Drugs (2015) 75:407–418
DOI 10.1007/s40265-015-0354-5

ADIS DRUG EVALUATION

Fluticasone Furoate/Vilanterol: a Review of Its Use in Patients with Asthma

Yahiya Y. Syed

Published online: 4 February 2015

Abstract Fluticasone furoate/vilanterol (Relvar®) is a once-daily, fixed combination of an inhaled corticosteroid (ICS) and a long-acting β_2-adrenoreceptor agonist (LABA), delivered via a dry powder inhaler (Ellipta®). It is approved for the treatment of asthma in the EU and Japan, and is the first once-daily ICS/LABA to be available for this indication. Fluticasone furoate is an enhanced-affinity glucocorticoid receptor agonist, with potent anti-inflammatory activity. Vilanterol produces rapid and prolonged bronchodilation. In phase III trials in adolescents and adults with various levels of asthma uncontrolled on ICS and/or ICS/LABA, fluticasone furoate/vilanterol 100/25 or 200/25 μg once daily (approved dosages in the EU) significantly improved pulmonary function compared with placebo or equivalent dosages of fluticasone furoate alone (in some trials) or fluticasone propionate. In similar trials, fluticasone furoate/vilanterol 100/25 μg once daily was as effective as fluticasone propionate/salmeterol 250/50 μg twice daily in improving pulmonary function and significantly reduced the risk of severe asthma exacerbation relative to fluticasone furoate alone. In clinical trials, fluticasone furoate/vilanterol was generally well tolerated with fewer than 15 % of patients experiencing treatment-related adverse events, the most common of which were oral/oropharyngeal candidiasis, dysphonia, extrasystoles and cough. The tolerability profile of fluticasone furoate/vilanterol was generally similar to that of fluticasone propionate/salmeterol. Thus, fluticasone furoate/vilanterol is an effective and generally well tolerated ICS/LABA option for the treatment of uncontrolled asthma.

Fluticasone furoate/vilanterol (Relvar® Ellipta®) in the treatment of asthma: a summary

Fixed combination of an inhaled corticosteroid (ICS) [fluticasone furoate] and a long-acting β_2-adrenoreceptor agonist (vilanterol)
Convenient once-daily administration
Fluticasone furoate has enhanced affinity for the glucocorticoid receptor compared with other ICS agents and a longer retention time than fluticasone propionate in respiratory tissues
Vilanterol produces rapid and sustained bronchodilation
Significantly improves pulmonary function versus placebo or equivalent dosages of fluticasone furoate or fluticasone propionate, and reduces the risk of severe asthma exacerbation versus fluticasone furoate
As effective as twice-daily fluticasone propionate/salmeterol
Generally well tolerated, with a tolerability profile similar to that of twice-daily fluticasone propionate/salmeterol

The manuscript was reviewed by: ***A. Bodzenta-Lukaszyk***, Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland; ***M. Cazzola***, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy; ***A. H. Mansur***, Respiratory Department, Birmingham Heartlands Hospital, Birmingham, United Kingdom.

Y. Y. Syed (✉)
Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand
e-mail: demail@springer.com

1 Introduction

British Thoracic Society (BTS) treatment guidelines [1] recommend a 5-step approach for the management of asthma, with modifications in treatments and/or regimens to meet the need for different age groups: short-term reliever therapy with an inhaled short-acting β_2-adrenoreceptor agonist (SABA) for mild intermittent asthma (step 1), regular preventer therapy with an inhaled corticosteroid (ICS) (step 2), initial add-on therapy (step 3), increased ICS dose or addition of a fourth drug for persistently poorly controlled asthma (step 4) and finally, continuous or frequent use of oral steroids (step 5). Treatment should be started at the step most appropriate to the initial severity of the disease, and then stepped up to improve disease control and down to find and maintain the lowest controlling step [1].

At step 3, for patients aged $\geq$12 years, the first choice of treatment is the addition of an inhaled long-acting β_2-adrenoreceptor agonist (LABA) to ICS, which has been shown to improve lung function and symptoms, and decrease exacerbation [1]. When co-administered, synergistic interactions can occur between an ICS and a LABA, resulting in greater clinical efficacy compared with an ICS alone [2, 3]. For asthma, LABAs should be used only as an add-on to ICS [1]. Combination inhalers that deliver an ICS plus a LABA are recommended over two separate inhalers to ensure that the LABA is not taken alone and to improve inhaler adherence [1]. Fixed-dose ICS/LABA combinations available for asthma in the EU (fluticasone propionate/salmeterol, fluticasone propionate/formoterol, budesonide/formoterol and beclometasone/formoterol) require twice-daily dosing. However, once-daily dosing of ICS/LABA can improve treatment adherence [4] and thereby has the potential to improve asthma control.

Fluticasone furoate (an ICS) and vilanterol trifenatate (a LABA, henceforth vilanterol) are novel compounds not previously available for the treatment of asthma [5]. A once-daily, fixed-dose combination of fluticasone furoate and vilanterol (Relvar®), delivered via a dry powder inhaler (Ellipta®) is approved in the EU [2] and Japan [6] for the treatment of asthma. Currently it is the only once-daily ICS/LABA available for this indication. Fluticasone furoate/vilanterol is available in two strengths, containing predispensed doses of 100/25 and 200/25 μg per inhalation (delivered doses of 92/22 and 184/22 μg, respectively) [2]. Doses referred to throughout this review are predispensed doses. In patients with asthma, fluticasone furoate 100 and 200 μg once daily is approximately equivalent to fluticasone propionate 250 and 500 μg twice daily, respectively [2].

This article reviews the clinical efficacy and tolerability of fluticasone furoate/vilanterol in adolescents and adults with asthma, and briefly summarizes their pharmacological properties. The use of this combination in chronic obstructive pulmonary disease has been reviewed previously [7] and is outside the scope of this review.

2 Pharmacodynamic Properties

2.1 Mechanism of Action

Fluticasone furoate is a synthetic, lipophilic, trifluorinated glucocorticoid receptor agonist [2, 8, 9]. It has enhanced affinity for the glucocorticoid receptor compared with other ICS agents [8, 9]. As reviewed earlier [7], fluticasone furoate shares some structural similarities with fluticasone propionate, but the two drugs have distinct physiochemical and pharmacological properties [8, 9]. The 17-α furoate ester occupies the lipophilic 17-α pocket on the glucocorticoid receptors more completely than dexamethasone or fluticasone propionate, which is likely the reason for the enhanced glucocorticoid receptor binding of fluticasone furoate [9]. In vitro, human lung glucocorticoid receptor binding kinetics of fluticasone furoate showed a fast association and slow dissociation, resulting in a higher relative receptor affinity than all other commonly used topical glucocorticoids, including fluticasone propionate [10]. In vitro, fluticasone furoate has a longer retention time in respiratory tissues than fluticasone propionate [8].

Although the precise anti-asthmatic action of fluticasone furoate is not known, it showed potent activity against the synthesis, release and activitiy of inflammatory cytokines [8, 11, 12]. For example, fluticasone furoate inhibited the nuclear factor-κB pathway and tumour necrosis factor-α release, and activated the glucocorticoid response element pathway, which plays a role in protecting respiratory epithelial cells from inflammation-mediated damage and enhancing the repair potential of damaged cells [8]. Fluticasone furoate has also demonstrated potent anti-inflammatory activity in the rat model of ovalbumin-induced respiratory allergic eosinophilia [8].

The LABA vilanterol is highly selective for β_2-adrenoreceptors and has 24-h activity [13, 14]. Activation of β_2-adrenergic receptors by LABAs such as vilanterol leads to relaxation of bronchial smooth muscle cells, causing bronchodilation [15]. This action, at least in part, results from stimulation of intracellular adenylate cyclase, which catalyzes the conversion of adenosine triphosphate to cyclic 3′-5′-cyclic adenosine monophosphate, which in turn activates protein kinase resulting in smooth muscle relaxation [15]. In vitro, vilanterol has greater affinity and selectivity for the β_2-adrenoreceptor than formoterol, and greater intrinsic β_2-adrenergic agonist activity, faster onset

of activity and longer duration of action than salmeterol [13]. In patients with asthma, inhaled vilanterol produced a statistically significant increase in forced expiratory volume in 1 s (FEV_1) versus placebo as early as 5 min post-dose and this was sustained for 24 h [16].

2.2 Pulmonary and Bronchoprotective Effects

Results from dose-ranging trials showed that fluticasone furoate 100 or 200 μg and vilanterol 25 μg provided an optimal balance between therapeutic effect [improvement over baseline in pre-dose evening (trough) FEV_1] and tolerability in patients with various levels of asthma severity [14, 17–20]. Furthermore, fluticasone furoate 200 μg once daily was non-inferior to a 100 μg twice daily dosage on day 28 in improving trough FEV_1 [21] and there was no significant difference between vilanterol 12.5 μg once daily and 6.25 μg twice daily groups in 0–24 h weighted mean (wm) FEV_1 on day 7 [18], suggesting that both drugs are suitable for once-daily administration. Thus, a combination of fluticasone furoate 100 or 200 μg plus vilanterol 25 μg once daily was selected for further evaluation.

In a 14-day, double-blind, crossover study, fluticasone furoate/vilanterol 100/25 μg once daily produced similar improvements in lung function in patients with persistent asthma, regardless of whether the combination was administered in the morning or evening [22]. The placebo-adjusted mean changes from baseline in 0–24 h wm FEV_1 on day 14 were 377 and 422 mL, respectively (treatment difference −44; 90 % CI −125 to 36) [22].

Fluticasone furoate/vilanterol provided bronchoprotection against early asthmatic response (EAR), late asthmatic response (LAR) and airway hyper-responsiveness (AHR) induced by an inhaled allergen challenge in patients with mild asthma in two double-blind, crossover studies [23, 24]. In one study ($n = 52$) [24], after 28 days of once-daily administration (in the evening), both fluticasone furoate/vilanterol 100/25 μg and fluticasone furoate 100 μg significantly suppressed the EAR (as assessed by adjusted mean change in minimum FEV_1 and wm FEV_1) relative to placebo, with no significant difference evident between the active treatment groups. However, in the other study ($n = 27$) [23], after 21 days of once daily administration (between 8 a.m. and noon), fluticasone furoate/vilanterol 100/25 μg significantly suppressed the EAR relative to fluticasone furoate 100 μg in terms of minimum FEV_1 and relative to vilanterol 25 μg in terms of minimum FEV_1 and wm FEV_1. Fluticasone furoate/vilanterol also significantly suppressed both the LAR (in terms of adjusted mean change in minimum FEV_1 and wm FEV_1) and AHR relative to placebo, and significantly suppressed AHR relative to vilanterol [23].

2.3 Effect on QT Interval

In a thorough QT study, fluticasone furoate/vilanterol 200/25 μg once daily for 7 days did not significantly prolong the corrected QT (QTc) interval in healthy volunteers [25]. Fluticasone furoate/vilanterol had no clinically relevant effect on QTc interval in a large phase III trial in patients with asthma (Sect. 5.3).

3 Pharmacokinetic Properties

Key pharmacokinetic parameters of fluticasone furoate and vilanterol are summarized in Table 1. The oral bioavailability of both drugs is low because of extensive first-pass metabolism and, therefore, systemic exposure is mainly due to absorption of the inhaled dose from the lungs [2].

Inhaled fluticasone furoate appeared to exhibit absorption rate-limited pharmacokinetics, and showed a longer lung retention time than that of fluticasone propionate in healthy volunteers [26]. The lung mean absorption time for each drug was ≈7 and ≈2.1 h, respectively, and the times for 90 % absorption from the lung were 19.1–31.7 and 10.5 h [26].

In patients with asthma, a single dose of inhaled vilanterol (25–100 or 6.25–100 μg) was rapidly absorbed, reaching the maximum plasma concentration (C_{max}) in a median 10 min; concentrations then declined rapidly [16]. Systemic exposure following the 25 μg dose was generally not quantifiable beyond 1 h post-dose and increased in an approximately dose-proportional manner. With repeated administration for 14 days in healthy volunteers, vilanterol accumulated in plasma marginally (≤30 %) over the first 7 days, with no further accumulation beyond day 7 [16].

Table 1 Summary of the pharmacokinetics of fluticasone furoate and/or vilanterol [2, 43]

Parameter	Fluticasone furoate	Vilanterol
Mean absolute bioavailability (%)[a]	15.2	27.3
Mean oral bioavailability (%)[a]	1.26	<2
Time to SS (days)[b]	6	6
Mean volume of distribution of at SS (L)[c]	661	165
Mean $t_{1/2}$ (h)[a]	24[b]	2.5
Effective half-life for accumulation (h)[d]		16.0

SS steady state, $t_{1/2}$ plasma elimination half-life

[a] Following inhalation of fluticasone furoate/vilanterol

[b] Following repeat inhalation of fluticasone furoate/vilanterol once daily

[c] Following intravenous administration

[d] Following repeat inhalation of vilanterol 25 μg in patients with asthma

In vitro plasma protein binding is high for both fluticasone furoate (99.6 %) and vilanterol (93.9 %) and the extent of binding was not decreased in subjects with renal or hepatic impairment [2].

In vitro data showed that fluticasone furoate and vilanterol are primarily metabolized by the cytochrome P450 (CYP) enzyme CYP3A4 [2]. Fluticasone furoate is primarily metabolized via hydrolysis of the *S*-fluoromethyl carbothioate moiety, yielding metabolites with significantly reduced corticosteroid activity [2, 27]. Vilanterol is primarily metabolized through *O*-dealkylation, yielding a range of metabolites with significantly reduced β_1- and β_2-agonist activity [2, 28]. Following oral administration, fluticasone furoate metabolites are almost exclusively excreted in faeces (<1 % is excreted via the urine) and vilanterol metabolites are excreted in faeces and urine ($\approx$30 and $\approx$70 %) [2].

Concomitant administration of fluticasone furoate/vilanterol 200/25 μg with a strong CYP3A4 inhibitor (ketoconazole 400 mg) increased the systemic exposure [area under the plasma concentration time curve (AUC)] to fluticasone furoate and vilanterol by 36 and 65 %, respectively, in healthy volunteers [29]. While the increase in fluticasone furoate exposure resulted in a 27 % decrease in 0–24 h wm serum cortisol, the increase in vilanterol exposure did not increase β_2-agonist systemic pharmacodynamic effects on heart rate, blood potassium or QTc [29]. However, caution should be exercised when co-administering fluticasone furoate/vilanterol with strong CYP3A4 inhibitors [2]. Fluticasone furoate and vilanterol are substrates for P-glycoprotein (P-gp); however, concomitant administration with P-gp inhibitors is unlikely to alter systemic exposure to fluticasone furoate or vilanterol because both drugs are well absorbed [2].

3.1 In Special Patient Populations

Severe renal impairment (creatine clearance <30 mL/min) did not have clinically relevant effects on the pharmacokinetics of fluticasone furoate or vilanterol in patients who received fluticasone furoate/vilanterol 200/25 μg once daily for 7 days [30].

In patients with mild, moderate or severe hepatic impairment (by Child-Pugh classification) who received fluticasone furoate/vilanterol 200/25, 200/25 and 100/12.5 μg, respectively, for 7 days, dose-normalized systemic exposure (AUC from time zero to 24 h on day 7) to fluticasone furoate increased by 34, 83 and 75 %, respectively; hepatic impairment did not significantly increase systemic exposure to vilanterol [30]. In patients with moderate hepatic impairment, the increase in fluticasone furoate exposure was associated with a mean 34 % decrease in 0–24 wm mean serum cortisol. Therefore, caution should be exercised when fluticasone furoate/vilanterol is given to patients with moderate or severe hepatic impairment (see Sect. 6) [30].

Systemic exposure to fluticasone furoate after inhalation was modestly (<50 %) higher in healthy East Asian (Chinese, Korean and Japanese) subjects than in healthy Caucasians [31]. However, the increased exposure was not associated with a clinically significant effect on serum cortisol; therefore, dose adjustment is not required in East Asian subjects [31]. Similar results are reported for fluticasone furoate in East Asian, Japanese and South East Asian patients with asthma; in these patients, vilanterol C_{max} is predicted to be 220–287 % higher than in other racial groups, with no evidence of clinically significant effect on heart rate because of the higher C_{max} [2].

Pharmacokinetics of fluticasone furoate or vilanterol were not affected by age, gender, body weight or body mass index in patients with asthma who received once-daily fluticasone furoate/vilanterol in phase III studies [2].

4 Therapeutic Efficacy

The efficacy of once-daily fluticasone furoate/vilanterol has been evaluated in adolescents and adults (age ≥12 - years) with asthma uncontrolled on ICS and/or ICS/LABA, in five randomized, double-blind, multicentre, phase III trials of 12 [32, 33], 24 [34, 35] or ≥24–78 [36] weeks' duration. Eligible patients had to have a prebronchodilator FEV_1 of 40–80 % [33], 40–85 % [34], 40–90 % [32, 35] or 50–90 % [36] of predicted and FEV_1 reversibility of ≥12 % and ≥200 mL following albuterol inhalation. Patients with a history of life threatening asthma, asthma exacerbation requiring oral corticosteroids and/or overnight hospitalization or emergency room visit were among those excluded.

Studies were primarily designed to assess pulmonary function [32–35] or asthma exacerbations [36]. Some trials compared the efficacy of once-daily fluticasone furoate/vilanterol with that of once-daily fluticasone furoate alone [32, 33, 35, 36], with additional analyses comparing it with placebo [32], twice-daily fluticasone propionate [35] or comparing the two approved fluticasone furoate/vilanterol dosages (100/25 and 200/25 μg) [33]. One trial compared once-daily fluticasone furoate/vilanterol with another dual therapy (twice-daily fluticasone propionate/salmeterol) [34]. Data for one study (HZA116863; NCT01686633) are available in clinical registries maintained by GlaxoSmithKline [33] and the US National Institutes of Health [37].

After a 4-week [32–35] or 2-week [36] run-in period during which patients received ICS only [34, 35] or continued their current regimen at a stable dose [36] and had their short-acting bronchodilator replaced with albuterol

[34, 35], patients were randomized to study treatments. At randomization, where reported, patients had to have the same degree of pre-bronchodilator FEV_1 as at screening [33, 34] or recorded asthma symptoms (a score of ≥3 on the asthma symptom scale [35]) and/or albuterol use on ≥3 [35] or ≥4 [36] of the 7 preceding days.

Primary efficacy analyses were conducted in intent-to-treat (ITT) populations [32–36]. Studies that evaluated pulmonary function applied a pre-defined statistical testing hierarchy, whereby statistical significance at the 0.05 level was required for (co)primary endpoints to infer significance for secondary endpoints and for each secondary endpoint in the sequence to infer significance for the subsequent endpoints [32–35].

The mean age of patients was approximately 40–46 years and 58–67 % were female [32–36]. Where reported, patients had had asthma for a mean 15.5 years [35, 36]. At screening, 24–59 % of patients were receiving ICS only and 41–76 % were receiving ICS/LABA [32, 34–36].

4.1 Pulmonary Function

4.1.1 Placebo, Dosage and Active Monotherapy Comparisons

Once-daily fluticasone furoate/vilanterol 100/25 μg was effective in improving pulmonary function over 12 weeks in adults and adolescents with asthma, as indicated by a significant increase in trough FEV_1 and 0–24 h serial wm FEV_1 relative to placebo (co-primary endpoints; Table 2) [32]. There were also improvements in the percentage of rescue-free and symptom-free 24-h periods in both active treatment groups versus placebo (Table 2).

When different dosages of fluticasone furoate/vilanterol were compared, 100/25 μg once daily was as effective as 200/25 μg once daily in improving pulmonary function, with no significant difference observed between the regimens in the 0–24 h serial wm FEV_1 (primary endpoint), trough FEV_1 or other measures (Table 2) [33].

In most trials comparing fluticasone furoate/vilanterol with fluticasone furoate alone, the dual regimen was associated with greater improvements in pulmonary function, as measured by trough FEV_1 and/or 0–24 h serial wm FEV_1. In one 12-week trial [32], there was no significant difference between furoate/vilanterol 100/25 μg and fluticasone furoate 100 μg for the co-primary endpoints of trough FEV_1 and 0–24 h serial wm FEV_1 (Table 2). In contrast, in another 12-week trial [33], improvement in 0–24 h serial wm FEV_1 was significantly greater with fluticasone furoate/vilanterol 100/25 μg than with fluticasone furoate 100 μg (primary endpoint) and there was also a significant (95 % CI did not include zero) between-group difference in trough FEV_1, a powered secondary endpoint (Table 2). In a 24-week trial [35], fluticasone furoate/vilanterol 200/25 μg was more effective than fluticasone furoate 200 μg alone, in that the mean changes from baseline in trough FEV_1 and 0–24 h serial wm FEV_1 (co-primary endpoints) were significantly greater with combination therapy than with monotherapy (Table 2). Similarly, in an exacerbation trial (Sect. 4.2) [36], once-daily fluticasone furoate 100/25 μg improved trough FEV_1 (secondary endpoint) to a significantly ($p < 0.001$) greater extent than fluticasone furoate 100 μg, at weeks 12, 36, 52 and treatment end [between-group differences in least squares mean (LSM) changes from baseline of 83–95 mL]. In two trials [33, 35], fluticasone furoate/vilanterol increased the percentage of rescue- and symptom-free 24 h periods significantly more than fluticasone furoate alone, while a statistical significance could not be inferred for these measures in one trial [32] (Table 2).

Fluticasone furoate/vilanterol 200/25 μg was more effective than fluticasone propionate 500 μg twice daily in terms of improvements in trough FEV_1 and 0–24 h serial wm FEV_1 over 24 weeks (Table 2) [35].

With respect to the onset of action, the treatment difference in 0–1 h serial FEV_1 on day zero between fluticasone furoate/vilanterol 100/25 μg and fluticasone furoate 100 μg or placebo (103 and 122 mL) was the largest at 1 h [32]. The median time to onset of bronchodilation (definition not provided) was 62, 270 and 272 min with fluticasone furoate/vilanterol, fluticasone furoate and placebo, respectively, with 81, 66 and 61 % of patients achieving the bronchodilator effect [32].

Descriptively, improvements from baseline in morning/evening peak expiratory flow (PEF) rate were seen at week 12 with once-daily fluticasone furoate/vilanterol 100/25 μg (LSM change 32.9/26.4 [32] or 44.3/39.7 L/min [33]), fluticasone furoate/vilanterol 200/25 μg (47.7/41.7 L/min) [33] and fluticasone furoate 100 μg (18.3/14.1 [32] or 19.1/15.2 L/min [33]) but not placebo (−0.4/−1.8 L/min) [32]. PEF improvements were also seen at 24 weeks with once-daily fluticasone furoate/vilanterol 200/25 μg (LSM change from baseline 51.8/39.8 L/min), once-daily fluticasone furoate 200 μg (18.2/9.1 L/min) and twice-daily fluticasone propionate 500 μg (18.8/13.6 L/min) [35].

Post hoc analyses of two trials showed that trough FEV_1 values at the end of treatment (i.e. at 12 [32] or 24 [35] weeks) were approaching post-albuterol FEV_1 values at screening in recipients of once-daily fluticasone furoate/vilanterol 100/25 [32] or 200/25 μg [35], fluticasone furoate 100 [32] or 200 μg [35], twice-daily fluticasone propionate 500 μg [35] or placebo [32].

Table 2 Efficacy of once-daily fluticasone furoate/vilanterol compared with fluticasone furoate alone (primary analyses) in patients with persistent asthma. Results from randomized, double-blind, multicentre trials

References	Treatment[a] (μg)	Pt no.[b]	BL pre-dose FEV_1 (L) [% predicted, % reversibility]	Comparison	Treatment difference [95 % CI] in least squares mean change from baseline versus comparator			
					Trough FEV_1 (mL)[c]	0–24 h serial wm FEV_1 (mL)[d]	Rescue-free 24 h periods (%)[e,f]	Symptom-free 24 h periods (%)[f]
Bleecker et al. [32]	FF/VI 100/25	201	2.344 [70.62, 27.98]	vs. FF	36 [−48 to 120][g]	116 [−5 to 236][g]	10.6 [4.3–16.8]	12.1 [6.2–18.1]
				vs. PL	172*** [87–528]	302*** [178–426]	19.3 [13.0–25.6]	18.0 [12.0–23.9]
	FF 100	205	2.290 [70.49, 30.66]	vs. PL	136** [51–222]	186** [62–310]	8.7 [2.4–15.0]	5.8 [−0.1 to 11.8]
	PL	203	2.334 [70.20, 27.47]					
O'Byrne et al. [35]	FF/VI 200/25	197	2.129 [66.59, 29.58]	vs. FF	193*** [108–277][g]	136* [1–270][g]	11.7*** [4.9–18.4]	8.4** [2.0–14.8]
				vs. FP	210*** [127–294]	206** [73–339]	6.3 [−0.4 to 13.1]	4.9 [−1.6 to 11.3]
	FF 200	194	2.190 [66.66, 29.17]	vs. FP	18 [−66 to 102][h]			
	FP 500	195	2.138 [67.57, 29.56]					
HZA116863 [33]	FF/VI 100/25	346		vs. FF	77 [16–138]	108*** [45–171][g]	12.2 [7.1–17.3]	7.8 [2.9–12.6]
	FF 100	347						
	FF/VI 200/25	346		vs. 100/25	16 [−46 to 77]	24 [−37 to 86]	0.9 [−4.2 to 6.1]	1.9 [−3.0 to 6.7]

BL baseline, *FEV_1* forced expiratory volume in 1 s, *FF* fluticasone furoate, *FP* fluticasone propionate, *PL* placebo, *SAL* salmeterol, *VI* vilanterol, *Wks* weeks, *wm* weighted mean

* $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs. comparator

[a] FF/VI or FF were administered once daily (evening) and FP or FP/SAL were administered twice daily (morning and evening)

[b] Intent-to-treat population

[c] Co-primary endpoint [32, 35] or a powered secondary endpoint [33] assessed at the end of treatment period

[d] Co-primary [32, 35] or primary [33] endpoint assessed at the end of treatment period

[e] Powered secondary endpoint [32, 33, 35]

[f] Calculated as a percentage of treatment period

[g] Primary analysis

[h] Non-inferiority was demonstrated as the lower limit of the 95 % CI exceeded the predefined margin of −125 mL

4.1.2 Compared with Fluticasone Propionate/Salmeterol

There was no significant difference between fluticasone furoate/vilanterol 100/25 μg once daily and fluticasone propionate/salmeterol 250/50 μg twice daily in the primary endpoint of LSM improvement from baseline in 0–24 h serial wm FEV_1 at 24 weeks [341 vs. 377 mL; treatment difference −37 (95 % CI −88 to 15)] [34]. This study was designed to demonstrate superiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol. Lung function was generally similar between the groups at baseline (pre-dose FEV_1 2.011 and 2.048 L; FEV_1 68.0 and 68.8 % of predicted normal value; FEV_1 reversibility 26.4 and 29.0 %) [34].

All secondary endpoints are descriptive only, as the primary endpoint was not statistically significant [34]. At 24 weeks, both treatments showed a sustained duration of action over 24 h, as evaluated by hourly assessment of serial FEV_1. The median time to onset of bronchodilator effect (≥12 and ≥200 mL increase from baseline in FEV_1 at randomization visit) was 61 and 59 min with fluticasone furoate/vilanterol and fluticasone propionate/salmeterol. In both treatment groups, ≥50 % of patients achieved bronchodilation at 12 and 24 h post-dose at week 24. Both treatments produced similar results with respect to 0–4 h wm FEV_1 and trough FEV_1 at week 24 [34].

4.2 Exacerbation

In an exacerbation study, patients received once-daily fluticasone furoate/vilanterol 100/25 μg or fluticasone furoate 100 μg alone for a planned minimum of 24 weeks and up to 78 weeks [36]. The mean duration of exposure was 52.7 and 52 weeks in the fluticasone furoate/vilanterol and fluticasone furoate groups, and 56 and 58 % of patients received ≥52 weeks' treatment. Overall, at baseline, 57, 24 and 19 % of patients had experienced 1, 2 or ≥3 asthma exacerbations, respectively, in the last 12 months. At screening, mean pre-bronchodilator FEV_1 was 2.11 L and was 68.9 % of predicted normal, and FEV_1 reversibility was 24.4 % [36].

Fluticasone furoate/vilanterol delayed the time to first severe asthma exacerbation, compared with fluticasone furoate alone [36]. The adjusted (for baseline FEV_1, sex, age and region) probability of experiencing a severe asthma exacerbation at 52 weeks was significantly ($p = 0.036$) lower with the combination than with fluticasone furoate alone [12.8 vs. 15.9 %; hazard ratio 0.795 (95 % CI 0.642–0.985); primary endpoint] [36].

When the primary endpoint was assessed across various patient subgroups, there was no significant (at the 0.05 level) interaction of treatment with baseline FEV_1, age, sex or region [36]. No significant between-treatment difference was evident in any of the subgroups tested, with the exception of baseline FEV_1 <2 L (hazard ratio 0.654; 95 % CI 0.482–0.888) [36].

The rate of severe asthma exacerbations per patient per year was significantly ($p = 0.014$) lower with fluticasone furoate/vilanterol than with fluticasone furoate (0.14 vs. 0.19), representing a 25 % (95 % CI 5–40) reduction in rate [36]. In the respective treatment groups, 15 and 18 % of patients experienced ≥1 on-treatment severe asthma exacerbation and the mean duration of severe asthma exacerbation was 11 days (both groups) [36].

In phase III trials, on-treatment severe asthma exacerbation was reported in 0–3 % of fluticasone furoate/vilanterol 100/25 or 200/25 μg recipients, 2–3 % of fluticasone furoate 100 or 200 μg recipients, 1–3 % of fluticasone propionate 500 μg recipients, 3 % of fluticasone propionate/salmeterol 250/25 μg recipients and 4 % of placebo recipients; few patients (<1 %) required hospitalization because of severe asthma exacerbation in most treatment groups [32, 34–36, 38].

4.3 Patient-Reported Outcomes

Asthma control (assessed using the Asthma Control Test score) and the impact of asthma on quality of life [assessed using the Asthma Quality of Life Questionnaire (AQLQ + 12) total score] improved from baseline with fluticasone furoate/vilanterol as well as with active comparators, with no statistically significant or minimal important difference between the groups [32, 34, 35].

Fluticasone furoate/vilanterol once daily and fluticasone propionate/salmeterol twice daily did not significantly differ in terms of improving health-related quality of life, as measured by the European Quality of Life-5 Dimension visual analogue scale score and the dimension scores for mobility, self-care, usual activities, pain/discomfort and anxiety/depression [34].

In the exacerbation trial [36], fluticasone furoate/vilanterol 100/25 μg provided significantly ($p < 0.001$) greater asthma control than fluticasone furoate 100 μg, as assessed by the Asthma Control Questionnaire (ACQ)-7 score at weeks 12, 36 and at the end of treatment period (e.g. odds ratio 1.5, 95 % CI 1.23–1.82 at the end of treatment). The proportion of patients achieving well-controlled asthma (i.e. ACQ-7 score ≤0.75) was 2 % in each treatment group at baseline and 44 versus 36 %, respectively, at the end of the treatment period [36].

5 Tolerability

The tolerability of once-daily fluticasone furoate/vilanterol 100/25 and 200/25 μg compared with twice-daily

Table 3 Tolerability of fluticasone propionate/vilanterol in double-blind, phase III trials in patients with uncontrolled asthma

Events (% of pts, unless specified otherwise)	Treatment regimen (μg) [no. of pts, ITT population]												
	Busse et al. [38]			Bleecker et al. [32]			Bateman et al. [36]		O'Byrne et al. [35]			Woodcock et al. [34]	
	FF/VI 100/25 [201]	FF/VI 200/25 [202]	FP 500 [100]	FF/VI 100/25 [201]	FF 100 [205]	Placebo [203]	FF/VI 100/25 [1009]	FF 100 [1010]	FF/VI 200/25 [197]	FF 200 [194]	FP 500 [195]	FF/VI 100/25 [403]	FP/SAL 250/50 [403]
Any on-treatment AEs	69	66	73	29	25	21	63	65	47	46	50	53	49
Treatment-related AEs	13	14	14	7[a]	5[a]	1[a]	7[a]	7[a]	9	4	8	5	4
AEs leading to discontinuation	2	1	6	<1	0	<1	2[a]	2[a]	4	2	1	1	2
SAEs[b]	1	<1	7	<1	<1	0	4	3	3	<1	1	<1	1
Treatment-related SAEs (no. of pts)	0	0	1	0	0		1[a]	3[a]	1		1	0	0
Death (no. of pts)	0	0	0	0	0	0	1[c]	2[c]	0	0	0	0	0

AE adverse event, *FF* fluticasone furoate, *FP* fluticasone propionate, *ITT* intent-to-treat, *Pts* patients, *SAE* serious adverse event *SAL* salmeterol, *VI* vilanterol

[a] On- and post-treatment

[b] On-treatment [35, 36, 38] or on- and post-treatment [32, 34]

[c] None treatment related

fluticasone propionate 500 μg was assessed in a 52-week, double-blind, multicentre trial in patients aged ≥12 years with uncontrolled asthma ($n = 503$; ITT population) [38]. Additional tolerability data are from the four fully published trials discussed in Sect. 4, supplemented with data from the EU SPC [2].

5.1 General Profile

Once-daily fluticasone furoate/vilanterol 100/25 or 200/25 μg was generally well tolerated in adolescents and adults with asthma [32, 34–36, 38]. On-treatment adverse events were reported in 29–69 % of patients receiving either dose; however, the incidence of treatment-related adverse events was 5–14 %, treatment-related serious adverse events <1 % and adverse events leading to treatment discontinuation ≤4 % (Table 3). The tolerability profile of fluticasone furoate/vilanterol 100/25 μg once daily was generally similar to that of fluticasone propionate/salmeterol 250/50 μg twice daily (Table 3) [34].

The most common adverse events reported in the tolerability trial are shown in Fig. 1 [38]. Headache, upper respiratory tract infection or nasopharyngitis occurred in >10 % of fluticasone furoate/vilanterol 100/25 or 200/25 μg recipients (Fig. 1). Headache and nasopharyngitis were also the two most commonly reported adverse events in other trials, although the incidences of these events with fluticasone furoate/vilanterol were generally similar to that with placebo, fluticasone furoate alone, fluticasone propionate alone or fluticasone propionate/salmeterol [32, 34–36]. For example, the incidence of headache with fluticasone furoate/vilanterol 100/25 μg,

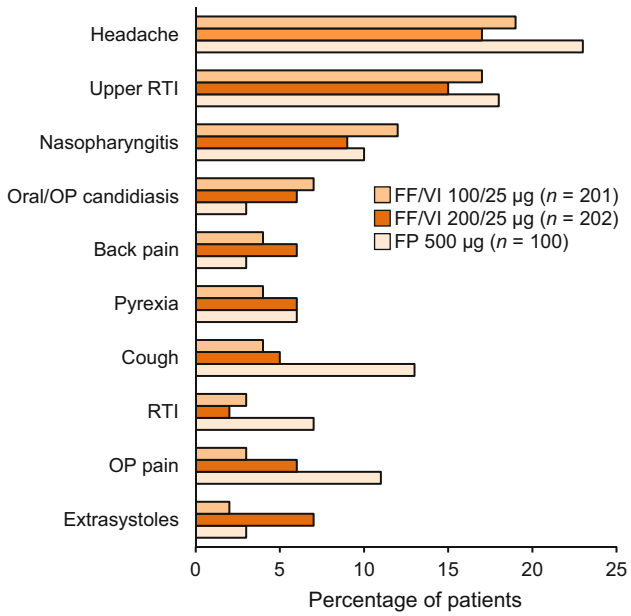

Fig. 1 The most common (incidence >5 % in any group) on-treatment adverse events that occurred with once-daily fluticasone furoate/vilanterol or twice-daily fluticasone propionate in patients aged ≥12 years with uncontrolled asthma in a 52-week trial [38]. *FF* fluticasone furoate, *FP* fluticasone propionate, *OP* oropharyngeal, *RTI* respiratory tract infection, *VI* vilanterol

fluticasone furoate 200 μg and fluticasone propionate 500 μg was 6, 7 and 8 %, respectively, and the corresponding incidence of nasopharyngitis was 13, 14 and 20 % [35].

The incidence of treatment-related adverse events was numerically higher with fluticasone furoate/vilanterol 100/25 μg than with placebo (Table 3); however, the incidences were similar between fluticasone furoate/vilanterol, fluticasone propionate and fluticasone propionate/salmeterol recipients; of note, treatment-related adverse events occurred at similar frequency in fluticasone furoate/vilanterol 100/25 and 200/25 μg groups (Table 3). In the tolerability trial, the most commonly (incidence ≥2 %) reported treatment-related events in fluticasone furoate/vilanterol 100/25 or 200/25 μg, or fluticasone propionate 500 μg were oral/oropharyngeal candidiasis (5, 4 and 2 %, respectively), dysphonia (3, <1 and 0 %), extrasystoles (<1, 2, 0 %) and cough (1, 0 and 2 %) [38]. In the trial comparing fluticasone furoate/vilanterol 100/25 μg with fluticasone furoate 100 μg or placebo, treatment-related adverse events occurring in more than one patient were oral/oropharyngeal candidiasis, headache, nasopharyngitis, dysphonia, epistaxis and oropharyngeal pain and were uncommon (0–2 % across treatment arms) [32].

Treatment-related serious adverse events reported in the clinical trials included: tachyarrhythmia in one fluticasone furoate/vilanterol 100/25 μg recipient [36], atrial fibrillation in one fluticasone furoate/vilanterol 200/25 μg recipient [35], pleurisy, asthma and non-cardiac chest pain each occurred in one fluticasone furoate 100 μg recipient [36], and worsening hepatitis B (possibly treatment-related) [38] and haemoptysis [35] each occurred in one fluticasone propionate 500 μg recipient.

5.2 Cortisol Suppression

In a double-blind, multicentre, phase III trial, fluticasone furoate/vilanterol 100/25 and 200/25 μg once daily did not significantly suppress serum cortisol in patients with persistent asthma ($n = 185$). Both dosages were noninferior to placebo with respect to change from baseline in 0–24 h wm serum cortisol at day 42, while the active comparator (oral prednisolone) substantially suppressed serum cortisol [39].

In other phase III trials, fluticasone furoate/vilanterol treatment was not associated with clinically relevant suppression in 24-h urinary cortisol (UC) [32, 34, 35, 38]. In the tolerability trial, fluticasone furoate/vilanterol 100/25 or 200/25 μg dosages caused only small changes from baseline in UC at weeks 12, 28 and 52; compared with either dosage, fluticasone propionate significantly ($p \leq 0.006$) suppressed UC at week 12 and 28 but not at week 52 [38]. In all treatment groups, UC was within the normal range or did not change from baseline at any post-baseline visit in the majority of patients (76, 81 and 70 % of patients in the fluticasone furoate/vilanterol 100/25 or 200/25 μg, or fluticasone propionate groups, respectively) [38]. Fluticasone furoate/vilanterol had no clinically relevant effects on UC in other trials [32, 34, 35], although statistically significant ($p = 0.032$) UC suppression was seen with the 100/25 μg dosage versus placebo (adjusted ratio relative to placebo 0.82 at week 12) [32]. Notably, there was no statistically significant difference between fluticasone furoate/vilanterol 100/25 μg once daily and fluticasone propionate/salmeterol 250/50 μg twice daily in terms of UC suppression [34].

5.3 Other Systemic Adverse Effects

There were no clinically relevant changes in vital signs, heart rate, clinical biochemical or haematological parameters with fluticasone furoate/vilanterol in phase III trials [32, 34–36, 38]. Of note, in the tolerability trial [38], there were no reports of clinically significant changes in Fridericia-corrected QT interval, non-fasting glucose, potassium, liver function or ophthalmic assessments (subcapsular opacity, cortical opacity, nuclear colour, nuclear opalescence, intraocular pressure and visual acuity).

Pneumonia and fractures were infrequent in patients with asthma receiving fluticasone furoate/vilanterol [2]. In an integrated analysis of 11 studies in patients with asthma ($n = 7,034$), the incidence of pneumonia per 1,000 patient-years was 9.6, 18.4 and 8.0 with fluticasone furoate/vilanterol 100/25 and 200/25 μg, and placebo, respectively [2]. The overall incidence of fractures in the same analysis was <1 % and was typically associated with trauma [2]. Where reported, pneumonia did not occur in phase III trials [32, 34].

6 Dosage and Administration

Fluticasone furoate/vilanterol is indicated in the EU for the regular treatment of asthma in adults and adolescents aged ≥12 years for whom a combination of ICS and LABA is appropriate (i.e. patients whose asthma is not adequately controlled with ICS and 'as needed' SABA) [2]. The efficacy and safety of fluticasone furoate/vilanterol is not established in children aged <12 years with asthma [2].

The recommended starting dosage of fluticasone furoate/vilanterol is one inhalation per day of 100/25 μg (delivered dose 92/22 μg) in patients who require a low to medium dose of ICS plus LABA or 200/25 μg (delivered dose 184/22 μg) in those who require a higher dose of ICS plus LABA, as determined by the severity of the disease [2]. In patients who start with the 100/25 μg dosage, if

asthma is not adequately controlled, the dosage can be increased to 200/25 μg, which may provide additional improvement in asthma control. Fluticasone furoate/vilanterol should be administered at the same time each day [2].

In patients with moderate or severe hepatic impairment, the maximum recommended dosage of fluticasone furoate/vilanterol is one inhalation per day of 100/25 μg and these patients should be monitored for systemic corticosteroid-related adverse reactions [2]. Dosage adjustment is not required in patients aged >65 years or in those with renal impairment. Fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease, as sympathomimetic drugs such as LABAs may cause cardiovascular events such as cardiac arrhythmias [2].

Local prescribing information should be consulted for further details regarding contraindications, possible drug interactions and precautions [2].

7 Current Status of Fluticasone Furoate/Vilanterol in Patients with Asthma

The fixed-dose combination of fluticasone furoate and vilanterol administered via the dry powder inhaler, Ellipta®, is approved in the EU [2] and Japan [6] for the treatment of asthma where use of an ICS/LABA combination is appropriate or required. Fluticasone furoate/vilanterol is also in pre-registration in the USA for the treatment of asthma [40]. In the EU, fluticasone furoate/vilanterol is not approved in patients with adequately controlled asthma [5], unlike the other available ICS/LABA combinations, which are indicated for patients with inadequately-controlled (with ICS and 'as needed' SABA) or adequately-controlled (with an ICS and a LABA) asthma.

Fluticasone furoate is a potent anti-inflammatory agent, with a greater binding affinity to the glucocorticoid receptor and a longer retention time in respiratory tissues than fluticasone propionate; vilanterol produces rapid and sustained bronchodilation; both compounds have ≥24-h duration of action and are hence suitable for once-daily dosing (Sect. 2).

When pulmonary function (trough FEV_1 and 0–24 h serial wm FEV_1) was assessed as a primary or secondary outcome in phase III trials of 12–24 weeks duration in adolescents and adults with asthma uncontrolled on ICS and/or ICS/LABA, fluticasone furoate/vilanterol was more effective than placebo, equivalent doses of fluticasone furoate (in three of four trials) or fluticasone propionate (Sect. 4.1). Fluticasone furoate/vilanterol was also associated with a significantly greater percentage of rescue- and symptom-free 24-h periods than fluticasone furoate in two of three trials.

In a 24-week trial designed to show superiority of fluticasone furoate/vilanterol 100/25 μg once daily to fluticasone propionate/salmeterol 250/50 μg twice daily in improving pulmonary function, no significant between-group difference was observed (Sect. 4.1.2). Both combinations had a similar time to onset of bronchodilator effect (≈1 h), with ≥50 % of patients receiving either combination achieving the bronchodilator effect at the end of the 24-week treatment period. The additional advantage of once-daily dosing with fluticasone furoate/vilanterol has the potential to improve treatment adherence, which may result in better asthma control, in some patients [4]. Furthermore, based on qualitative interviews with asthmatic patients, the Ellipta® device was associated with a high level of patient satisfaction and was preferred over other inhalers, which may also improve treatment adherence [41].

In a 24–78 week trial, fluticasone furoate/vilanterol 100/25 μg significantly reduced both the risk of severe asthma exacerbation (by 20 %; primary endpoint) and the rate per patient per year (by 25 %), compared with fluticasone furoate 100 μg alone (both endpoints were statistically significant). The combination was also associated with significantly greater asthma control.

Fluticasone furoate/vilanterol was generally well tolerated with fewer than 15 % of patients experiencing treatment-related adverse events (Sect. 5). Oral/oropharyngeal candidiasis, dysphonia, extrasystoles and cough were the most common treatment-related adverse events reported by fluticasone furoate/vilanterol recipients. Fluticasone furoate/vilanterol treatment was not associated with clinically relevant corticosteroid- and β_2-agonist-related systemic effects (Sects. 5.2, 5.3). Notably, the incidence of pneumonia and fractures was low among patients with asthma receiving fluticasone furoate/vilanterol. Overall, the tolerability profile of once-daily fluticasone furoate/vilanterol was similar to that of twice-daily fluticasone propionate/salmeterol (Table 3).

There are some limitations/gaps in the efficacy evidence base for fluticasone furoate/vilanterol including the use of individual drugs (particularly, fluticasone furoate which is not currently approved) as active comparators, limited efficacy data for the 200/25 μg dose and lack of studies that compare the combination with currently available ICS/LABAs using patient-oriented primary endpoints, such as exacerbation rate [5]. Furthermore, since fluticasone furoate is a new ICS, additional studies assessing its effect on cortisol suppression relative to other ICS is also required [5]. Currently, a pragmatic randomized controlled trial [Salford Lung Study (asthma)] is underway to compare the efficacy of fluticasone furoate/vilanterol with existing therapy in terms of asthma control in more than 4,000 patients with asthma [42]. Results from this study could provide real-world evidence for the efficacy of fluticasone furoate/vilanterol. To date, there are no published cost-

effectiveness analyses comparing this combination with other ICS/LABA combinations in the treatment of asthma. Such analyses would be of interest.

BTS guidelines recommend stepping down therapy in patients who have achieved asthma control, although this recommendation is not routinely implemented resulting in some patients being over-treated. Fluticasone furoate/vilanterol is not currently available at strengths lower than 100/25 μg, so the ability to step down treatment for patients stable on this dosage is limited [5].

In conclusion, once-daily fluticasone furoate/vilanterol is effective and generally well tolerated in patients with persistent asthma. It has similar overall efficacy and tolerability to twice-daily fluticasone propionate/salmeterol. However, further comparative studies are required to more definitively define the relative position of this combination to other available ICS/LABA treatment options. Meanwhile, fluticasone furoate/vilanterol is a useful treatment option for patients with asthma inadequately controlled with ICS plus as needed SABA.

Data selection sources: Relevant medical literature (including published and unpublished data) on fluticasone furoate/vilanterol was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 10 January 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: vilanterol, fluticasone furoate, fluticasone furoate + vilanterol, asthma
Study selection: Studies in patients with asthma who received fluticasone furoate/vilanterol. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. Yahiya Y. Syed is a salaried employee of Adis/Springer. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

References

1. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. 2008, revised January 2012. http://www.sign.ac.uk. Accessed 22 Dec 2014.
2. European Medicines Agency. Relvar Ellipta (fluticasone furoate/vilanterol): summary of product characteristics 2013. http://www.ema.europa.eu. Accessed 22 Dec 2014.
3. Kaur M, Chivers JE, Giembycz MA, et al. Long-acting β_2-adrenoceptor agonists synergistically enhance glucocorticoid-dependent transcription in human airway epithelial and smooth muscle cells. Mol Pharmacol. 2008;73(1):203–14.
4. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. J Manag Care Pharm. 2012;18(7):527–39.
5. National Institute for Health and Care Excellence. ESNM34: Asthma: fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler. 2014. http://www.nice.org.uk. Accessed 22 Dec 2014.
6. GlaxoSmithKline, Theravance Inc. Relvar™ Ellipta™ gains approval in Japan for the treatment of asthma [media release]. 20 Sept 2013. http://www.gsk.com.
7. McKeage K. Fluticasone furoate/vilanterol: a review of tts use in chronic obstructive pulmonary disease. Drugs. 2014. doi:10.1007/s40265-014-0269-6.
8. Salter M, Biggadike K, Matthews JL, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. Am J Physiol Lung Cell Mol Physiol. 2007;293(3):L660–7.
9. Biggadike K, Bledsoe RK, Hassell AM, et al. X-ray crystal structure of the novel enhanced-affinity glucocorticoid agonist fluticasone furoate in the glucocorticoid receptor-ligand binding domain. J Med Chem. 2008;51(12):3349–52.
10. Valotis A, Hogger P. Human receptor kinetics and lung tissue retention of the enhanced-affinity glucocorticoid fluticasone furoate. Respir Res. 2007;8:54.
11. Rossios C, To Y, To M, et al. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. Eur J Pharmacol. 2011;670(1):244–51.
12. Zhang N, Van Crombruggen K, Holtappels G, et al. Suppression of cytokine release by fluticasone furoate vs. mometasone furoate in human nasal tissue ex-vivo. PLoS One. 2014;9(4):e93754.
13. Slack RJ, Barrett VJ, Morrison VS, et al. In vitro pharmacological characterization of vilanterol, a novel long-acting β_2-adrenoceptor agonist with 24-hour duration of action. J Pharmacol Exp Ther. 2013;344(1):218–30.
14. Lotvall J, Bateman ED, Bleecker ER, et al. 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. Eur Respir J. 2012;40(3):570–9.
15. Cazzola M, Page CP, Calzetta L, et al. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012;64(3):450–504.
16. Kempsford R, Norris V, Siederer S. Vilanterol trifenatate, a novel inhaled long-acting beta2 adrenoceptor agonist, is well tolerated in healthy subjects and demonstrates prolonged bronchodilation in subjects with asthma and COPD. Pulm Pharmacol Ther. 2013;26(2):256–64.
17. Busse WW, Bleecker ER, Bateman ED, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012;67(1):35–41.
18. Sterling R, Lim J, Frith L, et al. Efficacy and optimal dosing interval of the long-acting beta$_2$ agonist, vilanterol, in persistent asthma: a randomised trial. Respir Med. 2012;106(8):1110–5.
19. Bleecker ER, Bateman ED, Busse WW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. Ann Allergy Asthma Immunol. 2012;109(5):353–358.e4.
20. Bateman ED, Bleecker ER, Lotvall J, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. Respir Med. 2012;106(5):642–50.
21. Woodcock A, Bleecker ER, Busse WW, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. Respir Res. 2011;12:160.
22. Kempsford RD, Oliver A, Bal J, et al. The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing. Respir Med. 2013;107(12):1873–80.

23. Oliver A, Bjermer L, Quinn D, et al. Modulation of allergen-induced bronchoconstriction by fluticasone furoate and vilanterol alone or in combination. Allergy. 2013;68(9):1136–42.
24. Oliver A, Quinn D, Goldfrad C, et al. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomised, controlled trial. Clin Transl Allergy. 2012;2(1):11.
25. Kempsford R, Allen A, Kelly K, et al. A repeat-dose thorough QT study of inhaled fluticasone furoate/vilanterol combination in healthy subjects. Br J Clin Pharmacol. 2014;77(3):466–79.
26. Allen A, Bareille PJ, Rousell VM. Fluticasone furoate, a novel inhaled corticosteroid, demonstrates prolonged lung absorption kinetics in man compared with inhaled fluticasone propionate. Clin Pharmacokinet. 2013;52:37–42.
27. Hughes SC, Shardlow PC, Hollis FJ, et al. Metabolism and disposition of fluticasone furoate, an enhanced-affinity glucocorticoid, in humans. Drug Metab Dispos. 2008;36(11):2337–44.
28. Harrell AW, Siederer SK, Bal J, et al. Metabolism and disposition of vilanterol, a long-acting β_2-adrenoceptor agonist for inhalation use in humans. Drug Metab Dispos. 2013;41(1):89–100.
29. Kempsford R, Allen A, Bal J. The effect of ketoconazole on the pharmacokinetics and pharmacodynamics of inhaled fluticasone furoate and vilanterol trifenatate in healthy subjects. Br J Clin Pharmacol. 2012;75(6):1478–87.
30. Allen A, Davis A, Hardes K, et al. Influence of renal and hepatic impairment on the pharmacokinetic and pharmacodynamic properties and tolerability of fluticasone furoate and vilanterol in combination. Clin Ther. 2012;34(12):2316–32.
31. Allen A, Bal J, Cheesbrough A, et al. Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. Br J Clin Pharmacol. 2014;77(5):808–20.
32. Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate–vilanterol 100–25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014. doi:10.1016/j.jaip.2014.02.010.
33. GlaxoSmithKline. GSK clinical study register. 2013. http://www.gsk-clinicalstudyregister.com. Accessed 22 Dec 2014.
34. Woodcock A, Bleecker ER, Lotvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144(4):1222–9.
35. O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43(3):773–82.
36. Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69(4):312–9.
37. US National Institutes of Health. ClinicalTrials.gov. 2012. http://clinicaltrials.gov. Accessed 22 Dec 2014.
38. Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β_2 agonist vilanterol administered once daily for 52 weeks in patients $\geq$12 years old with asthma: a randomised trial. Thorax. 2013;68(6):513–20.
39. Allen A, Schenkenberger I, Trivedi R, et al. Inhaled fluticasone furoate/vilanterol does not affect hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomised, double-blind, placebo-controlled study. Clin Respir J. 2013;7(4):397–406.
40. GlaxoSmithKline. GSK and Theravance announce submission to US regulatory authorities for fluticasone furoate/vilanterol in asthma [media release]. 30 June 2014. http://us.gsk.com/.
41. Svedsater H, Dale P, Garrill K, et al. Qualitative assessment of attributes and ease of use of the ELLIPTA dry powder inhaler for delivery of maintenance therapy for asthma and COPD. BMC Pulm Med. 2013;13:72.
42. New JP, Bakerly ND, Leather D, et al. Obtaining real-world evidence: the Salford Lung Study. Thorax. 2014. doi:10.1136/thoraxjnl-2014-205259.
43. GlaxoSmithKline. Breo Ellipta (fluticasone furoate and vilanterol inhalation powder): US prescribing information. 2014. http://www.fda.gov. Accessed 22 Dec 2014.