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# Fluticasone furoate/vilanterol (100/25; 200/25 μg) improves lung function in COPD: A randomised trial

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**KEYWORDS**
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**Summary**
*Background:* Once-daily combination treatment is an attractive maintenance therapy for COPD. However, the dose of inhaled corticosteroid to use in a once-daily combination is unknown. We compared two strengths of fluticasone furoate (FF) plus vilanterol (VI), the same strengths of the individual components, and placebo.
*Methods:* Multicentre, randomised, 24-week, double-blind, placebo-controlled, parallel-group study in stable, moderate-to-severe COPD subjects ($N = 1224$). Subjects were randomised to FF/VI (200/25 μg; 100/25 μg), FF (200 μg; 100 μg), VI 25 μg, or placebo, once daily in the morning. Co-primary efficacy endpoints; 0–4 h weighted mean (wm) $FEV_1$ on day 168, and change from baseline in trough (23–24 h post-dose) $FEV_1$ on day 169. The primary safety objective was adverse events (AEs).
*Results:* There was a statistically significant ($p < 0.001$) increase in wm $FEV_1$ (209 ml) and trough $FEV_1$ (131 ml) for FF/VI 200/25 μg vs. placebo; similar changes were seen for FF/VI 100/25 μg vs. placebo. Whereas the difference between FF/VI 200/25 μg and VI 25 μg in change from baseline trough $FEV_1$ (32 ml) was not statistically significant ($p = 0.224$), the difference between FF/VI 200/25 μg and FF 200 μg for wm $FEV_1$ (168 ml) was significantly different

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($p < 0.001$). VI 25 μg significantly improved wm and trough $FEV_1$ vs. placebo (209 ml and 131 ml, respectively). No increase was seen in on-treatment AEs or serious AEs (SAEs), with active therapy vs. placebo.

*Conclusions:* FF/VI provides rapid and significant sustained improvement in $FEV_1$ in subjects with moderate-to-severe COPD, which was not influenced by the dose of FF. These data suggest that FF/VI may offer clinical efficacy in COPD and warrants additional study.

**GSK study number**: HZC112207.

ClinicalTrials.gov: NCT01054885.



## Introduction

The efficacy and safety of combination inhaled corticosteroid (ICS) and long-acting $\beta_2$-agonist (LABA) therapy is well established[1–4] for the maintenance treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD), and this approach has been recognised by evidence based guidelines.[5–8] The most recent revision of the international GOLD statement further codifies such therapy by recommending that combination inhaled corticosteroid (ICS)/LABA therapy can be considered first-line in COPD patients at high risk for acute exacerbations.[5] There is increasing interest in moving to once-daily dosing for respiratory medications. One long-acting muscarinic antagonist (LAMA), tiotropium,[9] offers once-daily dosing, as does the phosphodiesterase-4 inhibitor roflumilast,[10] and the LABA indacaterol.[11] However, to date all ICS/LABA combination therapies require twice-daily dosing. Twice-daily dosing may result in lower adherence and greater COPD costs than once-daily dosing.[12]

Vilanterol (VI) is a LABA that can provide effective once-daily dosing in COPD at a dose of 25 μg.[13] Fluticasone furoate (FF) is a novel ICS whose effects as a monotherapy have not been investigated previously in COPD. In asthma the efficacy of FF as a once-daily therapy has been established in a series of studies investigating doses between 12.5 μg and 800 μg.[14–16] Also in asthma, FF at a dose of 100 μg once daily exhibited similar efficacy to fluticasone propionate at a dose of 250 μg twice daily over 24 weeks.[17]

In developing the combination FF/VI for clinical use, novel dose ranging of the ICS component of the combination was conducted in multiple phase III studies. In this report we describe the findings of one of the studies, which investigated the effect of FF at doses of 100 μg and 200 μg added to VI. The objectives of our study were to assess the bronchodilatory effect of FF/VI using two measures of lung function (weighted mean forced expiratory volume in 1 s [$FEV_1$] over the first 4 h post-dose, and trough $FEV_1$ assessed ~24 h after the final dose on day 168) to determine the effect of addition of FF to VI on those lung function outcomes; to assess whether any dose effect was observed with FF; to confirm the once-daily bronchodilatory capacity of VI; and to determine the safety and tolerability of all active treatments.

## Methods

A detailed description of all methods is provided in the Online Supplement.

### Subjects and ethics

The study was conducted between October 2009 and March 2011 at study centres in eight countries (Czech Republic, Germany, Japan, Poland, Romania, Russian Federation, Ukraine, and the United States). Participating subjects had a clinical diagnosis of COPD, an age ≥40 years, a smoking history of ≥10 pack-years, a post-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio of ≤0.70, a post-bronchodilator $FEV_1$ ≤70% predicted (NHANES III) and a score of ≥2 on the Modified Medical Research Council Dyspnoea Scale (mMRC). No prior history of COPD exacerbations was required for subjects to be eligible to enter the study. Reversibility to albuterol was assessed at the screening visit; both reversible and non-reversible subjects were eligible to enter the study.

Exclusion criteria included any respiratory disorder other than COPD; lung volume reduction surgery within the 12 months of screening; acute worsening (subject-managed corticosteroid or antibiotic treatment or physician prescription) of COPD within 6 weeks of screening, or a hospitalisation for COPD in the 12 weeks, or a lower respiratory tract infection that required the use of antibiotics in the 6 weeks before screening; the need for long-term oxygen therapy or nocturnal oxygen therapy (≥12 h/day).

All subjects gave written informed consent and the protocol was approved by the appropriate institutional review boards and conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

### Study design and treatments

This was a 24-week, multicentre, randomised, stratified (by smoking status), placebo-controlled, double-blind, parallel-group study (Fig. E1; GlaxoSmithKline study number HZC112207; ClinicalTrials.gov: NCT01054885). Study subjects were stratified by smoking status (former smoker = not smoked for 6 months prior to the screening visit). At visit 1 (screening), subjects entered a 2-week, single-blind run-in period during which they received placebo once daily in the morning via a dry powder inhaler (DPI) that contains two strips (GlaxoSmithKline, London, UK). The screening period was used to obtain a baseline assessment of symptoms (breathlessness, cough, sputum production and night-time awakenings requiring rescue medication [albuterol/salbutamol], rescue medication use and adherence to therapy). Eligible subjects were randomised (1:1:1:1:1:1) to one of six double-blind treatments

comprising FF/VI 200/25 μg, FF/VI 100/25 μg, FF 100 μg, FF 200 μg, VI 25 μg (representing emitted doses of FF/VI 184/22 μg, FF/VI 92/22 μg, FF 184 μg, FF 92 μg and VI 22 μg), or placebo taken once daily in the morning using a DPI. A central randomisation schedule was generated using a validated computerised system (RandAll; GlaxoSmithKline, London, UK) and subjects were randomised using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, London, UK) to register the subject, randomise the subject and receive medication assignment information. Subjects withheld study medication on the morning of clinic visits and rescue medication for at least 4 h prior to and during clinic visits. Albuterol (salbutamol) was allowed during the run-in and treatment periods for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward. Other permitted and prohibited co-medications are provided in the Online Supplement.

## Efficacy measurements

The co-primary efficacy outcomes were the weighted mean (wm) $FEV_1$ (0–4 h post-dose) on day 168 to assess bronchodilation by FF/VI and VI (vs. placebo) and FF/VI vs. FF; and the change from baseline in trough (23–24 h post-dose) $FEV_1$ on day 169 to assess the 24 h effect of VI and to determine the contribution of FF to lung function (i.e. FF/VI vs. VI). wm $FEV_1$ (0–4 h) is derived by calculating the AUC from $FEV_1$ measured 5 min, 15 min, 30 min, 1, 2 and 4 h post-dose, and then dividing the AUC by the time interval. The AUC is calculated using the trapezoidal rule. It acts as a more robust measure of post-dose lung function than peak $FEV_1$.

Secondary efficacy endpoints were the Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnoea domain on day 168, peak $FEV_1$ (0–4 h) on day 1 and time to $\geq$100 ml improvement from baseline in $FEV_1$ on day 1 (0–4 h).

Other endpoints were the time to $\geq$12% improvement in $FEV_1$ over the first 4 h post-dose on day 1; weighted mean $FEV_1$ 0–4 h post-dose on days 1, 14, 56, and 84; change from baseline in trough $FEV_1$ on treatment days 2, 7, 14, 28, 56, 84, 112, and 140; percentage of symptom-free 24-h periods; percentage of rescue-free 24-h periods; symptom scores (breathlessness scaled from 0 to 4, cough and sputum scores scaled from 0 to 3, with 0 indicating no impairment); number of occasions of rescue albuterol used; percentage of nights with no night-time awakenings requiring albuterol; number of night-time awakenings requiring albuterol; mean morning peak expiratory flow (AM PEF); and CRQ-SAS other domains and total score.

## Safety evaluation

Safety observations included the incidence of adverse events (AEs), COPD exacerbations, and all pneumonias. Exacerbations were defined as moderate (acute worsening of COPD requiring systemic corticosteroids and/or antibiotics) or severe (requiring hospitalisation). In addition, AEs of special interest were defined *a priori* as those known to be associated with ICS and/or LABA therapy. Change from baseline in pulse rate, systolic blood pressure (BP), diastolic BP, 12-lead electrocardiogram (ECG) assessments (for heart rate and QTcF [QT interval corrected using Friedericia's formula]) and clinical chemistry and haematology parameters (including glucose and potassium levels) were also assessed. An oropharyngeal examination was conducted at each treatment visit for all subjects, and in two subsets of subjects either Holter reading assessments ($n = 541$) or 24-h urinary cortisol (UC) excretion ($n = 406$; UC population) were assessed. The Holter and UC populations were recruited from selected sites to reduce the total burden of assessments on individual patients and sites.

## Spirometric measurements

Spirometry was performed using equipment that met or exceeded the minimum performance recommendations of the American Thoracic Society.[18] Reference values were those of NHANES III.[19]

## Statistical analysis

Assuming a standard deviation (SD) of 210 ml derived from prior studies of VI[13] and significance at the two-sided 5% level, a sample size of at least 146 evaluable subjects per arm was required for $\geq$90% power to detect a 100 ml difference between VI or FF/VI and placebo for wm or trough $FEV_1$ and between FF/VI and FF for wm $FEV_1$ and to detect an 80 ml difference between FF/VI and VI, for trough $FEV_1$. To allow for a 27% withdrawal rate based on prior trial experience (GlaxoSmithKline, Data on File), at least 200 subjects were to be randomised per arm (1200 were planned to be randomised in total).

The primary analyses were performed on the intent-to-treat (ITT) population, which comprised all subjects randomised to treatment and who had received at least one dose of study medication. Change from baseline trough $FEV_1$ recorded on days 2, 7, 14, 28, 56, 84, 112, 140, 168, and 169 was analysed using mixed models repeated measures (MMRM) with covariates of baseline $FEV_1$, smoking status (stratum), day, centre grouping, treatment, day by baseline interaction and day by treatment interaction, where day was nominal. wm $FEV_1$ recorded on days 1, 14, 56, 84 and 168 was analysed similarly. The CRQ-SAS was analysed using the same methodology as the co-primary endpoints, except the covariate of baseline dyspnoea score replaced that of baseline $FEV_1$. Peak $FEV_1$ was analysed using analysis of co-variance (ANCOVA) with covariates of baseline, smoking status, centre grouping and treatment.

This study included two co-primary endpoints and 6 treatment arms. As a consequence, there were 10 treatment comparisons of primary interest. Even if there were no differences between treatments then, by definition, 5% of treatment comparisons might be expected to be significant purely by chance. Hence, it was necessary to control for this when designing the trial. A pre-defined testing hierarchy was therefore employed (Fig. 1). Level 1 of the hierarchy comprised six key comparisons of the co-primary endpoints for VI 25 μg and FF/VI 200/25 μg, each of which

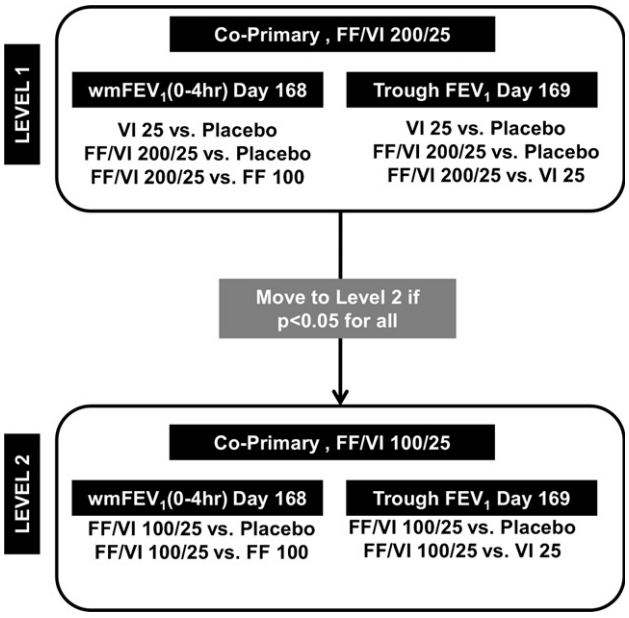


**Figure 1** Statistical hierarchy. $FEV_1$ = forced expiratory volume in 1 s, FF = fluticasone furoate, VI = vilanterol, wm = weighted mean.

was equally weighted. Significance with a $p < 0.05$ was required for all of these comparisons to allow statistical significance to be inferred for differences, with $p < 0.05$ for co-primary endpoints for the FF/VI 100/25 μg strength. Inferences could only be made for secondary endpoints if primary endpoints were significant at the 5% level.

## Results

### Subject characteristics

Of 1909 subjects screened, 1224 comprised the ITT population. In total, 924 (75%) subjects completed the study; subject disposition and reasons for discontinuation are shown in Fig. 2. In total 683 subjects were excluded, 332 at the screening stage and a further 351 during the run-in period. The primary reason for exclusion at screening or during run-in was that the subject did not meet the entry ($n = 323$) or continuation ($n = 246$) criteria, respectively. The principle reason for not meeting entry criteria was severity of disease ($n = 283$), while the principle reasons for not meeting continuation criteria were abnormal Holter ($n = 108$) or ECG ($n = 75$) findings. A summary of screening demographics, lung function and dyspnoea is shown in Table 1.

### Efficacy: co-primary

Combination therapy with FF/VI 200/25 μg resulted in significant increases in adjusted wm $FEV_1$ (0—4 h) on day 168 of 209 ml (95% CI: 157, 261; $p < 0.001$) and adjusted mean trough $FEV_1$ on day 169 of 131 ml (95% CI: 80, 183;

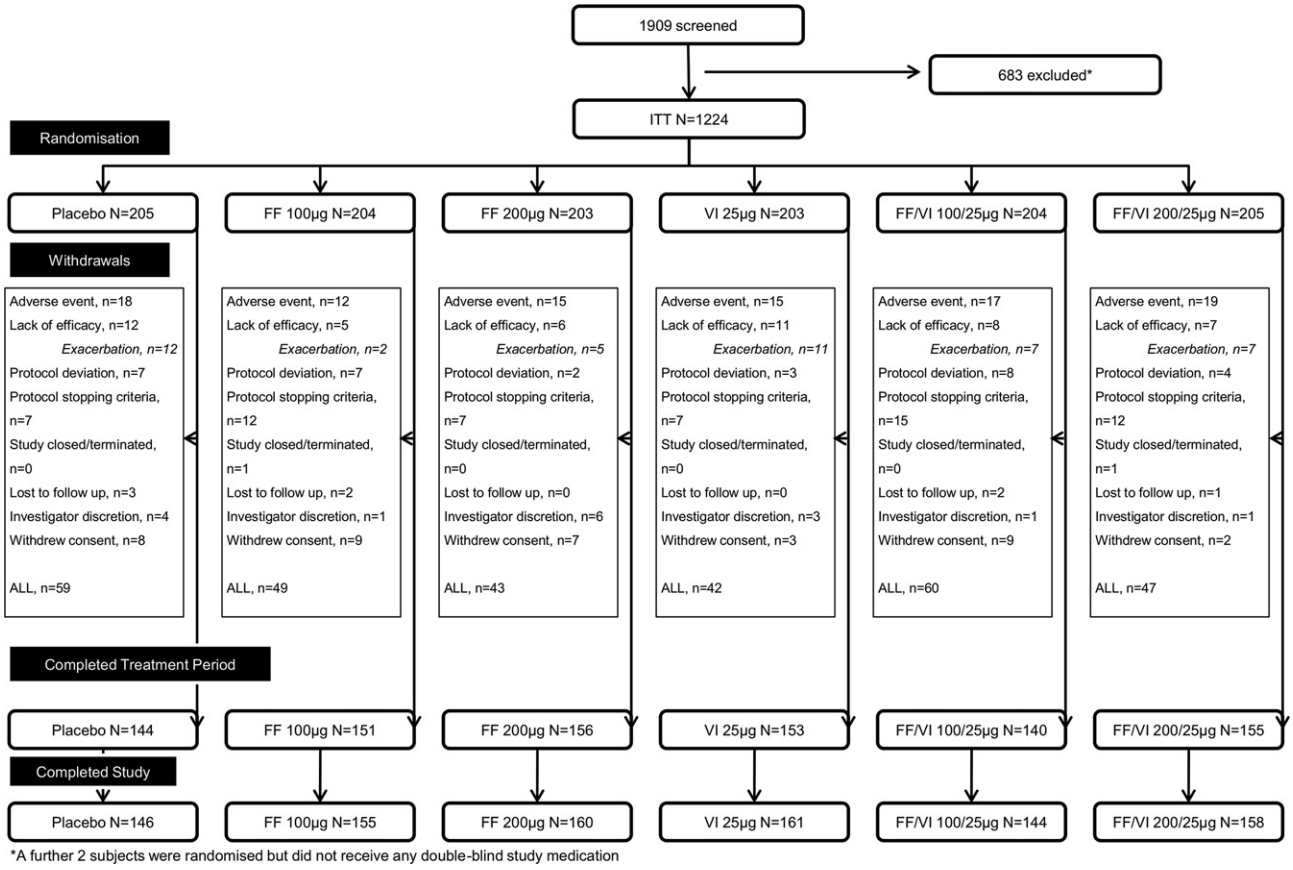


**Figure 2** Consort diagram. FF = fluticasone furoate, ITT = intention to treat, VI = vilanterol.

**Table 1** Subject characteristics.

| | Placebo $N = 205$ | FF 100 μg $N = 204$ | FF 200 μg $N = 203$ | VI 25 μg $N = 203$ | FF/VI 100/25 μg $N = 204$ | FF/VI 200/25 μg $N = 205$ |
|---|---|---|---|---|---|---|
| Age, yr (SD) | 61.9 (8.14) | 61.8 (8.28) | 61.8 (9.02) | 61.2 (8.62) | 61.9 (8.79) | 61.1 (8.58) |
| Male sex, *n* (%) | 152 (74) | 150 (74) | 151 (74) | 151 (74) | 144 (71) | 137 (67) |
| Race, *n* (%) | | | | | | |
| White | 197 (96) | 197 (97) | 183 (90) | 196 (97) | 190 (93) | 192 (94) |
| Asian | 8 (4) | 5 (2) | 14 (7) | 4 (2) | 8 (4) | 11 (5) |
| Other | 0 | 2 (<1) | 6 (3) | 3 (1) | 6 (3) | 2 (<1) |
| Current smoker, *n* (%) | 108 (53) | 114 (56) | 112 (55) | 111 (55) | 109 (53) | 112 (55) |
| Smoking history, pack-yr (SD) | 45.7 (25.8) | 39.8 (21.3) | 43.5 (22.5) | 42.0 (23.3) | 42.8 (23.9) | 41.5 (23.4) |
| COPD type, *n* (%) | | | | | | |
| Chronic bronchitis | 133 (65) | 152 (75) | 137 (67) | 140 (69) | 143 (70) | 138 (67) |
| Emphysema | 126 (61) | 118 (58) | 129 (64) | 113 (56) | 109 (53) | 129 (63) |
| Pre-study COPD therapy, *n* (%) | | | | | | |
| SABA | 125 (61) | 128 (63) | 128 (63) | 123 (61) | 136 (67) | 124 (60) |
| SAMA | 76 (37) | 61 (30) | 61 (30) | 72 (35) | 67 (33) | 77 (38) |
| LABA | 77 (38) | 64 (31) | 66 (33) | 81 (40) | 74 (36) | 66 (32) |
| LAMA | 49 (24) | 49 (24) | 42 (21) | 44 (22) | 46 (23) | 61 (30) |
| ICS | 47 (23) | 50 (25) | 53 (26) | 55 (27) | 37 (18) | 46 (22) |
| On-treatment non-COPD medication, *n* (%) | 151 (74) | 150 (74) | 149 (73) | 151 (74) | 150 (74) | 142 (69) |
| Screening pre-BD $FEV_1$, l (SD) | 1.349 (0.4512) | 1.412 (0.4839) | 1.304 (0.4870) | 1.371 (0.4755) | 1.357 (0.5188) | 1.330 (0.5025) |
| Screening post-BD $FEV_1$, l (SD) | 1.504 (0.4675) | 1.532 (0.4814) | 1.436 (0.4744) | 1.519 (0.4719) | 1.491 (0.5094) | 1.458 (0.5117) |
| Screening % predicted pre-BD $FEV_1$, % (SD) | 43.5 (13.00) | 44.6 (12.98) | 42.7 (12.72) | 43.7 (12.85) | 43.8 (13.81) | 43.0 (13.01) |
| Screening % predicted post-BD $FEV_1$, % (SD) | 48.3 (12.71) | 48.4 (12.17) | 47.1 (11.98) | 48.5 (12.89) | 48.1 (12.85) | 47.1 (12.76) |
| Screening $FEV_1$ reversibility, ml (SD) | 153.1 (165.94) | 128.9 (188.76) | 130.0 (157.57) | 143.7 (177.89) | 134.9 (188.31) | 113.3 (175.58) |
| Reversible at screening[a] *n* (%) | 61 (30) | 57 (29) | 54 (27) | 60 (30) | 58 (29) | 54 (27) |
| Screening mMRC dyspnoea scale, units (SD) | 2.4 (0.55) | 2.4 (0.54) | 2.4 (0.54) | 2.4 (0.51) | 2.4 (0.52) | 2.4 (0.50) |
| Moderate exacerbation in the year prior to screening, *n* (%) | | | | | | |
| 0 | 166 (81) | 156 (76) | 140 (69) | 152 (75) | 154 (75) | 152 (74) |
| ≥1 | 39 (19) | 48 (24) | 63 (31) | 51 (25) | 50 (25) | 53 (26) |
| Severe exacerbation in the year prior to screening, *n* (%) | | | | | | |
| 0 | 185 (90) | 186 (91) | 180 (89) | 186 (92) | 180 (88) | 185 (90) |
| ≥1 | 20 (10) | 18 (9) | 23 (11) | 17 (8) | 24 (12) | 20 (10) |

Moderate exacerbation required oral/systemic corticosteroids and/or antibiotics but did not involve hospitalisation; severe exacerbation required hospitalisation; BD = twice daily, COPD = chronic obstructive pulmonary disorder, $FEV_1$ = forced expiratory volume in 1 s, FF = fluticasone furoate, ICS = inhaled corticosteroid, LABA = long-acting $\beta_2$-agonist, LAMA = long-acting muscarinic antagonist, mMRC = Modified Medical Research Council Dyspnoea Scale, SABA = short-acting $\beta_2$-agonist, SAMA = short-acting muscarinic antagonist, SD = standard deviation, VI = vilanterol.

[a] Reversible to albuterol/salbutamol as defined by ≥12% and ≥200 ml improvement in $FEV_1$ post-dose.

$p < 0.001$), compared with placebo (Table 2). No significant increase in adjusted mean trough $FEV_1$ was observed for the comparison of FF/VI 200/25 μg with VI 25 μg (32 ml, 95% CI: −19, 83; $p = 0.224$), while the comparison of FF/VI 200/25 μg with FF 200 μg indicated a significant improvement with the combination vs. the ICS alone for adjusted wm $FEV_1$ (168 ml, 95% CI: 117, 219; $p < 0.001$) (Table 2). VI 25 μg monotherapy significantly improved both lung function parameters (wm and trough $FEV_1$) by 185 ml (95% CI: 133, 237; $p < 0.001$) and 100 ml (95% CI: 48, 151; $p < 0.001$) respectively, compared with placebo. Due to the pre-defined statistical testing hierarchy no inference can be drawn for comparisons of the 100/25 μg strength with placebo or its components, as there was no significant difference in the change in lung function between VI and the highest strength of FF/VI. However the differences observed with FF/VI 100/

**Table 2** Primary and secondary efficacy comparisons.

| Comparisons | wm $FEV_1$ (0–4 h) day 168 | Trough $FEV_1$ day 169 | CRQ-SAS dyspnoea day 168 | Peak $FEV_1$[a] day 1 |
|---|---|---|---|---|
| VI vs. PBO | **0.185* (0.133, 0.237)** | **0.100* (0.048, 0.151)** | 0.07 (−0.14, 0.28) | 0.147 (0.117, 0.177) |
| *FF 200 comparisons* | | | | |
| FF/VI 200/25 μg vs. PBO | **0.209* (0.157, 0.261)** | **0.131* (0.080, 0.183)** | 0.1 (−0.12, 0.31) | 0.141 (0.111, 0.171) |
| FF/VI 200/25 μg vs. VI 25 μg | 0.024 (−0.027, 0.075) | **0.032** (−0.019, 0.083)** | 0.03 (−0.18, 0.23) | −0.006 (−0.036, 0.024) |
| FF/VI 200/25 μg vs. FF 200 μg | **0.168* (0.117, 0.219)** | 0.123 (0.072, 0.174) | 0.1 (−0.11, 0.31) | 0.134 (0.104, 0.164) |
| FF 200 μg vs. PBO | 0.041 (−0.011, 0.093) | 0.008 (−0.044, 0.060) | −0.01 (−0.22, 0.21) | 0.007 (−0.023, 0.037) |
| *FF 100 comparisons* | | | | |
| FF/VI 100/25 μg vs. PBO | 0.214 (0.161, 0.266) | 0.144 (0.091, 0.197) | 0.24 (0.02, 0.46) | 0.152 (0.122, 0.182) |
| FF/VI 100/25 μg vs. VI 25 μg | 0.029 (−0.023, 0.081) | 0.045 (−0.008, 0.097) | 0.17 (−0.04, 0.38) | 0.005 (−0.025, 0.036) |
| FF/VI 100/25 μg vs. FF 100 μg | 0.168 (0.116, 0.220) | 0.1 (0.047, 0.152) | 0.36 (0.14, 0.57) | 0.128 (0.098, 0.158) |
| FF 100 μg vs. PBO | 0.046 (−0.006, 0.098) | 0.044 (−0.008, 0.097) | −0.12 (−0.33, 0.10) | 0.024 (−0.006, 0.055) |

Values are differences in least square mean (95% CI); $FEV_1$ is expressed in litres; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized, $FEV_1$ = forced expiratory volume in 1 s, FF = fluticasone furoate, PBO = placebo, VI = vilanterol, wm = weighted mean.
*$p < 0.001$.
**$p = 0.224$.
[a] Peak $FEV_1$ represents maximum post-dose $FEV_1$ from assessments taken at 5 min, 15 min, 30 min, 1 h, 2 h and 4 h post-dose. CRQ-SAS dyspnoea domain is scaled from 0 to 7, with 0 indicating no impairment.

25 μg were typically numerically greater than those recorded with the 200/25 μg strength of the combination (Table 2). Results from the per-protocol population analysis (data not shown) were consistent with those of the ITT population.

## Efficacy: secondary

As an outcome of the statistical hierarchy used to analyse results (Fig. 1), no significance can be inferred for secondary endpoints. Thus, all differences reported must be regarded as descriptive only.

From day 1 of the study both measures of lung function were greater (CIs not including zero) with FF/VI and VI compared with FF and placebo. Both parameters (wm and trough $FEV_1$) increased rapidly from day 1 to day 14 and were generally maintained thereafter (Figs. 3 and 4). Time-course plots of wm $FEV_1$ and trough $FEV_1$ compared with placebo and active comparator are shown in Figs. E2 and E3.

Over 6 months, scores on the dyspnoea domain of the CRQ-SAS declined relative to placebo with both strengths of FF, but improved with both strengths of FF/VI and with VI 25 μg (Table 2). None of the treatment comparisons assessed achieved the minimal clinically important difference of 0.5 units. Peak post-dose adjusted mean $FEV_1$ on day 1 was 120 ml in the placebo arm, relative to baseline. In the FF 100 μg and 200 μg arms adjusted mean peak $FEV_1$ was 24 ml (95% CI: −6, 55) and 7 ml (95% CI: −23, 37) respectively, greater than placebo while for VI 25 μg the adjusted mean increase from placebo was 147 ml (95% CI: 117, 177). The equivalent values for FF/VI 100/25 μg and FF/VI 200/25 μg were 152 ml (95% CI: 122, 182) and 141 ml (95% CI: 111, 171) respectively (Table 2). The time at which 50% of subjects (median time) achieved a ≥100 ml improvement in $FEV_1$ from baseline on day 1 was 17 min for VI 25 μg, 16 min for FF/VI 100/25 μg and 17 min for FF/VI 200/25 μg. No median time could be determined for placebo as insufficient subjects in each arm had achieved the improvement by 4 h on day 1. Serial $FEV_1$ in all arms containing

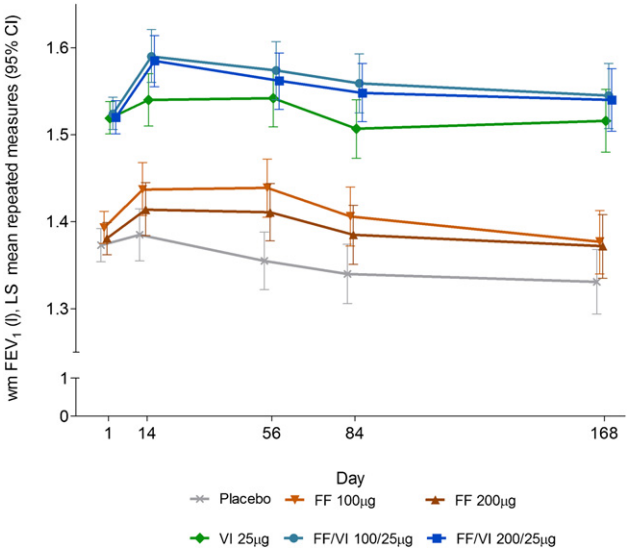


**Figure 3** Least squares weighted mean (0–4 h) $FEV_1$ from day 1 to day 168. CI = confidence interval, $FEV_1$ = forced expiratory volume in 1 s, FF = fluticasone furoate, LS = least squares, VI = vilanterol, wm = weighted mean.

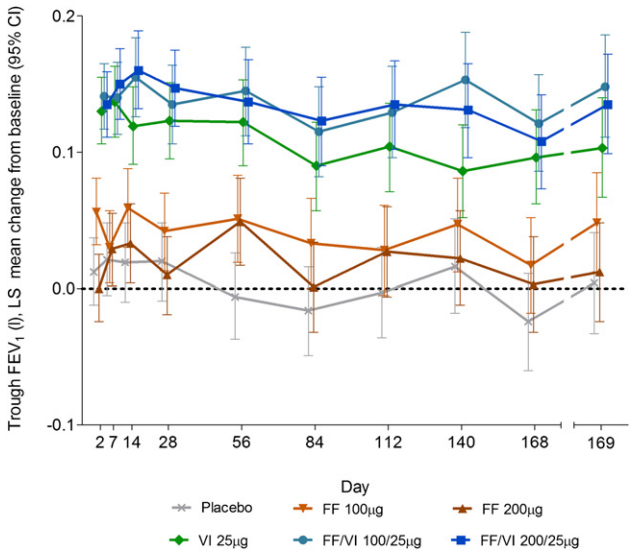


**Figure 4** Least squares mean trough $FEV_1$, change from baseline from day 2 to day 169. CI = confidence interval, $FEV_1$ = forced expiratory volume in 1 s, FF = fluticasone furoate, LS = least squares, VI = vilanterol.

VI was similar during the first h post-dose on day 1; but a numerical increase was apparent in the FF/VI arms on day 168 over the VI monotherapy arm (Fig. E4).

### Efficacy: other

Symptomatic endpoints, as assessed by diary card and CRQ-SAS for all treatments and comparisons are presented in Table E1. Compared with placebo, greater improvements (CIs excluding zero) were observed with FF/VI 100/25 µg for all endpoints except the CRQ-SAS mastery domain. With FF/VI 200/25 µg no difference from placebo was observed on any domain, total score of CRQ-SAS, nor occasions of rescue use per 24-h period; all other comparisons were greater with FF/VI 200/25 µg compared with placebo. As per the hierarchy of analysis, statistical significance could not be inferred for any comparisons of 'other' outcomes.

### Safety

No increase in the incidence of on-treatment AEs or serious AEs (SAEs), whether drug-related or not, was observed with active therapy vs. placebo (Table 3). Detailed summaries of drug-related AEs, on-treatment SAEs and all AEs or SAEs leading to withdrawal of study treatment or discontinuation from the study are provided in Tables E2—E4. As with the overall AE profile, no trend was observed for AEs of special interest, related to known LABA- or ICS-mediated effects, in the active therapy arms relative to the placebo arm (Table 3).

Exacerbations were infrequent but occurred more often in the placebo arm (21 events) than in any active treatment arm and more frequently in the VI arm (18 events) than in the FF-containing arms (14—4 events; Table E5). No pneumonia events were reported as an AE in the placebo arm. With active therapy, the number of pneumonia events was low and none of these resulted in fatality (Table E5). Chest X-rays were conducted in 11 of the 12 subjects with pneumonia; of these, 10 showed infiltrates.

No clinically important abnormality was recorded for clinical chemistry or haematology variables over the course of the study, nor was any treatment effect observed on blood levels of potassium or glucose. Analysis of the day 168 to baseline ratio of UC (UC population) showed no clinical effect of any treatment on UC excretion (Fig. E5). QTcF and ECG heart rate were assessed post-dose on days 1 and 84 and pre-dose on days 1, 84 and 168. No clinical difference was observed from baseline in either of these measures (Figs. E6 and E7).

A total of six deaths were reported during the study, none of which were considered to be drug-related by the investigator. One subject in the placebo arm died consequent to myocardial infarction. Two subjects died during VI 25 µg therapy, 1 due to anaphylaxis secondary to nuclear stress test injection, and 1 due to accidental intoxication with methanol. One subject each receiving FF/VI 100/25 µg or FF/VI 200/25 µg died, due to thrombotic stroke and myocardial infarction, respectively. One post-treatment death was reported in a subject who received FF/VI 100/25 µg. In that subject the cause of death is unknown; however, the subject did have a history of congestive heart failure coronary heart disease and hypertension.

## Discussion

Combination ICS/LABA therapy has been incorporated into evidence based guidelines for the management of COPD.[5—8] Relatively few data have been published regarding dose-ranging for ICS in COPD patients.[20] Furthermore, there is now an interest in moving to once-daily dosing for respiratory medications, an approach that is possible with FF/VI therapy. To date, FF/VI has been assessed in COPD in a small safety study,[21] and in a 28-day crossover study[22] while the VI component has only been assessed in one dose-ranging study[13]; in all these studies significant improvements in lung function were observed compared with placebo. In the novel approach presented here, the further development of this combination therapy in COPD included dose-ranging of the ICS component during phase IIIa studies. As such, we describe the efficacy and safety of two strengths of FF/VI (200/25 µg and 100/25 µg) in subjects with moderate-to-severe COPD.

This report documents (1) an improvement in wm $FEV_1$ and trough $FEV_1$ with VI 25 µg compared with placebo; (2) an improvement in wm $FEV_1$ and trough $FEV_1$ with FF/VI 200/25 µg and 100/25 µg compared with placebo, for both strengths the improvements observed were numerically greater than those seen with VI 25 µg (3) there was no statistical difference in trough $FEV_1$ in change from baseline to day 169 for FF/VI 200/25 µg vs. VI 25 µg; (4) a rapid onset of action was seen in all VI-containing arms; and (5) no increase in on-treatment AEs, SAEs or AEs of special interest (defined *a priori* and known to be related to LABA or ICS therapy) was observed with active therapy compared with placebo. These results suggest that once-daily therapy with FF/VI results in clinically relevant bronchodilation in subjects with moderate-to-severe COPD and requires further study to fully define its physiological and clinical benefits.

**Table 3** Adverse events.

| *n* (%) | Placebo *N* = 205 | FF 100 μg *N* = 204 | FF 200 μg *N* = 203 | VI 25 μg *N* = 203 | FF/VI 100/25 μg *N* = 204 | FF/VI 200/25 μg *N* = 205 |
|---|---|---|---|---|---|---|
| *Summary* | | | | | | |
| Any on-treatment AEs | 96 (47) | 78 (38) | 96 (47) | 85 (42) | 92 (45) | 93 (45) |
| AEs leading to permanent discontinuation from the study or withdrawal of study treatment[a] | 23 (11) | 14 (7) | 15 (7) | 14 (7) | 20 (10) | 23 (11) |
| Any on-treatment SAEs | 10 (5) | 6 (3) | 10 (5) | 16 (8) | 12 (6) | 15 (7) |
| Any on-treatment fatal SAEs | 1 (<1) | 0 | 0 | 2 (<1) | 1 (<1) | 1 (<1) |
| *AEs of special interest* | | | | | | |
| Cardiovascular effects | 30 (15) | 17 (8) | 20 (10) | 12 (6) | 20 (10) | 15 (7) |
| Local steroid effects | 8 (4) | 5 (2) | 17 (8) | 8 (4) | 11 (5) | 13 (6) |
| LRTI excluding pneumonia | 8 (4) | 7 (3) | 6 (3) | 5 (2) | 5 (2) | 2 (<1) |
| Effects on glucose | 2 (<1) | 1 (<1) | 3 (1) | 5 (2) | 2 (<1) | 3 (1) |
| Hypersensitivity | 2 (<1) | 1 (<1) | 3 (1) | 3 (1) | 2 (<1) | 2 (<1) |
| Pneumonia | 0 | 2 (<1) | 3 (1) | 2 (<1) | 1 (<1) | 4 (2) |
| Bone disorders | 0 | 1 (<1) | 4 (2) | 2 (<1) | 4 (2) | 0 |
| Tremor | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Effects on potassium | 0 | 0 | 0 | 0 | 0 | 1 (<1) |
| Ocular effects | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Systemic steroid effects | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| *All on-treatment AEs occurring in ≥3% of subjects in any treatment group* | | | | | | |
| Nasopharyngitis | 17 (8) | 14 (7) | 20 (10) | 19 (9) | 13 (6) | 13 (6) |
| Headache | 15 (7) | 13 (6) | 11 (5) | 20 (10) | 11 (5) | 15 (7) |
| Upper respiratory tract infection | 5 (2) | 3 (1) | 5 (2) | 9 (4) | 8 (4) | 7 (3) |
| Oral candidiasis | 2 (<1) | 5 (2) | 5 (2) | 2 (<1) | 8 (4) | 4 (2) |
| Back pain | 6 (3) | 1 (<1) | 2 (<1) | 3 (1) | 4 (2) | 2 (<1) |
| Oropharyngeal candidiasis | 3 (1) | 0 | 7 (3) | 1 (<1) | 3 (1) | 4 (2) |
| Hypertension | 3 (1) | 3 (1) | 7 (3) | 0 | 3 (1) | 1 (<1) |

AEs = adverse events, FF = fluticasone furoate, LRTI = lower respiratory tract infection, SAEs = serious adverse events, VI = vilanterol.
[a] Includes on-treatment and post-treatment.

We confirm that a once-daily dose of FF combined with VI led to a sustained improvement in $FEV_1$. These data showed an improvement in wm $FEV_1$ that relates predominantly to the LABA component. Importantly, trough $FEV_1$ also improved with these three therapeutic arms in comparison with placebo. The lack of any statistical or clinical difference between either of the two strengths of FF/VI and VI suggest that any physiological improvement contributed by FF was modest. This may have been further confounded statistically in that the treatment differences observed were smaller in magnitude than anticipated when designing the trial, while the variability observed was larger than that assumed in the calculation of sample size. However, it is notable that while treatment with VI alone met the putative minimal clinically important difference from placebo of 100 ml for trough $FEV_1$,[23] both combination treatments exceeded this value. Furthermore, the lack of any clear differentiation between FF 200 μg and FF 100 μg in terms of lung function suggests no additional benefit of the higher dose of FF. This finding differs from the results reported with twice-daily fluticasone propionate,[2,24] and may reflect the timing of physiological assessment, differences in the study arms, or differences in the underlying steroid molecule and its pharmacokinetics. Whether this lack of demonstration of a statistically significant contribution of FF to the combination on lung function effect precludes an impact on clinically relevant outcomes such as exacerbations remains to be determined.

We document a series of beneficial effects for the combination of FF and VI with respect to patient-reported outcomes as compared with both placebo and the combination components. However, these results should be interpreted with caution given the predefined statistical hierarchy for analyses. Similarly, changes for some of these parameters were not above the minimal clinically important difference, suggesting that the improvements in lung function observed did not confer a reduction in symptoms, most notably dyspnoea. Notably a lack of a clinically important change in the dyspnoea domain of the CRQ-SAS has also been reported in patients with a comparable level of baseline dyspnoea treated with fluticasone propionate/salbutamol or fluticasone propionate/salbutamol + tiotropium, despite notable improvements in lung function.[25]

Our data suggest there is little difference in on-treatment AEs or SAEs with any of the active therapies compared with placebo, at least over a 6-month comparison period. This

conclusion also applies to assessments of events known to be related to LABA- or ICS-mediated effects. There were numerically fewer exacerbations in the corticosteroid-containing regimens, with varying distribution of moderate and severe events, although the number of events seen was low and may be a consequence of the study entry criteria, which did not require subjects to have a history of exacerbations. As such, this finding should be interpreted with caution since our study was not designed or powered to examine the impact of FF added to VI on acute exacerbations. Additional study will be needed to better define this potential therapeutic benefit. As in other reports of ICS in COPD,[26,27] there were numerically more pneumonias reported as AEs (none of which were fatal) in the corticosteroid containing regimens compared with placebo, although similar numbers were reported in the LABA alone therapeutic arm. Further prospective data are required to define the risk of this rare event with FF in COPD patients during longer term studies.

This was a 24-week study, a period long enough to determine clinically meaningful bronchodilatory effects of both the combination and its components. Additionally, it recruited a clinically appropriate cohort of subjects and assessed appropriate lung function endpoints. The statistical hierarchy used can be regarded as both a strength and a limitation. It is a rigorous approach for accounting for multiplicity; however, it also limits the ability to infer statistical significance for comparisons that fall behind the 'point of failure' in the hierarchy. In the present case, this means that significance cannot be inferred for differences of FF/VI 100/25 μg vs. its components or placebo, nor for any comparisons of any secondary or 'other' endpoints. Finally, the only symptomatic assessment conducted at the secondary endpoint level was that of the dyspnoea domain of the CRQ-SAS. As such, our ability to assess the impact of adding FF to VI in terms of symptom assessment is limited.

This report confirms that the combination of FF/VI results in a sustained improvement in $FEV_1$ in COPD subjects with moderate-to-severe airflow obstruction. The predominant effect seems to come from the LABA with little effect of the inhaled corticosteroid, independent of dose, on lung function. Despite this, there appeared to be modest improvements in patient reported outcomes for the FF/VI combination compared with its components. There were numerically less exacerbations in the corticosteroid-treated subjects, but interpretation of these data is limited by the small number of exacerbations in this study population. Whether the lack of lung function effect precludes an impact on relevant outcomes such as exacerbations should be determined in future studies. Overall, an evaluation of safety identified the anticipated ICS and LABA effects. Taken together our data suggest that a once-daily combination of FF/VI may offer an alternative to improve lung function in COPD patients.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2012.12.016.

## Conflict of interest

The study sponsor (GlaxoSmithKline) provided support for study design, collection, analysis and interpretation of data. The sponsor no part in the decision of the authors to submit this manuscript for publication.

**FM** has participated in advisory boards in COPD development for Actelion, Almirall, American Institutes for Research, AstraZeneca, Bayer, BoomComm, Forest, GlaxoSmithKline, Ikaria, MedImmune, Merck, Novartis, Nycomed, Pearl, Pfizer, and Schering. He has been a member of the steering committee for COPD studies sponsored by Actelion, GlaxoSmithKline, Forest, MPex, and Nycomed. He has participated in Food and Drug Administration mock panels for Boehringer Ingelheim and Forest. The University of Michigan received funds from Boehringer Ingelheim for a COPD study. He has served on speaker's bureaus or in continuing medical education activities sponsored by American College of Chest Physicians, American Lung Association, Almirall, AstraZeneca, Beaumont, Boehringer Ingelheim, Center for Health Care Education, CME Incite, ePocrates, Forest, France Foundation, GlaxoSmithKline, Lovelace, MedEd, NACE, Nycomed, Potomac, Prescott, Sanofi Aventis, St Luke's, and UpToDate. He has received royalties from Associates in Medical Marketing and Castle Connolly.

**JB** is on the speakers' bureau of GlaxoSmithKline and was an investigator in this clinical trial, which was sponsored by GlaxoSmithKline and administered by his employer CU Pharmaceutical Research.

**GF** received funds as an investigator in this clinical trial sponsored by GlaxoSmithKline, which was administered by his employer S. Carolina Pharmaceutical Research.

**CS-W, SK** and **CC** are employees of GlaxoSmithKline and hold shares/share options in GlaxoSmithKline.

**LF** has received payment for consultancy from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Beech, Merck Sharp and Dohme, Novartis, Nycomed, Pearl Therapeutics, SigmaTau, Sterna, Peer Voice Europe, Pearl Therapeutic, OM Pharma Sa, and TEVA. He has received payment for lectures, advisory boards, or travel expense reimbursements from AstraZeneca, Dey Pharma, Novartis, Schering Plough, SigmaTau, Roche, German Aerospace Center, Mundipharma International, Genetech Inc, Elevation Pharmaceutical, and Ferrer Group. His institution received grants from Boehringer Ingelheim, SheringPlough, Pfizer, Nycomed, Menarini Industrie Farmaceutiche, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Roche, AstraZeneca, Novartis, SigmaTau, Italian Ministry for University and Research, and Italian Ministry of Health.

**PMAC** has advised on the design and conduct of clinical trials undertaken by GlaxoSmithKline and received honoraria for this and speaking at meetings supported by GlaxoSmithKline. He has performed similar functions for

AstraZeneca, Boehringer Ingelheim, Novartis and Takeda-Nycomed.

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