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Fluticasone furoate/vilanterol versus fluticasone propionate in patients with asthma and exercise-induced bronchoconstriction

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ABSTRACT

Objective: To investigate whether once-daily (OD) fluticasone furoate (FF)/vilanterol (VI) provides greater long-term protection from postexercise fall in forced expiratory volume in 1 s (FEV₁) than twice-daily (BD) fluticasone propionate (FP) in patients with asthma and exercise-induced bronchoconstriction. **Methods:** A randomized, double-blind, crossover study was conducted in patients (aged 12–50 years) on low-/mid-dose maintenance inhaled corticosteroid. Following a 4-week run-in period (FP 250 µg BD), patients with a $\geq 20\%$ decrease in postexercise FEV₁ received FF/VI 100/25 µg OD or FP 250 µg BD for 2 weeks. Exercise challenges were carried out 23 h after the first dose of study medication, and 12 and 23 h after evening clinic dose at the end of the 2-week treatment period. After a 2-week washout period (FP 250 µg), patients crossed over treatments, with procedures and tests repeated. The primary endpoint was mean maximal percentage decrease from pre-exercise FEV₁ following exercise challenge 12-h postevening dose on Day 14. **Results:** The mean maximal percentage decrease from pre-exercise FEV₁ after the 12-h exercise challenge (Day 14) was 15.02% with FF/VI, and 16.71% with FP (difference, -1.69 ; 95% confidence interval, -3.76 to 0.39 ; $p = 0.109$). After the 23-h exercise challenge (Day 14), respective mean maximal decreases were 11.90% and 14.05% (difference, -2.15 ; 95% confidence interval, -4.31 to 0.01). **Conclusion:** The study failed to show a difference between FF/VI and FP at providing long-term protection from exercise-induced bronchoconstriction.

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Introduction

Exercise-related symptoms affect up to 90% of individuals with asthma, and exercise is one of the most common triggers of bronchoconstriction in patients with asthma [1–3]. However, the predisposition toward exercise-induced bronchoconstriction varies greatly among patients with asthma [4]. The diagnosis is based on a fall in lung function, measured by forced expiratory volume in 1 s (FEV₁) [5]. American Thoracic Society guidelines define exercise-induced bronchoconstriction as a $\geq 10\%$ decline in FEV₁ from pre-baseline levels, recorded within 30 min following exercise [4].

For many patients, standard maintenance therapy with an inhaled corticosteroid (ICS) will reduce exercise-induced bronchoconstriction [6], and the relationship between this phenomenon, airway inflammation, and steroid responsiveness has been clearly

demonstrated [7]. If exercise symptoms persist, ICS can be supplemented with the prophylactic use of a short-acting β_2 -agonist (SABA). For those patients requiring daily or more frequent use of a SABA, a second controller agent is generally added to ICS, such as a long-acting β_2 -agonist (LABA). ICS/LABA combinations have been shown to be the most effective step-up option to gain improved asthma control [6,8–10], and are recommended for the daily management of asthma [11]. ICS, alone and in combination with a LABA, can reduce the incidence and severity of exercise-induced bronchoconstriction when measured shortly after dosing [12]. However, results have been inconsistent as to whether the ICS/LABA combination is superior to ICS alone at reducing the severity of exercise-induced bronchoconstriction over a more prolonged time period. There have been contradictory results as to whether fluticasone propionate (FP)/salmeterol is superior to FP

alone at time periods up to 8-h post-dose [13–15]. It remains unclear whether LABAs would confer longer bronchoprotection.

Fluticasone furoate/vilanterol (FF/VI) is a once-daily (OD) ICS/LABA combination that has been shown to provide improvements in lung function for up to 72 h in adults and adolescents with persistent asthma [16]. Therefore, this study was designed to see whether the longer duration of bronchodilation offered by this medication would also confer a longer duration of bronchoprotection. We compared the bronchoprotective effect against exercise-induced bronchoconstriction of OD FF/VI 100/25 µg with twice-daily (BD) FP 250 µg over a 24-h dosing interval in adult and adolescent patients with asthma. Safety was also compared between treatments. FP was used as the comparator because it is commonly used globally as an ICS monotherapy for the treatment of asthma, and its ability to prevent exercise-induced bronchoconstriction when used as a maintenance therapy has been previously demonstrated [13,17]. Additionally, FF monotherapy is not available for the treatment of asthma in a number of markets, including the European Union.

Methods

Patients

Adult and adolescent patients aged 12–50 years with a diagnosis of asthma according to the National Institutes of Health guidelines [18], pre-bronchodilator FEV₁ ≥70% of the predicted normal value [19], who had been taking maintenance low-/mid-dose ICS for ≥12 weeks (no change in dose for 4 weeks prior) were eligible. Additionally, patients needed to respond “yes” to at least two of the following questions: “Are you short of breath during exercise or other physical exertion?”, “Do you wheeze after exercise or other physical exertion?”, and “Do you cough after exercise or other physical exertion?” Patients with significant smoking history or asthma symptoms that were seasonal, intermittent, or only present during exercise were excluded. As this was a short-term study, patients with seasonal symptoms were excluded so that the results were not influenced by the time of year that the study was conducted. Additionally, intermittent and exercise-only symptoms are treatable with β₂-agonists, and do not meet Global Initiative for Asthma criteria for persistent disease [11]; therefore, patients with these conditions do not qualify for long-term ICS or ICS/LABA therapy and, as such, were not included in the study. Patients with symptomatic allergic rhinitis at screening were

excluded but could attend a second enrollment screening after 4 weeks of treatment with nasal corticosteroids and were enrolled only if asymptomatic. Female patients of childbearing potential were required to have a negative pregnancy test at screening and agree to use an acceptable contraceptive method. Other exclusion criteria included an asthma exacerbation within the previous 12 weeks that required treatment and any history of life-threatening asthma within the previous 10 years. Although a postexercise decrease of ≥20% in FEV₁ within 30 min of completing the challenge was required for randomization, patients with a decrease of 15% to <20% could repeat the eligibility exercise challenge once within a week while continuing run-in medication.

The study was reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with International Council for Harmonisation Good Clinical Practice and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study design and conduct

This was a randomized, double-blind, double-dummy, multicenter, crossover study comparing the effects of FF/VI 100/25 µg OD (evening, delivered via the ELLIPTA inhaler) versus FP 250 µg BD (morning and evening, delivered via the DISKUS inhaler) on exercise-induced bronchoconstriction in patients with persistent asthma (NCT02730351/GSK study 201832). The study took place between May 2016 and February 2017, with patients randomized at 14 treatment centers in the United States and Canada (recruitment period, May 2016 to November 2016; follow-up period, November 2016 to February 2017). Patients were enrolled by study investigators, and randomization to one of two treatment sequences was achieved by the investigators assigning each patient a number from a computer-generated randomization schedule provided by the sponsor.

The study design is shown in Figure 1. After Visit 1 (screening), patients began a 4-week run-in period on FP 250 BD, followed by a standardized exercise challenge (Visit 2). A postexercise decrease of ≥20% in FEV₁ within 30 min of completing the challenge was required for randomization.

The first double-blind 2-week treatment period was followed by a 2-week single-blind washout period with FP 250 BD (started at Visit 4). Patients then crossed over to the alternative treatment for

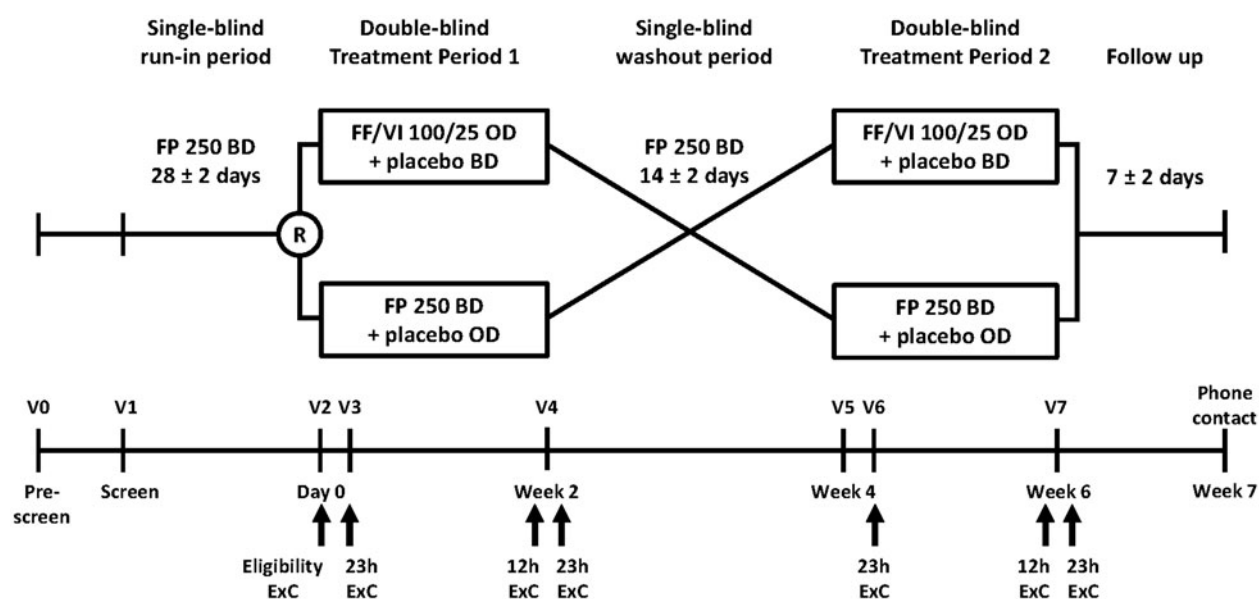


Figure 1. Study schematic. BD: twice daily; ExC: exercise challenge; FF: fluticasone furoate; FP: fluticasone propionate; OD: once daily; R: randomization; V: visit; VI: vilanterol.

the second double-blind 2-week treatment period (started at Visit 5). To maintain study drug blinding, patients were provided with relevant active and placebo ELLIPTA and DISKUS inhalers for each treatment period. Run-in and washout phases were single-blind only because investigators and site staff, due to their knowledge of the study design, were not blinded to the allocation of FP 250 BD to all patients. In addition to the study medication, patients were provided with a SABA (albuterol/salbutamol) for rescue use as needed throughout the study.

Patients took standardized exercise challenge tests with spirometry testing 23-h postfirst dose at the start (Day 1), and 12 and 23-h postevening dose at the end of each 2-week treatment period (Day 14). Exercise challenges comprised 10-min stepped treadmill challenges, with the patients spending ≥ 6 min at 80–95% of their maximum predicted heart rate. Patients breathed medical-grade dry air at ambient temperature. Postexercise FEV₁ measurements were taken using serial spirometry 5, 10, 15, 30, 45, and 60 min after every challenge. Asthma control was assessed using the Asthma Control Questionnaire-5 (ACQ-5) at the beginning of each study visit. Patients were followed up by telephone 7 days after Visit 7.

FEV₁ measurements were taken using standardized spirometry equipment at all visits. Centers were standardized using the CompleWare spirometry system. Patients were not permitted to consume highly caffeinated beverages ≤ 4 h prior to the exercise challenge

(before any FEV₁ measurement) and had to refrain from exercise in cold air for 24 h before the exercise challenge. Patients were instructed to withhold their daily study drug dose on clinic visit days before arriving at the clinic and to withhold albuterol for ≥ 6 h before a visit.

Endpoints

The primary endpoint was the maximum percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12-h postevening dose on Day 14. Secondary endpoints included the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 23-h postevening dose on Day 14, and, following the exercise challenges at 12 and 23-h postevening dose on Day 14, the proportion of patients with a 30-min postchallenge FEV₁ $\leq 5\%$ lower than their pre-exercise FEV₁, and the weighted mean (0–60 min) for percentage decrease from pre-exercise FEV₁.

Other endpoints (Day 14) included the maximal percentage decrease from treatment-period baseline FEV₁ following the exercise challenges at 12 and 23-h postevening dose, the mean change from baseline in ACQ-5 score [20], the percentage of patients with controlled asthma (ACQ-5 score ≤ 0.75), and the percentage of patients achieving an improvement of ≥ 0.5 in ACQ-5 score. Safety was assessed by monitoring adverse events (AEs) and measuring vital signs at each visit. There was a 12-lead electrocardiogram and physical examination at screening.

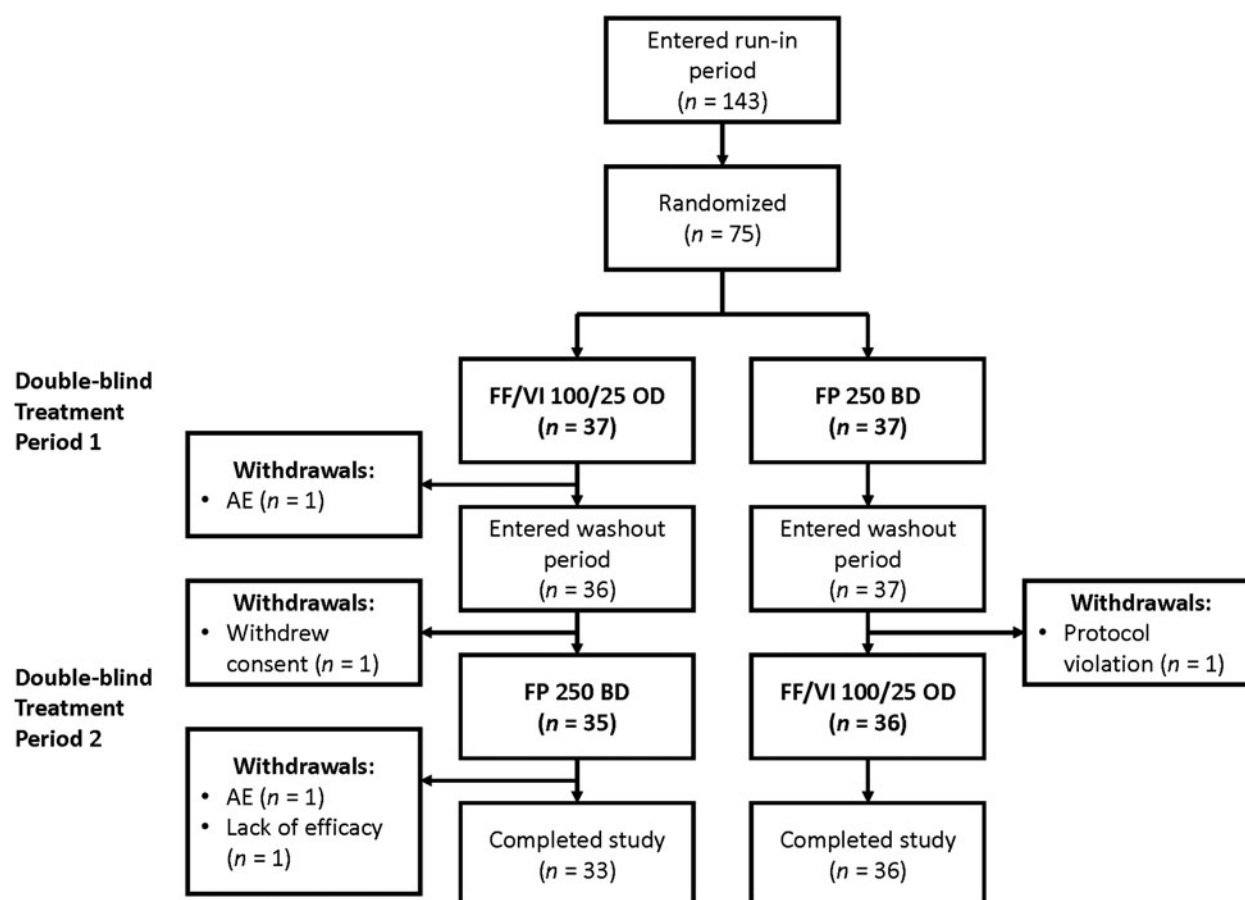


Figure 2. Disposition of patients during the study. AE: adverse event; BD: twice daily; FF: fluticasone furoate; FP: fluticasone propionate; OD: once daily; VI: vilanterol.

Statistical analyses

The primary population for efficacy analysis was the intent-to-treat (ITT) population (all patients randomized to treatment who received ≥ 1 dose of study medication). The primary treatment comparison was FF/VI versus FP for the primary endpoint of maximal percentage decrease from pre-exercise FEV₁ following an exercise challenge at 12-h postdose at the end of the 2-week treatment period. A sample size of 56 evaluable patients for each treatment was calculated to provide a study power of $\sim 90\%$ for the primary endpoint, assuming a true population difference of 5% in maximal percentage decrease in FEV₁ between the two groups and a within-subject standard deviation of 8%. Based on a potential 20% dropout rate, 66 patients were planned for each group.

The analysis of maximal percentage decrease in FEV₁ postexercise was performed using a mixed-model repeated-measures model (fixed effect covariates: treatment, sex, age, treatment period, smoking history [pack-years], period baseline FEV₁, and mean baseline FEV₁ across both periods). Subject was fitted as a random effect. For the analysis of the proportion

of patients with a 30-min postchallenge FEV₁ $\leq 5\%$ lower than their pre-exercise FEV₁, a repeated measures logistic regression model with parameters estimated using the Generalized Estimating Equation method was used (covariates: treatment, sex, age, treatment period, and period baseline FEV₁). For all endpoints, the null hypothesis of no difference between treatments was tested at a 2-sided significance level of 5%. A stepwise gatekeeping procedure was used during the statistical significance testing of the multiple endpoints in the study.

Results

Study conduct

Seventy-four patients were randomized and received study medication (37 patients in each treatment sequence; Figure 2). One patient randomized to receive FF/VI during Treatment Period 1 discontinued the study prior to completion of Treatment Period 1. One patient in each treatment sequence did not complete the washout period. Of the 35 patients entering Treatment Period 2 who were randomized to receive

Table 1. Patient demographics and baseline clinical characteristics (intent-to-treat population).

Parameter	N = 74
Mean age, years (SD)	27.8 (10.35)
Sex, n (%)	
Female	43 (58)
Male	31 (42)
Race, n (%)	
White/Caucasian/European heritage	42 (57)
African American/African heritage	28 (38)
Other	4 (5)
Mean pre-challenge FEV ₁ , L (SD)	3.025 (0.7714)
Mean pre-challenge FEV ₁ , % predicted (SD)	91.28 (13.804)
Mean maximal decrease from pre-exercise FEV ₁ , % (SD)	28.55 (5.827)

Note. FEV₁: forced expiratory volume in 1 s; SD: standard deviation.

FP during that period, two did not complete study treatment (Figure 2). The clinical trial was completed as planned.

Patient demographics and baseline clinical characteristics are shown in Table 1. The mean age of the ITT population was 27.8 years, and there was a slightly higher proportion of female patients (58%). A substantial proportion of patients were of African American/African heritage (38%). The mean prechallenge FEV₁ at baseline (Visit 2) was 91.28% (standard deviation [SD] 13.804) of predicted and the mean maximal decrease after baseline exercise challenge was 28.55% (SD 5.827).

Efficacy

Exercise challenge testing

After the 12-h postevening dose exercise challenge on Day 14, the mean maximal percentage decrease from pre-exercise FEV₁ was 15.02% with FF/VI and 16.71% with FP (Table 2). The difference was -1.69 (95% confidence interval [CI] -3.76 to 0.39) and was not statistically significant ($p = 0.109$). Because of the gatekeeper hierarchy beginning with the primary endpoint as defined in the statistical analysis plan, no inference of statistical significance can be made for the other endpoints, which should be interpreted as descriptive only.

After the 23-h postevening dose exercise challenge on Day 14, the values for the mean maximal decrease from pre-exercise FEV₁ with FF/VI and FP, respectively, were 11.90% and 14.05% (difference -2.15 ; 95% CI -4.31 to 0.01). For recovery of FEV₁ to pre-exercise levels, only minimal differences were present between the two treatments. At the 12-h postdose exercise challenge on Day 14, 49% of patients had FEV₁ values $\geq 95\%$ of the prechallenge value at the 30-min postchallenge time point with FF/VI, compared with 42% with FP. The odds ratio for FF/VI versus FP was 1.34 (95% CI 0.80–2.26; Table 2). The

weighted mean values of the 0–60 min percentage decrease in FEV₁ from pre-exercise levels showed differences numerically favoring FF/VI of -0.65 (95% CI -2.01 to 0.71) at 12-h postdose and -1.75 (95% CI -3.42 to -0.07) at 23-h postdose on Day 14. The maximal percentage decrease in FEV₁ from the treatment period baseline also numerically favored the FF/VI group; after the 12-h and 23-h postdose exercise challenges on Day 14, the treatment differences were -5.49% (95% CI -8.23 to -2.74) and -4.06% (95% CI -6.75 to -1.37), respectively (Table 2).

At period baseline, the majority of patients did not meet the definition of well-controlled asthma (defined as an ACQ-5 score of ≤ 0.75). Mean period baseline ACQ-5 scores in the FF/VI and FP arms were 1.27 and 1.26, respectively. Least squares mean ACQ-5 scores at the end of each crossover period numerically favored FF/VI over FP (0.92 versus 1.12, respectively; difference -0.20 [95% CI -0.35 to -0.05]; Table 3). For the percentage of patients with asthma control (ACQ-5 score ≤ 0.75), the FF/VI versus FP odds ratio was 3.07 (95% CI 1.35 – 6.93), but there was no between-group difference in patients with a decrease in ACQ-5 score of ≥ 0.5 points (Table 3; Figure 3).

Comparisons between study periods (post-hoc analysis)

To examine the possible role of study design in the lack of demonstrated efficacy, we assessed the change in FEV₁ over time for each on-treatment exercise challenge (Figure 4). The difference between FF/VI and FP was smaller during the second treatment period than during the first, largely resulting from smaller declines in postchallenge FEV₁ in the FP-treated group during Treatment Period 2 versus Treatment Period 1. In contrast, post-exercise fall in FEV₁ was relatively consistent across both treatment periods with FF/VI.

Safety

Overall, the number of patients with AEs was low for both treatments, and there was no between-treatment difference in the incidence of AEs. On study drug, 16% and 15% of patients experienced ≥ 1 AE with FF/VI and FP, respectively. Only one nonserious AE (increased tendency to bruise) was thought to be related to study treatment (FF/VI). One patient in each arm reported non-serious AEs that resulted in withdrawal from the study (worsening of asthma and sinusitis for one patient in the FF/VI arm, and cough for one patient in the FP arm). One serious AE

Table 2. Results of the study primary, secondary, and other endpoints.

Endpoint	FF/VI 100/25 OD (n = 73)	FP 250 BD (n = 72)
Maximal decrease in FEV ₁ from pre-exercise value following exercise challenge		
Day 14 ^a , 12-h postdose	n = 70	n = 69
LS mean (SE) ^b , %	15.02 (1.058)	16.71 (1.095)
Difference (95% CI), %	−1.69 (−3.76 to 0.39)	
p-value	0.109 ^c	
Day 14 ^a , 23-h postdose	n = 68	n = 69
LS mean (SE) ^b , %	11.90 (1.020)	14.05 (1.051)
Difference (95% CI), %	−2.15 (−4.31 to 0.01)	
Day 1 ^d , 23-h postdose	n = 66	n = 70
LS mean (SE) ^b , %	16.42 (1.189)	16.99 (1.185)
Difference (95% CI), %	−0.57 (−3.39 to 2.25)	
Post-challenge FEV ₁ following exercise challenge (30 min post-challenge) ^e		
Day 14 ^a , 12-h postdose	n = 70	n = 69
FEV ₁ ≥95% of pre-exercise value, n (%)	34 (49)	29 (42)
Odds ratio (95% CI)	1.34 (0.80 – 2.26)	
Day 14 ^a , 23-h postdose	n = 68	n = 69
FEV ₁ ≥95% of pre-exercise FEV ₁ , n (%)	42 (62)	37 (54)
Odds ratio (95% CI)	1.37 (0.73 – 2.58)	
Day 1 ^d , 23-h postdose	n = 66	n = 70
FEV ₁ ≥95% of pre-exercise FEV ₁ , n (%)	22 (33)	37 (53)
Odds ratio (95% CI)	0.43 (0.22–0.84)	
Weighted mean 0 – 60 min for decrease from pre-exercise FEV ₁ following exercise challenge		
Day 14 ^a , 12-h postdose	n = 67	n = 66
LS mean (SE) ^b , %	5.87 (0.663)	6.52 (0.680)
Difference (95% CI), %	−0.65 (−2.01 to 0.71)	
Day 14 ^a , 23-h postdose	n = 68	n = 67
LS mean (SE) ^b , %	3.98 (0.699)	5.73 (0.747)
Difference (95% CI), %	−1.75 (−3.42 to −0.07)	
Day 1 ^d , 23-h postdose	n = 65	n = 67
LS mean (SE) ^b , %	6.96 (0.676)	6.14 (0.678)
Difference (95% CI), %	0.83 (−0.88 to 2.53)	
Maximal decrease from period baseline FEV ₁ following exercise challenge		
Day 14 ^a , 12-h postdose	n = 70	n = 69
LS mean maximal decrease (SE) ^b , %	11.21 (1.171)	16.70 (1.227)
Difference (95% CI), %	−5.49 (−8.23 to −2.74)	
LS mean maximal decrease (SE) ^b , L	0.358 (0.0376)	0.519 (0.0392)
Difference (95% CI), L	−0.161 (−0.244 to −0.078)	
Day 14 ^a , 23-h postdose	n = 69	n = 69
LS mean maximal decrease (SE) ^b , %	8.58 (1.130)	12.64 (1.173)
Difference (95% CI), %	−4.06 (−6.75 to −1.37)	
LS mean maximal decrease (SE) ^b , L	0.279 (0.0332)	0.396 (0.0343)
Difference (95% CI), L	−0.118 (−0.191 to −0.044)	
Day 1 ^d , 23-h postdose	n = 66	n = 70
LS mean maximal decrease (SE) ^b , %	12.00 (1.274)	17.37 (1.270)
Difference (95% CI), %	−5.38 (−8.53 to −2.22)	
LS mean maximal decrease (SE) ^b , L	0.361 (0.0396)	0.514 (0.0395)
Difference (95% CI), L	−0.153 (−0.243 to −0.062)	

Notes. BD: twice daily; CI: confidence interval; FEV₁: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once daily; SE: standard error; VI: vilanterol.

^aVisits 4 and 7.

^bRepeated-measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history (number of pack-years), period baseline FEV₁, and the mean of the two period baseline FEV₁ values. Subject is fitted as a random effect.

^cThe failure to achieve $p < 0.05$ for the FF/VI vs FP comparison on the primary endpoint meant that significance could not be inferred for any subsequent endpoint per the closed step-down statistical hierarchy employed. As such, differences and associated 95% CI values only are shown for subsequent endpoints.

^dVisits 3 and 6.

^eRepeated-measures logistic regression model with parameters estimated using the Generalized Estimating Equation method. Covariates of treatment, sex, age, treatment period, and period baseline FEV₁ were included. Smoking history (number of pack-years) could not be included as a covariate.

(gastroenteritis reported with FF/VI) was not considered related to study treatment.

Discussion

In this study, FF/VI did not confer significantly greater bronchoprotection to patients following exercise challenges 12 and 23 h after evening dose, when

compared with regular use of FP. Although there was a smaller maximal percentage decrease from pre-exercise FEV₁ with FF/VI than with FP following the exercise challenge 12-h postdose on Day 14, the between-treatment difference was not significant and, as such, the primary endpoint of the study was not met. Because a gatekeeper approach was used for the statistical testing, it was not possible to infer statistical

Table 3. Assessment of ACQ-5 score following a 2-week treatment period.

Assessment of ACQ-5	FF/VI 100/25 OD (n = 73)	FP 250 BD (n = 72)
Change in ACQ-5 score	n = 72	n = 71
LS mean at Day 14 ^a	0.92	1.12
LS mean change from period baseline (SE), %	−0.33 (0.057)	−0.12 (0.058)
Difference (95% CI) ^b	−0.20 (−0.35 to −0.05)	
Number of patients with controlled asthma	n = 72	n = 71
ACQ-5 score ≤ 0.75 at Day 14 ^a , n (%)	34 (47)	22 (31)
Odds ratio (95% CI) ^c	3.07 (1.35 to 6.93)	
Number of patients with improving asthma control	n = 72	n = 71
Decrease in ACQ-5 score ≥ 0.5 from period baseline at Day 14 ^a , n (%)	20 (28)	18 (25)
Odds ratio (95% CI) ^c	1.08 (0.49 to 2.40)	

Notes. ACQ-5: Asthma Control Questionnaire-5; BD: twice daily; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once daily; SE: standard error; VI: vilanterol.

^aVisits 4 and 7.

^bRepeated Measures analysis adjusted for fixed effects of treatment, sex, age, treatment period, smoking history, period baseline ACQ-5 score and the mean of the two period baseline ACQ-5 scores. Participant was fitted as a random effect.

^cRepeated measures logistic regression model with parameters estimated using the GEE method. Covariates of treatment, sex, age, treatment period, smoking history and period baseline ACQ-5 score were included. Period baseline was defined as the pretreatment value taken at the start of each treatment period.

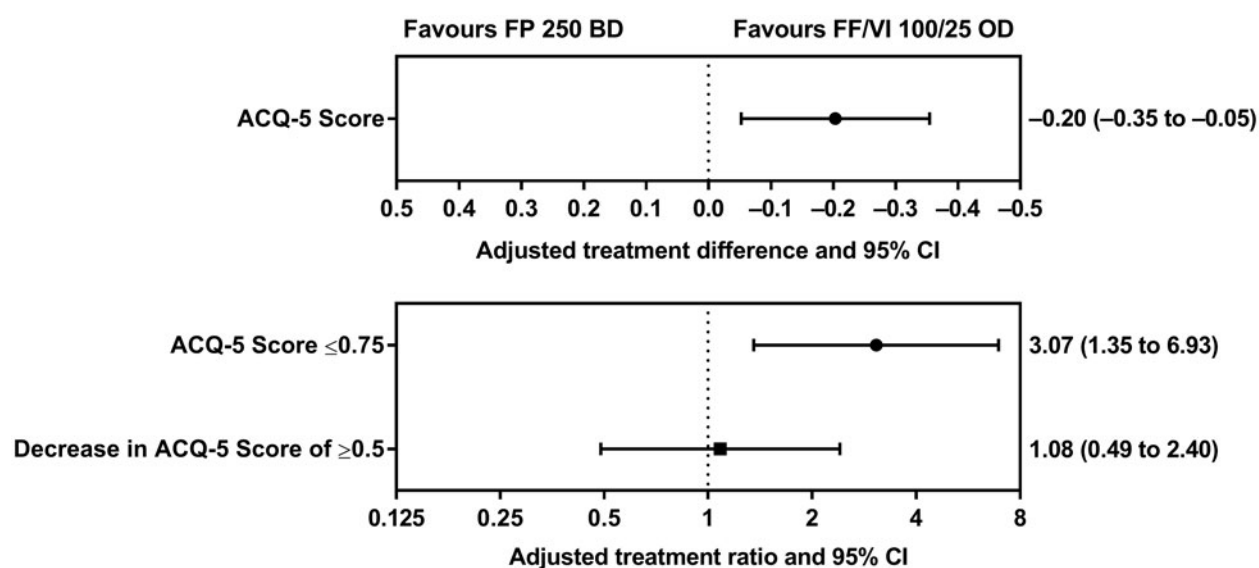


Figure 3. Difference in ACQ-5 score with FF/VI versus FP. ACQ-5: Asthma Control Questionnaire-5; BD: twice daily; CI: confidence interval; FF: fluticasone furoate; FP: fluticasone propionate; OD: once daily; VI: vilanterol.

significance for the secondary and other endpoints. Patients had a numerically smaller reduction in maximal percentage fall from pre-exercise FEV₁ with FF/VI versus FP following the exercise challenge 23-h postdose on Day 14, while the number of patients with postexercise FEV₁ values $\geq 95\%$ of pre-exercise levels was marginally higher with FF/VI at the 30-min postchallenge time point following both exercise challenges on Day 14. Pre-exercise, patients had numeric improvements in FEV₁ and in ACQ-5 score with FF/VI versus FP. There is a suggestion that FF/VI provided an improvement in asthma control in these patients with exercise-induced bronchoconstriction, as the change from baseline in ACQ-5 and the proportion of patients that achieved control (a score of ≤ 0.75) were numerically in favor of FF/VI compared with FP. In both treatment arms, there was a low

number of patients with on-treatment AEs and serious AEs.

The bronchoprotective effects of ICS/LABA versus ICS alone have previously been assessed using approximately similar steroid doses to the current study [13]. In a parallel-group study, FP/salmeterol provided significantly greater bronchoprotection versus FP alone 1 h and 8.5 h after dosing following 4 weeks of treatment (both $p \leq 0.01$) [13]. Although the current study did not demonstrate a significant bronchoprotective effect with ICS/LABA versus ICS alone, there were key differences in the study design from that of Weiler et al. [13], particularly the crossover versus parallel design, and the later timing of the exercise challenges (12 and 23 vs 1 and 8.5 h postdose). Additionally, the less restrictive inclusion criterion of the current study regarding patient FEV₁ at screening

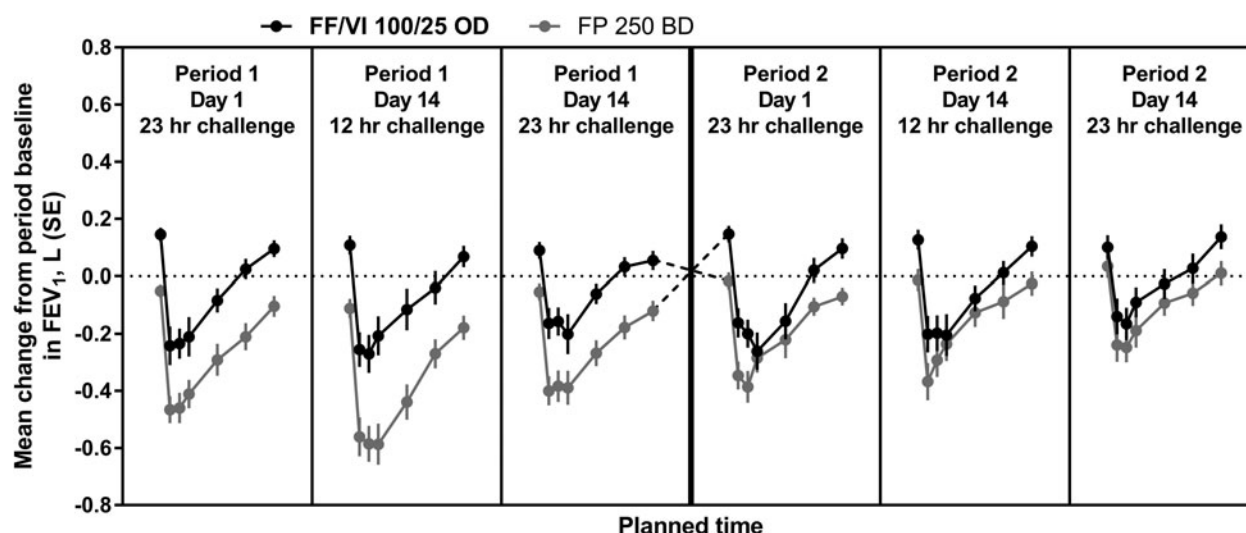


Figure 4. Change from period baseline in individual serial FEV_1 measurements (L) by period (*post hoc*). BD: twice daily; FEV_1 : forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; OD: once daily; SE: standard error; VI: vilanterol.

($\geq 70\%$ vs 65–90% predicted) [13] led to patient populations with distinctly different average lung functions (mean $FEV_1\%$ predicted 91% vs 78%), with considerably more heterogeneity among patients in the current study.

Post hoc analysis of individual time points showed that there was a greater difference in post-exercise fall in FEV_1 between the FF/VI and FP groups in Treatment Period 1 versus Treatment Period 2, largely due to a reduction in postexercise fall in FEV_1 with FP in Treatment Period 2 versus Treatment Period 1. This may have resulted from a positive effect on airway responsiveness and exercise bronchoconstriction due to the long-term use of FP. Subbarao et al. [21], have demonstrated both time-related and dose-response effects with ICS treatment on the magnitude of exercise bronchoconstriction. Although patients were prescribed low- to moderate-dose steroids before inclusion in the study and received a 4-week FP run-in, the long-term effects of good adherence to inhaled steroid medication may still have been apparent; this effect may have been amplified in patients whose adherence to ICS treatment was poor at baseline. Additionally, analysis of FEV_1 measurements over time across the treatment periods showed that, although postexercise falls in FEV_1 were similar in magnitude between FF/VI and FP, the initial pre-exercise measurements consistently showed that patients on FF/VI had improved lung function and asthma control scores versus FP.

Although tachyphylaxis to the bronchoprotective effects of LABA therapy has been observed in other studies, with and without concomitant ICS use [22–28], the constant effect of FF/VI on exercise-

induced bronchoconstriction observed in the current trial suggests that it was not a factor in this study. It should be noted that an individual patient may have markedly different airway responses to exercise challenges on a day-to-day basis [29], and this was apparent in the current study. At screening (Visit 2), the mean post-exercise maximal percentage decrease in FEV_1 was 28.55%. However, following the exercise challenge the next day (Visit 3, 23 h after first dose of study medication), this value dropped to 16.29% in the FF/VI arm and 17.48% in the FP arm. As this reduction in post-exercise fall in FEV_1 was observed in the FP arm, where patients' treatments had not altered from the 4-week run-in period, it cannot be attributed to the first dose of study treatment. This within-patient variability has the potential to reduce study power; however, it remains clear that the overall long-term bronchodilator effect of FF/VI, as previously reported [17], has been established.

The mechanisms that confer bronchoprotection as opposed to bronchodilation may be very different, and indeed the results of this study suggest this to be the case. In particular, the duration of action required for bronchodilation is likely to be significantly less than that for bronchoprotection, although the full mechanistic process here is not yet understood. Recent work on ligand specificity and β_2 -adrenoceptors indicates that the various ligands that interact with these receptors can have antagonistic, agonistic, or inverse agonistic activity [30]. Differences between partial and complete agonists may be particularly relevant. There has also been previous clear demonstration that the duration of bronchoprotection with LABAs is variable and, though often quite marked at

1–4 h post-dose, remains inconsistent >6 h after dosing [9,13]. Therefore, there is the potential for asthma drugs to offer long-term bronchodilation, while providing less prolonged bronchoprotection; so even an OD ICS/LABA may require an additional bronchoprotective agent, such as salbutamol, to be used prophylactically before exercise. In some short studies, it has even been questioned whether the addition of a LABA to ICS therapy is detrimental to patients' exercise-induced bronchoconstriction [31]; however, data from the current study showed a numerically lower postexercise fall in FEV₁ in patients treated with ICS/LABA compared with ICS alone.

The strengths of this study include that it was conducted rigorously with the training of site personnel on conducting the exercise challenges, and the timing of visits and dosing. Weaknesses of the study include the choice to not perform any exercise challenges earlier than 12-h postdose, and at Treatment Period 2 baseline; these data may have provided useful insights into the mechanisms and duration of bronchoprotection with FF/VI and FP. Moreover, the treatment comparison may have been obscured by the use of FP as both a run-in/washout drug and the study drug. Additionally, as there was no exercise challenge 12-h postfirst dose, tachyphylaxis of FF/VI could not be fully assessed. Patients only performed a single pre-randomization challenge, and the influence of a learning effect cannot be ruled out for the subsequent challenges. Additionally, although the choice to include only individuals with postexercise falls in FEV₁ ≥20% meant that all enrolled patients demonstrated unequivocal exercise-induced bronchoconstriction, current guidelines state that a ≥10% post-exercise fall in FEV₁ is sufficient for a positive diagnosis [4]. While the selection criteria for this study helped to provide patients with clearly defined exercise-induced bronchoconstriction, extrapolation of the study results may not necessarily be applicable to those with milder exercise-induced bronchoconstriction.

The efficacy of FF/VI on improving lung function and asthma control remains evident, but the biology around long-term bronchoprotection with OD drugs remains to be fully elucidated and requires further mechanistic study.

Conclusion

This double-blind, crossover study failed to show a difference between FF/VI and FP in providing protection from exercise-induced bronchoconstriction 12 h after dosing. Patients generally had numerically better

symptom control and lung function with FF/VI versus FP but not statistically significant differences in bronchoprotection. The number of patients with on-treatment AEs and serious AEs was low with both treatments.

Disclosure statement

No potential conflict of interest was reported by the authors.

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