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ORIGINAL ARTICLE

Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma

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Abstract

Objectives: Fluticasone furoate (FF; inhaled corticosteroid) combined with vilanterol (VI; long-acting beta₂ agonist) is a once-daily therapy for asthma and chronic obstructive pulmonary disease. This 12-week phase III study compared the efficacy and safety of once-daily (evening dosing) FF/VI 100/25 mcg versus FF 100 mcg (primary objective) and FF/VI 100/25 mcg versus FF/VI 200/25 mcg (descriptive comparison only) in patients ($n=1039$) ≥ 12 years with moderate-to-severe persistent asthma. **Methods:** The primary end point was weighted mean (wm) 0–24-h serial forced expiratory volume in 1 s (FEV₁) at week 12. Secondary end points (change from baseline) were trough FEV₁ and the proportion (%) of rescue-free 24-h periods (both powered), the proportion (%) of symptom-free 24-h periods, and morning and evening peak expiratory flow (PEF). Safety data (adverse events, AEs) were collected throughout. **Results:** Compared with FF 100 mcg, FF/VI 100/25 mcg significantly improved wmFEV₁ ($p<0.001$), trough FEV₁ ($p=0.014$), % rescue-free ($p<0.001$), % symptom-free ($p=0.002$) 24-h periods, and morning and evening PEF ($p<0.001$). FF/VI 200/25 mcg produced small numerical improvements versus FF/VI 100/25 mcg for all end points. Incidence of AEs was similar across groups. **Conclusions:** FF/VI 100/25 mcg resulted in significant improvements in all primary and secondary end points versus FF 100 mcg. Numerical improvements occurred with FF/VI 200/25 mcg versus FF/VI 100/25 mcg. All treatments were well tolerated.

Keywords

Efficacy, inhaled corticosteroid, long-acting beta-agonist, lung function, safety

History

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Introduction

Inhaled corticosteroids (ICS) are the mainstay of the treatment for asthma [1–3]; their introduction in the 1970s represented a leap forward in the management of asthma. However, the role of inflammation in asthma was not fully understood until the 1990s, when guidelines were developed that recommended ICS as first-line treatment for patients with asthma not controlled with intermittent short-acting beta₂ agonist (SABA) use. For patients whose asthma symptoms persist when treated with ICS, addition of an inhaled long-acting beta₂ agonist (LABA) is now the preferred treatment option [1–6]. Addition of a LABA to ICS has been reported to reduce the rate of exacerbations requiring oral corticosteroids, improve lung function, improve symptoms and decrease the use of rescue SABAs, compared with the same dose of ICS alone. If asthma control is not achieved with low dose ICS/LABA, guidelines recommend that the ICS dose should be

increased; therefore it is important to have more than one strength of ICS/LABA available.

The ICS/LABA combination fluticasone furoate (FF)/vilanterol (VI) is a once-daily asthma treatment, and efficacy over a full 24-h period in asthma has been demonstrated for both FF [7] and VI [8]. In asthma, the optimal doses of once-daily FF are 100 and 200 mcg [9–12], and the optimal dose of VI is 25 mcg [13]. Despite the widespread availability of medications for asthma, suboptimal control remains an issue, which may be linked to poor adherence to therapy [14]. Once-daily regimens have the potential to improve adherence compared with twice-daily regimens [15–17]. Good adherence to asthma medication can improve asthma control and contribute to better quality of life for patients, with, for example, fewer unscheduled visits to physicians or fewer missed work/school days [18].

The primary objective of this study was to examine the efficacy and safety of once-daily FF/VI 100/25 mcg versus once-daily FF 100 mcg, over 12 weeks, in patients ≥ 12 years of age with moderate-to-severe persistent asthma. The secondary objective was to descriptively assess the relative efficacy of once-daily FF/VI 100/25 mcg versus once-daily

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FF/VI 200/25 mcg. Preliminary results have been presented in abstract form [19].

Methods

Patients

The study was approved by local ethics review committees and conducted in accordance with applicable regulatory requirements, the Declaration of Helsinki [20], and Good Clinical Practice guidelines [21]. All patients (or guardians for patients <18 years) gave written informed consent prior to any study procedures being performed.

Key inclusion criteria were age ≥ 12 years and moderate-to-severe asthma treated with an ICS $\pm$ LABA for ≥ 12 weeks; a dose that was equivalent to twice-daily fluticasone propionate (FP) >250 mcg or twice-daily FP/salmeterol 250/50 mcg that was stable for ≥ 4 weeks. Patients had to have a pre-bronchodilator forced expiratory volume in 1 s (FEV₁) 40–80% of predicted normal and FEV₁ reversibility of $\geq 12\%$ and ≥ 200 mL following salbutamol/albuterol at randomization (historical reversibility, i.e. documented evidence of reversibility within the previous 6 months, was accepted at screening). Key exclusion criteria were: history of life-threatening asthma within 5 years; any asthma exacerbation requiring oral corticosteroids within 12 weeks or resulting in hospitalization within 6 months; concurrent respiratory disease; use of tobacco products within 3 months or historical use of ≥ 10 pack-years (calculated by the number of packs of cigarettes smoked per day multiplied by the number of years, e.g. 10 pack-years is equivalent to smoking 1 pack [20 cigarettes] per day for 10 years).

At screening, patients on ICS continued taking their current daily dose and those using ICS/LABA switched to their current daily dose of ICS alone (LABAs were not permitted from screening onwards) for the 4-week run-in period. All patients replaced their current SABA with salbutamol, which was to be withheld for ≥ 6 h prior to study visits. At randomization, eligible patients had to have reported (via an electronic diary) asthma symptoms (a score of ≥ 3 on the combined day- and night-time asthma symptom scale) and/or daily salbutamol use on ≥ 4 of the last 7 days of the run-in period. Compliance with ICS during the run-in period was reported by the patient via an electronic diary.

Study design and treatments

This phase III, randomized, double-blind, stratified, parallel-group (i.e. treatment comparison) study (GSK study number HZA116863; www.clinicaltrials.gov registration number NCT01686633) was conducted at 125 centers in 11 countries (USA, Russia, Argentina, Ukraine, Romania, Chile, Germany, Poland, Mexico, Netherlands and Sweden) between 20 September 2012 and 15 October 2013.

Randomization was carried out centrally by the sponsor using a validated computer system (RandAll; GSK, Brentford, UK) and registration and medication ordering system (RAMOS; GSK).

Patients were stratified by asthma severity (severe: baseline FEV₁ $\leq 65\%$; or moderate: baseline FEV₁ $>65\%$ of predicted normal) and randomized to one of three groups in a

1:1:1 ratio: FF 100 mcg (emitted dose of 92 mcg); or FF/VI 100/25 mcg (emitted dose of 92/22 mcg); or FF/VI 200/25 mcg (emitted dose of 184/22 mcg). Each medication was to be taken once-daily in the evening for 12 weeks. FF and FF/VI were administered via the ELLIPTA[®] dry powder inhaler.¹ The inhaler dose counters were reviewed at each visit to assess treatment compliance.

If any patients met the following criteria, indicating lack of efficacy, they were withdrawn from the study: FEV₁ measurement $<80\%$ of pre-bronchodilator FEV₁ at randomization; in the 7 days preceding any visit, ≥ 4 days in which the peak expiratory flow (PEF) was $<80\%$ of the mean morning PEF measured in the week prior to randomization; in the 7 days preceding any visit, ≥ 3 days in which ≥ 12 inhalations/day of salbutamol/albuterol were used; severe exacerbation, defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥ 3 days, or an in-patient hospitalization/emergency department visit due to asthma that required systemic corticosteroids; or clinical asthma worsening, which in the opinion of the investigator, required additional asthma treatment other than study medication or study-supplied salbutamol/albuterol.

At the randomization visit, patients were trained by the investigator (or a delegate) in the correct use of the inhaler. Placebo inhalers were used as demonstration inhalers. Following the demonstration, the patient's competence with a demonstration inhaler was assessed. If the patient did not use the inhaler correctly, further instructions were given before assessing competence again. If the patient was still unable to use the inhaler correctly after three demonstrations, the patient was considered ineligible to enter the study. The correct use of the inhaler was reassessed at the second and fourth weeks of treatment using the demonstration inhaler. If the patient did not perform the correct technique, the procedure was demonstrated again.

Outcome measurements

The primary end point was the mean change in the 0–24-h post-dose weighted mean (wm) serial FEV₁ from baseline to week 12. The 0–24-h post-dose wmFEV₁ represents the average FEV₁ from a series of measurements taken over a 24-h period (5, 15 and 30 min, and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24-h post-dose) and gives an indication of lung function over the 24-h period.

Secondary efficacy end points that were statistically powered to detect predefined differences between treatments were: change from baseline in (a) trough FEV₁ at week 12 and (b) the proportion of rescue [medication]-free 24-h periods as a percentage of the overall study period during the 12 weeks.

Remaining secondary end points were: (a) change from baseline in the proportion (%) of symptom-free 24-h periods during the 12 weeks; (b) change from baseline in daily morning and evening PEF, averaged over the 12 weeks. Other end points included: the 12-h post-bronchodilator FEV₁ at week 12; the number of withdrawals due to lack of efficacy during the 12-week period and change from baseline in the

¹ELLIPTA[®] is a trademark of the GSK group of companies.

Asthma Quality of Life Questionnaire (AQLQ12+) and the Asthma Control Test™ (ACT) scores at week 12.

Safety evaluations

Safety and tolerability assessments included recording of adverse events (AEs), serious AEs (SAEs), AEs of special interest (class effects of ICS or LABA) and severe asthma exacerbations requiring treatment with systemic/oral corticosteroids for ≥ 3 days or an in-patient hospitalization or an emergency department visit due to asthma that required systemic corticosteroids (the latter were not recorded as AEs unless considered to be an SAE). AEs were coded according to the Medical Dictionary for Regulatory Activities.

Statistical analyses

There is no established minimal important difference (MID) for wmFEV_1 in patients with asthma; an assumed treatment difference of 135 mL was based on the largest difference (136 mL) observed in previous studies for the comparison of FF/VI 200/25 mcg versus FF 200 mcg at week 24 [22]. Assuming a true population effect of 135 mL, a sample size of 290 evaluable patients per group would have 97% power in wmFEV_1 over 24 h post-dose.

For the powered secondary end points, 316 evaluable patients per group would have 95% power, assuming a true population effect of 120 mL, to detect a treatment difference in change from baseline in trough FEV_1 , and $>99\%$ power, assuming a true population effect of 15%, for the treatment difference in change from baseline in the proportion of rescue-free 24-h periods. The overall power of the study to detect treatment differences between FF/VI 100/25 mcg and FF 100 mcg in the primary and powered secondary end points was 94%. This study was not powered to compare FF/VI 100/25 mcg with FF/VI 200/25 mcg.

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study medication. The per-protocol (PP) population included all ITT patients without any full protocol deviations. The primary and powered secondary end points were analyzed using an analysis of covariance (ANCOVA) model (covariates were baseline, region, sex, age and treatment group).

A step-down, closed-testing procedure was used to account for multiplicity across treatment comparisons and key end points. If the primary end point achieved significance, the secondary end points were tested according to the following priority: trough FEV_1 , rescue-free 24-h periods, symptom-free 24-h periods, morning PEF and evening PEF. A p value < 0.05 was required to permit inference of significance for the next comparison in the hierarchy. If significance was achieved for each of the secondary efficacy end points, then all other efficacy end points were tested without further multiplicity adjustment.

Results

Study population

Of 2019 patients screened, 1039 were randomized and included in the ITT population, and 931 patients completed the study (Figure 1). The most common reason for withdrawal

post-randomization was lack of efficacy. At baseline, patient demographics and characteristics were well balanced across groups, and prior to study entry, the majority of patients (64%) were using ICS/LABA (Table 1). Baseline lung function according to asthma severity is shown in online Supplementary Table S1. Eleven patients used concomitant asthma medication (prescribed or over the counter) during the study, with prednisolone (used by four patients in the FF 100 mcg group and one patient in the FF/VI 100/25 mcg group) being the most common. Non-asthma medication was used by 58–61% of patients pre-study and 65–69% during the study. In all treatment groups, median exposure to study treatment was 84 days and mean overall compliance was approximately 99%.

Efficacy

Primary end point

At week 12, there was a mean improvement from baseline in wmFEV_1 0–24 h of 0.366 L with FF 100 mcg and 0.474 L with FF/VI 100/25 mcg; the treatment difference for FF/VI 100/25 mcg versus FF 100 mcg (0.108 L) was statistically significant ($p < 0.001$; Table 2 and Figure 2A). Results in the PP population supported the ITT population (Figure 2A). A larger change from baseline in serial wmFEV_1 occurred in patients with more severe asthma ($\text{FEV}_1 \leq 65\%$) at baseline versus those with $\text{FEV}_1 > 65\%$ (Supplementary Table S2 and Supplementary Figure S1), although for FF/VI 100/25 mcg versus FF 100 mcg, the treatment difference was greater in the $\text{FEV}_1 > 65\%$ stratum. The adjusted mean change from baseline of the serial FEV_1 measurements at week 12 showed a relatively flat profile over the 24-h duration, suggesting that respective efficacy levels were maintained during this time for each of the three once-daily treatments (Figure 3).

Powered secondary end points

At week 12, change from baseline in trough FEV_1 was 0.365 L for FF 100 mcg and 0.441 L for FF/VI 100/25 mcg; the treatment difference for FF/VI 100/25 mcg versus FF 100 mcg of 0.077 L was statistically significant ($p = 0.014$; Table 2 and Figure 2). The increased trough FEV_1 benefit of FF/VI 100/25 mcg versus FF 100 mcg occurred by week 2 and was sustained (Figure 4A). A greater change from baseline in trough FEV_1 at week 12 was seen in patients with $\text{FEV}_1 \leq 65\%$ at baseline, but the treatment difference for FF/VI 100/25 mcg versus FF 100 mcg was higher in the $\text{FEV}_1 > 65\%$ than in the $\text{FEV}_1 \leq 65\%$ stratum (Supplementary Table S2).

Over 12 weeks, the proportion of rescue-free 24-h periods increased from baseline in all groups (Table 2 and Figure 4B). The treatment difference was 12.2% ($p < 0.001$) between FF/VI 100/25 mcg and FF 100 mcg (Table 2 and Figure 2A), equivalent to 0.9 additional rescue-free days per week.

Secondary and other end points

The proportion of symptom-free 24-h periods increased from baseline over 12 weeks in all groups (Supplementary Table S3). The treatment difference was 7.8% ($p = 0.002$) for FF/VI 100/25 mcg versus FF 100 mcg (Supplementary Table S3).

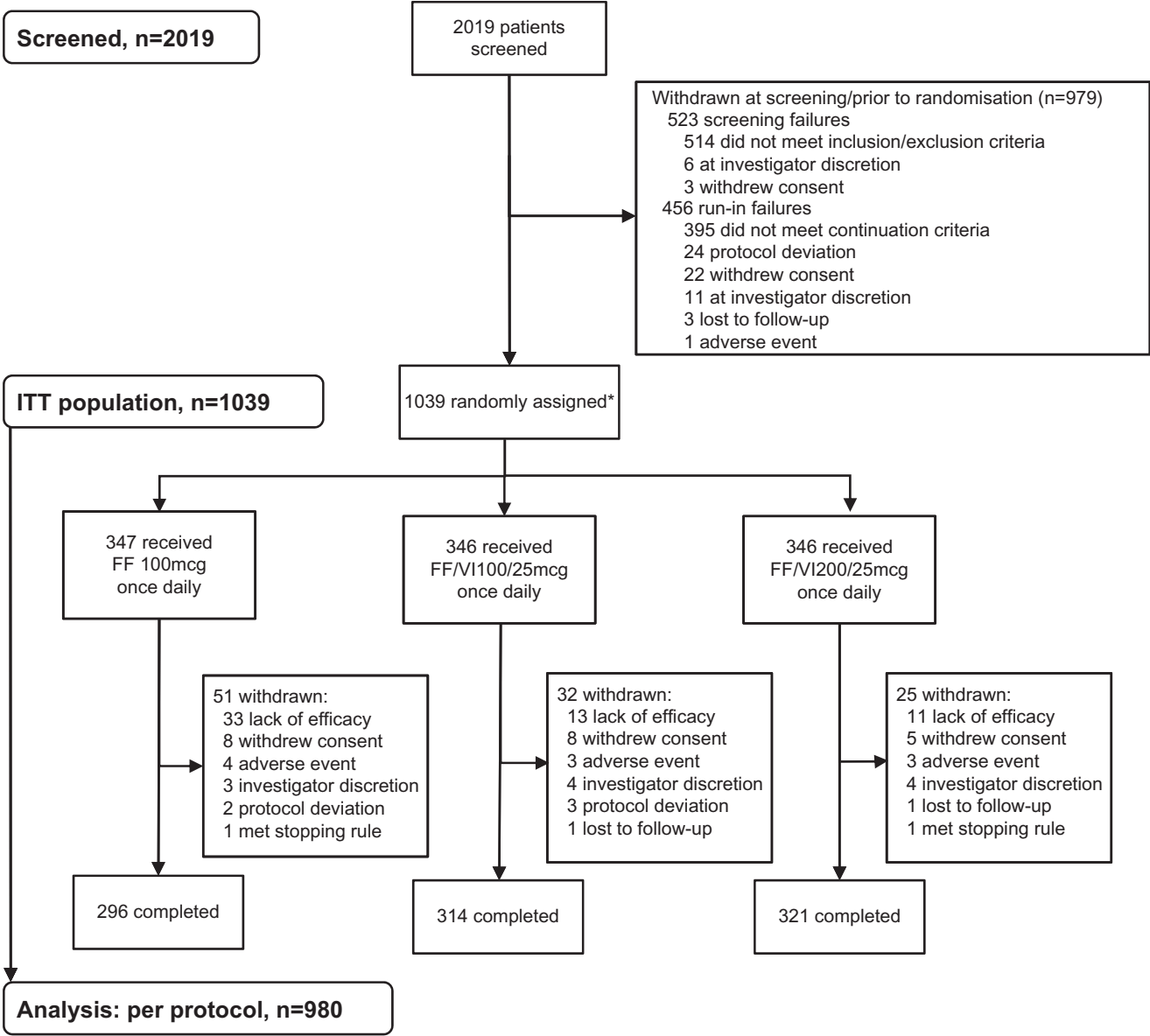


Figure 1. Patient flow diagram. FF, fluticasone furoate; ITT, intent-to-treat; PP, per-protocol; VI, vilanterol. *One patient had enrolled at each of two US sites which was discovered after randomization and this patient was withdrawn from both sites.

and Figure 2A), which equated to 0.5 additional symptom-free 24-h periods per week.

Morning PEF was increased from baseline in all groups (Supplementary Table S3 and Supplementary Figure S2A), and there was a statistically significant ($p < 0.001$) treatment difference (25.2 L/min) between FF/VI 100/25 mcg and FF 100 mcg (Supplementary Table S3 and Figure 2A). Similarly, evening PEF was increased from baseline (Supplementary Table S3 and Supplementary Figure S2B); the treatment difference for FF/VI 100/25 mcg versus FF 100 mcg of 24.2 L/min was statistically significant ($p < 0.001$; Supplementary Table S3 and Figure 2A).

Data for other end points are shown in Supplementary Table S3 and Figure 2(A). The treatment difference for FF/VI 100/25 mcg versus FF 100 mcg for the change from baseline in 12 h post-dose FEV₁ at week 12 (0.124 L) was statistically significant ($p < 0.001$). Although increases from baseline in AQLQ12+ score at week 12 in all groups were greater than the MID of 0.5 [23,24], the treatment difference of 0.08

($p = 0.303$) between the FF/VI 100/25 mcg and FF 100 mcg groups was smaller than the MID. Significantly fewer patients withdrew due to lack of efficacy in the FF/VI 100/25 mcg group versus FF 100 mcg ($p = 0.003$); this is supported by the cumulative incidence of time to withdrawal (Supplementary Figure S3). A statistically significant ($p = 0.002$) treatment difference for FF/VI 100/25 mcg versus FF 100 mcg of 0.9 in ACT score was observed at week 12. The proportion of patients with well-controlled asthma (ACT score ≥ 20) at week 12 was 40% (FF 100 mcg) and 46% (FF/VI 100/25 mcg). The odds ratio for achieving ACT score ≥ 20 was 1.42 (95% CI: 1.01–1.99; $p = 0.043$) for patients treated with FF/VI 100/25 mcg versus FF 100 mcg.

FF/VI 200/25 mcg versus FF/VI 100/25 mcg

FF/VI 200/25 mcg treatment resulted in small numerical improvements for all study end points versus FF/VI 100/25 mcg (Figure 2B and Supplementary Tables S2 and S3).

Table 1. Patient demographics and lung function at baseline (ITT population).

	FF 100 mcg OD (N = 347)	FF/VI 100/25 mcg OD (N = 346)	FF/VI 200/25 mcg OD (N = 346)	Total (N = 1039)
Age (years), mean $\pm$ SD (range)	44.7 $\pm$ 15.89 (12–78)	45.9 $\pm$ 16.14 (12–82)	46.6 $\pm$ 14.72 (12–79)	45.7 $\pm$ 15.60 (12–82)
Age group, n (%)				
<18 years	26 (7)	23 (7)	16 (5)	65 (6)
$\geq$ 18 to <65 years	288 (83)	284 (82)	296 (86)	868 (84)
$\geq$ 65 years	33 (10)	39 (11)	34 (10)	106 (10)
Gender: female, n (%)	199 (57)	205 (59)	224 (65)	628 (60)
Race, n (%) ^a				
White	305 (88)	307 (89)	300 (87)	912 (88)
African American/African Heritage	26 (7)	20 (6)	28 (8)	74 (7)
American Indian or Alaska Native and White	11 (3)	15 (4)	12 (3)	38 (4)
Japanese/East Asian Heritage/ South East Asian Heritage	4 (1)	2 (<1)	2 (<1)	8 (<1)
Other	1 (<1)	2 (<1)	3 (<1)	6 (<1)
Ethnicity, n (%)				
Hispanic/Latino	67 (19)	76 (22)	65 (19)	208 (20)
Not Hispanic/Latino	280 (81)	270 (78)	281 (81)	831 (80)
Duration of asthma (years), mean (SD)	17.87 (13.557)	17.77 (14.161)	19.27 (14.684)	18.31 (14.144)
Baseline lung function, mean (SD)	(n = 342)	(n = 342)	(n = 344)	(n = 1028)
Pre-bronchodilator FEV ₁ , L	1.965 (0.5980)	1.985 (0.5563)	1.954 (0.5819)	1.968 (0.5786)
% Predicted FEV ₁	61.13 (10.348)	62.64 (10.148)	62.12 (10.050)	61.96 (10.192)
Pre-bronchodilator FVC, L	3.045 (0.9370)	3.027 (0.8891)	3.035 (0.9224)	3.035 (0.9155)
Pre-bronchodilator FEV ₁ /FVC, %	65.46 (11.430)	66.72 (11.434)	65.31 (10.655)	65.83 (11.185)
% reversibility FEV ₁ ^b	30.79 (19.153)	29.10 (16.537)	29.33 (15.701)	29.74 (17.198)
Pre-study ICS regimen, n (%)				
Mid-dose ICS alone ^c	91 (26)	96 (28)	104 (30)	291 (28)
High-dose ICS alone ^d	24 (7)	26 (8)	29 (8)	79 (8)
ICS/LABA combination	232 (67)	224 (65)	213 (62)	669 (64)

FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta₂ agonist; OD, once daily; SD, standard deviation; VI, vilanterol.

^aRace data available for 345 and 1038 patients in the FF/VI 200/25 mcg and Total groups, respectively.

^bData available for 346 (FF 100 mcg) and 1032 (total) patients.

^c>250–500 mcg FP daily, or equivalent.

^d>500 mcg FP daily, or equivalent.

Table 2. Results from the analyses of the primary, secondary, and other end points at week 12 (ITT population).

End point	FF 100 mcg OD (n = 347)	FF/VI 100/25 mcg OD (n = 346)	FF/VI 200/25 mcg OD (n = 346) ^a
Primary end point			
wm 0–24-h FEV ₁			
n	288	312	312
LS mean	2.347	2.455	2.479
LS mean (SE) change from baseline, L	0.366 (0.0231)	0.474 (0.0221)	0.499 (0.0222)
Treatment difference versus FF 100 mcg (95% CI)		0.108 (0.045, 0.171) $p < 0.001$	
Treatment difference versus FF/VI 100/25 mcg (95% CI)			0.024 (–0.037, 0.086)
Powered secondary end points			
Change from baseline in trough FEV ₁			
n	336	334	337
LS mean	2.334	2.411	2.426
LS mean (SE) change from baseline, L	0.365 (0.0220)	0.441 (0.0221)	0.457 (0.0220)
Treatment difference versus FF 100 mcg (95% CI)		0.077 (0.016, 0.138) $p = 0.014$	
Treatment difference versus FF/VI 100/25 mcg (95% CI)			0.016 (–0.046, 0.077)
Change from baseline in % rescue-free 24 h periods during 12-week treatment period			
n	346	345	346
LS mean (SE) change from baseline	22.6 (1.84)	34.8 (1.85)	35.8 (1.85)
Treatment difference versus FF 100 mcg (95% CI)		12.2 (7.1, 17.3) $p < 0.001$	
Treatment difference versus FF/VI 100/25 mcg (95% CI)			0.9 (–4.2, 6.1)
Equivalent number of additional rescue-free days per week			
LS mean change from baseline	1.6	2.4	2.5
LS mean difference to FF 100 mcg OD		0.9	
LS mean difference to FF/VI 100/25 mcg OD			0.1

Analyses performed using ANCOVA with covariates of baseline, region, sex, age and treatment. AM, morning; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily; PEF, peak expiratory flow; PM, evening; SE, standard error; VI, vilanterol; wm, weighted mean.

^aDescriptive comparison between FF/VI 200/25 mcg and FF/VI 100/25 mcg only (no formal inference made).

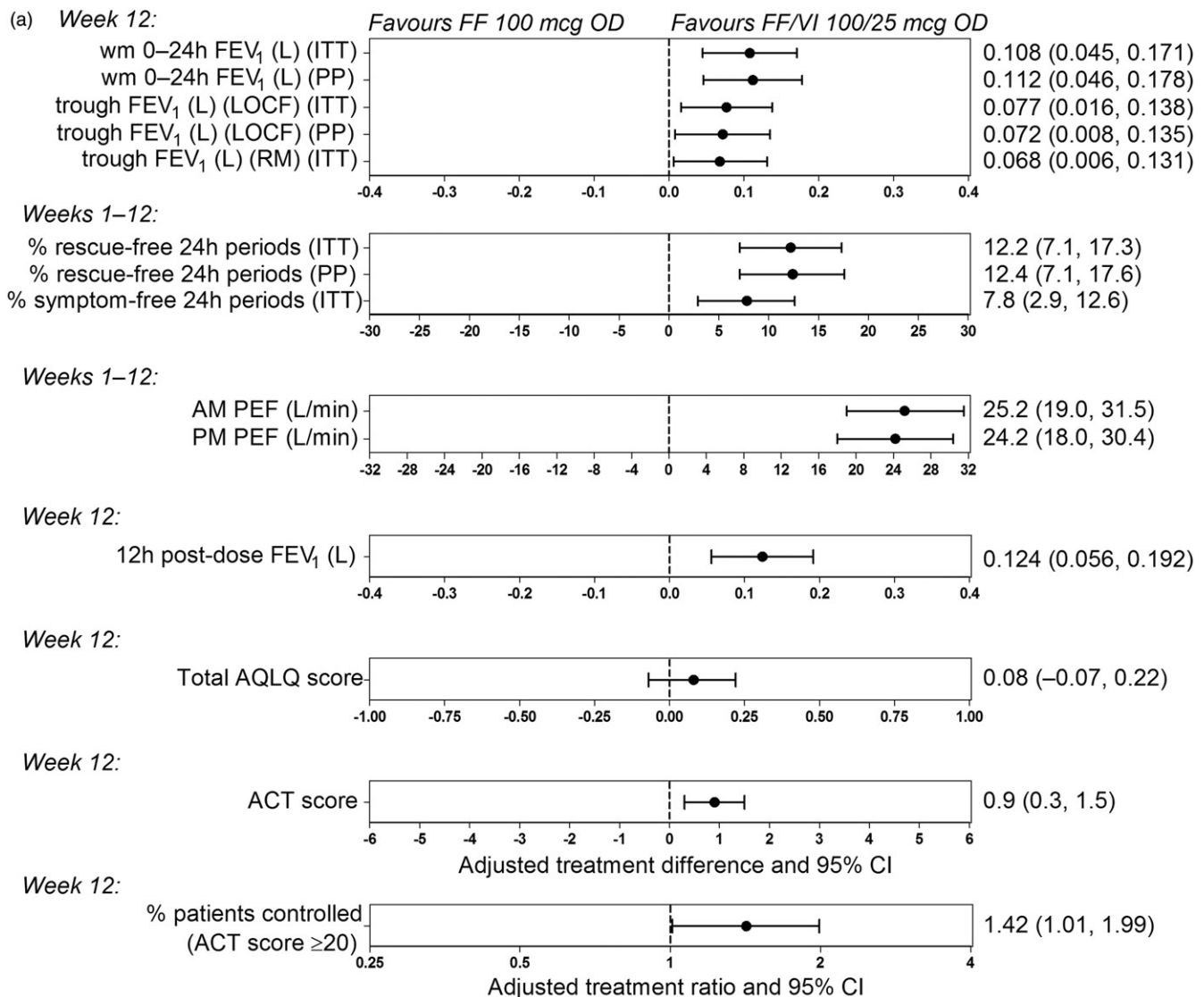


Figure 2. Adjusted treatment differences and ratios for primary, secondary and other efficacy end points comparing (A) FF/VI 100/25 mcg with FF 100 mcg; (B) FF/VI 200/25 mcg with FF/VI 100/25 mcg (ITT population, unless otherwise stated). ACT, asthma control test; AM, morning; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; OD, once daily; PEF, peak expiratory flow; PM, evening; PP, per-protocol; VI, vilanterol; wm, weighted mean.

Safety assessments

The incidence of on-treatment AEs was similar across groups. Treatment-related AEs (as assessed by the investigator) occurred in 3% (FF 100 mcg), 2% (FF/VI 100/25 mcg) and 4% (FF/VI 200/25 mcg) of patients (Table 3). On-treatment SAEs were: pneumonia ($n=2$) and borderline mucinous ovarian tumor ($n=1$) for FF 100 mcg; biliary colic, acute pancreatitis, thermal burn and occipital neuralgia ($n=1$ for each) with FF/VI 100/25 mcg; and abortion threatened ($n=1$) in the FF/VI 200/25 mcg group. The incidence of on-treatment drug-related AEs was low (3% in the FF 100 mcg group, 2% in the FF/VI 100/25 mcg group and 2% in the FF/VI 200/25 mcg group), and driven mainly by oral/oropharyngeal candidiasis ($n=2$ [$<1\%$] for FF 100 mcg, $n=1$ [$<1\%$] for FF/VI 100/25 mcg, and $n=5$ [1%] in the FF/VI 200/25 mcg group), headache ($n=1$ [$<1\%$] in each group) and dysphonia ($n=1$ [$<1\%$] for FF 100 mcg, $n=2$ [$<1\%$] for FF/VI 100/25 mcg, and $n=1$

[$<1\%$] for FF/VI 200/25 mcg). There were no post-treatment SAEs, and there were no deaths during the study. The most frequent AE of special interest (Supplementary Table S4) was local steroid effects in 3% (FF), 4% (FF/VI 100/25 mcg) and 4% (FF/VI 200/25 mcg) of patients. Fourteen patients experienced severe asthma exacerbations on treatment: seven (2%) on FF 100 mcg, three ($<1\%$) on FF/VI 100/25 mcg and four (1%) on FF/VI 200/25 mcg; all but one (FF/VI 200/25 mcg) of these patients discontinued the study. All severe asthma exacerbations were treated with systemic/oral corticosteroids, and one patient (FF/VI 100/25 mcg) visited an emergency room, but none were hospitalized. In contrast, in the year prior to the study 29% of patients experienced an exacerbation requiring oral corticosteroids and 7% had an exacerbation requiring hospitalization. Three patients had pneumonia (FF 100 mcg $n=2$; FF/VI 100/25 mcg $n=1$). One patient (FF 100 mcg) withdrew from the study due to pneumonia which resolved after 23 days.

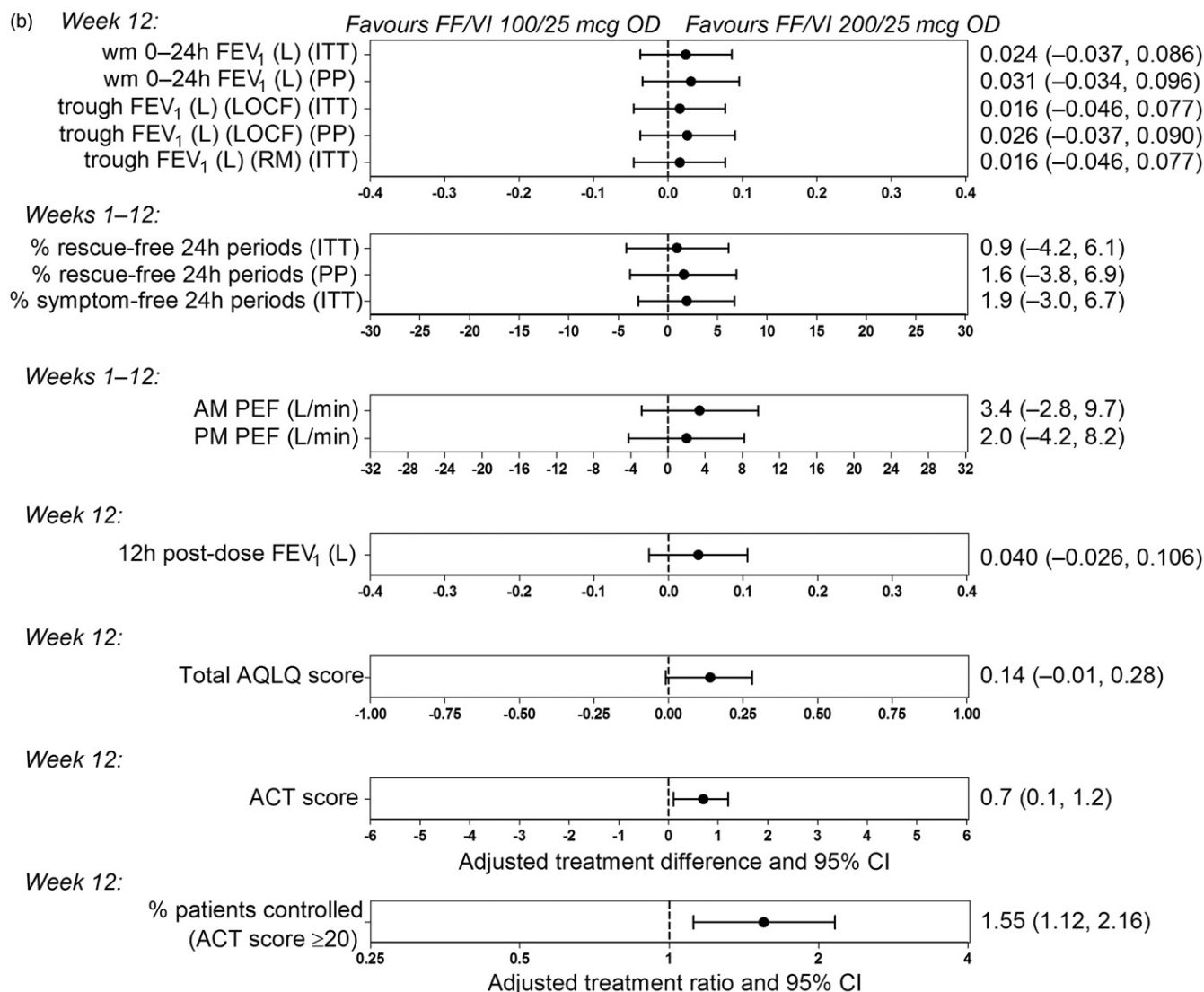


Figure 2. Continued.

Discussion

In this study, once-daily FF/VI 100/25 mcg significantly improved wmFEV₁ 0-24h, an important measure of lung function over the 24-h dosing interval, versus FF 100 mcg in patients with asthma previously uncontrolled on mid-to-high dose ICS or mid-dose ICS/LABA. This was supported by significant improvements in trough FEV₁ and the proportion of 24-h periods that patients did not have to use rescue medication and the proportion of 24-h periods that patients did not have symptoms.

Previous studies comparing FF/VI 100/25 mcg and FF 100 mcg have shown mixed results for FEV₁ end points. In a 12-week study, Bleecker et al. were not able to show statistically significant treatment differences in wm and trough FEV₁ end points for once-daily FF/VI 100/25 mcg over FF 100 mcg [16] in patients uncontrolled on low-to-mid-dose ICS or low-dose ICS/LABA; in our study, however, patients using low-dose ICS ± LABA were not included. In a study by Bateman et al., which recruited patients receiving ≥200 mcg FP daily or equivalent, or 200/100-500/100 mcg FP/salmeterol daily or equivalent, improvements from

baseline in trough FEV₁ were significant for FF/VI 100/25 mcg versus FF 100 mcg [25]. Our study provides further information on the contribution of VI to the efficacy of FF/VI 100/25 mcg compared with FF 100 mcg alone, particularly with respect to the serial measurement of wmFEV₁ 0-24h (which was not assessed by Bateman et al.). It is worth noting that the treatment difference in wmFEV₁ 0-24h for FF/VI 100/25 mcg versus FF 100 mcg in the Bleecker et al. study (116 mL) was slightly larger than in the present study (108 mL) [12]. Thus, a more likely explanation for the discrepant results in wmFEV₁ is the difference in statistical power between the studies; fewer patients in the Bleecker et al. study underwent serial FEV₁ evaluations than in our study.

For wmFEV₁ and trough FEV₁, the change from baseline with FF 100 mcg and FF/VI 100/25 mcg was larger for patients with baseline FEV₁ ≤ 65% predicted compared with those with FEV₁ > 65% predicted. These observations indicate that patients with poorer lung function at baseline may have a greater potential to improve lung function in response to anti-inflammatory treatments.

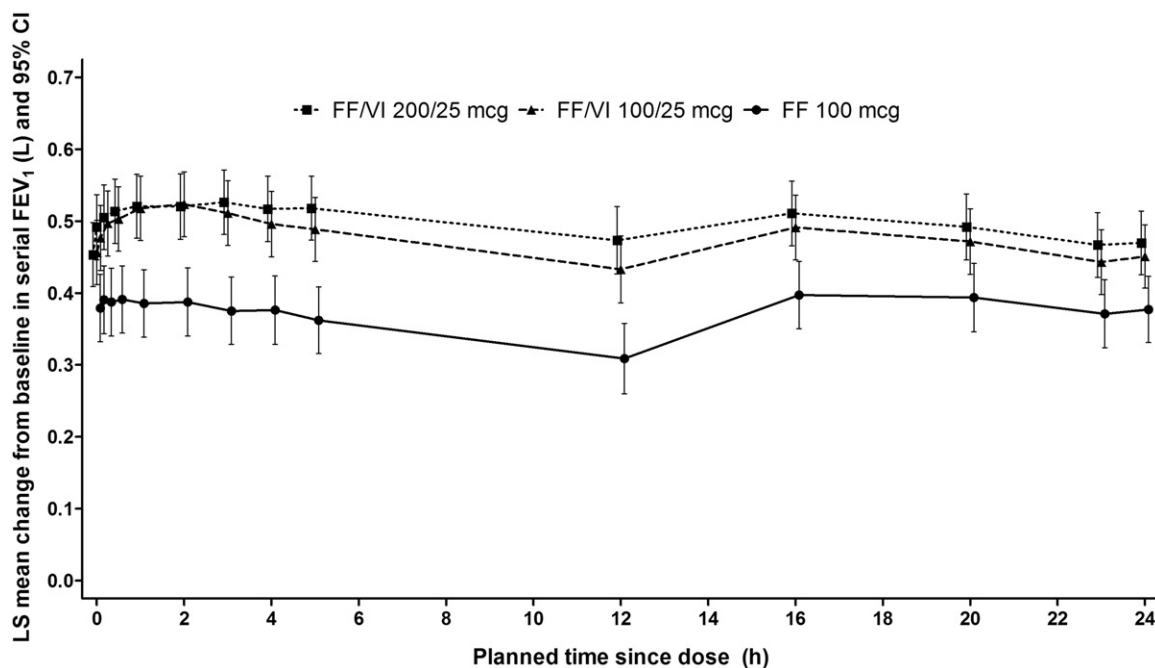


Figure 3. Adjusted mean change from baseline of individual serial FEV₁ assessments at week 12 (ITT population). CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily; VI, vilanterol.

FF/VI 100/25 mcg significantly improved all secondary and other end points (except change from baseline in AQLQ at week 12) versus FF 100 mcg. These findings are consistent with previous studies comparing FF/VI with FF [12,22] and with meta-analyses comparing ICS/LABA with ICS only in patients with persistent asthma [6,26]. Improvements in the proportion of rescue-free 24-h periods and symptom-free 24-h periods seen with FF/VI 100/25 mcg versus FF 100 mcg were clinically meaningful, being within the MIDs previously identified (8–16% and 8–15%, respectively) [27]. Although the change from baseline values for each treatment exceeded the MIDs (0.5 [23,24] and 3 units [28], respectively), indicating that patients had improved quality of life and asthma control with each of the once-daily treatments, the treatment differences between FF/VI 100/25 mcg and FF 100 mcg in AQLQ and ACT scores failed to reach the MIDs [21,22,26]. However, the odds of being well-controlled at week 12 (ACT score ≥ 20) were 42% greater for patients treated with FF/VI 100/25 mcg compared with FF 100 mcg. A previous study that recruited patients with a history of severe exacerbations [25] reported that FF/VI 100/25 mcg was associated with greater improvements in Asthma Control Questionnaire 7 (ACQ7) than FF 100 mcg ($p < 0.001$ at all time points) with the odds of a patient having well-controlled asthma (ACQ7 score ≥ 0.75) being greater for FF/VI compared with FF. At the study endpoint, patients receiving FF/VI were 50% more likely to have their asthma well-controlled than those on FF alone [25].

A secondary objective of this study was to descriptively assess the relative efficacy of once-daily FF/VI 200/25 mcg versus FF/VI 100/25 mcg. Small numerical improvements were seen with FF/VI 200/25 mcg versus FF/VI 100/25 mcg for all end points. It can be difficult to show a dose-response to ICS, especially in the presence of a LABA; however, the odds of a patient being well-controlled (ACT score ≥ 20) were

55% higher with FF/VI 200/25 mcg compared with FF/VI 100/25 mcg. These results are supported by those of a study of different doses of FF monotherapy, which showed numerical increases in lung function end points for once-daily FF 200 mcg compared with once-daily FF 100 mcg [29]. In that study, the odds of being well-controlled (ACT score ≥ 20) were 42% greater with FF 200 mcg compared with FF 100 mcg. In the present study, for $wmFEV_1$ and trough FEV₁, the change from baseline with FF/VI 200/25 mcg versus FF/VI 100/25 mcg was greater for patients with FEV₁ $> 65\%$ than those with FEV₁ $\leq 65\%$ at baseline (62 mL versus –1 mL and 57 mL versus –12 mL, respectively). These observations suggest that ICS dose-response may be dependent on the level of airway inflammation, which may be reflected by the severity of airflow limitation.

Overall, no new safety concerns were raised with any treatments; all options were well-tolerated and represent valid treatment choices for patients. The AEs with FF/VI 100/25 mcg and FF/VI 200/25 mcg were consistent with those reported in a 12-month safety study [30]. The incidences of AEs expected with ICS (e.g. local steroid effects, respiratory tract infections, bone disorders [1,31]) or LABA (e.g. glucose increase, cardiovascular effects [1]) were low across all groups. As expected, local steroid effects were observed in all groups, although the incidence was low and similar across all treatment groups. There was no evidence of an increased risk of cardiovascular effects due to the addition of VI to the regimen. Although some patients experienced severe asthma exacerbations requiring oral corticosteroids during the study, the incidence was less than that recorded in the year prior to the study.

The study strengths include enrollment of suitable patients with persistent moderate-to-severe asthma; i.e. patients with uncontrolled asthma and requiring Step 3 treatment or above, as per the Global Initiative for Asthma (GINA) guidelines [1].

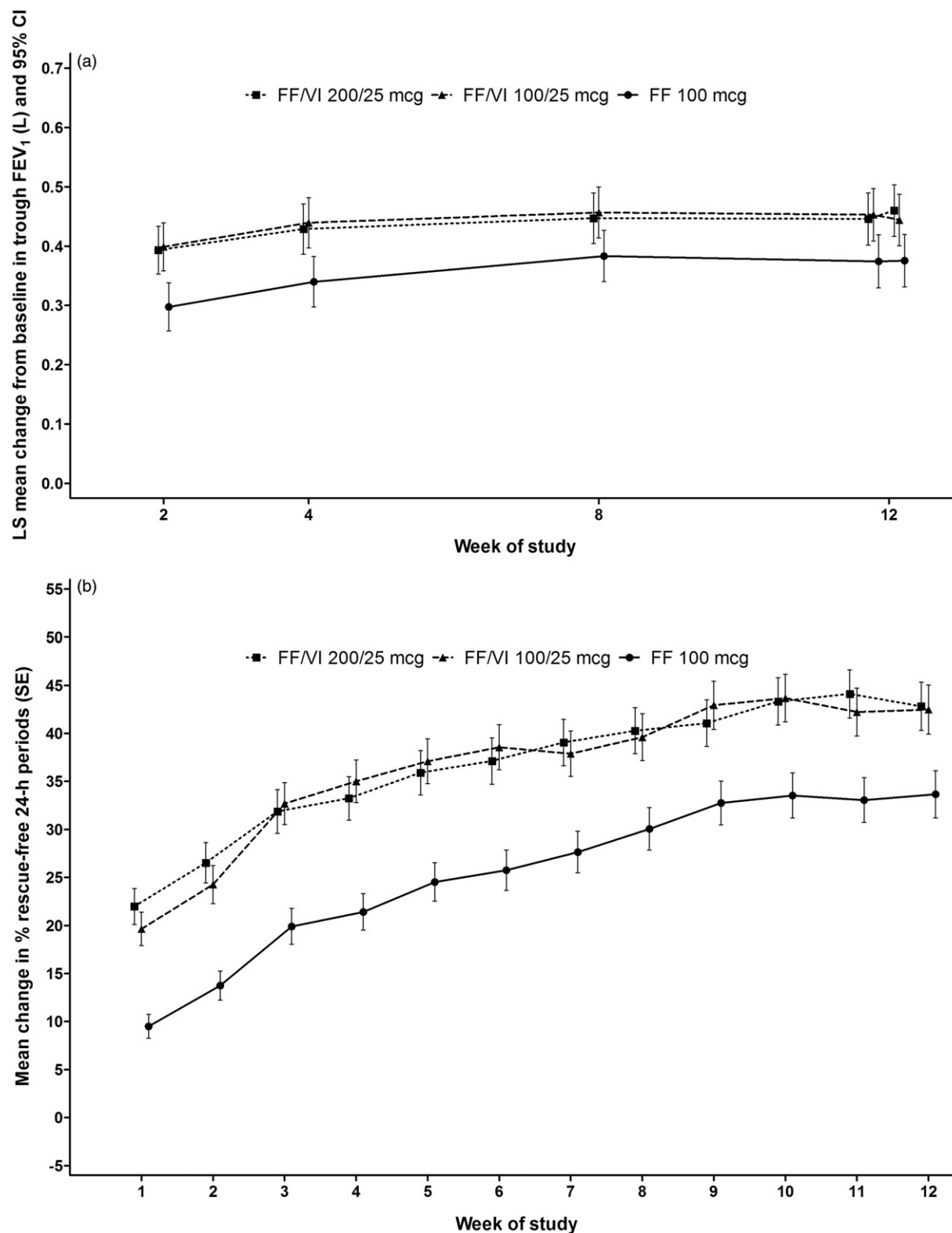


Figure 4. Repeated measures analysis of (A) change from baseline in trough FEV₁; (B) change from baseline in % rescue-free 24-h periods over weeks 0–12 (ITT population). CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily (evening); VI, vilanterol.

Compliance with study medication in all groups was very high ($\approx 99\%$). Moreover, this study is one of the first to assess two doses of the same ICS (i.e. FF) in the corresponding ICS/LABA combination. Potential limitations of our study include the lack of a placebo arm, the relatively short duration and the fact that the comparison of FF/VI 200/25 mcg versus FF/VI

100/25 mcg was not powered and could only be interpreted descriptively. There were only a few patients on high-dose ICS pre-study, so an evaluation of the potential dose response between the two doses of FF/VI in such patients was not feasible. Additionally, the proportion of patients with childhood-onset asthma or allergic rhinitis, neither taking

Table 3. Summary of incidence of AEs, serious AEs and most frequent on-treatment AEs (ITT population).

	FF 100 mcg OD (N = 347)	FF/VI 100/25 mcg OD (N = 346)	FF/VI 200/25 mcg OD (N = 346)
AEs			
Any on-treatment	127 (37)	127 (37)	123 (36)
Any post-treatment	3 (<1)	6 (2)	4 (1)
Drug-related	11 (3)	7 (2)	8 (2)
Leading to permanent discontinuation or withdrawal	4 (1)	3 (<1)	3 (<1)
Serious AEs			
Any on-treatment	3 (<1)	4 (1)	1 (<1)
Any post-treatment	0	0	0
On-treatment AEs occurring in ≥3% patients in any treatment group			
Any event	127 (37)	127 (37)	123 (36)
Headache	32 (9)	29 (8)	29 (8)
Nasopharyngitis	26 (7)	22 (6)	25 (7)
Upper respiratory tract infection	12 (3)	8 (2)	7 (2)
Influenza	4 (1)	10 (3)	9 (3)

All data are *n* (%). AE, adverse event; FF, fluticasone furoate; ITT, intent-to-treat; OD, once daily; VI, vilanterol.

intranasal corticosteroids was not recorded, nor were any environmental controls specified in the current study. Allergic rhinitis and environmental factors (e.g. second-hand smoke) are known to affect asthma control [32,33] and could potentially confound the interpretation of our results.

Conclusions

This study demonstrated that, in patients with moderate-to-severe persistent asthma, once-daily FF/VI 100/25 mcg was significantly more effective in improving lung function and symptoms than once-daily FF 100 mcg, over 12 weeks. Small numerical improvements occurred with FF/VI 200/25 mcg versus FF/VI 100/25 mcg. AEs were in line with the class effects expected for ICS and LABA treatment. The incidence of drug-related AEs was low with each of the studied treatment options. Very few drug-related AEs led to withdrawal of treatment, suggesting that FF/VI 100/25 mcg, FF/VI 200/25 mcg and FF 100 mcg are all valid treatment options for moderate-to-severe persistent asthma, providing further choice for patients.

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Declaration of interest

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Supplementary Table S1. Baseline lung function by asthma severity (ITT population).

	FF 100 mcg OD (N=347)	FF/VI 100/25 mcg OD (N=346)	FF/VI 200/25 mcg OD (N=346)	Total (N=1039)
Baseline lung function, mean (SD)				
FEV ₁ ≤65% predicted	(n=207)	(n=204)	(n=205)	(n=616)
Pre-bronchodilator FEV ₁ , L	1.709 (0.4655)	1.784 (0.4948)	1.713 (0.4645)	1.735 (0.4756)
% predicted FEV ₁	54.32 (6.979)	55.85 (6.828)	55.32 (6.523)	55.16 (6.799)
Pre-bronchodilator FVC, L	2.805 (0.8164)	2.874 (0.8805)	2.817 (0.8195)	2.832 (0.8383)
Pre-bronchodilator FEV ₁ /FVC, %	62.18 (11.718)	63.60 (11.593)	61.93 (10.306)	62.57 (11.231)
% reversibility FEV ₁	36.18 (21.861)	32.61 (18.906) ^a	33.51 (17.504) ^b	34.11 (19.549)
FEV ₁ >65% predicted	(n=135)	(n=138)	(n=139)	(n=412)
Pre-bronchodilator FEV ₁ , L	2.358 (0.5659)	2.282 (0.5088)	2.311 (0.5550)	2.316 (0.5433)
% predicted FEV ₁	71.59 (3.971)	72.67 (4.129)	72.15 (4.256)	72.14 (4.136)
Pre-bronchodilator FVC, L	3.412 (0.9922)	3.253 (0.8558)	3.355 (0.9738)	3.340 (0.9422)
Pre-bronchodilator FEV ₁ /FVC, %	70.50 (8.894)	71.32 (9.514)	70.29 (9.125)	70.70 (9.171)
% reversibility FEV ₁	22.17 (8.576)	23.74 (10.051)	23.11 (9.804)	23.01 (9.505)

FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; FVC, forced vital capacity; ITT, intent-to-treat; OD, once daily; SD, standard deviation; VI, vilanterol.

^an=203.

^bn=204.

Supplementary Table S2. Results from the analyses of wm 0–24-h FEV₁ (primary end point) and change from baseline in trough FEV₁ (first powered secondary end point) by severity of baseline lung function, at Week 12 (ITT population).

End point	FF 100 mcg OD (N=347)	FF/VI 100/25 mcg OD (N=346)	FF/VI 200/25 mcg OD (N=346) ^a
Primary end point			
wm 0–24-h FEV₁ (in baseline % predicted FEV₁ ≤65%)			
<i>n</i>	169	186	182
LS mean	2.440	2.532	2.531
LS mean (SE) change from baseline, L	0.460 (0.0318)	0.552 (0.0294)	0.551 (0.0300)
Treatment difference vs. FF 100 mcg (95% CI)		0.092 (0.011, 0.173)	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			–0.001 (–0.080, 0.078)
wm 0–24-h FEV₁ (in baseline % predicted FEV₁ >65%)			
<i>n</i>	119	126	130
LS mean	2.222	2.339	2.401
LS mean (SE) change from baseline, L	0.241 (0.0379)	0.358 (0.0366)	0.420 (0.0367)
Treatment difference vs. FF 100 mcg (95% CI)		0.117 (0.020, 0.214)	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			0.062 (–0.033, 0.157)
First powered secondary end point			
Change from baseline in trough FEV₁ (in baseline % predicted FEV₁ ≤65%)			
<i>n</i>	203	199	200
LS mean	2.418	2.487	2.474
LS mean (SE) change from baseline, L	0.449 (0.0302)	0.517 (0.0293)	0.505 (0.0294)
Treatment difference vs. FF 100 mcg (95% CI)		0.069 (–0.010, 0.147)	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			–0.012 (–0.091, 0.066)
Change from baseline in trough FEV₁ (in baseline % predicted FEV₁ >65%)			
<i>n</i>	133	135	137
LS mean	2.217	2.293	2.350
LS mean (SE) change from baseline, L	0.248 (0.0371)	0.324 (0.0367)	0.381 (0.0368)
Treatment difference vs. FF 100 mcg (95% CI)		0.076 (–0.020, 0.171)	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			0.057 (–0.038, 0.152)

Analyses performed using ANCOVA with covariates of baseline, region, sex, age, and treatment.

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily; SE, standard error; VI, vilanterol; wm, weighted mean.

^aDescriptive comparison between FF/VI 200/25 mcg and FF/VI 100/25 mcg only (no formal inference made).

Supplementary Table S3. Results from the analyses of the other secondary and other end points at Week 12 (ITT population).

End point	FF 100 mcg OD (N=347)	FF/VI 100/25 mcg OD (N=346)	FF/VI 200/25 mcg OD (N=346) ^a
Secondary efficacy end points (non-powered)			
Change from baseline in % symptom-free 24-h periods			
<i>n</i>	346	345	346
LS mean (SE) change from baseline	19.4 (1.74)	27.2 (1.74)	29.0 (1.74)
Treatment difference vs. FF 100 mcg (95% CI)		7.8 (2.9, 12.6) <i>p</i> =0.002	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			1.9 (-3.0, 6.7)
Equivalent number of additional symptom-free days per week			
LS mean change from baseline	1.4	1.9	2.0
LS mean difference to FF 100 mcg OD		0.5	
LS mean difference to FF/VI 100/25 mcg OD			0.1
Change from baseline in AM PEF			
<i>n</i>	346	345	345
LS mean	346.1	371.3	374.8
LS mean (SE) change from baseline, L/min	19.1 (2.25)	44.3 (2.25)	47.7 (2.25)
Treatment difference vs. FF 100 mcg (95% CI)		25.2 (19.0, 31.5) <i>p</i> <0.001	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			3.4 (-2.8, 9.7)
Change from baseline in PM PEF			
<i>n</i>	346	345	346
LS mean	350.5	374.6	376.6
LS mean (SE) change from baseline, L/min	15.5 (2.24)	39.7 (2.24)	41.7 (2.24)
Treatment difference vs. FF 100 mcg (95% CI)		24.2 (18.0, 30.4) <i>p</i> <0.001	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			2.0 (-4.2, 8.2)
Other efficacy end points			
12 h post-dose FEV₁ at Week 12			
<i>n</i>	284	311	309
LS mean (SE) change from baseline, L	2.292 (0.0249)	2.416 (0.0238)	2.457 (0.0239)

Treatment difference vs. FF 100 mcg (95% CI)		0.124 (0.056, 0.192) $p<0.001$	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			0.040 (-0.026, 0.106)
Change from baseline in Total AQLQ score			
<i>n</i>	300	317	326
LS mean	5.28	5.36	5.49
LS mean (SE) change from baseline	0.76 (0.053)	0.84 (0.051)	0.97 (0.051)
Treatment difference vs. FF 100 mcg (95% CI)		0.08 (-0.07, 0.22) $p=0.303$	
Treatment difference vs. FF/VI 100/25 mcg (95% CI)			0.14 (-0.01, 0.28)
Withdrawals due to lack of efficacy			
Patients whose primary reason for withdrawal was lack of efficacy, <i>n</i> (%)	33 (10)	13 (4)	11 (3)
Comparison vs. FF 100 mcg		$p=0.003$	
Change from baseline in ACT score			
<i>n</i>	300	318	326
LS mean (SE) change from baseline	3.8 (0.22)	4.7 (0.21)	5.4 (0.21)
Treatment difference vs. FF 100 mcg (95% CI)		0.9 (0.3, 1.5) $p=0.002$	
Comparison vs. FF/VI 100/25 mcg (95% CI)			0.7 (0.1, 1.2)
Patients controlled			
<i>n</i>	300	318	326
ACT score <20, <i>n</i> (%)	179 (60)	171 (54)	143 (44)
ACT score ≥20, <i>n</i> (%)	121 (40)	147 (46)	183 (56)
Treatment ratio vs. FF 100 mcg, odds ratio (95% CI)		1.42 (1.01, 1.99) $p=0.043$	
Treatment ratio vs. FF/VI 100/25 mcg, odds ratio (95% CI)			1.55 (1.12, 2.16)

Analyses performed using ANCOVA with covariates of baseline, region, sex, age and treatment.

AM, morning; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily; PEF, peak expiratory flow; PM, evening; SE, standard error; VI, vilanterol; wm, weighted mean.

^aDescriptive comparison between FF/VI 200/25 mcg and FF/VI 100/25 mcg only (no formal inference made).

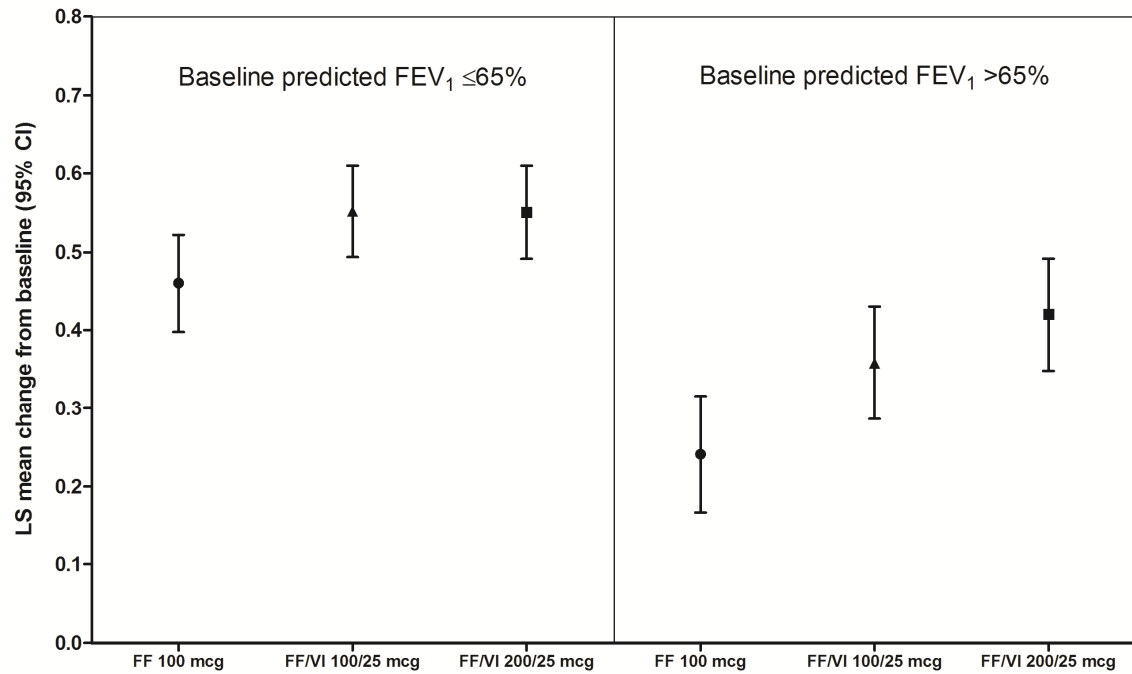
Supplementary Table S4. Summary of on-treatment and post-treatment FF/VI AEs of special interest (ITT population).

	FF 100 mcg OD (N=347)	FF/VI 100/25 mcg OD (N=346)	FF/VI 200/25 mcg OD (N=346)
Any event	27 (8)	27 (8)	25 (7)
Local steroid effects	10 (3)	14 (4)	15 (4)
LRTI excluding pneumonia	9 (3)	3 (<1)	7 (2)
Cardiovascular effects	3 (<1)	6 (2)	1 (<1)
Hypersensitivity	2 (<1)	4 (1)	3 (<1)
Bone disorders	1 (<1)	1 (<1)	1 (<1)
Pneumonia	2 (<1)	1 (<1)	0
Effects on glucose	1 (<1)	1 (<1)	0

All data are n (%). AE, adverse event; FF, fluticasone furoate; ITT, intent-to-treat; LRTI, lower respiratory tract infection; OD, once daily; VI, vilanterol.

Supplementary Figure S1. Analyses of wm 0–24-h FEV₁ by asthma severity (ITT population).

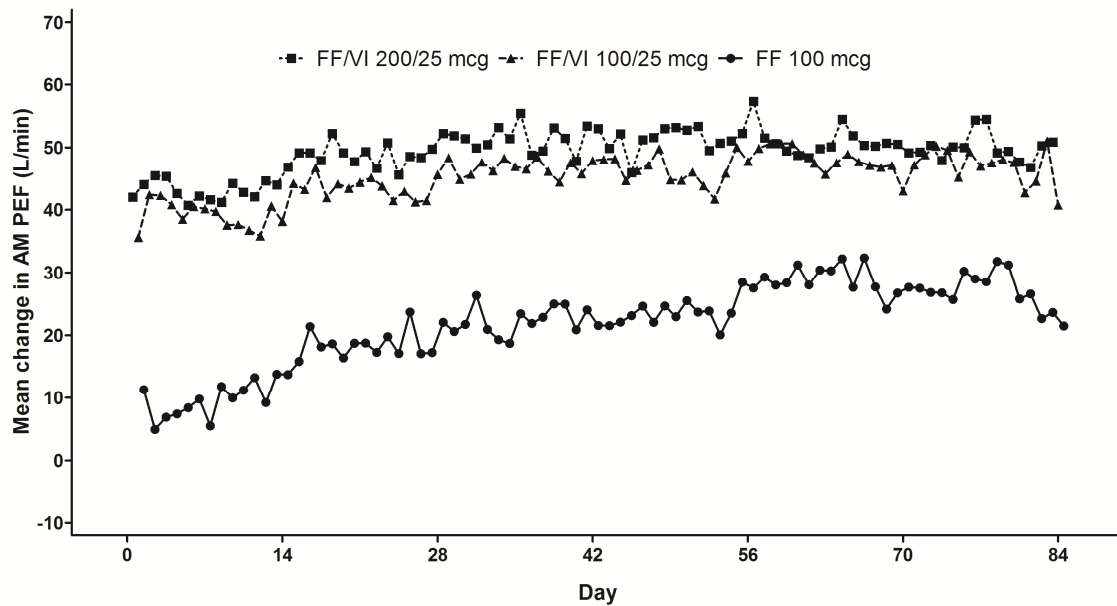
CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; OD, once daily (evening); VI, vilanterol; wm, weighted mean.



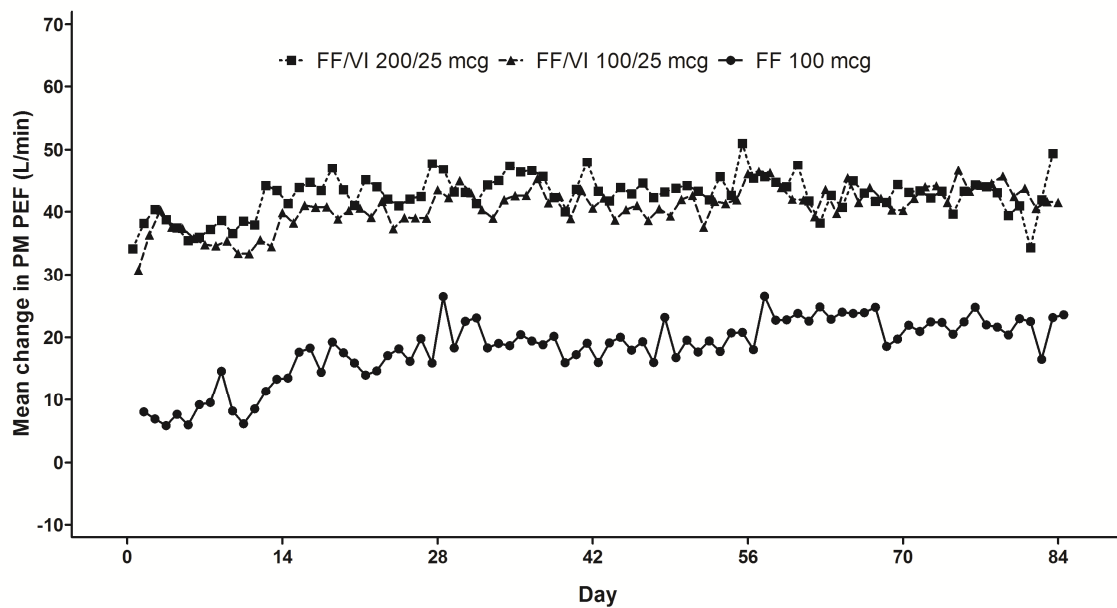
Supplementary Figure S2. Mean change from baseline in (A) AM PEF (L/min) and (B) PM PEF (L/min) (ITT population).

AM, morning; FF, fluticasone furoate; ITT, intent-to-treat; OD, once daily; PEF, peak expiratory flow; PM, evening; VI, vilanterol.

A



B



Supplementary Figure S3. Cumulative incidence curve of time to withdrawal due to lack of efficacy (ITT population).

FF, fluticasone furoate; ITT, intent-to-treat; OD, once daily; VI, vilanterol.

