, two-way crossover study in 26 children aged 5–11 years with asthma, treatment included once-daily FF/VI (100/25 µg) or FF (100 µg) by inhalation for 14 days followed by a 7-day washout period before crossover. The trial lasted a total of 11 weeks [Oliver *et al.* 2014a]. The primary endpoints were peak expiratory flow rates (PEFs), blood pressure, clinical laboratory measurements, maximum heart rate and electrocardiogram (EKG) parameters. Secondary endpoints included pharmacokinetic and pharmacodynamic properties. No clinically significant difference was found in the primary endpoints between FF/VI and FF. The combination dosing of FF/VI was well tolerated and no significant differences were seen in the pharmacokinetic or pharmacodynamics of FF. No adverse events were judged to be serious or treatment related [Oliver *et al.* 2014a] in this pediatric population.

A series of efficacy trials with inhaled once-daily FF/VI were reported in patients aged 12 years and over with persistent asthma. A moderately

Table 3. Major clinical trials using inhaled vilanterol trifenate in asthma.

Type of study	Number of patients	Design	Outcomes	Conclusions	Reference
1. R, DB, MC, X, PC	201	(patients with asthma, healthy subjects and patients with COPD) VI (6.25, 25, 50 or 100 µg) daily <i>versus</i> P daily, × 14 days	No changes in EKG, glucose, potassium levels. All doses resulted in improved FEV ₁ for up to 24 h in patients with asthma or COPD	VI well tolerated and improved FEV ₁ for 24 h	[Kempford <i>et al.</i> 2013b]
2. R, DB, MC, PC	614	Patients with asthma on an ICS given VI (3, 6.25, 12.5, 25 or 50 µg) once each evening or P once each evening, × 28 days	Statistically significant VI dose–response effect seen with trough FEV ₁ compared with P. Well tolerated, <2% AEs (tremor, palpitations and glucose or potassium effects)	Once daily inhaled VI doses (12.5–50 µg) resulted in prolonged bronchodilator for at least 24 h	[Lotvall <i>et al.</i> 2012]
3. R, DB, X, MC, PC	75	Patients with asthma patients treated with VI (6.25, 12.5 or 25 µg) once each evening or VI (6.25 µg) twice daily or P once each evening, × 7 days	All VI doses showed statistically significant increases in trough FEV ₁ compared with P. Dose-dependent once-daily VI effect seen. Low incidence of AEs. The VI dose (6.25 µg) twice daily and VI (12.5 µg) once each evening had similar changes in trough FEV ₁	Once-daily inhaled VI appears to be an effective bronchodilator in patients with asthma	[Sterling <i>et al.</i> 2012]
4. R, DB, MC, PC	347	Patients with asthma on ICS given VI (25 µg) once each evening or SAL (50 µg) twice daily <i>versus</i> P twice daily, × 12 weeks	Improvement seen in trough FEV ₁ in all three groups, VI (359 ml), SAL (283 ml) and P (289 ml): all well tolerated	Study failed to show a bronchodilator effect difference with either SAL or VI compared with P because of a large placebo effect	[Lotvall <i>et al.</i> 2014a]
5. R, DB, MC, PC, X	28	Patients with asthma aged 5–11 years on ICS treated with P or VI (25 µg) × 1 then 7-day washout then once each morning × 7 days then cycle repeated but with other drug. AEs, pharmacodynamics and pharmacokinetics were followed	AEs in 33% with VI and 23% P. No serious AEs. No age-related change in pharmacokinetics. No clinically relevant changes in heart rate, QTc, glucose or potassium	VI well tolerated and the pharmacokinetic profile of VI was not age or sex dependent in these children	[Oliver <i>et al.</i> 2014b]

AE, adverse event; COPD, chronic obstructive lung disease; DB, double blind; EKG, electrocardiogram; FEV₁, forced expiratory volume 1 s; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; MC, multicenter; P, placebo; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; QTc, corrected QT interval; R, randomized; SAL, salmeterol; VI, vilanterol; X, crossover.

large randomized, double-blind (DB), double-dummy, parallel group study of 806 patients demonstrated FF/VI (100/25 µg) once daily in the evening was similar to FP/SAL (250/50 µg) given twice daily in improving lung function [Woodcock *et al.* 2013] and no safety issues were noted. A similar comparative study evaluated FF/VI (200/25 µg) once daily for 24 weeks in 587 patients with asthma aged 12 years and over

[O’Byrne *et al.* 2014a]. This study used change from baseline in trough *wm* FEV₁ as the primary endpoint. The secondary endpoints included percentage change in rescue inhaler use (rescue-free 24 h periods), symptom-free 24 h periods, and Asthma Quality of Life Survey (AQLS) scores. In this study, once-daily FF/VI significantly improved trough FEV₁ and *wm* FEV₁ *versus* once-daily FF or twice-daily FP. Significantly

Table 4. Major clinical trials using combined inhaled fluticasone furoate/vilanterol trifenatate in patients with asthma.

Type of study	Number of patients	Design	Outcomes	Conclusions	Reference
1. DB, R, PC, X, MC	52, aged 18–65 years	P <i>versus</i> FF 100 µg <i>versus</i> FF/VI 100/25 µg daily once each evening, × 28 days then challenged against inhaled allergen and EAR on FEV ₁	Both FF 100 µg and FF/VI 100/25 µg daily provided significant protection in EAR using FEV ₁ changes 2 h after allergen challenge compared with P	FF and FF/VI daily provide reactive airway protection against EAR in subjects with mild asthma	[Oliver <i>et al.</i> 2012]
2. DB, R, DD, MC	503, aged ≥ 12 years already on ICS	Daily FF/VI 100/25 µg <i>versus</i> FF/VI 200/25 µg <i>versus</i> FP 500 µg twice daily, followed adverse events for 52 weeks	Oral candidiasis was more common with FF/VI (6–7%) <i>versus</i> FP (3%). 12 serious AEs with one thought to be drug related seen (FP, worsening hepatitis B). Small but significant increase in cortisol suppression with FP compared with FF/VI at weeks 12 and 28 but not week 52	FF/VI 100/25 µg daily was well tolerated	[Busse <i>et al.</i> 2013]
3. DB, R, DD, MC	806, aged ≥ 12 years with persistent asthma	FF/VI 100/25 µg daily once each evening <i>versus</i> FP/SAL 250/50 µg twice daily, wm FEV ₁ after 24 weeks	0–24 h wm FEV ₁ improved by both FP/VI (341 ml) and FP/SAL (377 ml), NS different. No difference in QOLS, exacerbation rate or urinary cortisol excretion	FF/VI 100/25 µg once each evening was similar to FP/SAL 250/25 µg twice daily. No safety issues identified	[Woodcock <i>et al.</i> 2013]
4. DB, R, PC, X	26, aged 18–70 years	FF/VI 100/25 µg daily once each morning or once each evening <i>versus</i> P daily for 14 days. The wm FEV ₁ was followed	Compared with P, the difference in wm FEV ₁ for morning was 337 ml (95% CI 293–463 ml) and for evening dosing was 422 ml (95% CI 337–507). The difference in improvement between once each morning and once each evening wm FEV ₁ was –49 ml (95% CI –125 to 36 ml)	FF/VI 100/25 µg daily improved wm FEV ₁ with comparable improvement between once each morning <i>versus</i> once each evening dosing	[Kempford <i>et al.</i> 2013c]
5. DB, R, PC, X	27, aged 18–65 years	FF/VI 100/25 µg, FF 100 µg, VI 25 µg and P all given daily were compared using FEV ₁ evaluating both EAR and LAR to allergen challenge, AHR was measured 1 h post dose on day 21 using methacholine challenge	Compared with P, FF/VI, FF and VI all reduced the reduction in EAR (decrease in FEV ₁) after allergen challenge. Similar LAR response was measured by wm FEV ₁ which showed all therapies better than P with FF/VI showing the least decrease. FF/VI showed the best protection when AHR was evaluated after allergen challenge and methacholine challenge	FF/VI provided additive protection against allergic reactions in FEV ₁ in EAR, in wm FEV ₁ in LAR and in AHR with methacholine challenge	[Oliver <i>et al.</i> 2013]
6. DB, R, DD, MC	587, aged ≥ 12 years	FF/VI 200/25 µg daily, FF 200 µg daily or FP 500 µg twice daily for 24 weeks co endpoints were trough FEV ₁ and wm FEV ₁ . AQLS and safety also monitored	FF/VI significantly improved trough FEV ₁ and wm FEV ₁ compared with FF or FP alone. No difference in AQLS, EKG, vital signs or 24 h urinary cortisol seen	High-dose FF/VI resulted in statistically significant improvement in lung function compared with FF or FP alone	[O'Byrne <i>et al.</i> 2014a]

(Continued)

Table 4. (Continued)

Type of study	Number of patients	Design	Outcomes	Conclusions	Reference
7. DB, R, MC	2019, aged \geq 12 years with at least one recorded asthma exacerbation in the last year	FF/VI 100/25 μ g daily <i>versus</i> FF 100 μ g daily were evaluated for time to first asthma exacerbation and change in trough FEV ₁ for minimum of 24 weeks and up to 72 weeks	Compared with FF alone, FF/VI delayed time to first exacerbation HR 0.795 (95% CI 0.642–0.9850). Significantly greater trough FEV ₁ seen with FF/VI.	Once-daily FF/VI reduced the risk of asthma exacerbation compared with FF alone	[Bateman <i>et al.</i> 2014]
8. DB, R, X	26, aged 5–11 years	FF/VI 100/25 μ g or FF 100 μ g daily \times 14 days followed by a 7-day washout period then switched to other treatment \times 14 days. Primary endpoints were AEs	No clinically significant AEs or clinical laboratory, EKG or vital sign changes reported	No serious AEs with FF/VI or FF in pediatric population were found	[Oliver <i>et al.</i> 2014a]
9. DB, R, MC	609, aged \geq 12 years with persistent asthma	FF/VI 100/25 μ g, FF 100 μ g or P once each evening \times 12 weeks. Trough FEV ₁ and wm FEV ₁ were the coprimary endpoints. Rescue-free 24 h periods and safety were also assessed	An increase in trough FEV ₁ (196 ml) and wm FEV ₁ (212 ml) were seen with P. Compared with P, FF/VI and FF both had further significantly increased trough FEV ₁ (respectively, 172 and 136 ml). Similarly, wm FEV ₁ increased with FF/VI by 301 and 186 ml with FF compared with P. Rescue-free 24 h periods were increased 10.6% with FF/VI compared with FF and 19.3% compared with P. Statistically significant ($p = 0.032$) increase in urinary cortisol suppression was seen in the FF/VI group relative to P	Significant lung function improvement was seen with both FF/VI and FF compared with P. High P effect was noted and may have been a confounder	[Bleecker <i>et al.</i> 2014]
10. DB, R, DD, MC	309, > 12-year-old Asian patients with persistent asthma uncontrolled with high-dose ICS or mid-dose ICS/LABA	FF/VI 200/25 μ g once each evening <i>versus</i> FP 500 μ g twice daily \times 12 weeks. Primary endpoint was change in daily evening PEF with secondary endpoints of daily morning PEF, AQLS change and the number of rescue-free 24 h periods	Evening PEF 28.5 liter/min greater with FF/VI compared with FP ($p \leq 0.001$). No differences in rescue-free 24 h periods were noted	FF/VI improved evening PEF compared with FP in Asian populations.	[Lin <i>et al.</i> 2015]
11. DB, PC, R, X	16, healthy Chinese subjects aged 18–45 years	FF/VI 50/20 μ g, FF/VI 100/25 μ g, FF/VI 200/25 μ g or P once each morning \times 7 days. Pharmacodynamic endpoints of wm serum cortisol level, wm QTc and potassium levels were monitored	wm serum cortisol level reductions of 15% and 25% seen with FF/VI 100/25 μ g and 200/25 μ g <i>versus</i> P. Minor increase (<10 ms) in maximum QTc was seen with FF/VI 50/25 μ g and FF/VI 200/25 μ g, F accumulation ranged from 38% to 54% at day 7 compared with day 1 for FF/VI doses of 50/25 μ g to 200/25 μ g	In daily doses of FF/VI from 50/25 μ g to 200/25 μ g, nonclinically significant β -adrenergic pharmacodynamic effects were seen. Serum cortisol levels were decreased 15–25% over 7 days and were well clinically tolerated	[Chen <i>et al.</i> 2015]

(Continued)

Table 4. (Continued)

Type of study	Number of patients	Design	Outcomes	Conclusions	Reference
12. DB, R, MC	1039, \geq 12 years old with persistent asthma	FF/VI 100/25 μ g <i>versus</i> FF 100 μ g and FF/VI 100/25 μ g <i>versus</i> FF/VI 200/25 μ g \times 12 weeks with the primary endpoint of wm FEV ₁ and secondary endpoints of trough FEV ₁ and rescue-free 24 h periods were used	Compared with FF 100 μ g, FF/VI 100/25 μ g significantly ($p \leq 0.001$) improved wm FEV ₁ , trough FEV ₁ ($p = 0.014$), and % rescue-free 24 h periods ($p < 0.001$). The higher dose of FF/VI 200/25 μ g produced only small numerical improvements over the FF/VI 100/25 μ g dose. The incidences of AEs were similar across all groups	The use of FF/VI 100/25 μ g provides significant improvements over FF 100 μ g. Only small further improvement is seen with FF/VI 200/25 μ g	[Bernstein <i>et al.</i> 2015]

AE, adverse event; AHR, airway hyper responsiveness; AQLS, asthma quality of life survey; AE, adverse event; CI, confidence interval; DB, double blind; DD, double dummy; EAR, early asthmatic response; FEV₁, forced expiratory volume 1 s; FF, fluticasone furoate; FP, fluticasone propionate; HR, hazard ratio; LAR, late asthmatic response; MC, multicenter; NS, nonsignificant; P, placebo; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; QTc, corrected QT interval; R, randomized; wm, weighted mean; VI, vilanterol; X, crossover.

more 24 h periods without use of rescue medication and without symptoms were reported with FF/VI compared with FF alone [O'Byrne *et al.* 2014a]. No difference in AQLS scores or adverse events were noted. Using the endpoints of severe exacerbations in asthma, a study of 2019 patients greater than 12 years old who had at least one recorded exacerbation within the prior year found that once-daily FF/VI (100/25 μ g) significantly delayed the time to the first asthma exacerbation and reduced the rate of annualized severe exacerbations compared with FF (100 μ g) once daily [Bateman *et al.* 2014]. The study also found improved trough FEV₁ with FF/VI compared with FF alone with no difference in adverse event rates. Similar findings were reported in a study of 609 patients with asthma aged 12 years and over when FF/VI (100/25 μ g) once daily was compared with placebo and FF (100 μ g) once daily [Bleecker *et al.* 2014]. FF/VI and FF both showed significant improvement in both trough FEV₁ and wm FEV₁ compared with placebo. In a recent trial, 1039 patients aged 12 years and over with persistent asthma were randomized to once-daily FF/VI (100/25 μ g), FF (100 μ g) or FF/VI (200/25 μ g) for over 12 weeks [Bernstein *et al.* 2015]. Compared with FF (100 μ g) alone, FF/VI (100/25 μ g) significantly improved wm FEV₁, trough FEV₁, % time rescue inhalers used, % time symptom free, and morning and evening PEFs. Little further improvement was seen at the higher dose of FF/VI (200/25 μ g) [Bernstein *et al.* 2015]. Examining 309 Asian patients with asthma

aged 12 years and over, Lin and colleagues found that FF/VI (200/25 μ g) once daily provided statistical improvements in morning and evening PEFs, symptom-free days and AQLS scores compared with twice-daily FP (500 μ g) [Lin *et al.* 2015]. Together, these studies provide strong evidence of the efficacy of FF/VI in the maintenance treatment of asthma.

Tolerability of inhaled FF/VI

When FF/VI (100/25 μ g) was dosed once daily in the morning and compared with once daily in the evening, comparable improvement in lung function was seen in patients with persistent asthma [Kempsford *et al.* 2013c]. A 52-week trial focusing on safety and tolerability was performed in patients with asthma aged 12 years and over who were treated with either once-daily FF/VI (100/25 or 200/25 μ g) or FP (500 μ g) twice daily [Busse *et al.* 2013]. Statistically significant greater cortisol suppression was seen with FP compared with both doses of FF/VI at weeks 12 and 28, but not at week 52. No clinically important changes in nonfasting glucose, potassium, corrected QT intervals on EKG or ophthalmic assessments were reported at week 52. The lack of significant changes in corrected QT intervals was also seen with FF/VI (200/25 μ g) in a study of 85 healthy volunteers [Kempsford *et al.* 2014]. In these same patients, moxifloxacin alone, given orally, increased corrected QT intervals greater than 10 ms 1–8 h after ingestion. Supratherapeutic doses

Table 5. Adverse effects of fluticasone furoate/vilanterol trifenate inhalation.

In decreasing frequency:
Headache
Upper respiratory infection
Nasopharyngitis
Oropharyngeal candidiasis
Back pain
Pyrexia
Cough
Respiratory tract infection
Oropharyngeal pain/dysphonia
Extrasystoles
Other adverse effects:
Decreased cortisol level/adrenal suppression
Worsening hepatitis B
Hemoptysis
Epistaxis
Similar rates tended to be seen in adverse events for FF/VI as in FF, VI and FP alone. Based in part on Busse <i>et al.</i> [2013] and Syed [2015].
FF, fluticasone furoate; FP, fluticasone propionate; VI, vilanterol.

of FF/VI (800/100 µg) in the same study also demonstrated a small transient increase in the corrected QT interval. Small increases in heart rate 10 min after the last dose during week 52 were seen with FF/VI (100/25 µg) (3.4 bpm, 95% CI 1.3–5.6, $p = 0.002$) and with FF/VI (200/25 µg) (3.4 bpm, 95% CI 1.2–5.6, $p = 0.003$) both compared with FP alone. Overall, daily mean heart rates decreased in all groups when 24 h Holter Monitor results were compared with baseline rates [Busse *et al.* 2013].

Healthy Chinese subjects were enrolled to study the pharmacodynamics and pharmacokinetics of various doses of FF/VI (50/25, 100/25 or 200/25 µg) or placebo [Chen *et al.* 2015]. Minimal and nonclinically significant β -adrenergic pharmacodynamic effects were seen with FF/VI. Inhaled daily doses of FF (200 or 800 µg) for 7 days or a single intravenous dose of FF (250 µg) showed only modestly higher serum levels in healthy East Asian subjects compared with white subjects without significant effect on cortisol levels [Allen *et al.* 2014]. Severe renal impairment had no significant effect on FF/VI pharmacokinetic or pharmacodynamic properties, while liver impairment increased FF levels and decreased serum cortisol levels [Allen *et al.* 2012].

A 12-week study of FF/VI (100/25 µg or 200/25 µg) once-daily or placebo was performed in 185 patients

with a history of asthma [Allen *et al.* 2013b]. The doses of FF/VI were found to be ‘noninferior’ to placebo in affecting the hypothalamic–pituitary–adrenal axis with no significant suppression of cortisol after 42 days. A meta-analysis on FF systemic exposure and cortisol suppression demonstrated the absorbed dose of FF correlated with reductions in serum and urine cortisol levels [Allen, 2013]. When computer modelling was used, it was suggested that clinical doses of FF less than 200 µg daily are unlikely to provide significant cortisol suppression and that supratherapeutic range doses would be required to consistently suppress cortisol levels [Allen, 2013]. A study of 48 healthy Japanese male subjects exposed to inhaled single doses of FF (200, 400 or 800 µg) and VI (25 or 12.5 µg) for 7 days found that repeat dosing of FF (200, 400 or 800 µg) reduced serum cortisol levels by 32%, 38% and 97%, respectively [Nakahara *et al.* 2013]. No significant changes in heart rate were seen in the repeated dose or single dose arm of the study. Serum cortisol levels decreased by 27% when 400 mg of oral ketoconazole was added to daily inhaled FF/VI (200/25 µg) for 11 days [Kempsford *et al.* 2013a]. Table 5 summarizes the major adverse effects associated with the use of inhaled FF/VI.

The delivery system used for the inhaled dry powder FF/VI is the ELLIPTA (GlaxoSmithKline, England) system. Using qualitative interviews, this

system was associated with high patient satisfaction and was preferred over other systems in 75 patients with COPD and asthma aged 18 years and over [Svedsater *et al.* 2013]. At the time of survey, 44 of the 75 patients were on DISKUS (GlaxoSmithKline, England) inhalers or the DISKUS and Handi-Haler (Boehringer Ingelheim, Germany) systems. The others were on metered dose inhalers or other dry-powdered inhalation systems. From these limited data, acceptance of the FF/VI dry powder once-daily inhaler delivery system appears high.

Conclusion

The dry powder inhaler of FF/VI is an effective and well tolerated once-daily maintenance treatment for patients with persistent asthma. Both FF and VI have demonstrated efficacy in asthma. The combination of FF/VI has also proven efficacy in the treatment of COPD. The once-daily dosing of FF/VI offers efficacy and increased convenience, and possible increased adherence for patients with asthma.

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