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Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma

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ABSTRACT

The inhaled corticosteroid fluticasone furoate (FF) and the long-acting β_2 agonist vilanterol (VI) are in development as a combined once-daily therapy for asthma and COPD. Study objectives were to compare the efficacy and safety of once-daily FF/VI with FF alone and twice-daily fluticasone propionate (FP) in patients ≥12 years of age with moderate-to-severe persistent asthma.

Patients (N=586) received FF/VI 200/25µg or FF 200µg once-daily (evening dosing), or FP 500µg twice-daily for 24 weeks. Co-primary endpoints: change from baseline in trough FEV_1; weighted mean (wm) 0–24h serial FEV_1. Secondary endpoints included change from baseline in percentage rescue-free 24-h periods, percentage symptom-free 24-h periods and Total Asthma Quality of Life Questionnaire (AQLQ). Safety assessments included adverse events (AEs), 24h urinary cortisol (UC) excretion, vital signs and ECG.

FF/VI significantly improved trough FEV_1 and $wmFEV_1$ *versus* FF and FP. Significantly more rescue-free and symptom-free 24-h periods were reported with FF/VI *versus* FF. Treatment differences for AQLQ were not significant. Incidence of AEs was similar across groups. No clinically significant differences were seen for 24h UC excretion, vital signs or ECG.

FF/VI resulted in statistically greater improvements in lung function and symptomatic endpoints *versus* FF, and was well tolerated in this asthma population.

INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory treatments for all severities of persistent asthma [1]. The benefits of ICS include better control of asthma symptoms, improvement in lung function and fewer exacerbations [2]. Once-daily dosing of ICS can improve treatment adherence relative to twice-daily treatments [3], potentially improving asthma control. Fluticasone furoate (FF) is an ICS with 24h activity approved for intranasal treatment of allergic rhinitis [4, 5] and is under development as a once-daily treatment for asthma. FF is structurally distinct from fluticasone propionate (FP) [6] and has both greater affinity for the glucocorticoid receptor and longer retention in respiratory tissues than FP [7]. FF has been shown to be effective in asthma in earlier trials, with daily doses of 100µg and 200µg having a favourable therapeutic index [8–10]. Additionally, non-inferiority of FF 200µg once-daily to FF 100µg twice-daily has been shown, providing clinical evidence that FF is suitable for once-daily dosing [11].

The benefits of adding long-acting β_2 agonists (LABA) to an ICS in twice-daily treatments are well documented for lung function, symptom control, rescue medication use, and asthma exacerbation frequency [1, 12]. Vilanterol (VI) is a novel once-daily inhaled LABA shown to provide bronchodilation for at least 24h; 25µg is considered the optimal dose [13]. Once-daily FF/VI is being investigated as a combination therapy for asthma at strengths of 100/25µg and 200/25µg.

The aims of this study were to compare the efficacy and safety of once-daily FF/VI 200/25µg with once-daily FF 200µg alone in patients aged ≥12 years with moderate-to-severe persistent asthma; twice-daily FP 500µg was included as an active comparator. Additionally, the study sought to demonstrate non-inferiority of FF 200µg once-daily compared with FP 500µg twice-daily. Preliminary results have been published in abstract form [14].

METHODS

Patients

The study enrolled asthma patients [15] aged ≥12 years with documented use of ICS, with or without LABA, for ≥12 weeks with stable ICS dose (FP 500µg twice daily [or equivalent], or mid-dose ICS/LABA [FP/salmeterol 250/50µg twice daily or equivalent]) for ≥4 weeks. Eligible patients were required to demonstrate an evening pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of 40–90% of predicted normal and FEV_1 reversibility of ≥12% and ≥200mL on inhalation of albuterol/salbutamol. Patients were ineligible if they had a history of life-threatening asthma in the previous 10 years, an asthma exacerbation requiring overnight hospitalisation or emergency room attendance within 6 months of screening, and/or an asthma exacerbation requiring oral corticosteroids within 12 weeks of screening.

At screening, eligible patients entering the study on ICS/LABA therapy were switched to the same ICS at the same dose contained in the ICS/LABA combination for the 4-week run-in period prior to randomisation. No LABA was taken on the day of screening. Patients on ICS alone continued ICS-only therapy during run-in. All patients had to be able to replace their current short-acting bronchodilator with albuterol/salbutamol and to withhold albuterol/salbutamol for at least 6 h prior to study visits. At randomisation, all eligible patients were required to have recorded asthma symptoms (equating to a score of ≥3 on the asthma symptom scale) and/or daily albuterol/salbutamol use on ≥4 of the 7 preceding days. Electronic diary cards were used to capture daily measurements of peak expiratory flow (PEF), symptom scores and rescue use.

Written informed consent from each adult (≥18 years) patient was obtained prior to performing any study-specific procedures, as was assent and written parental consent for each

adolescent (12–17 years) patient. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki [16], Good Clinical Practice guidelines [17] and all applicable regulatory requirements.

Study design and treatments

This phase III, randomised, multicentre, double-blind, double-dummy, parallel-group study (GSK study number HZA106829; ClinicalTrials.gov registration number NCT01134042) was conducted between 10 June, 2010 and 18 October, 2011 at 63 centres in six countries (Germany, Japan, Poland, Romania, Russia, United States). Patients were randomised (1:1:1) to FF/VI 200/25µg (representing an emitted dose of 184/22µg), FF 200µg once daily in the evening, or FP 500µg twice daily (morning and evening) for 24 weeks.

FF/VI and FF were administered via a dry powder inhaler and FP was administered via DISKUS™/ACCUHALER™. Treatment compliance was assessed at each study visit after randomisation by reviewing the dose counters on the inhalers. Patients were randomised using Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system, following the generation of a central randomisation schedule generated by the sponsor using a validated computerised system (RandAll; GlaxoSmithKline, UK).

Details of medication prohibited during the study are given in the Online Supplement.

Outcome measurements

The co-primary endpoints were mean change from baseline in pre-dose (trough) FEV_1 and weighted mean (wm) FEV_1 (0–24h post-dose) after 24 weeks of treatment. Secondary efficacy endpoints were mean change from baseline in the percentage of rescue-free 24-h

periods during the 24-week treatment period (a nominated powered endpoint), change from baseline in the percentage of symptom-free 24-h periods during the 24-week treatment period, and change from baseline in Total Asthma Quality of Life Questionnaire (AQLQ+12) score after 12 and 24 weeks of treatment.

'Other' endpoints included 12 h post-dose FEV_1 at week 24; $wmFEV_1$ (0–4 h post-dose) at week 24; mean change from baseline in daily morning and evening PEF over weeks 1–12 and 1–24; change from baseline in the Asthma Control Test™ (ACT) at weeks 12 and 24; number of withdrawals due to lack of efficacy over 24 weeks; and unscheduled healthcare resource utilisation for severe asthma exacerbations and other asthma-related healthcare. A *post-hoc* analysis was performed to assess week 24 trough FEV_1 as a percentage of the post-salbutamol screening value.

Safety

Safety and tolerability of study treatments were assessed by monitoring adverse events (AEs), serious AEs (SAEs), and incidence of severe asthma exacerbations (not recorded as an AE unless they met the definition of SAE). AEs were coded using the Medical Dictionary for Regulatory Activities dictionary. Safety parameters including vital signs, ECG measurements (recorded after 5min rest before measurement of the clinic lung function tests), clinical chemistry and haematology, routine liver function assessments and 24-h urinary cortisol (UC) excretion were also assessed.

Statistical analysis

A sample size of 588 randomised patients (196 per treatment arm) had 95% power to detect a treatment difference of 150mL in change from baseline in trough FEV_1 between FF/VI and

FF; 96% power to detect a treatment difference of 175mL in 0–24-h wm serial FEV_1 in the subset of patients performing serial FEV_1 measurements; and greater than 99% power to detect a treatment difference of 15% in change from baseline in percentage of rescue-free 24-h periods between FF/VI and FF. The overall power of the study to detect treatment differences for the co-primary endpoints and the nominated powered secondary endpoint was 92%. The sample size also provided 80% power to test for non-inferiority on change from baseline in trough FEV_1 only for the comparison of FF 200µg to FP 500µg with a non-inferiority bound of –125mL.

Co-primary and powered secondary endpoints were analysed using an ANCOVA model with covariates for baseline, region, sex, age and treatment group. Imputation of missing data for the change from baseline in trough FEV_1 endpoint was carried out by last observation carried forward (LOCF). Change from baseline in trough FEV_1 was also analysed using a repeated measures model. $wmFEV_1$ was calculated in a subset of patients (~45% per arm) who performed serial FEV_1 at week 24.

The intent-to-treat (ITT) population comprised all patients randomised to treatment and who received at least one dose of study medication. The per protocol (PP) population comprised all patients in the ITT population who did not have any full protocol deviations. The UC population comprised all patients whose urinary samples did not have confounding factors considered to affect the interpretation of 24-h UC data. The ITT population was the primary population for all efficacy and safety analyses other than the UC analysis. The PP population was of equal importance to the ITT in the assessment of non-inferiority of FF 200µg once daily to FP 500µg twice daily on change from baseline in trough FEV_1.

To account for multiplicity across treatment comparisons and key endpoints, a step-down, closed-testing procedure was applied whereby treatment comparisons for the co-primary

endpoints (trough and $wmFEV_1$) were required to be significant at the 0.05 level in order to infer significance for key secondary endpoints percentage of rescue-free and percentage of symptom-free 24-h periods and AQLQ+12 (fig. S1). Significance at the 0.05 level was required for each secondary endpoint in sequence to allow significance to be inferred for comparison of all remaining secondary and 'Other' endpoints. If $p>0.05$ for any comparison in the hierarchy then statistical significance could not be inferred for comparisons below that point in the hierarchy. The analysis of non-inferiority for FF 200µg once daily compared with FP 500µg twice daily on the endpoint of trough FEV_1 was not part of this statistical procedure.

Following routine quality control surveillance by the study sponsor, data quality issues were identified for one trial site. A *post-hoc* sensitivity analysis was therefore conducted after the blind was broken for the co-primary and powered secondary efficacy endpoints that excluded all patients randomised at this site (n=48). The decision to keep the ITT population as the primary population for presentation of results was documented prior to conducting the sensitivity analysis.

RESULTS

Study population

Of 1206 patients screened, 587 were randomised, 586 comprised the ITT population, 515 comprised the PP population and 476 (81%) completed the study (Figure 1). Patient demographics and baseline characteristics were well balanced across treatment groups (Table 1). FP/SAL was the most common pre-study treatment (taken by 50–54% of patients). During run-in, FP was the most common ICS (taken by 59–64% of patients); mean daily doses of run-in FP ranged from 551.1µg to 583.2µg.

Co-primary endpoints

Trough FEV_1 at week 24 was improved from baseline with all therapies. The differences between FF/VI and FF, and FF/VI and FP were both significant, while FF was non-inferior to FP (Table 2). Change from baseline in trough FEV_1 by treatment showed sustained benefit with FF/VI over FF and FP at all study time points (Figure 2).

0–24-h $wmFEV_1$ at 24 weeks was assessed in 89, 83 and 86 patients in the FF/VI, FF and FP arms, respectively. In all arms 0–24-h $wmFEV_1$ was improved at week 24 compared with baseline and there were statistically significant treatment differences between FF/VI and FF or FP (Table 2). A 24-h time-course of FEV_1 at week 24 is shown in Figure 3.

Results for both co-primary endpoints in the PP population supported those of the ITT population (Figure S2).

Powered secondary endpoints

The percentage of rescue-free 24-h periods increased over the study with all therapies. The difference in improvement was significant for the comparison of FF/VI with FF, but not for

FF/VI compared with FP (Table 3). The number of additional rescue-free 24-h periods per week compared with baseline was 2.7 with FF/VI, 1.9 with FF, and 2.2 with FP.

Sensitivity analysis

The results for the sensitivity analysis excluding the site with quality issues gave results consistent with the full ITT population for trough FEV_1 and for 24h rescue-free periods (Table S1; Figure S2). For 0–24-h $wmFEV_1$ at 24 weeks, the treatment difference for FF/VI *versus* FF was smaller than observed in the ITT population and was no longer statistically significant; the treatment difference for FF/VI *versus* FP remained statistically significant (Table S1; Figure S2).

Secondary and 'Other' endpoints

The percentage of symptom-free 24-h periods increased over the course of the study and a significant effect of FF/VI over FF, but not over FP, was observed (Table 3). Patients experienced an additional 2.1 symptom-free 24-h periods per week in the FF/VI arm; these values were 1.5 for FF and 1.7 for FP.

Improvements from baseline in the AQLQ+12 score were seen in all treatment groups at week 24. The improvements were similar in each arm and were not statistically significant (Table 3). As statistical significance was not achieved on this endpoint, statistical inference could not be drawn on any of the 'Other' efficacy endpoints (Table 3; Figure S3 for morning PEF data). At baseline, the proportion of patients rating themselves as controlled (ACT ≥20) was 2% (3/197), 6% (12/194) and 8% (15/195) in the FF/VI, FF and FP arms, respectively. At week 24, this proportion increased to 50% (85/170; FF/VI), 51% (75/147; FF) and 48% (77/162; FP).

Over the 24-week treatment period, fewer patients withdrew due to lack of efficacy in the FF/VI group (3%) compared with FF (11%) or FP (9%)(Figure 4).

In *post-hoc* analysis, the mean percentage of trough FEV_1 at week 24 relative to post-salbutamol FEV_1 (screening) was 96.1% (FF/VI), 85.7% (FF) and 85.6% (FP) (Table S2; Figure S4).

Safety assessment

On-treatment AEs were similar across treatment groups (46–50%). Nasopharyngitis (13–20%) and headache (6–8%) occurred most frequently (table S3). More patients withdrew from the study due to an AE in the FF/VI group (7 [4%]), compared with FF (3 [2%]) and FP (2 [1%]). The incidence of treatment-related AEs was greater with FF/VI (9%) and FP (8%) than FF (4%). The incidence of on-treatment SAEs was greater for FF/VI (3%) than FF (<1%) or FP (1%). Two SAEs (atrial fibrillation, FF/VI group; haemoptysis, FP group) were considered treatment-related. There were no statistically significant differences at week 24 in systolic or diastolic blood pressure or pulse rate, or clinically significant differences for ECG measurements (QTcF or QTcB). No deaths occurred during the study.

Eight patients reported severe asthma exacerbations during treatment: 6 (3%) in the FF group, 0 in the FF/VI group and 2 (1%) in the FP group. All were treated with systemic/oral corticosteroids; only one patient in the FF group was hospitalised due to a severe asthma exacerbation.

The ratio to baseline for 24-h UC excretion at week 24 was slightly lower for FP (0.84) than FF (0.91) or FF/VI (0.98); treatment differences were not statistically significant for any comparison (Figure S5).

DISCUSSION

This study demonstrates the benefit of combining the new once-daily LABA VI with the once-daily ICS FF, *versus* once-daily FF or twice-daily FP alone, in patients with moderate-to-severe asthma. The main aims of this study, involving patients with moderate-to-severe asthma [1], were to compare the efficacy and safety of once-daily FF/VI 200/25µg to once-daily FF 200µg alone. An additional comparison of once-daily FF 200µg to twice-daily FP 500µg assessed the non-inferiority of the two treatments on trough FEV_1. A significantly greater improvement in lung function was observed with FF/VI *versus* FF for both co-primary endpoints and the powered secondary endpoint of change in percentage of rescue-free 24-h periods, as well as *versus* FP for both co-primary endpoints. Additionally, FF 200µg once daily was shown to be non-inferior to FP 500µg twice daily. All treatments were generally well-tolerated and no safety signals were observed.

The inclusion criteria in this study selected for patients whose asthma was uncontrolled on high-dose ICS or medium-dose ICS/LABA therapy. FF 200µg has previously been shown to be effective for patients with moderate to severe persistent asthma, with higher doses not offering further benefits [10]. The active control (FP 500µg twice daily) represents the maximum dose of FP recommended for use in patients with moderate-to-severe persistent asthma [1]. Therefore, doses of FF/VI, FF and FP used were appropriate for the patient population assessed.

FF/VI was statistically significantly better than FF and FP for both co-primary FEV_1 endpoints, with FF being non-inferior to FP on trough FEV_1. The improvements in trough FEV_1 with FF/VI over FF (193mL) and FP (210mL) were in the range considered to be clinically relevant. These findings indicate that good efficacy is achievable with less frequent

administration. Together with previous findings that VI produces prolonged bronchodilation of at least 24h duration at an optimal dose of 25µg [13], this suggests FF/VI is suitable for once-daily dosing, thereby offering greater convenience to patients. This is an important consideration for a maintenance therapy in asthma; poor adherence is associated with inadequate control and occurrence of severe asthma exacerbations [18], often due to poor patient motivation [19]. Simpler dosing regimens with reduced frequency of dosing have been shown to improve adherence for a variety of treatments [20].

Adding VI to FF significantly increased the percentage of rescue-free and symptom-free 24-h periods compared with FF alone. These findings are consistent with those of two large Cochrane meta-analyses that compared twice-daily ICS/LABA *versus* ICS-only therapies in ICS-experienced [12] or ICS-naïve [21] patients with persistent asthma. In addition, there were numerical improvements in these outcomes for FF/VI compared with FP. The AQLQ+12 score was improved with FF/VI compared with FF and FP, but the differences were not statistically significant. There was a numerically greater benefit with FF/VI *versus* FF or FP for 12 h FEV_1, $wmFEV_1$ 0–4 h post dose, morning and evening PEF, and the ACT (for which all treatments achieved the minimally clinically important difference of 3 compared with baseline [22]). Fewer withdrawals due to lack of efficacy were seen with the combination and no severe asthma exacerbations were reported for patients on FF/VI compared with FF (n=6) and FP (n=2).

The study was conducted in a clinically appropriate cohort of patients for the dose of FF/VI used and was sufficiently long enough to allow clinically meaningful conclusions to be drawn from the data. An additional strength of the study was that its powering was sufficient to show non-inferiority of once-daily FF to the maximum recommended dose of FP (500µg

twice daily), thereby providing a robust active treatment against which the effects of FF/VI and FF could be assessed. The use of electronic daily diary provided a standardised method of capturing accurate date- and time-stamped information. The statistical hierarchy methodology represents both a strength and potential limitation. While it accounts for multiple comparisons and multiplicity, it also means statistical significance could not be inferred for treatment differences for any comparison following AQLQ+12. The sponsor's quality control processes identified a study site with data quality issues and a sensitivity analysis of the co-primary and powered secondary endpoints was subsequently performed. The results of the sensitivity analysis did not affect the overall study conclusions.

In conclusion, the findings of this study demonstrate the efficacy of FF/VI in this patient population. Additionally, non-inferiority (on trough FEV_1) of once-daily FF 200µg to twice-daily FP 500µg was shown. Treatment with once-daily FF/VI was associated with statistically greater improvements in lung function and symptomatic endpoints *versus* FF, showing that the addition of the LABA VI confers significant clinical benefit in this patient population relative to high-dose ICS monotherapy. The incidence of treatment-related AEs was low and there were no apparent treatment effects on UC levels or safety parameters.

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Statement of interest

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P.M.O'B. has served as a consultant for AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, and Merck; has served on advisory boards for AIM, Altair, Boehringer, GlaxoSmithKline, Medimmune and Merck; has received lecture fees from Chiesi; and has received research funding from Amgen, Asmacure, AstraZeneca, Genentech and Ono. **E.R.B.** has served as a consultant for AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Johnson and Johnson, and Merck; and has performed clinical trials for AstraZeneca, Boehringer Ingelheim, Cephalon, Forest, Genentech, GlaxoSmithKline, KalaBios, MedImmune, Novartis and Sanofi-Aventis which have been administered by his employer Wake Forest University School of Medicine. **E.D.B.** has served as a consultant for AlkAbello, Almirall, Cephalon, Hoffman la Roche, ICON and MS Consulting Group; been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis and Nycomed; and received lecture fees

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TABLES

Table 1 Patient demographics and baseline characteristics (ITT population)

	FF/VI 200/25µg OD (N=197)	FF 200µg OD (N=194)	FP 500µg BD (N=195)	Total (N=586)
Age, years	46.6 (15.05)	44.6 (14.33)	47.3 (14.06)	46.2 (14.51)
Female gender (%)	116 (59)	113 (58)	116 (59)	345 (59)
Duration of asthma, years	17.01 (13.227)	14.71 (11.920)	14.85 (12.533)	15.53 (12.597)
Baseline pre-bronchodilator FEV_1, L	2.129 (0.6539)	2.190 (0.6756)	2.138 (0.6725)	2.153 (0.6668)
Baseline % predicted FEV_1	66.59 (12.614)	66.66 (12.388)	67.57 (12.185)	66.94 (12.383)
Screening % reversibility FEV_1	29.58 (19.828)	29.17 (17.035)	29.56 (16.375)	29.44 (17.790)
Screening absolute reversibility FEV_1, mL	561.7 (367.91)	583.3 (346.30)	568.0 (313.08)	570.9 (342.77)
Baseline % rescue-free 24-h periods	7.6 (19.22)	7.8 (20.68)	6.3 (18.03)	
Baseline % symptom-free 24-h periods	5.1 (15.20)	4.7 (16.06)	2.7 (9.83)	
Pre-study ICS regimen, n (%)				
ICS alone	47 (24)	44 (23)	49 (25)	140 (24)
ICS + salmeterol	106 (54)	102 (53)	98 (50)	306 (52)
ICS + formoterol	44 (22)	48 (25)	48 (25)	140 (24)

Values are mean (SD) unless otherwise stated.

BD: twice-daily; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; ICS: inhaled corticosteroids; OD: once-daily; VI: vilanterol.

TABLE 2 Mean change from baseline and treatment differences in trough FEV_1 (last observation carried forward) and weighted mean 0–24h FEV_1 (subset of patients who performed serial FEV_1) (mL) at week 24 (ITT population)

	FF/VI 200/25µg OD (N=197)	**FF 200µg OD (N=194)**	**FP 500µg BD (N=195)**
Trough FEV_1 (week 24)			
n	187	186	190
LS mean change from baseline, mL (SE)	394 (30.2)	201 (30.3)	183 (30.0)
Treatment difference *vs* FF 200µg OD, mL (95% CI)	193 (108, 277) p<0.001		
Treatment difference *vs* FP 500µg BD, mL (95% CI)	210 (127, 294) p<0.001	18 (–66, 102)[a]	
0–24-h $wmFEV_1$ (week 24)			
n	89	83	86
LS mean change from baseline, mL (SE)	464 (47.0)	328 (49.3)	258 (48.3)
Treatment difference *vs* FF 200µg OD, mL (95% CI)	136 (1, 270) p=0.048		
Treatment difference *vs* FP 500µg BD, mL (95% CI)	206 (73, 339) p=0.003		

ANCOVA model with covariates for baseline, region, age, sex and treatment.

[a]Non-inferiority comparison. Non-inferiority shown as lower bound of comparison 95% CI exceeded margin of –125mL.

BD: twice-daily; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; LOCF: last observation carried forward; LS: least squares; OD: once-daily; SE: standard error; VI: vilanterol; wm: weighted mean.

TABLE 3 Mean change from baseline and treatment differences for powered secondary and 'Other' efficacy endpoints (ITT population)

	FF/VI 200/25µg OD (N=197)	**FF 200µg OD (N=193)**	**FP 500µg BD (N=194)**
% rescue-free 24-h periods (weeks 1–24)			
LS mean change from baseline (SE)	38.2 (2.42)	26.6 (2.45)	31.9 (2.45)
Treatment difference *vs* FF 200µg OD (95% CI)	11.7 (4.9, 18.4) p<0.001		
Treatment difference *vs* FP 500µg BD (95% CI)	6.3 (–0.4, 13.1) p=0.067		
% symptom-free 24-h periods (weeks 1–24)			
LS mean change from baseline (SE)	29.3 (2.29)	21.0 (2.32)	24.5 (2.31)
Treatment difference *vs* FF 200µg OD (95% CI)	8.4 (2.0, 14.8) p=0.010		
Treatment difference *vs* FP 500µg BD (95% CI)	4.9 (–1.6, 11.3) p=0.137		
AQLQ+12 (week 24)			
LS mean change from baseline (SE)	0.93 (0.065)	0.88 (0.071)	0.90 (0.068)
Treatment difference *vs* FF 200µg OD (95% CI)	0.05 (–0.14, 0.24) p=0.587[a]		
Treatment difference *vs* FP 500µg BD (95% CI)	0.03 (–0.16, 0.21) p=0.786		
12 h post-dose FEV_1 (week 24)			
LS mean (SE)	2.645 (0.0489)	2.477 (0.0513)	2.390 (0.0497)

Treatment difference *vs* FF 200µg OD (95% CI)	0.167 (0.027, 0.307)		
Treatment difference *vs* FP 500µg BD (95% CI)	0.254 (0.117, 0.392)		
0–4 h wmFEV$_1$ (week 24)			
LS mean change from baseline (SE)	0.484 (0.0469)	0.342 (0.0492)	0.285 (0.0483)
Treatment difference *vs* FF 200µg OD (95% CI)	0.142 (0.008, 0.276)		
Treatment difference *vs* FP 500µg BD (95% CI)	0.198 (0.066, 0.331)		
AM PEF (weeks 1–24)			
LS mean change from baseline (SE)	51.8 (2.94)	18.2 (2.97)	18.8 (2.95)
Treatment difference *vs* FF 200µg OD (95% CI)	33.5 (25.3, 41.7)		
Treatment difference *vs* FP 500µg BD (95% CI)	32.9 (24.8, 41.1)		
PM PEF (weeks 1–24)			
LS mean change from baseline (SE)	39.8 (2.93)	9.1 (2.98)	13.6 (2.96)
Treatment difference *vs* FF 200µg OD (95% CI)	30.7 (22.5, 38.9)		
Treatment difference *vs* FP 500µg BD (95% CI)	26.2 (18.0, 34.3)		
ACT (week 24)			
LS mean change from baseline (SE)	5.5 (0.28)	5.2 (0.30)	4.7 (0.29)

Treatment difference *vs* FF 200µg OD (95% CI)	0.3 (–0.5, 1.1)
Treatment difference *vs* FP 500µg BD (95% CI)	0.7 (–0.1, 1.5)

ANCOVA model with covariates for baseline, region, age, sex and treatment

[a]The failure to achieve p<0.05 for the FF/VI *versus* FF comparison on the AQLQ+12 endpoint in the ITT population analysis meant that significance could not be inferred for any subsequent comparisons per the closed step-down statistical hierarchy employed. As such differences and associated 95% CI values only are shown for subsequent comparisons.

ACT: Asthma Control Test™; AM: morning; AQLQ+12: Total Asthma Quality of Life Questionnaire; BD: twice-daily; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; PEF: peak expiratory flow; PM: evening; SE: standard error; VI: vilanterol; wm: weighted mean.

FIGURE LEGENDS

FIGURE 1. CONSORT/patient flow diagram.

BD: twice-daily; FF: fluticasone furoate; FP: fluticasone propionate; ITT: intent to treat; OD: once-daily; VI: vilanterol.

*One patient was randomised to the FP 500mcg group in error, but did not receive study drug and was thus not included in the ITT population.

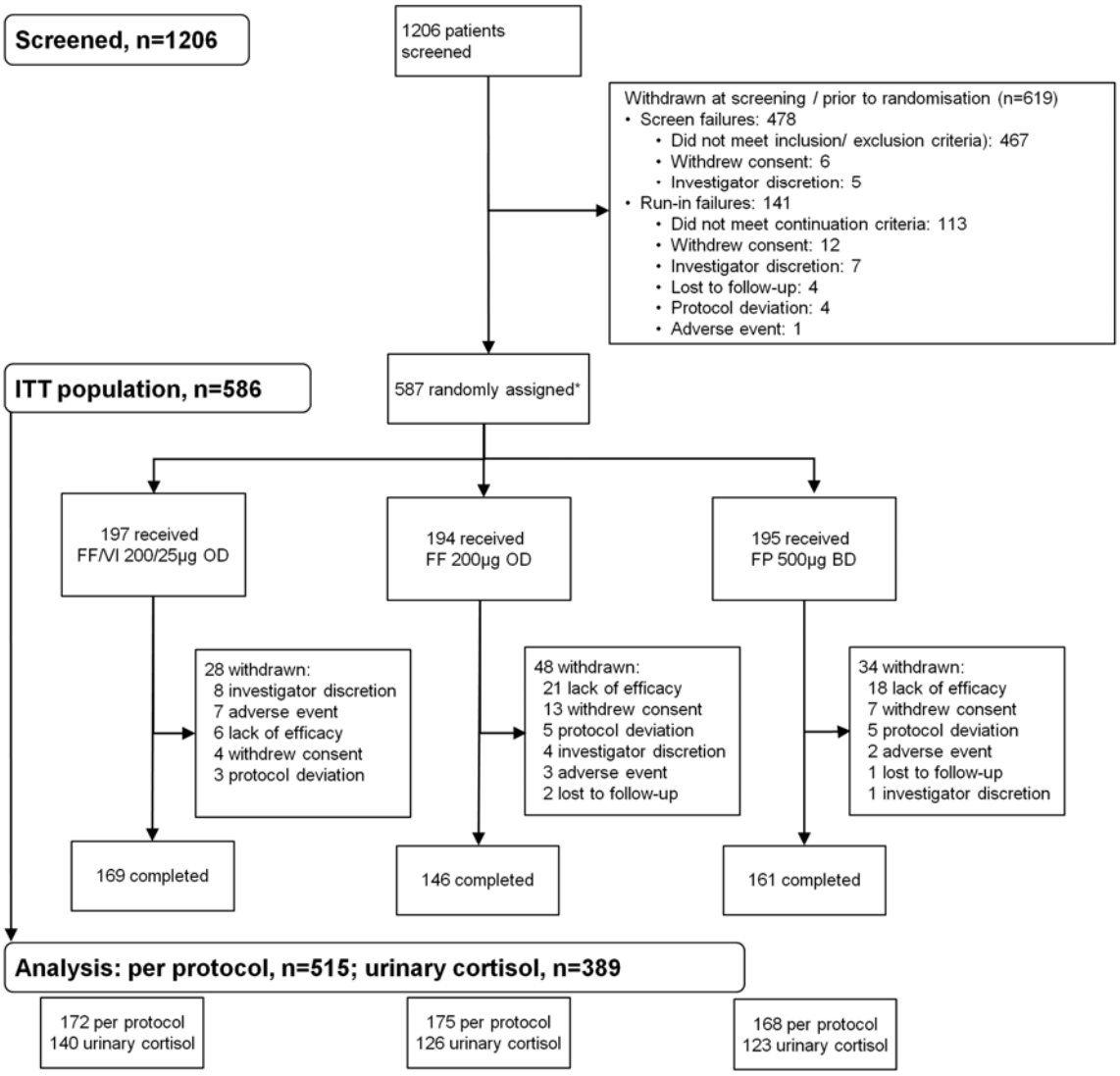

Screened, n=1206
1206 patients screened
Withdrawn at screening / prior to randomisation (n=619)
• Screen failures: 478
• Did not meet inclusion/ exclusion criteria): 467
• Withdrew consent: 6
• Investigator discretion: 5
• Run-in failures: 141
• Did not meet continuation criteria: 113
• Withdrew consent: 12
• Investigator discretion: 7
• Lost to follow-up: 4
• Protocol deviation: 4
• Adverse event: 1
ITT population, n=586
587 randomly assigned*
197 received FF/VI 200/25µg OD
194 received FF 200µg OD
195 received FP 500µg BD
28 withdrawn:
8 investigator discretion
7 adverse event
6 lack of efficacy
4 withdrew consent
3 protocol deviation
48 withdrawn:
21 lack of efficacy
13 withdrew consent
5 protocol deviation
4 investigator discretion
3 adverse event
2 lost to follow-up
34 withdrawn:
18 lack of efficacy
7 withdrew consent
5 protocol deviation
2 adverse event
1 lost to follow-up
1 investigator discretion
169 completed
146 completed
161 completed
Analysis: per protocol, n=515; urinary cortisol, n=389
172 per protocol
140 urinary cortisol
175 per protocol
126 urinary cortisol
168 per protocol
123 urinary cortisol

FIGURE 2. Repeated measures analysis for the primary endpoint of change from baseline in trough FEV_1 over 24 weeks of treatment (ITT population).

BD: twice-daily; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; VI: vilanterol.

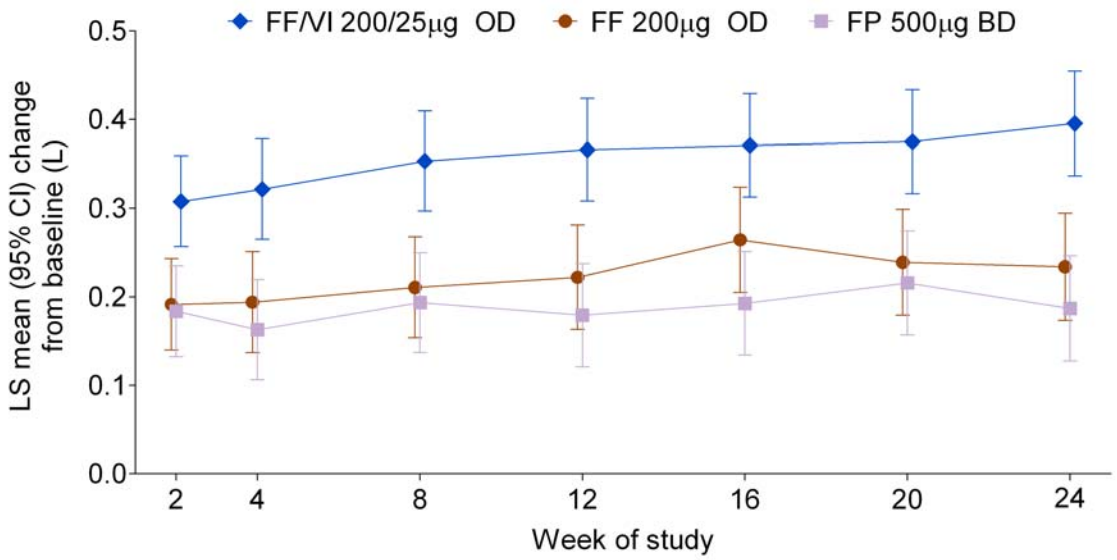


FIGURE 3. Adjusted mean change from baseline of individual serial FEV_1 (L) assessments following 24 weeks of treatment (ITT population).

BD: twice-daily; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; VI: vilanterol.

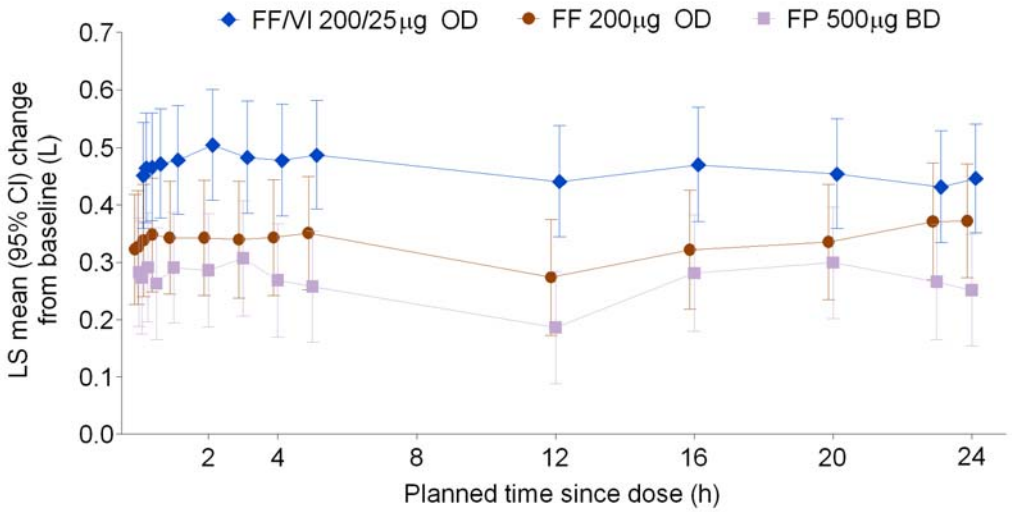
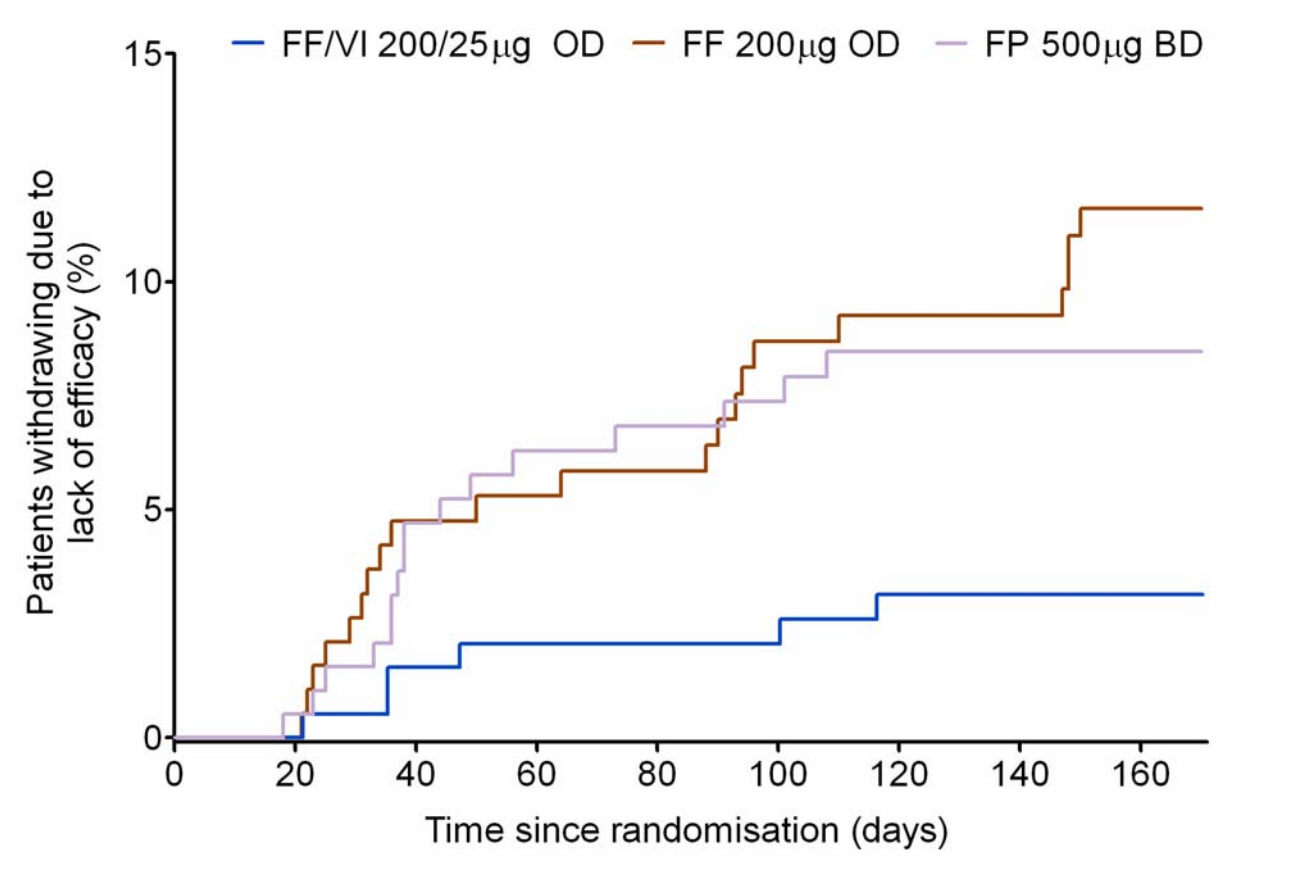


FIGURE 4. Cumulative incidence curves for withdrawals due to lack of efficacy over the 24-week treatment period (ITT population).

BD: twice-daily; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; VI: vilanterol.



Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma

Paul M. O'Byrne, Eugene R. Bleecker, Eric D. Bateman, William W. Busse, Ashley Woodcock, Richard Forth, William T. Toler, Loretta Jacques, and Jan Lötvall

ONLINE SUPPLEMENT

Prohibited medication during the study

Any prescription or non-prescription medication that could affect the course of asthma was prohibited during the study. This included all corticosteroids (with the exception of intranasal sprays and mild topical creams), long-acting β_2 agonists (LABAs), leukotriene modifiers, slow-release bronchodilators, and any medication that could interact with corticosteroid or sympathomimetic amines.

TABLE S1 Mean change from baseline and treatment differences for the co-primary endpoints of trough forced expiratory volume in 1 s (FEV_1; last observation carried forward) and weighted mean 0–24h FEV_1 (subset of patients who performed serial FEV_1) at week 24 and the powered secondary endpoint of percentage rescue-free 24-h periods during the 24-week treatment period (sensitivity analysis population)

	FF/VI 200/25µg OD (N=197)	**FF 200µg OD (N=194)**	**FP 500µg BD (N=195)**
Trough FEV_1 (week 24)			
n	169	172	179
LS mean change from baseline, mL (SE)	329 (29.3)	165 (29.1)	156 (28.4)
Treatment difference *vs* FF 200µg OD, mL (95% CI)	164 (83, 245) p<0.001		
Treatment difference *vs* FP 500µg BD, mL (95% CI)	173 (93, 253) p<0.001	9 (–71, 89)	
0–24-h wmFEV_1 (week 24)			
n	72	69	76
LS mean change from baseline, mL	339 (44.6)	261 (46.1)	215 (43.7)
Treatment difference *vs* FF 200µg OD, mL (95% CI)	78 (–49, 205) p=0.230		
Treatment difference *vs* FP 500µg BD, mL (95% CI)	124 (1, 247) p=0.047		
Percentage rescue-free 24-h periods (weeks 1–24)			

n	176	177	183
LS mean change from baseline (SE)	38.8 (2.55)	25.6 (2.54)	31.7 (2.49)
Treatment difference *vs* FF 200µg OD (95% CI)	13.2 (6.2, 20.3) p<0.001		
Treatment difference *vs* FP 500µg BD (95% CI)	7.1 (0.1, 14.1) p=0.046		

ANCOVA model with covariates for baseline, region, age, sex and treatment.

BD: twice-daily; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; SE: standard error; VI: vilanterol; wm: weighted mean.

TABLE S2 Summary of percentage of trough FEV_1 (L) at week 24 relative to post-salbutamol FEV_1 at screening using the last observation carried forward method (intent-to-treat [ITT] population)

Treatment	N	n	Mean	SD	Median	Min.	Max.
FF/VI 200/25µg OD	197	193	96.1	12.78	96.8	54	136
FF 200µg OD	194	186	85.7	24.28	90.5	–100	138
FP 500µg BD	195	191	85.6	19.47	88.5	–22	131

BD: twice-daily; FF: fluticasone furoate; FP: fluticasone propionate; OD: once-daily; SD: standard deviation; VI: vilanterol.

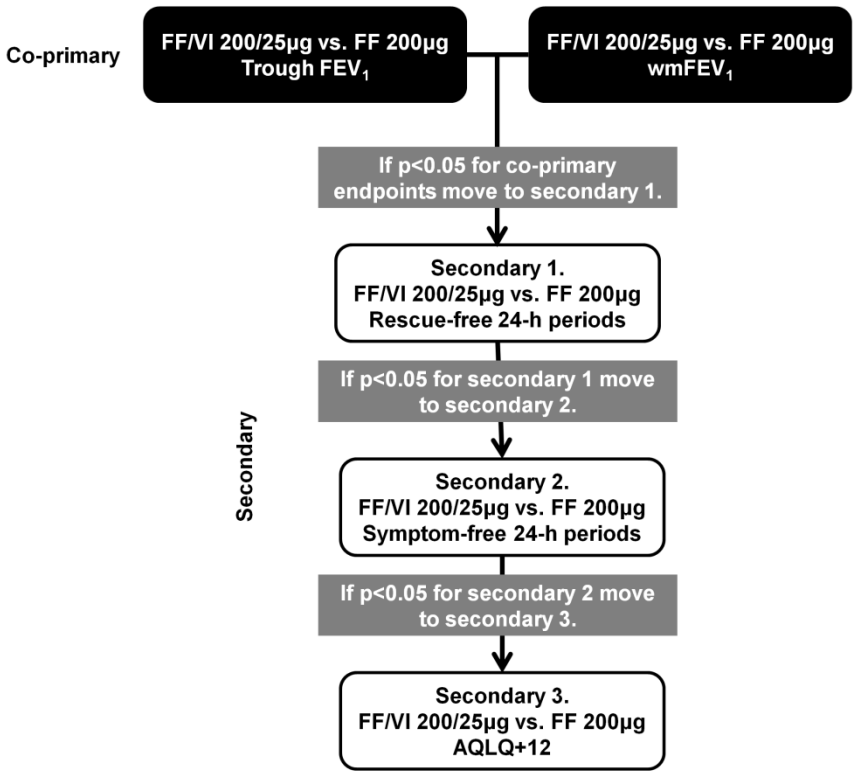
TABLE S3 Summary of adverse events by treatment group (ITT population)

	FF/VI 200/25µg OD (N=197)	FF 200µg OD (N=194)	FP 500µg BD (N=195)
AEs, n (%)			
On-treatment	92 (47)	90 (46)	97 (50)
Treatment-related AEs	17 (9)	8 (4)	16 (8)
AEs leading to permanent discontinuation of study drug or withdrawal from study	7 (4)	3 (2)	2 (1)
Most frequent on-treatment AEs, n (%)[a]			
Nasopharyngitis	25 (13)	27 (14)	39 (20)
Headache	11 (6)	13 (7)	15 (8)
Cough	3 (2)	6 (3)	13 (7)
Respiratory tract infection, viral	7 (4)	7 (4)	7 (4)
Influenza	5 (3)	8 (4)	7 (4)
Bronchitis	7 (4)	6 (3)	6 (3)
Oropharyngeal pain	4 (2)	8 (4)	7 (4)
Sinusitis	3 (2)	7 (4)	4 (2)
Dysphonia	6 (3)	2 (1)	4 (2)
Pharyngitis	4 (2)	2 (1)	6 (3)
Rhinitis	1 (<1)	2 (1)	7 (4)
Oropharyngeal candidiasis	5 (3)	1 (<1)	2 (1)

[a]Occurring in ≥3% of patients in any treatment group.

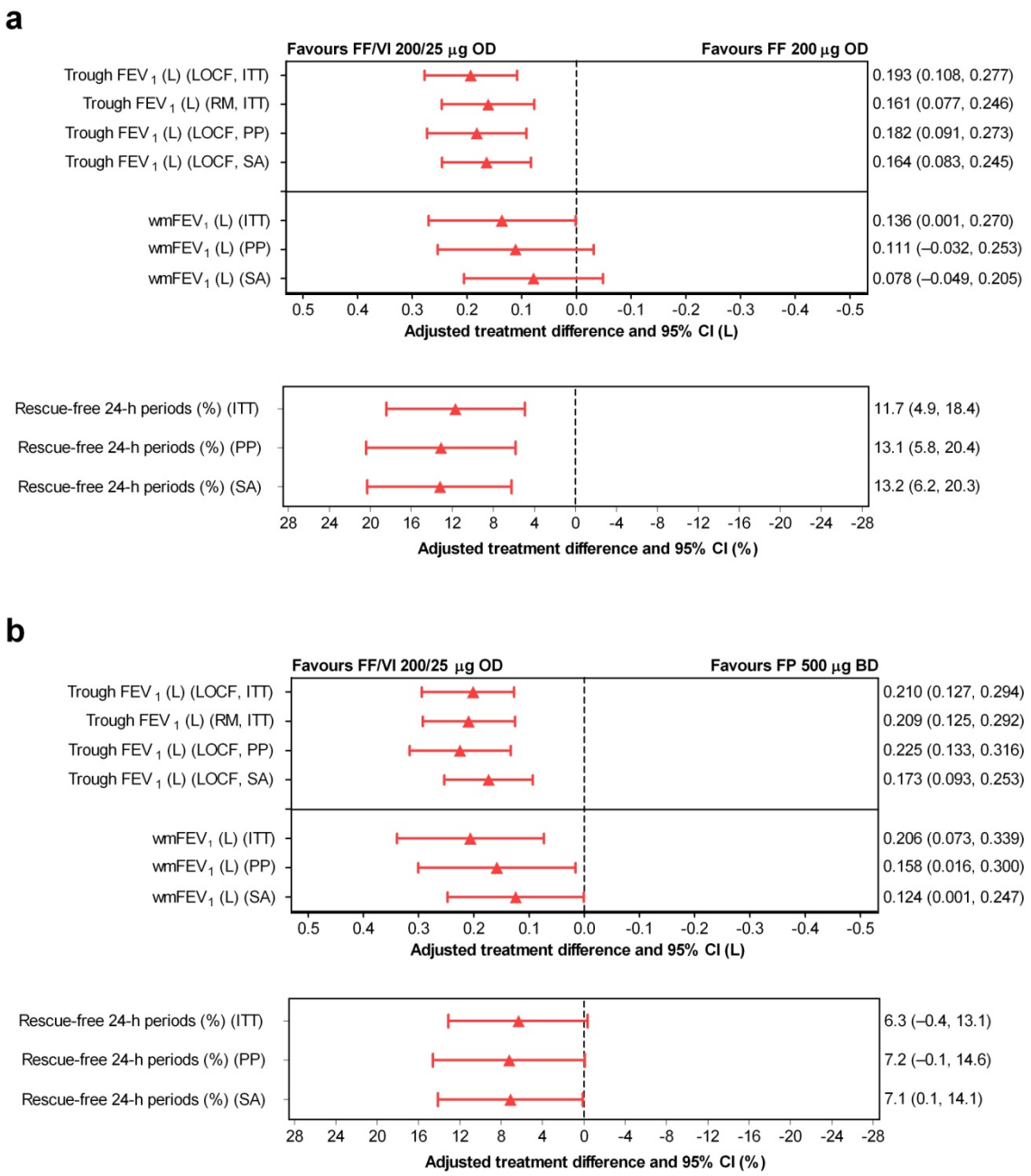
AEs: adverse events; BD: twice-daily; FF: fluticasone furoate; FP: fluticasone propionate; OD: once-daily; VI: vilanterol.

FIGURE S1. Statistical hierarchy.



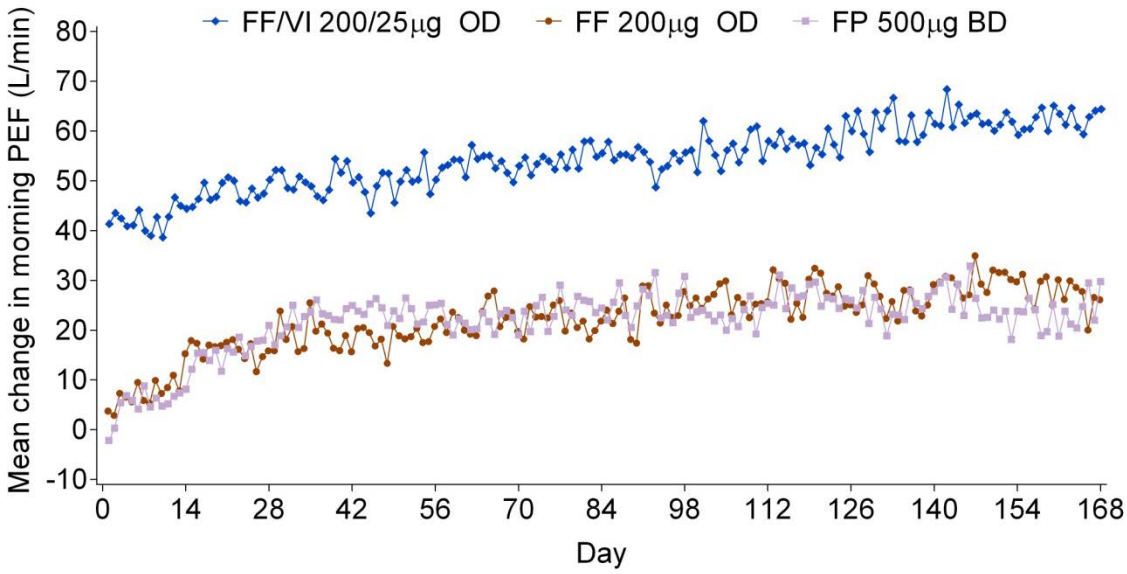
AQLQ+12: Asthma Quality of Life Questionnaire; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; VI: vilanterol; wm: weighted mean.

FIGURE S2 Summary of adjusted treatment differences for the co-primary endpoints of trough FEV_1 and weighted mean (wm) FEV_1, and powered secondary endpoint of percentage rescue-free 24-h periods for (**a**) fluticasone furoate/vilanterol (FF/VI) 200/25µg *versus* FF 200µg and (**b**) FF/VI 200/25µg *versus* fluticasone propionate (FP) 500µg in the ITT last observation carried forward population, ITT repeat measures population (trough FEV_1 only), per protocol population and sensitivity analysis population.



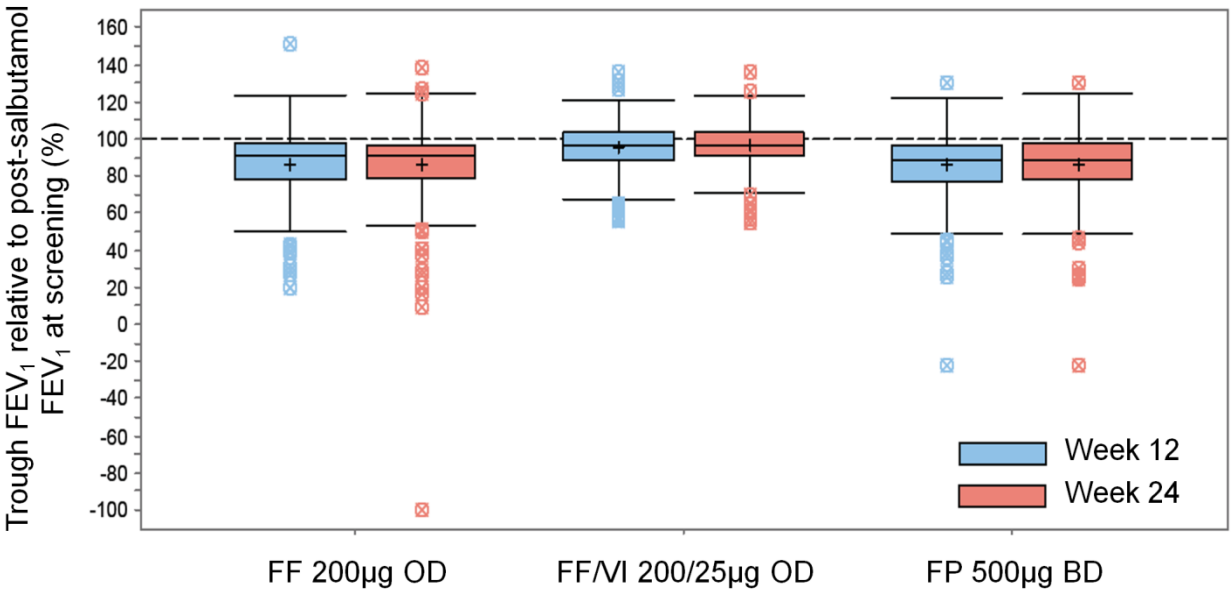
BD: twice-daily; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; ITT: intent to treat; LOCF: last observation carried forward; LS: least squares; OD: once-daily; PP: per protocol; RM: repeat measures; SA: sensitivity analysis; VI: vilanterol; wm: weighted mean.

FIGURE S3. Mean change from baseline in morning peak expiratory flow (ITT population).



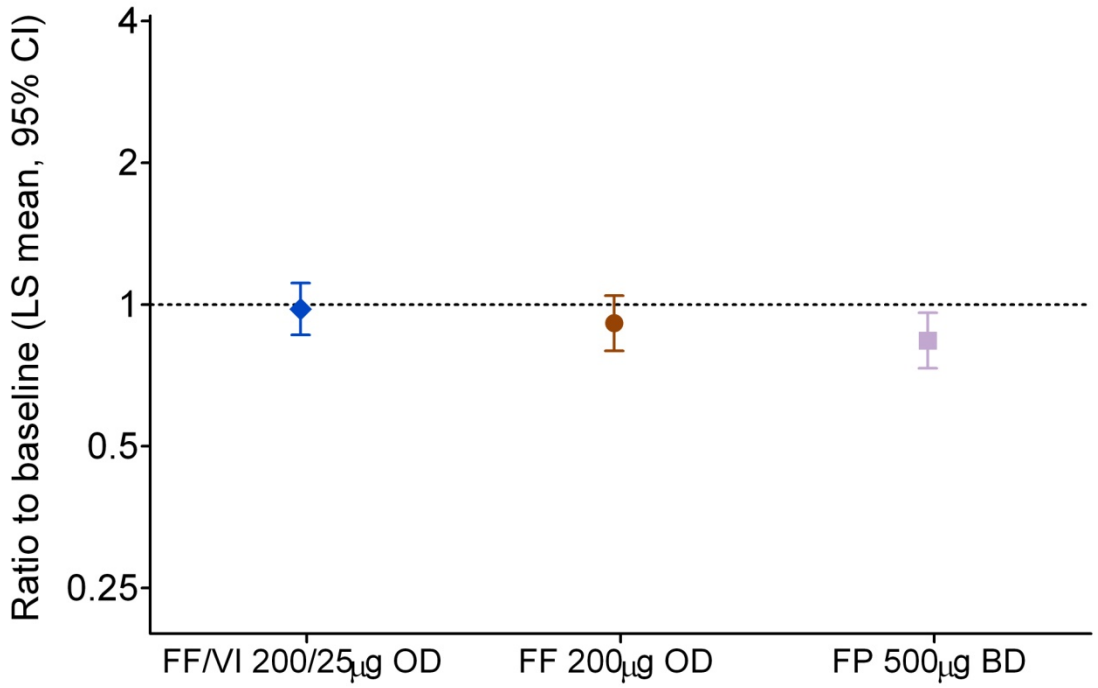
BD: twice-daily; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; PEF: peak expiratory flow; VI: vilanterol.

FIGURE S4. Box plot of percentage of trough FEV_1 at week 24 relative to post-salbutamol FEV_1 at screening using last observation carried forward method (ITT population)



BD: twice-daily; FEV_1: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; OD: once-daily; VI: vilanterol.

FIGURE S5. Adjusted LS mean ratio to baseline 24-h urinary cortisol (UC) excretion by treatment group at week 24 (UC population).



BD: twice-daily; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once-daily; VI: vilanterol.