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Original Research

ASTHMA

Efficacy and Safety of Fluticasone Furoate/Vilanterol Compared With Fluticasone Propionate/Salmeterol Combination in Adult and Adolescent Patients With Persistent Asthma

A Randomized Trial

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Background: **The combination of fluticasone furoate (FF), a novel inhaled corticosteroid (ICS), and vilanterol (VI), a long-acting β_2 agonist, is under development as a once-daily treatment of asthma and COPD. The aim of this study was to compare the efficacy of FF/VI with fluticasone propionate (FP)/salmeterol (SAL) in patients with persistent asthma uncontrolled on a medium dose of ICS.**

Methods: **In a randomized, double-blind, double-dummy, parallel group study, 806 patients received FF/VI (100/25 μg, n = 403) once daily in the evening delivered through ELLIPTA (GlaxoSmithKline) dry powder inhaler, or FP/SAL (250/50 μg, n = 403) bid through DISKUS/ACCUHALER (GlaxoSmithKline). The primary efficacy measure was 0- to 24-h serial weighted mean (wm) FEV_1 after 24 weeks of treatment.**

Results: **Improvements from baseline in 0- to 24-h wmFEV_1 were observed with both FF/VI (341 mL) and FP/SAL (377 mL); the adjusted mean treatment difference was not statistically significant (−37 mL; 95% CI, −88 to 15, *P* = 0.162). There were no differences between 0- to 4-h serial wmFEV_1, trough FEV_1, and asthma control and quality-of-life questionnaire scores. There was no difference in reported exacerbations between treatments. Both treatments were well tolerated, with no clinically relevant effect on urinary cortisol excretion or vital signs and no treatment-related serious adverse events.**

Conclusions: **The efficacy of once-daily FF/VI was similar to bid FP/SAL in improving lung function in patients with persistent asthma. No safety issues were identified.**

Trial registry: **ClinicalTrials.gov; No.: NCT01147848; URL: www.clinicaltrials.gov**

CHEST 2013; 144(4):1222–1229

Abbreviations: AE = adverse event; AQLQ+12 = Asthma Quality of Life + 12 Questionnaire; EQ-5D = European Quality of Life-5 Dimensions; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; SAE = serious adverse event; SAL = salmeterol; UC = urinary cortisol; VI = vilanterol; wm = weighted mean

For patients with asthma who remain uncontrolled despite inhaled corticosteroid (ICS) therapy, a long-acting inhaled β_2-agonist (LABA) may be added.[1,2] Combination therapy improves symptoms, reduces severe exacerbation rate and achieves better asthma control in more patients than ICS monotherapy.[1,3-5] However, poor adherence to bid therapy may account for poor asthma control in some patients. For these patients, once-daily therapy could offer them greater convenience, thereby improving adherence.[6]

Vilanterol (VI) (GW642444M) is a LABA with inherent 24-h activity in development as a once-daily treatment in combination with the novel ICS fluticasone furoate (FF) for asthma and COPD. Three dose-ranging

FF studies in patients with persistent asthma showed significant improvements from baseline in lung function relative to placebo, with the 100 and 200 μg doses of FF (over 8 weeks) providing optimal efficacy with an acceptable tolerability profile.[7-9] A VI dose-ranging study with concurrent ICS, also in persistent asthma, showed that the 25-μg dose of VI administered once daily over 4 weeks provided the most beneficial therapeutic ratio.[10]

The main aim of the current study was to compare the efficacy of FF/VI 100/25 μg administered once daily in the evening with fluticasone propionate (FP)/salmeterol (SAL) 250/50 μg administered bid over a 24-week treatment period in patients aged ≥ 12 years with persistent asthma uncontrolled on medium-dose of ICS. The dose of FP/SAL selected was considered suitable for the patient population to be studied.

Materials and Methods

Patients

Patients aged ≥ 12 years with asthma[1] were eligible if they could demonstrate a ≥ 12% and ≥ 200-mL reversibility of FEV_1 following albuterol inhalation at screening and had a best evening FEV_1 of 40% to 85% of the predicted normal value at screening and at randomization.[11] Before screening, patients had been taking ICS for ≥ 12 weeks, with a stable medium dose of ICS (FP 250 μg bid or equivalent) for ≥ 4 weeks. Key exclusion criteria are outlined in e-Appendix 1. The study was approved by the local ethics review committees (e-Table 1) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent.

Study Design and Treatments

This phase 3, multicenter, randomized, double-blind, double-dummy, parallel group study was conducted between June 16, 2010, and July 27, 2011. After screening, eligible patients entered a 4-week run-in period during which they replaced their current asthma medication with FP 250 μg bid, and their short-acting bronchodilator with albuterol delivered through a metered-dose inhaler. After the run-in period, patients received (1:1) either FF/VI 100/25 μg (emitted dose, 92/22 μg) once daily in the evening, administered through an ELLIPTA dry powder inhaler (GlaxoSmithKline), or FP/SAL 250/50 μg bid (morning and evening) through DISKUS/ACCUHALER (GlaxoSmithKline) for 24 weeks. The central randomization schedule was generated by the sponsor with a validated computerized system (RandAll; GlaxoSmithKline). Patients were randomized by the Registration and Medication Ordering System. Neither the patients nor the investigator knew which study medication the patient was receiving. A summary of permitted and prohibited medications is provided in e-Appendix 2. Compliance with study medication was measured by reviewing the dose counter on the dry powder inhaler and DISKUS/ACCUHALER.

Outcome Measurements

The primary end point was change from baseline in 0- to 24-h serial weighted mean (wm) FEV_1 after 24 weeks of treatment. Secondary end points were individual serial FEV_1 assessments at week 24 (FEV_1 at each time point on day 168), time to onset of bronchodilator effect (the time point when FEV_1 first exceeded the 12% and 200-mL increase over baseline [taken from serial measurements]) at randomization visit only, 0- to 4-h serial $wmFEV_1$ postdose at the randomization visit and at week 24, percentage of patients experiencing a ≥ 12% and ≥ 200-mL increase from baseline in FEV_1 at 12 and 24 h at week 24, and change from baseline in clinic visit trough (prebronchodilator and predose) FEV_1 at week 24.

Other efficacy end points were scores on the Asthma Quality of Life + 12 Questionnaire (AQLQ+12), the Asthma Control Test, and the European Quality of Life-5 Dimensions (EQ-5D) test, and unscheduled health-care resource utilization. Patients were asked to complete questionnaires at baseline and end of treatment. A post hoc analysis of the individual AQLQ+12 domains and minimally important difference (≥0.5-point improvement in AQLQ+12 score) was also performed. Results from this analysis are shown in e-Appendix 3.

Safety Evaluations

Adverse events (AEs) could be reported throughout the study. Other safety assessments were 24-h urinary cortisol (UC) excretion at baseline and at the end of the 24-week treatment period (subset of patients); vital signs (diastolic and systolic BP, pulse rate); incidence of severe asthma exacerbations; liver safety; and ECG, clinical chemistry, and hematology screening assessments.

Patients were withdrawn from the study because of lack of efficacy if they experienced a severe exacerbation or worsening of asthma or at the investigator's discretion. A severe exacerbation was defined as deterioration of asthma requiring treatment with systemic or oral corticosteroids for ≥3 days or an inpatient hospitalization or ED visit that required systemic corticosteroids. Worsening asthma was defined as a requirement for any treatment other than study medication or use of rescue albuterol. Severe asthma exacerbations were not recorded as an AE unless they met the definition of a serious adverse event (SAE).

Manuscript received January 23, 2013; revision accepted May 16, 2013.
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Data contained in this article were presented at the European Respiratory Society Annual Congress, Vienna, Austria, September 1-5, 2012.
Funding/Support: This study was funded by GlaxoSmithKline [HZA113091].
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DOI: 10.1378/chest.13-0178

Statistical Analysis

Sample size calculations were based on the primary end point of 0- to 24-h serial wmFEV$_1$ at the end of the 24-week treatment period for the treatment comparison of FF/VI 100/25 μg once daily vs FP/SAL 250/50 μg bid. It was estimated that approximately 348 patients with evaluable data per treatment group would provide 90% power to detect a difference of 80 mL between FF/VI 100/25 μg and FP/SAL 250/50 μg; this assumed an SD of 325 mL. Details about the analysis populations and power calculation are provided in e-Appendix 4.

The primary analysis was performed on the intention-to-treat population with an analysis of covariance model allowing for the effects of baseline FEV$_1$, region, sex, age, and treatment group. A two-sided 5% risk (significance level) associated with incorrectly rejecting the null hypothesis was considered acceptable for this study. For the secondary and other efficacy end points, if the statistical test for the primary end point failed to reject the null hypothesis of no treatment difference at the 0.05 significance level, the tests for the secondary and other efficacy end points were to be interpreted as descriptive only.

As a consequence of site audits conducted by the study sponsor GlaxoSmithKline, concerns about the quality of data supplied were identified for two study centers. These centers contributed 57 patients (7% of enrolled patients) to the study. Because of these concerns, analysis of the primary end point was repeated, excluding the data from these two centers. Results were consistent with the primary analysis. The authors and study sponsor are satisfied that the exclusion of data derived from these centers did not materially change the findings of the study; therefore, we present a complete data set from all the centers.

Results

Study Population

Patient disposition is shown in Figure 1. Most patients (89%) in both treatment groups completed the 24-week treatment period (Fig 1). Patient demographics and baseline lung function are shown in Table 1.

Efficacy Assessments

Lung Function: Improvements from baseline in 0- to 24-h serial wmFEV$_1$ were seen with both FF/VI (341 mL) and FP/SAL (377 mL); however, the adjusted mean treatment difference was not statistically significant (−37 mL; 95% CI, −88 to 15 mL; $P = .162$) (Fig 2). There were no differences in key secondary end points, including the change from baseline in individual serial FEV$_1$ assessments over time at week 24. These showed sustained 24-h duration of action for both once-daily FF/VI and bid FP/SAL at all time points (Fig 3). The adjusted mean treatment differences between FF/VI and FP/SAL ranged from 2 to 58 mL. No important differences were seen between FF/VI vs FP/SAL for the secondary end points of time to onset of bronchodilator effect, 0- to 4-h serial wmFEV$_1$ postdose at randomization and at week 24, percentage

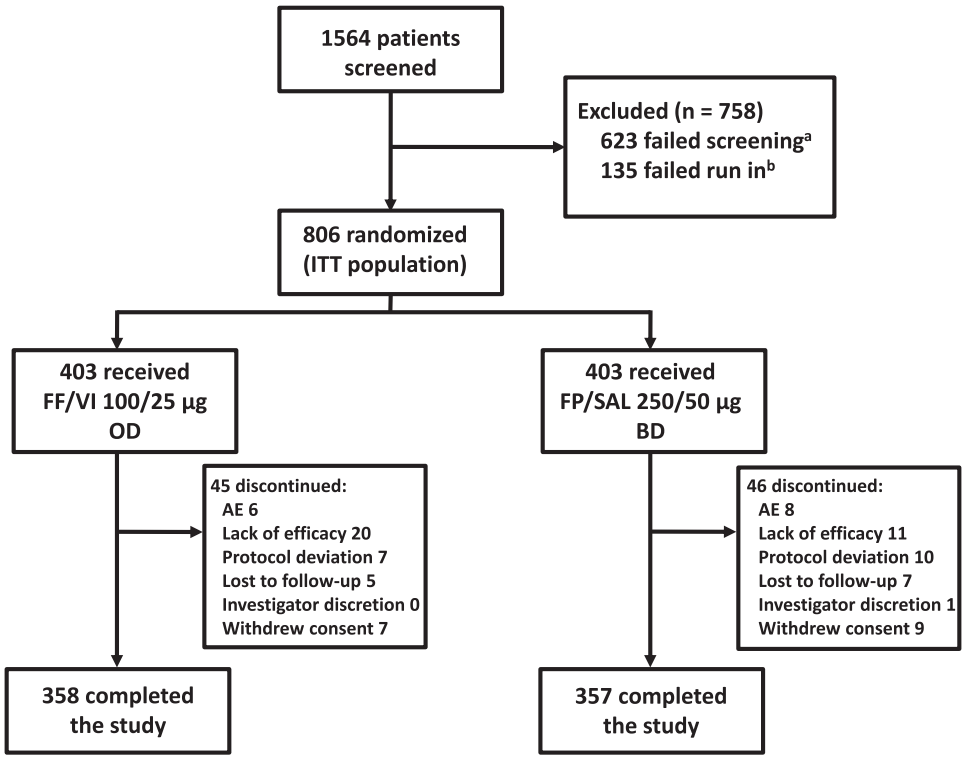

Figure 1. Consolidated Standards of Reporting Trials patient flow diagram. AE = adverse event; BD = twice daily; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intention to treat; OD = once daily; SAL = salmeterol; VI = vilanterol. [a]Main reason was that patients did not meet inclusion/exclusion criteria (n = 613 [39%]). [b]Main reason was that patients did not meet continuation criteria (n = 103 [7%]).

Table 1—*Patient Demographics and Baseline Lung Function (Intention-to-Treat Population)*

Characteristic	FF/VI 100/25 μg OD PM (n = 403)	FP/SAL 250/50 μg bid (n = 403)
Age, y	43.8 ± 15.9	41.9 ± 16.9
Range	12-79	12-80
Female sex	244 (61)	245 (61)
Race		
White	242 (60)	232 (58)
Asian	124 (31)	125 (31)
Black/African heritage	36 (9)	43 (11)
Other[a]	1 (< 1)	3 (< 1)
Percent reversibility of FEV_1,[b] L	26.4 ± 14.4	29.0 ± 18.0
Predose FEV_1, L	2.011 ± 0.639	2.048 ± 0.625
FEV_1 % predicted	68.0 ± 11.7	68.8 ± 11.0
ICS use[c] at screening	125 (31)	123 (31)
ICS/LABA use at screening	279 (69)	279 (69)

Data are presented as mean ± SD or No. (%) unless otherwise indicated. FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; OD = once daily; SAL = salmeterol; VI = vilanterol.

[a]Native Hawaiian or other Pacific Islander, African American/African heritage and white.

[b]Measured at screening.

[c]Patients needed to have been maintained on a medium dose of ICS (eg, FP 250 μg bid) for ≥ 4 wk before screening.

of patients obtaining a ≥ 12% and ≥ 200-mL increase from baseline in FEV_1 at 12 and 24 h at week 24, and change from baseline in clinic visit trough (prebronchodilator and predose) FEV_1 at week 24 (Table 2). Change from baseline in predose FEV_1 over the 24-week treatment period is shown in e-Figure 1.

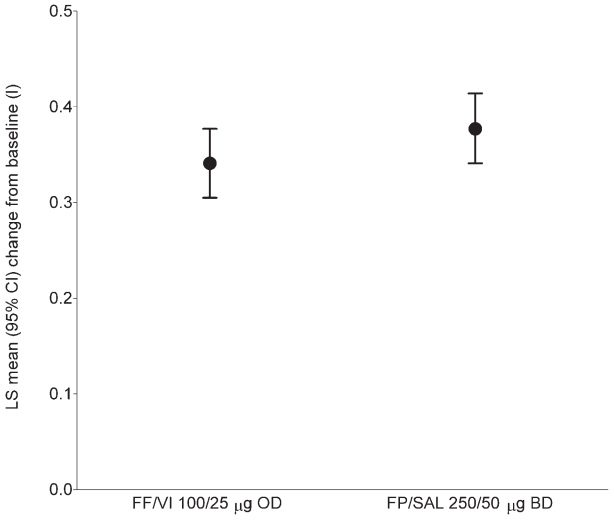

FIGURE 2. Adjusted means for 0- to 24-h serial weighted mean FEV_1 at week 24 (intention-to-treat population). LS = least squares. See Figure 1 legend for expansion of other abbreviations.

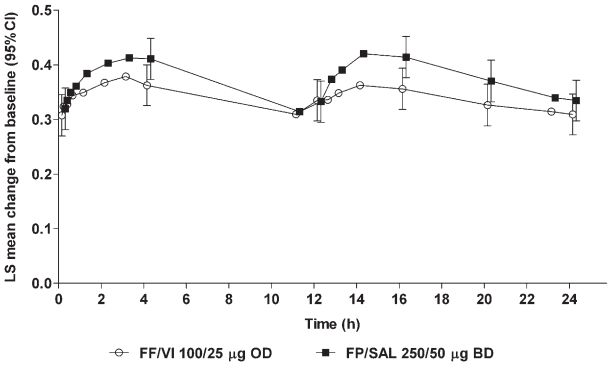

FIGURE 3. Adjusted mean change from baseline in FEV_1 over time at week 24 for FF/VI dosed OD in the evening and FP/SAL dosed BD (intention-to-treat population). See Figure 1 and 2 legends for expansion of abbreviations.

Health Outcomes

Improvements from baseline in the AQLQ+12, Asthma Control Test, and EQ-5D asthma health outcomes assessments were observed for both FF/VI and FP/SAL. There was no difference between treatments (Table 3).

Safety Assessments

The overall incidence of AEs and SAEs reported while on treatment are presented in Table 4. The most frequently occurring AEs reported by both groups were nasopharyngitis and headache; treatment-related AEs were similar between groups (Table 4). Nine patients reported on-treatment SAEs (four receiving FF/VI and five receiving FP/SAL) (Table 4). SAEs were single events with the exception of asthma exacerbation and pneumonia (one pretreatment and one on treatment [FP/SAL]). None of the SAEs was considered treatment related. No deaths were reported during the study.

There was no statistically significant difference between FF/VI and FP/SAL in 24-h UC excretion at week 24 (adjusted treatment ratio, 0.85; 95% CI, 0.72-1.02; $P = .075$) (Fig 4). However, 24-h UC excretion did increase in both groups from baseline to week 24 (ratio to baseline, 1.11 and 1.21 for FF/VI and FP/SAL, respectively).

The incidence of asthma exacerbations was low, and there was no difference between groups (3% vs 2% on FP/SAL vs FF/VI, respectively [on-treatment events]). Eight (2%) patients in the FF/VI group and seven (2%) in the FP/SAL group withdrew because of their exacerbation. One patient in the FF/VI group and two in the FP/SAL group were hospitalized because of their exacerbations. None of the exacerbations were considered treatment related. No clinically relevant treatment effects on vital signs (e-Appendix 5) or liver function

Table 2—*Secondary End Points*[a]

Secondary End Point	Treatment Value	Difference FF/VI OD PM vs FP/SAL bid, (95% CI)
Time to onset of bronchodilator effect (median time to ≥ 12% and ≥ 200 mL FEV_1 over baseline at randomization visit), min		0.948[b] (0.797 to 1.128)
FF/VI	61	
FP/SAL	59	
0- to 4-h serial wmFEV_1 postdose at randomization visit, L		−0.030 (−0.071 to 0.012)
FF/VI	0.316 ± 0.0149	
FP/SAL	0.346 ± 0.0149	
0- to 4-h serial wmFEV_1 postdose at week 24, L		−0.034 (−0.086 to 0.017)
FF/VI	0.360 ± 0.0184	
FP/SAL	0.394 ± 0.0186	
% patients obtaining ≥ 12% and ≥ 200 mL increase from baseline in FEV_1 at 12 h and at 24 h at week 24		
12-h FF/VI	56	1.31[c] (0.96 to 1.78)
12-h FP/SAL	50	…
24-h FF/VI	51	1.09[c] (0.80 to 1.48)
24-h FP/SAL	50	…
Change from baseline in clinic visit trough (prebronchodilator and predose) FEV_1 at week 24		−0.019 (−0.073 to 0.034)
FF/VI	0.281 ± 0.0191	
FP/SAL	0.300 ± 0.0193	

Data are presented as least squares mean ± SE change from baseline unless otherwise indicated. Intention-to-treat population, n = 403 (FF/VI 100/25 μg OD PM) and n = 403 (FP/SAL 250 μg bid). HR = hazard ratio; wm = weighted mean. See Table 1 legend for expansion of other abbreviations.

[a]Results are for all secondary end points other than the end point individual serial FEV_1 assessments at week 24 (see Fig 3).

[b]HR.

[c]OR.

parameters were found, with the exception of one patient in the FP/SAL group who met liver stopping criteria of alanine aminotransferase levels more than eight times the upper limit of normal, which was reported as an AE but was not considered treatment related.

Discussion

In this study of patients aged ≥ 12 years with persistent asthma uncontrolled on a medium dose of ICS, FF/VI 100/25 μg once daily in the evening was not significantly different from FP/SAL 250/50 μg bid for the primary end point of 0- to 24-h serial wmFEV_1 at week 24 or for any of the secondary end points. The AE profiles for both treatments were similar, and those AEs reported with FP/SAL were consistent with those previously reported with this drug combination.[12,13]

Patients were symptomatic on a medium dose of ICS at baseline. According to current asthma guidelines, these patients would require a step up in their asthma treatment from step 3 to 4.[2] Lack of asthma control in the patient population at baseline was evident by an FEV_1 of approximately 68% of the predicted normal value for both groups and by the fact that ≥ 50% of patients had an Asthma Control Test score of < 20. The goal of asthma treatment is to control asthma symptoms.[2] A number of studies have shown that nonadherence to asthma therapy is an important reason for loss of asthma control in some patients.[14-16] Adherence to the treatment schedule was high during the study (> 94% in both groups), although the artificial setting of a clinical trial may have encouraged normally nonadherers to take their medication. If poor adherence to the dosing schedule is an important factor in loss of asthma control, then once-daily dosing (as opposed to bid dosing) such as that provided by FF/VI may represent a more-convenient treatment option for patients in a real-world setting.[17]

No differences in Asthma Control Test scores or in measures of quality of life (AQLQ+12 and EQ-5D) were shown in the present study. A difference of 1.4 was observed between groups on the EQ-5D test, but this difference was not statistically significant. The outcomes of the post hoc analysis (e-Appendix 3) suggest that FF/VI may provide clinically relevant improvements in certain patient-reported quality-of-life measures (environmental domain of the AQLQ+12 in the present study), as well as in the percentage of patients who improved by at least the minimally important difference of 0.5,[18] that were not reported with FP/SAL. However, this statement is speculative and requires further evaluation in real-world studies outside the environment of a clinical trial.

Table 3—*Health Outcomes Assessments*

Assessment	Mean Score at Baseline	Mean Score at Week 24	LS Mean Change ± SE From Baseline[a]	Difference FF/VI OD PM vs FP/SAL bid, (95% CI)[a]
AQLQ+12 (total score)				0.09 (−0.03 to 0.21)
FF/VI	5.35	5.85	0.46 ± 0.043	
FP/SAL	5.37	5.79	0.37 ± 0.043	
ACT				0.2 (−0.2 to 0.7)
FF/VI	18.9	21.2	2.3 ± 0.16	
FP/SAL	18.8	20.9	2.0 ± 0.16	
EQ-5D dimensions, % reporting no problems				
Mobility			N/A	1.37[b] (0.86 to 2.18)
FF/VI				
FP/SAL	83	85		
Self-care	83	84	N/A	1.14[b] (0.38 to 3.41)
FF/VI	97	98		
FP/SAL	98	98		
Usual activities			N/A	1.44[b] (0.93 to 2.24)
FF/VI	75	84		
FP/SAL	74	82		
Pain/discomfort			N/A	1.12[b] (0.80 to 1.58)
FF/VI	67	69		
FP/SAL	60	66		
Anxiety/depression			N/A	0.79[b] (0.52 to 1.19)
FF/VI	78	77		
FP/SAL	77	81		
EQ-5D VAS score				
VAS score				1.4 (−0.3 to 3.0)
FF/VI	80.4	85.6	5.5 ± 0.60	
FP/SAL	80.0	84.2	4.1 ± 0.60	

Intention-to-treat population, n = 403 (FF/VI 100/25 μg OD PM) and n = 403 (FP/SAL 250 μg bid). ACT = Asthma Control Test; AQLQ+12 = Asthma Quality of Life + 12 Questionnaire; EQ-5D = European Quality of Life-5 Dimensions; N/A = not applicable; VAS = visual analog scale. See Table 1 legend for expansion of other abbreviations.

[a]AQLQ+12, ACT, and EQ-5D VAS score, analysis of covariance was used, with covariates of baseline score, country, sex, age, and treatment; EQ-5D, logistic regression analysis was used, with covariates of baseline, region, sex, age, and treatment.

[b]OR.

FF/VI and FP/SAL were well tolerated, and FF/VI had a similar AE profile to FP/SAL. The AE profile with FF/VI reported in the present study is consistent with that seen in the two FF dose-ranging studies that included the 100 μg once-daily dose[7,8] and the two studies of VI 25 μg plus concurrent ICS.[10,19] Most of the SAEs reported in the present study were single events, and none were considered treatment related. Asthma exacerbations requiring hospitalization occurred in one patient receiving FF/VI and two patients receiving FP/SAL.

A potential effect of ICS treatment is reduction in UC levels as a result of suppression of the hypothalamic-pituitary-adrenal axis, although this usually only occurs at higher doses of ICS.[9,20,21] In earlier phase dose-ranging studies, once-daily FF 100 or 200 μg did not significantly inhibit 24-h UC levels relative to placebo.[7,8] In the current study, clinically insignificant increases in UC levels from baseline were reported, and no statistically significant differences were observed between the groups at week 24. LABAs have occasional side effects, such as headache, tremor, and hypertension.[22] In the present study, no clinically relevant effects of FF/VI or FP/SAL were found in measures of BP or pulse rate.

It may be considered a limitation that the study duration was too short to reliably collect information on important end points such as exacerbations. Also, while a once-daily dosing schedule could provide greater convenience to the patient and may therefore increase compliance to treatment,[23] the double-blind, double-dummy nature of the study, together with the very high compliance levels during the study, means that the full benefit of once-daily dosing compared with bid dosing could not be realized in this study. This can only be investigated in a real-world effectiveness study, such as the Salford Lung Study, which is now under way.[24] It is possible that prestudy ICS adherence was lower than anticipated by the protocol, as suggested by the high degree of FEV_1 reversibility seen at screening. Patient compliance with run-in medication was not formally assessed. Once-daily FF/VI had similar treatment effects to bid FP/SAL in improving lung function and health status in this double-blind

Table 4—*On-Treatment AEs ≥ 3% in Any Treatment Group, All SAEs, and Treatment-Related AEs (Intention-to-Treat Population)*

Event	FF/VI 100/25 μg OD PM (n = 403)	FP/SAL 250/50 μg bid (n = 403)
Any event	213 (53)	198 (49)
Nasopharyngitis	46 (11)	46 (11)
Headache	34 (8)	41 (10)
URTI	26 (6)	16 (4)
Cough	15 (4)	13 (3)
Back pain	11 (3)	11 (3)
Oropharyngeal pain	11 (3)	9 (2)
Sinusitis	12 (3)	7 (2)
Pyrexia	13 (3)	5 (1)
Productive cough	11 (3)	5 (1)
Treatment-related AEs (any)	19 (5)	15 (4)
SAEs		
Any event	4 (< 1)	5 (1)
Pneumonia	0	1 (< 1)
URTI	1 (< 1)	0
Urinary tract infection	0	1 (< 1)
Asthma	1 (< 1)	2 (< 1)
Myocardial ischemia	1 (< 1)	0
Cholelithiasis	1 (< 1)	0
CO poisoning	0	1 (< 1)
Disorientation	0	1 (< 1)
Treatment-related SAEs (any)	0	0

Data are presented as No. (%). AE = adverse event; SAE = serious adverse event; URTI = upper respiratory tract infection. See Table 1 legend for expansion of other abbreviations.

randomized study. It remains to be seen whether it will be superior in a real-world setting. In conclusion, there was no difference in efficacy or safety between FF/VI 100/25 μg administered once daily in the evening and FP/SAL 250/50 μg administered bid.

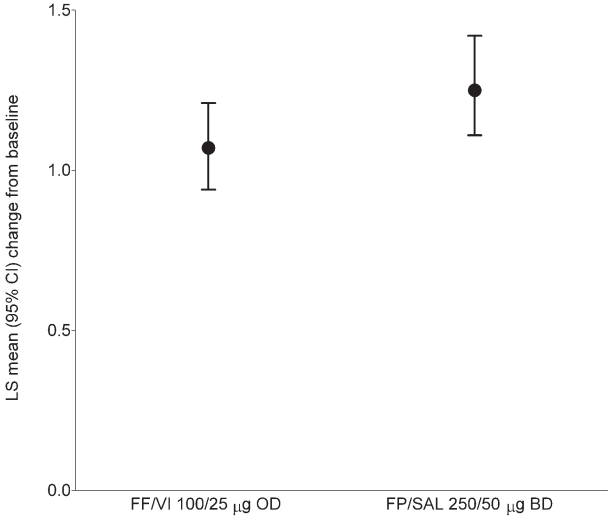

FIGURE 4. Adjusted ratios to baseline for 24-h urinary cortisol excretion at week 24 (urinary cortisol population). See Figure 1 and 2 legends for expansion of abbreviations.

ACKNOWLEDGMENTS

Author contributions: Dr Woodcock had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Woodcock: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Bleecker: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Lötvall: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr O'Byrne: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Bateman: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Ms Medley: contributed to the study concept and design, data collection, critical review of the manuscript, and approval of the final version to be published.

Ms Ellsworth: contributed to the study design, data analysis and interpretation, critical review of the manuscript, and approval of the final version to be published.

Dr Jacques: contributed to the study design; data collection, analysis, and interpretation; critical review of the manuscript; and approval of the final version to be published.

Dr Busse: contributed to the study design, data interpretation, critical review of the manuscript, and approval of the final version to be published.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Woodcock has served as consultant to Almirall SA, Chiesi Farmaceutici SpA, Cytos Biotechnology AG, and GlaxoSmithKline and has received lecture fees and research grants from GlaxoSmithKline. Dr Bleecker has served as a consultant to AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline, Johnson & Johnson, and Merck Sharp & Dohme Corp. He has received reimbursement for travel from GlaxoSmithKline and has performed clinical trials for AstraZeneca; Boehringer Ingelheim GmbH; Cephalon; Forest Laboratories, Inc; Genentech, Inc; GlaxoSmithKline; Kalabios; MedImmune; Novartis Corporation; and Sanofi-Aventis, which have been administered by his employer, Wake Forest School of Medicine. Dr Lötvall has served as a consultant to and received lecture fees from AstraZeneca; GlaxoSmithKline; Merck Sharp and Dohme Corp; Novartis Corporation; and UCB, Inc. He has been partly covered by some of these companies to attend previous scientific meetings, including those of the European Respiratory Society and the American Academy of Allergy, Asthma & Immunology; has provided expert testimony for Barr Pharmaceuticals, Inc; and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme Corp, and Novartis Corporation. Dr O'Byrne has served as a consultant to Almirall SA, AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline, and Merck Sharp & Dohme Corp. He has served on advisory boards for AIM Pharmaceuticals; Altair Therapeutics; Boehringer Ingleheim GmbH; GlaxoSmithKline; MedImmune, LLC; and Merck Sharp & Dohme Corp; has received lecture fees from Chiesi Farmaceutici SpA; and has received research funding from Amgen Inc; AstraZeneca; Asmacure Ltée; Genentech, Inc; and Ono Pharmaceutical Co, Ltd. Dr Bateman has served as a consultant to ALK, Almirall SA, Boehringer Ingelheim, Cephalon Inc, Hoffmann-La Roche Inc, ICON plc, and MS Consulting Group. He has been on advisory boards for Almirall SA; AstraZeneca; Boehringer Ingelheim GmbH; Elevation Pharmaceuticals Inc; Forest Laboratories, Inc; GlaxoSmithKline; Merck Sharp & Dohme Corp; NAPP Pharmaceuticals Limited; Novartis Corporation; and Nycomed. Dr Bateman has also received lecture fees from ALK; AstraZeneca; Boehringer Ingelheim GmbH; Chiesi Farmaceutici SpA; GlaxoSmithKline; Novartis Corporation; Pfizer, Inc Takeda Pharmaceuticals International GmbH and Teva, and his institution has received remuneration for participation in clinical trials sponsored by Actelion Pharmaceuticals US, Inc; Aeras; Almirall SA; AstraZeneca; Boehringer Ingelheim GmbH; Forest Laboratories,

Inc; GlaxoSmithKline; Hoffmann-La Roche Inc; Merck Sharp & Dohme Corp; Novartis Corporation; Takeda Pharmaceuticals International GmbH; and Teva Pharmaceutical Industries Ltd. Dr Busse has served as a consultant to Amgen Inc; AstraZeneca; Boehringer Ingelheim GmbH; Genentech, Inc; GlaxoSmithKline; MedImmune, LLC; Novartis Corporation; and Teva Pharmaceutical Industries Ltd. He has served on advisory boards for Altair Therapeutics; Amgen Inc; Centocor Ortho Biotech, Inc; GlaxoSmithKline; Johnson & Johnson Services, Inc; Merck Sharp & Dohme Corp; and Pfizer, Inc. Dr Busse has also received lecture fees from Merck Sharp & Dohme Corp and research funding from AstraZeneca; Ception Therapeutics; GlaxoSmithKline; MedImmune, LLC; and Novartis Corporation. Mss Medley and Ellsworth and Dr Jacques are employees of and hold stock in GlaxoSmithKline.

Role of sponsors: Employees of the sponsor GlaxoSmithKline, collected the data (Mss Medley and Ellsworth and Dr Jacques), and performed the statistical analysis (Ms Ellsworth), contributed to the study design, interpreted the data, and developed the manuscript. The sponsor did not place any restriction on authors about the statements made in the final article. Editorial support (in the form of development of the draft outline in consultation with the authors, development of the manuscript first draft in consultation with the authors, editorial suggestions to draft versions of this article, assembly of tables and figures, collating author comments, copyediting, fact checking, referencing, and graphic services) was provided by Lisa Moore, PhD, and Ian Grieve, PhD, Gardiner-Caldwell Communications (Macclesfield, England) and was funded by GlaxoSmithKline. The fee for open access was paid by GlaxoSmithKline.

Other contributions: The authors thank all the patients who took part in the study and all of the investigators at the 65 participating centers.

Additional information: The e-Appendixes, e-Tables, and e-Figure can be found in the "Supplemental Materials" area of the online article.

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