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A randomised, phase III trial of once-daily fluticasone furoate/vilanterol 100/25 μg versus once-daily vilanterol 25 μg to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD

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ABSTRACT

Background: The contribution of fluticasone furoate (FF) on lung function in the FF/vilanterol (VI) 100/25 μg combination has been demonstrated numerically, but not statistically.
Methods: This multicentre, randomised, double-blind, controlled trial (GlaxoSmithKline study number 200820; clinicaltrials.gov NCT02105974) enrolled ≥40-year-old patients with chronic obstructive pulmonary disease (COPD), a ≥10-pack-year smoking history, a post-bronchodilator forced expiratory volume in 1 s (FEV_1) 30–70% of the predicted value, a FEV_1/forced vital capacity ratio of ≤0.70, ≥1 COPD exacerbation in the previous 12 months requiring corticosteroids, antibiotics and/or hospitalisation, and current COPD symptoms. Participants received FF/VI 100/25 μg or VI 25 μg once daily. The primary endpoint was the change from baseline in trough FEV_1 at day 84.
Findings: 1620 patients were randomised and received at least one dose of FF/VI 100/25 μg (n = 806) or VI 25 μg (n = 814). At day 84, the FF/VI 100/25 μg group showed an adjusted mean treatment difference of 34 mL over VI 25 μg in change from baseline trough FEV_1 (95% confidence interval [CI] 14–55; p = 0.001). There was no significant difference between the groups in the percentage of rescue medication-free 24-h periods. The FF/VI 100/25 μg group demonstrated a 42% risk reduction compared with the VI 25 μg group in time to first moderate/severe COPD exacerbation (95% CI 22–57; nominal p < 0.001). The incidence of on-treatment adverse events was similar between the groups.
Interpretation: The contribution of FF in the FF/VI 100/25 μg combination on lung function in COPD was statistically significant.
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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [1]. It is characterised by progressive airflow limitation and often an accelerated decline in forced expiratory volume in 1 s (FEV_1) as a result of chronic inflammation and narrowing of the peripheral airways [2,3]. Inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) combination therapy is more effective than the individual components alone in improving lung function, reducing the frequency of exacerbations, and improving quality of life in patients with COPD [4–9]. The ICS/LABA combination fluticasone furoate (FF)/vilanterol (VI) is currently approved as a once-daily treatment for COPD and asthma in more than 80 countries, including all 28 European Union Member States and the USA [10,11]. FF/VI has been associated with a reduced rate of moderate/severe COPD exacerbations in patients with a history of exacerbations, compared with VI alone [12]. Other

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currently available ICS/LABA combinations require twice-daily administration; a once-daily combination with a 24-h duration of effect in improving lung function could confer additional benefits, including improved adherence and outcomes.

The contribution of FF 100 μg to the FF/VI 100/25 μg combination on lung function has been demonstrated numerically, but not statistically, in two similarly designed, 6-month, phase III, multicentre, randomised, placebo-controlled, double-blind, parallel-group trials in patients with moderate/severe COPD. However, these two studies excluded patients who had a history of COPD exacerbations within 6 months (exacerbations that required corticosteroids or antibiotics, or that required treatment prescribed by a physician) or 12 months (exacerbations that required hospitalisation) prior to screening. The treatment differences in change from baseline trough FEV_1 on day 169 were 48 mL (95% CI −6 to 102; p = 0.082) and 45 mL (95% CI −8 to 97; p = 0.093) [13,14]. Statistical significance may not have been achieved for these comparisons, as the studies were not adequately powered to detect the treatment differences that were observed, and the observed variability was larger than that assumed in the sample size calculations.

This study aimed to evaluate the contribution on lung function of FF 100 μg in the FF/VI 100/25 μg combination, by comparing FF/VI 100/25 μg and VI 25 μg (both treatments administered once daily in the morning via the ELLIPTA® inhaler) in patients with COPD.

2. Material and methods

2.1. Study design

This phase IIIa study (GlaxoSmithKline study number 200820; clinicaltrials.gov NCT02105974) was a multicentre, randomised, stratified (reversibility status), double-blind, parallel-group trial conducted in 11 countries that aimed to evaluate the efficacy and safety of FF/VI 100/25 μg once daily compared with VI 25 μg once daily in patients with moderate-to-severe COPD with a history of moderate/severe COPD exacerbations and current COPD symptoms. Participants were centrally randomised (1:1) by country using RAMOS, an Interactive Voice Response System, and were stratified according to reversibility status; both the participants and investigators did not know which study medication the participant received. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by applicable independent ethics committees/institutional review boards. Safety was monitored (blinded) by the Project Physician Leader, Medical Monitor, and the GlaxoSmithKline Safety Review team.

Eligible participants visited a study clinic at least seven times over a 14-week period: screening (day −14), and study days 1, 2, 14, 28, 56, and 84. At screening, eligible participants entered a 2-week, single-blind (placebo), run-in period to obtain baseline assessments of albuterol (salbutamol) use and symptom scores. Adherence with the use of the run-in inhaler (single-blind placebo administered once daily in the morning via the ELLIPTA® inhaler) and study procedures, diary card completion, and assessment of disease stability were evaluated. After the run-in period, eligible participants entered the treatment period and were randomised to receive FF/VI 100/25 μg or VI 25 μg, administered as one inhalation via the ELLIPTA® inhaler each morning for 12 weeks. Participants received supplemental albuterol (salbutamol) on an as-needed basis as rescue medication throughout the run-in and treatment periods.

2.2. Participants

Participants aged ≥40 years, with a COPD diagnosis (American Thoracic Society [ATS]/European Respiratory Society definition) [15] and a smoking history of ≥10 pack-years were eligible. All participants had a post-albuterol (salbutamol) FEV_1 ≥30–≤70% of predicted normal values (calculated using the Global Lung Function Initiative 2012 reference equations) [16] and a FEV_1/forced vital capacity (FVC) ratio of ≤0.70 at screening, ≥1 COPD exacerbation in the previous 12 months that required corticosteroids, antibiotics, and/or hospitalisation, and current symptoms of COPD (patient diary combined symptom score [breathlessness, cough, sputum, and night-time awakenings requiring rescue medication] of ≥4 on at least 5 of the 7 days immediately preceding randomisation [appendix p 4]). Exclusion criteria included: current diagnosis of asthma/active pulmonary disease other than COPD; lung volume reduction surgery within the previous 12 months; clinically significant abnormality on chest x-ray/computerised tomography scan not related to COPD; hospitalisation due to poorly controlled COPD that had not resolved at least 4 weeks prior to screening and at least 6 weeks following the last dose of systemic corticosteroids; poorly controlled COPD or a lower respiratory tract infection (LRTI) requiring antibiotics within the last 6 weeks; and a COPD exacerbation or LRTI (including pneumonia) during the run-in period.

2.3. Study assessments

Spirometry was performed at each scheduled clinic visit to assess FEV_1 and FVC (ATS guidelines). Sites were provided with training, standardised spirometric equipment, and centralised overread of these assessments by an external vendor (Biomedical Systems, EU Headquarters: Brussels, Belgium; US Headquarters: St Louis, Missouri; Japan Headquarters: Tsukuba-shi, Ibaraki-ken, Japan). Participants' reversibility status was assessed at screening (further details are provided in the appendix p 2).

COPD exacerbations were defined as a worsening of COPD symptoms requiring additional treatment, and were classified as mild (self-managed [data not collected]), moderate (required antibiotics and/or systemic/oral corticosteroids), or severe (required in-patient hospitalisation). Antibiotic use was not considered a COPD exacerbation unless associated with treatment of worsening COPD symptoms. According to the study protocol, COPD exacerbations were not to be recorded as an adverse event (AE), unless they met the definition of a serious AE (SAE; an SAE was defined as any untoward medical occurrence that results in death or disability/incapacity, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, or is a congenital anomaly/birth defect, and all events of possible drug-induced liver injury with hyperbilirubinaemia); however, some moderate exacerbations were still recorded as AEs. Moderate/severe COPD exacerbations were recorded in the electronic case report form.

A daily diary was completed by participants each morning prior to taking study/rescue medication to report the following over the previous 24 h: COPD symptoms (appendix p 4); number of occasions of rescue medication use; number of night-time awakenings requiring rescue medication; and any medical problems and medications used to treat those problems.

Health-related quality of life (HRQoL) was assessed using the St George's Respiratory Questionnaire – COPD (SGRQ-C), a validated, 40-item, paper-administered, COPD-specific questionnaire that measures the impact of COPD and its treatment on HRQoL [17]. An improvement of four units is the accepted minimum clinically important difference (MCID) [18]. COPD-related health status was assessed using the COPD Assessment Test™ (CAT; a validated, eight-item, paper-administered, patient-completed questionnaire for use

in routine clinical practice) [19]. Participants rated their experience on a six-point scale, ranging from 0 (no impairment) to 5 (maximum impairment), with a scoring scale of 0–40; an improvement of two units is the MCID [20]. COPD symptoms of cough and sputum production were assessed using the Cough and Sputum Assessment Questionnaire (CASA-Q; a validated, 20-item, paper-administered, 7-day recall period, questionnaire with four domains: cough symptoms, cough impact, sputum symptoms, and sputum impact). Scores range from 0 to 100, with lower scores indicating higher symptom/impact levels [21]. The CASA-Q was completed by all randomised participants at participating sites in countries for which a validated and translated version of the questionnaire was available at the time of study initiation (Germany, Japan, Republic of Korea, Romania, Russian Federation, Taiwan, and the USA). Participants were instructed to complete procedures in the following order: CAT, SGRQ-C, CASA-Q, and then any other procedures.

2.4. Study outcomes

The primary endpoint was the change from baseline in trough (pre-bronchodilator/pre-dose) FEV_1 on treatment day 84, to evaluate the contribution on lung function of FF 100 μg in the FF/VI 100/25 μg combination. Baseline FEV_1 was the mean of two assessments conducted at 30 min pre-dose and immediately pre-dose on treatment day 1. Trough FEV_1 on day 84 was the mean of two assessments conducted 23 and 24 h after dosing on day 83 (if one of the two timepoints was missing, the available timepoint was used).

Secondary endpoints were the percentage of rescue-free 24-h periods over the entire 12-week treatment period and time to first moderate/severe COPD exacerbation. Other efficacy endpoints included the number of occasions of rescue medication use during a 24-h period averaged over the entire 12-week treatment period; symptom scores (breathlessness, cough, and sputum production) averaged over the entire 12-week treatment period; the percentage of symptom-free 24-h periods over the entire 12-week treatment period; the percentage of nights with no night-time awakenings requiring rescue medication in participants who had at least one night-time awakening requiring rescue medication during baseline; the number of night-time awakenings requiring rescue medication over the entire 12-week treatment period in participants who had at least one night-time awakening requiring rescue medication during baseline; change in health status using the CAT at randomisation and week 12 or early withdrawal; and the proportion of responders on the SGRQ total score at day 84. Responder status was defined as a change from baseline score of −4 units or lower (MCID) [18]. Participants with an SGRQ total score higher than four units below baseline, or a missing change from baseline in SGRQ total score were classified as non-responders. The effect of FF/VI 100/25 μg on cough and sputum symptoms assessed using CASA-Q was an exploratory endpoint.

2.5. Safety

The occurrence of AEs was solicited from the participants at each study visit and coded using the Medical Dictionary for Regulatory Activities® (Version 18.0; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland). Participants also recorded any medical conditions and any change in medications in the daily diary.

2.6. Statistical analysis

Sample size calculations were based on the primary endpoint of trough FEV_1 on day 84. Using a two sample *t*-test and two-sided 5% significance level, 696 evaluable participants in each treatment group would have 90% power to detect a 40 mL difference between FF/VI 100/25 μg and VI 25 μg in trough FEV_1 at week 12, assuming a residual standard deviation of 230 mL (based upon the integrated results of the two phase III studies of FF/VI in patients with COPD) [13,14]. To allow for an estimated 12% post-randomisation withdrawal rate, 791 participants were to be randomised per arm. The primary population used for all data analyses comprised of all participants randomised to treatment who received at least one dose of randomised study medication in the treatment period (intent-to-treat [ITT] population).

The primary analysis of the change from baseline in trough FEV_1 on day 84 (primary endpoint) was performed using mixed models repeated measures, with covariates of baseline FEV_1, reversibility status (stratum), day, region, treatment, day by baseline interaction, and day by treatment interaction (where day was nominal). The model used all available trough FEV_1 values recorded on study days 2, 14, 28, 56, and 84. Missing data were not directly imputed in this analysis; however, all non-missing data for a participant were used within the analysis to estimate the treatment effect for trough FEV_1 on day 84.

An analysis of covariance (ANCOVA) model, with covariates of baseline, reversibility status at screening, region, and treatment, was used to analyse the percentage of rescue-free 24-h periods, the mean number of occasions on which rescue medication was used, the mean symptom score for breathlessness, cough and sputum production, and the mean number of night-time awakenings requiring rescue medication. The time to first moderate/severe exacerbation was analysed using a Cox proportional hazards regression model, which included terms for reversibility status, baseline disease severity (as % predicted FEV_1) and treatment. SGRQ total score, CAT, and CASA-Q scores were analysed using ANCOVA with covariates of baseline, reversibility status at screening, region, and treatment. The proportion of responders according to SGRQ total score at treatment day 84 was analysed using a separate logistic regression model, with treatment as an explanatory variable and baseline total SGRQ score, reversibility status at screening, and region as covariates.

In order to make inferences for pre-defined secondary endpoints while controlling for the overall type I error, the secondary endpoints were nested under the primary endpoint; multiplicity across these endpoints was controlled using a closed testing procedure. If superiority was concluded for the primary analysis of the primary endpoint, then testing was to be performed for the secondary endpoint of percentage of rescue-free 24-h periods over the entire treatment period. If superiority was concluded for this secondary endpoint, then testing was to be performed for the secondary endpoint of time to first moderate/severe exacerbation. However, if superiority was not concluded for the primary endpoint, then testing for the secondary endpoints was interpreted as descriptive only. For ‘other’ and ‘exploratory’ endpoints, statistical inference was contingent on significance having been achieved for the primary and secondary endpoints.

3. Results

3.1. Participants

A total of 2423 participants were enrolled, of whom 1620 completed the screening and run-in periods, were randomised, and received at least one dose of double-blind study medication (ITT population). Two participants were randomised in error; neither received study medication and they were not included in the ITT population. The withdrawal rate was similar between treatment groups (5% and 7% for FF/VI 100/25 μg and VI 25 μg, respectively); the most common primary reason for withdrawal was an AE (2% per group) (Fig. 1). Baseline demographics were comparable between

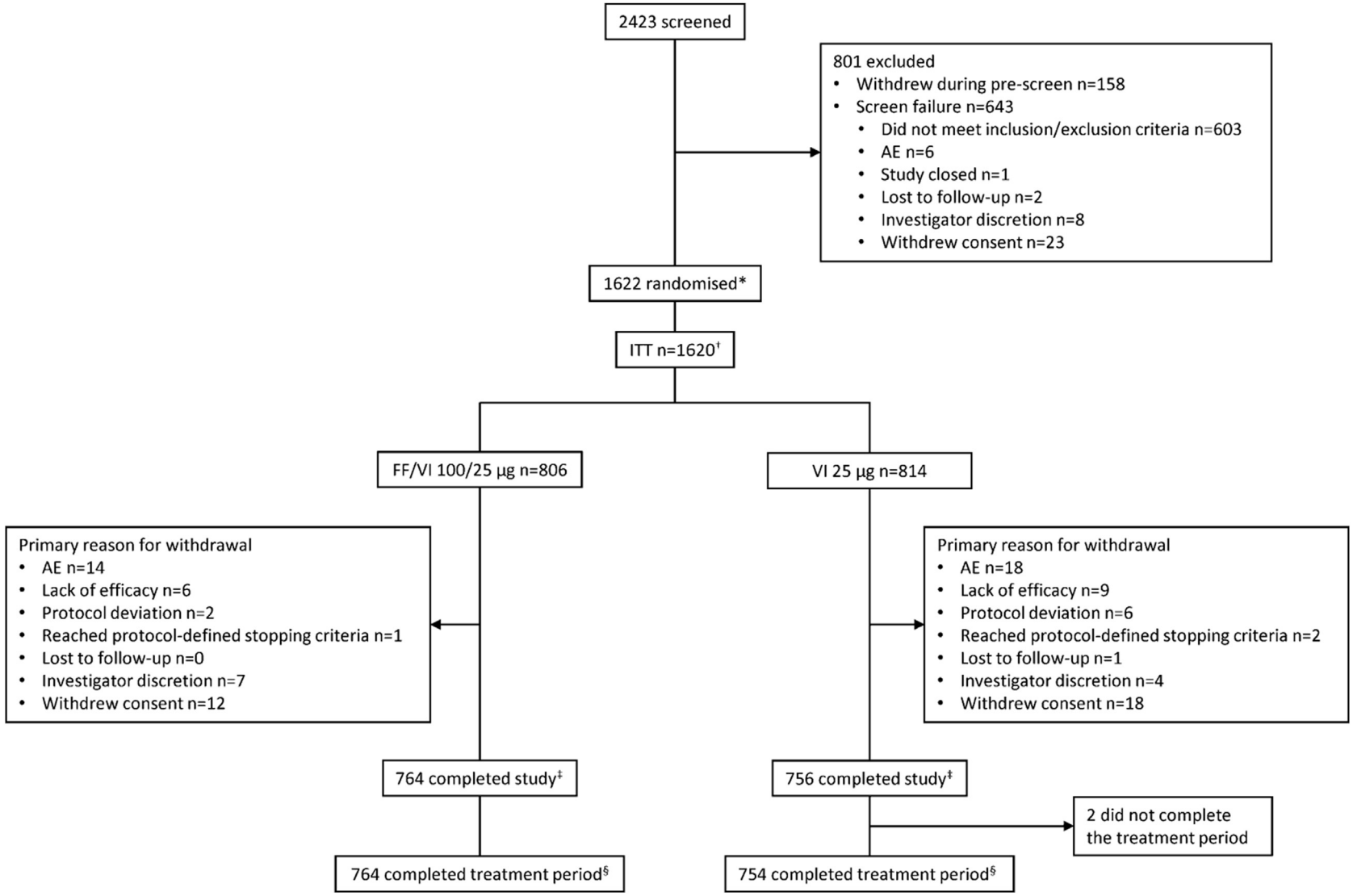

Fig. 1. CONSORT flow diagram.
AE = adverse event; FF = fluticasone furoate; ITT = intent-to-treat; VI = vilanterol. *Two participants were randomised in error. Neither took double-blind study medication and they were not included in the ITT population. †Participants who were randomised to a treatment group and received at least one dose of study medication (USA, n = 170; Asia Pacific, n = 522, of whom 370 were in Japan; Eastern Europe, n = 348; Western Europe, n = 505; other, n = 75). ‡Participants were considered to have completed the study if they attended the last clinic visit (visit 7), had a follow-up phone contact and did not have an early withdrawal visit. §Participants were considered to have completed the treatment period if they attended the last clinic visit (visit 7), and did not withdraw at the visit, and had an exposure stop date on or after the day prior to visit 7.

Table 1
ITT population characteristics.

Characteristic	FF/VI 100/25 μg (n = 806)	VI 25 μg (n = 814)	Total (N = 1620)
Screening			
Mean age, years (SD)	65.3 (8.58)	65.4 (9.02)	65.3 (8.80)
Male, n (%)	605 (75)	625 (77)	1230 (76)
Race, n (%)			
African American/African heritage	6 (<1)	10 (1)	16 (<1)
Asian (total)	262 (33)	262 (32)	524 (32)
East Asian heritage	77 (10)	77 (9)	154 (10)
Japanese heritage	185 (23)	185 (23)	370 (23)
White/Caucasian/European heritage	538 (67)	541 (66)	1079 (67)
African American/African heritage and White	0	1 (<1)	1 (<1)
Mean BMI, kg/m^2 (SD)	25.90 (5.421)	25.95 (5.664)	25.93 (5.543)
Current smoker, n (%)[a]	367 (46)	363 (45)	730 (45)
Smoking history, pack-years			
n	806	811	1617
Mean (SD)	43.7 (25.75)	44.1 (26.39)	43.9 (26.06)
Cardiovascular history/risk factors, n (%)			
Any history/risk factors[b]	583 (72)	553 (68)	1136 (70)
Coronary artery disease	165 (20)	135 (17)	300 (19)
Myocardial infarction	49 (6)	34 (4)	83 (5)
Arrhythmia	73 (9)	76 (9)	149 (9)
Congestive heart failure	45 (6)	51 (6)	96 (6)
Hypertension	491 (61)	457 (56)	948 (59)
Cerebrovascular accident	41 (5)	33 (4)	74 (5)
Diabetes mellitus	110 (14)	105 (13)	215 (13)
Hypercholesterolaemia	205 (25)	202 (25)	407 (25)
COPD type, n (%)[c]			
Chronic bronchitis	508 (63)	527 (65)	1035 (64)
Emphysema	528 (66)	536 (66)	1064 (66)
Unknown	0	1 (<1)	1 (<1)
Pre-study COPD therapy, n (%)[d]			
SABA	553 (69)	560 (69)	1113 (69)
SAMA	222 (28)	244 (30)	466 (29)
LABA	510 (63)	515 (63)	1025 (63)
LAMA	360 (45)	400 (49)	760 (47)
ICS	397 (49)	389 (48)	786 (49)
Number of patients with a moderate and/or severe COPD exacerbation in the last 12 months, n (%)[e]			
0	0	1 (<1)[f]	1 (<1)[f]
1	626 (78)	619 (76)	1245 (77)
2	139 (17)	141 (17)	280 (17)
>2	41 (5)	53 (7)	94 (6)
Number of patients with a moderate COPD exacerbation in the last 12 months, n (%)[e]			
0	158 (20)	143 (18)	301 (19)
1	533 (66)	544 (67)	1077 (66)
2	82 (10)	91 (11)	173 (11)
>2	33 (4)	36 (4)	69 (4)
Number of patients with a severe COPD exacerbation in the last 12 months, n (%)[e]			
0	583 (72)	604 (74)	1187 (73)
1	205 (25)	188 (23)	393 (24)
2	18 (2)	19 (2)	37 (2)
>2	0	3 (<1)	3 (<1)
Lung function, mean (SD)			
Pre-bronchodilator FEV_1, L	1.296 (0.4170)	1.303 (0.4321)	1.300 (0.4245)
Post-bronchodilator FEV_1, L	1.427 (0.4137)	1.438 (0.4311)	1.433 (0.4224)
Percent predicted pre-bronchodilator FEV_1, %	45.7 (10.92)	45.7 (10.86)	45.7 (10.89)
Percent predicted post-bronchodilator FEV_1, %	50.3 (10.33)	50.5 (10.33)	50.4 (10.32)
Post-bronchodilator FEV_1/FVC, %	45.8 (10.01)	45.9 (10.19)	45.8 (10.10)
Percent reversibility FEV_1, %	11.7 (12.34)	12.1 (12.49)	11.9 (12.41)
Reversibility status, n (%)[g]			
Reversible	218 (27)	218 (27)	436 (27)
Non-reversible	588 (73)	596 (73)	1184 (73)
GOLD classification, n (%)			
GOLD 1: $FEV_1 \geq 80\%$	0	0	0
GOLD 2: $50\% \leq FEV_1 < 80\%$	411 (51)	443 (54)	854 (53)
GOLD 3: $30\% \leq FEV_1 < 50\%$	395 (49)	371 (46)	766 (47)
GOLD 4: $FEV_1 < 30\%$	0	0	0
GOLD Patient Group, n (%)[h]			
A	35 (4)	43 (5)	78 (5)
B	222 (28)	226 (28)	448 (28)
C	35 (4)	29 (4)	64 (4)
D	514 (64)	515 (63)	1029 (64)
Unknown	0	1 (<1)[i]	1 (<1)[i]
Baseline			

Table 1 (*continued*)

Characteristic	FF/VI 100/25 μg (n = 806)	VI 25 μg (n = 814)	Total (N = 1620)
FEV_1, L			
n	804	813	1617
Mean (SD)	1.281 (0.4377)	1.293 (0.4585)	1.287 (0.4482)
Total symptom score[j]			
n	805	812	
Mean (SD)	5.56 (1.315)	5.52 (1.323)	

BMI = body mass index; CAT=COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FF = fluticasone furoate; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; ITT = intent-to-treat; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic-antagonists; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic-antagonists; SD = standard deviation; VI = vilanterol.

[a] Two patients with unknown smoking status in VI group.

[b] A participant with one or more of the following terms recorded as a current or past medical condition at the screening visit is considered to have cardiovascular history/risk factors.

[c] Participants could be classified as 'chronic bronchitis', 'emphysema', or both for COPD type.

[d] The following respiratory medication classes were the most common reported by participants (participants could be counted in multiple medication options).

[e] Moderate COPD exacerbation: worsening symptoms of COPD that required treatment with oral/systemic corticosteroids and/or antibiotics. Severe COPD exacerbation: worsening symptoms of COPD that required treatment with in-patient hospitalisation.

[f] One patient was reported with a full protocol deviation.

[g] Reversibility was defined as an increase in FEV_1 of ≥200 mL and ≥12% following administration of albuterol (salbutamol).

[h] GOLD Group A (low risk, less symptoms): CAT score <10 and GOLD classification 1 or 2 and exacerbation history of 0–1 exacerbations that required oral/systemic corticosteroids and/or antibiotics in the previous year, and no hospitalisation for exacerbation in the previous year. GOLD Group B (low risk, more symptoms): CAT score ≥10 and GOLD classification 1 or 2 and exacerbation history of 0–1 exacerbations that required oral/systemic corticosteroids and/or antibiotics in the previous year, and no hospitalisation for exacerbation in the previous year. GOLD Group C (high risk, less symptoms): CAT score <10 and one of the following: GOLD classification 3 or 4, or exacerbation history of ≥2 exacerbations that required oral/systemic corticosteroids and/or antibiotics in the previous year, or ≥1 severe exacerbation involving hospitalisation in the previous year. GOLD Group D (high risk, more symptoms): CAT score ≥10 and one of the following: GOLD classification 3 or 4, or exacerbation history of ≥2 exacerbations that required oral/systemic corticosteroids and/or antibiotics in the previous year, or ≥1 severe exacerbation involving hospitalisation in the previous year.

[i] The missing participant had no baseline CAT data, which is required to derive the GOLD patient group classification.

[j] Total symptom score for breathlessness, cough, and sputum production.

treatment groups (Table 1). Participants had a mean age of 65 years and most were White (67%) and male (76%). The mean body mass index of 26 kg/m^2 indicated that participants tended to be slightly overweight. Almost half of the participants were current smokers (45%; the mean number of pack-years was 43.9). All but one participant (in the VI 25 μg group and reported as a protocol deviation) had one or more COPD exacerbations that required oral/systemic corticosteroids and/or antibiotics and/or hospitalisation in the 12 months prior to screening.

Screening and baseline (pre-dose on day 1) lung function data were comparable between groups (ITT; Table 1). At screening, the mean post-bronchodilator FEV_1 (1.433 L), mean percent predicted post-bronchodilator FEV_1 (50.4%), and the mean post-bronchodilator FEV_1/FVC ratio (45.8%) was indicative of a population with moderate-to-severe airflow obstruction. The majority of participants (73% in each group) had non-reversible COPD; 53% of participants were Global Initiative for Obstructive Lung Disease (GOLD) classification 2 (moderate) and 47% were GOLD classification 3 (severe) at screening. For all participants in the ITT population, 64% were in GOLD Patient Group D (high risk, more symptoms), followed by 28% of participants included in GOLD Patient Group B (low risk, more symptoms); GOLD Patient Group distribution was similar between the two groups.

3.2. Lung function (primary endpoint)

The median exposure to treatment was the same in the FF/VI 100/25 μg and VI 25 μg groups (84.0 days). At treatment day 84, the FF/VI 100/25 μg group showed a statistically significant adjusted mean treatment difference of 34 mL over the VI 25 μg group in change from baseline trough FEV_1 (95% CI 14–55; p = 0.001) (Table 2). Statistically significant improvements in the FF/VI 100/25 μg group, compared with the VI 25 μg group, were observed at all timepoints (Fig. 2). No statistical evidence of an interaction (at the 10% level) of treatment, with covariates included in the primary analysis model (baseline, region, reversibility status) or with additional parameters of interest (percent predicted FEV_1 categories, cardiovascular history/risk factors), was observed for trough FEV_1 at day 84.

Table 2
Analysis of the difference in change from baseline trough FEV_1 (L) between FF/VI 100/25 μg and VI 25 μg (ITT population).

Day 84	FF/VI 100/25 μg (n = 806)	VI 25 μg (n = 814)
n[a]	802	811
n[b]	759	749
LS mean trough FEV_1, L (SE)	1.404 (0.0074)	1.370 (0.0075)
LS mean change in trough FEV_1 from baseline, L (SE)	0.116 (0.0074)	0.082 (0.0075)
Difference, L (95% CI)	0.034 (0.014–0.055)	
p value	0.001	

Analysis performed using a repeated measures model with covariates of treatment, reversibility status (stratum), baseline − mean of the two assessments made 30 min pre-dose and immediately pre-dose on day 1, region, day, day by baseline, and day by treatment interactions.CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; FF = fluticasone furoate; ITT = intent-to-treat; LS = least squares; SE = standard error; VI = vilanterol.

[a] Number of patients with analysable data for one or more timepoints.

[b] Number of patients with analysable data at the given timepoint.

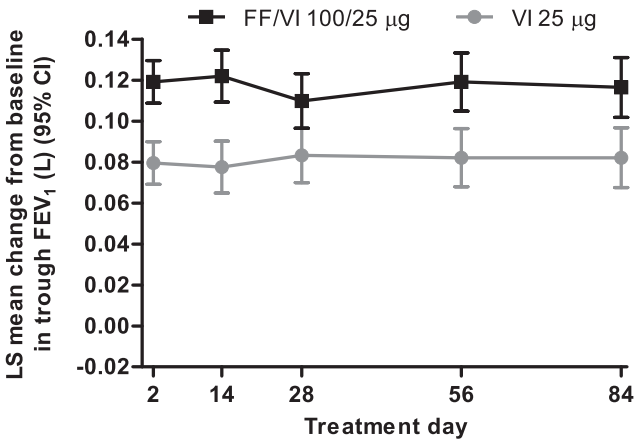

Fig. 2. Analysis of change from baseline trough FEV_1 at each clinic visit.
CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; FF = fluticasone furoate; LS = least squares; VI = vilanterol. Analysis performed using a repeated measures model with covariates of treatment, reversibility status (stratum), baseline – mean of the two assessments made 30 min pre-dose and immediately pre-dose on day 1, region, day, day by baseline, and day by treatment interactions.

3.3. Percentage of rescue-free 24-h periods and time to first moderate/severe COPD exacerbation (secondary endpoints)

The percentage of rescue-free 24-h periods over the entire treatment period was greater in the FF/VI 100/25 μg group (adjusted mean: 47.03% [standard error [SE] 1.070]), compared with the VI 25 μg group (adjusted mean: 44.41% [SE 1.069]), but the difference between the groups was not statistically significant (2.62% [95% CI −0.35 to 5.59; p = 0.084]). Since the comparison of FF/VI 100/25 μg versus VI 25 μg did not achieve statistical significance at the 5% level for the percentage of rescue-free 24-h periods, the conditions of the step-down testing procedure were not met, and therefore, the results of the statistical analyses for the second secondary endpoint (time to first moderate/severe COPD exacerbation) and the other endpoints were interpreted descriptively. The FF/VI 100/25 μg group showed a 42% risk reduction in time to first moderate/severe COPD exacerbation, compared with the VI 25 μg group (95% CI 22–57; nominal p < 0.001) (Fig. 3).

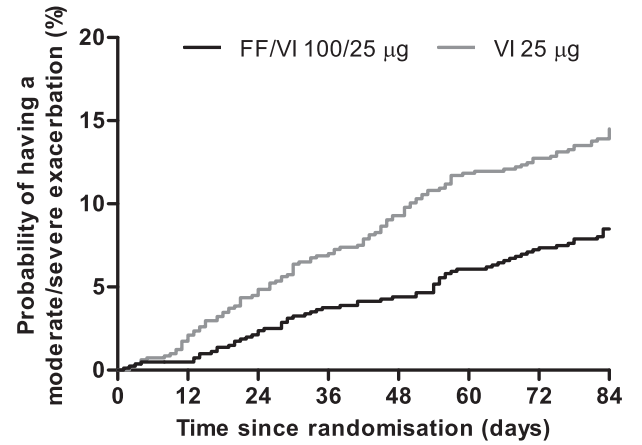

Fig. 3. Kaplan-Meier plot of time to first on-treatment moderate or severe COPD exacerbation.
COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; VI = vilanterol. All participants who did not experience an exacerbation during the double-blind treatment period were censored.

3.4. Daily diary and HRQoL/health outcomes ('other' endpoints)

Baseline values for the number of occasions of rescue medication use, symptom scores, night-time awakenings requiring rescue medication, SGRQ score, and CAT score were similar between treatment groups. The adjusted mean number of occasions of rescue medication use in a 24-h period over the 12-week treatment period was lower in the FF/VI 100/25 μg group (1.15 [SE 0.035]), compared with VI 25 μg (1.27 [SE 0.035]); this difference was nominally significant (−0.12 [95% CI −0.21 to −0.02; nominal p = 0.020]). Over weeks 1–12, the FF/VI 100/25 μg group showed a reduction in mean breathlessness score, compared with the VI 25 μg group (nominal p = 0.043). The adjusted mean change from baseline in SGRQ total score exceeded the MCID of four units in both the FF/VI 100/25 μg (−6.02; SE 0.407) and VI 25 μg (−5.39; SE 0.409) groups; patients in the FF/VI 100/25 μg group with a non-missing baseline/post-baseline assessment were 1.3 times more likely to be a responder than a non-responder compared with the VI 25 μg group. There was no significant difference between the treatment groups for cough and sputum production symptom scores, the number of night-time awakenings requiring rescue medication use, or CAT score (Table 3). Further information can be found in the appendix p 2.

3.5. Safety assessments

The number of participants who experienced an on-treatment AE, drug-related AE, AE of special interest, SAE, AE leading to permanent discontinuation of study drug or withdrawal from study, drug-related SAE, or fatal SAE was comparable between the treatment groups (Table 4). The most frequently reported on-treatment AE was nasopharyngitis (6% per group). The most common on-treatment SAEs were COPD (FF/VI 100/25 μg: 1%; VI 25 μg: 2%) and pneumonia (<1% in each group). Four participants died during the study. One participant in the FF/VI 100/25 μg group had three events that were considered by the investigators to have contributed to the patient's death (COPD, chronic respiratory failure, and pulmonary embolism) and three participants in the VI 25 μg group had one fatal event each (myocardial infarction, cardiac failure congestive, and aortic dissection). COPD was the most frequently reported AE leading to discontinuation of study drug or study withdrawal (<1% of participants per group). The most common on-treatment AEs of special interest were cardiovascular effects (FF/VI 100/25 μg: 3%; VI 25 μg: 2%; Table 4). The number of participants who had a pneumonia AE was low and the same in each group (n = 7 [<1%]). No pneumonia-related fatalities were reported (further information can be found in the appendix p 3). The number of participants with ≥1 COPD exacerbation during the treatment period was lower in the FF/VI 100/25 μg group, compared with the VI 25 μg group (Table 5). Fewer exacerbations in the FF/VI 100/25 μg group led to withdrawal (4/78 [5%]) or resulted in hospitalisation (10/78 [13%]) compared with the VI 25 μg group (11/144 [8%] and 21/144 [15%], respectively).

4. Discussion

This study evaluated the efficacy and safety of FF/VI 100/25 μg compared with VI 25 μg in patients with COPD who had a history of at least one COPD exacerbation that required treatment with corticosteroids, antibiotics and/or required hospitalisation in the past year, and who had current COPD symptoms. Participants treated with FF/VI 100/25 μg had a significant improvement over the VI 25 μg group in change from baseline trough FEV_1 at all assessment timepoints (day 2 through day 84). At day 84, there was an adjusted mean treatment difference of 34 mL in favour of FF/VI 100/25 μg,

Table 3
Summary of daily diary and health-related quality of life/health outcome endpoints.

Weeks 1–12 (unless otherwise noted)	Difference in adjusted mean values for FF/VI 100/25 μg versus VI 25 μg (95% CI)
Number of occasions of rescue medication use in a 24-h period	−0.12 (−0.21 to −0.02); p = 0.020 (nominal)[a]
Symptom scores	
Breathlessness[b]	−0.06 (−0.11 to 0.00); p = 0.043 (nominal)[a]
Cough[c]	0.01 (−0.04 to 0.06); p = 0.643
Sputum production[d]	0.01 (−0.04 to 0.06); p = 0.696
Total symptoms	−0.04 (−0.17 to 0.09); p = 0.564
Number of night-time awakenings requiring rescue medication use[e]	−0.02 (−0.10 to 0.06); p = 0.653
Proportion of responders on SGRQ total score at week 12[f]	OR: 1.3 (1.1–1.7); p = 0.006 (nominal)[a,g]
CAT score at week 12[h]	−0.2 (−0.7 to 0.4); p = 0.577

All endpoints were analysed using an ANCOVA model with covariates of baseline, reversibility status at screening, region, and treatment, except for the analysis of the proportion of responders on SGRQ total score at week 12, which used a logistic regression with covariates of treatment, baseline SGRQ total score (score on day 1), geographical region and reversibility status (stratum). ANCOVA = analysis of covariance; CAT=COPD Assessment Test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; OR = odds ratio; SGRQ=St Georges Respiratory Questionnaire; SGRQ-C=St Georges Respiratory Questionnaire – COPD; VI = vilanterol.

[a] The results for the 'other' endpoints were interpreted descriptively as the comparison of percentage of rescue-free 24-h periods between the groups (secondary endpoint) did not achieve statistical significance at the 5% level.

[b] Five-point scale: 0 (not breathless at rest/on exertion) to 4 (breathless at rest).

[c] Four-point scale: 0 (no cough) to 3 (severe cough, eg, coughing in the morning and throughout the day).

[d] Four-point scale: 0 (none) to 3 (severe sputum production, eg, throughout the day).

[e] Only includes patients who had at least one night-time awakening requiring rescue medication during baseline.

[f] SGRQ total score was derived from the SGRQ-C, which is a 40-item questionnaire, lower scores indicate better health status. Responders were defined as participants who had a change from baseline of −4 units or lower (minimum clinically important difference). Non-responders were defined as participants with a SGRQ total score higher than four units below baseline, or a missing change from baseline in SGRQ total score.

[g] Results for patients with a non-missing baseline/post-baseline assessment (similar results were observed for patients with a non-missing baseline only).

[h] The CAT is an eight-item questionnaire, six-point scale: 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0–40, lower scores indicate better health status.

Table 4
Summary of AEs.

n (%)	FF/VI 100/25 μg (n = 806)	VI 25 μg (n = 814)
Summary		
Any on-treatment AEs	260 (32)	244 (30)
Any on-treatment drug-related AEs	20 (2)	16 (2)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study[a]	16 (2)	20 (2)
Any on-treatment SAEs	27 (3)	35 (4)
Any on-treatment drug-related SAEs	1 (<1)	1 (<1)
Any on-treatment fatal SAEs	1 (<1)	3 (<1)
On-treatment AEs reported by ≥ 3% of participants in any treatment group		
Nasopharyngitis	49 (6)	48 (6)
COPD	19 (2)	33 (4)
Headache	29 (4)	19 (2)
On-treatment AEs of special interest[b]		
Any event	71 (9)	58 (7)
Adrenal suppression	0	0
Corticosteroid-associated eye disorders	3 (<1)	0
Decreased bone mineral density and associated fractures	3 (<1)	4 (<1)
Pneumonia	7 (<1)	7 (<1)
LRTI excluding pneumonia	13 (2)	14 (2)
Local steroid effects	15 (2)	12 (1)
Effects on potassium	0	1 (<1)
Tremor	0	0
Cardiovascular effects[c]		
Any events	22 (3)	18 (2)
Cardiac arrhythmias	4 (<1)	3 (<1)
Cardiac failure	3 (<1)	3 (<1)
Cardiac ischaemia	4 (<1)	3 (<1)
Hypertension	10 (1)	9 (1)
Stroke	2 (<1)	2 (<1)
Effects on glucose[d]	5 (<1)	5 (<1)
Hypersensitivity[e]	11 (1)	5 (<1)

AE = adverse event; COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LRTI = lower respiratory tract infection; SAE = serious adverse event; VI = vilanterol.

[a] Includes both on-treatment and post-treatment AEs.

[b] On-treatment AEs of special interest associated with the known pharmacological action of ICS or LABA therapy were identified using standardised Medical Dictionary for Regulatory Activities® (Version 18.0; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland) queries (SMQs) and sponsor-defined special interest terms where no SMQ was available.

[c] Defined using SMQ terms (stroke included the SMQ terms of central nervous system haemorrhages and cerebrovascular conditions).

[d] Defined using the SMQ terms of hyperglycaemia/new-onset diabetes mellitus.

[e] Defined using the SMQ terms of anaphylactic reaction, angioedema, and hypersensitivity.

Table 5
Summary of on-treatment moderate or severe COPD exacerbations in ITT population.

	FF/VI 100/25 μg (n = 806)	VI 25 μg (n = 814)
Patients with ≥1 exacerbations, n (%)[a]	69 (9)	114 (14)
Total number of exacerbations	78	144
Severity, n (%)[b]		
Moderate[c]	68 (87)	123 (85)
Severe[d]	10 (13)	21 (15)
Outcome, n (%)[b]		
Resolved	76 (97)	139 (97)
Fatal	1 (1)	0
Not resolved	1 (1)	5 (3)
Duration of exacerbation, days[e]		
n	77	139
Mean (SD)	12.4 (8.68)	14.4 (10.83)
Median	10.0	10.0
Minimum	1	1
Maximum	53	61
Withdrawn due to an exacerbation, n (%)[b]	4 (5)	11 (8)

COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; ITT = intent-to-treat; SD = standard deviation; VI = vilanterol.
[a] Percentage calculated using n as the denominator.
[b] Percentage calculated using the number of exacerbations as the denominator.
[c] COPD exacerbation that required oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation).
[d] COPD exacerbation that required hospitalisation.
[e] Summary only includes exacerbations for which a date of resolution or death is provided.

suggesting that there is a small contribution on lung function of FF in the FF/VI 100/25 μg combination that is sustained over time, in addition to its effect on COPD exacerbations [12].

These results are in the range of treatment differences that have been shown in previous studies of FF/VI and other ICS/LABA combinations [4,12–14,22,23]. Two 6-month, randomised, controlled trials that included a comparison of FF/VI 100/25 μg versus VI 25 μg in COPD reported FEV_1 treatment differences of 52 mL and 26 mL at day 84 in favour of FF/VI 100/25 μg (in these trials, the effect on lung function had reached a plateau by day 84) [13,14]. However, unlike this study, these trials excluded participants who had a history of COPD exacerbations. Comparable treatment differences between FF/VI 100/25 μg and VI 25 μg (36 mL and 40 mL) were also observed at day 84 in two replicate, 1-year, randomised trials designed to evaluate the contribution of FF 100 μg in the FF/VI 100/25 μg combination in reducing the annual rate of moderate/severe COPD exacerbations in patients with moderate-to-severe airflow limitation, and a documented history of at least one COPD exacerbation that required antibiotics and/or systemic/oral corticosteroids, or hospitalisation in the year prior to screening [12]. The magnitude of these effects on trough FEV_1 demonstrated for FF/VI versus VI is in the range of treatment differences observed in studies comparing budesonide/formoterol with formoterol alone [4,22,24].

In contrast to patients with asthma, where improvements in lung function are observed with ICS [25], the predominant role of ICS in COPD is to reduce the rate of exacerbations [2,4,13,14]. However, FF may reduce the rate of decline in FEV_1 in patients with COPD, when used alone or in combination with VI [9], and there is evidence to suggest that ICSs and LABAs have a synergistic effect when used in combination [26,27].

The percentage of rescue-free 24-h periods was numerically, but not significantly, greater in the FF/VI 100/25 μg group compared with the VI 25 μg group. The difference in the number of occasions of rescue medication use over the 12-week treatment period was nominally significant in favour of FF/VI 100/25 μg.

In this 12-week study, the FF/VI 100/25 μg group demonstrated a 42% risk reduction in time to first moderate/severe COPD exacerbation, compared with the VI 25 μg group. The 1-year exacerbation studies of FF/VI reported a 24% risk reduction in favour of FF/VI 100/25 μg [12]. These trials had similar inclusion criteria to the current study, with the exception that there was no lower limit for percent predicted FEV_1 and no requirement for participants to have current COPD symptoms. The 12-week study of budesonide/formoterol versus formoterol alone showed a 32% risk reduction in time to first moderate/severe exacerbation in favour of budesonide/formoterol [4].

There was a nominally significant reduction in breathlessness score in favour of the FF/VI 100/25 μg group over the VI 25 μg group. However, there were no significant differences between the treatment groups for cough and sputum symptoms, or the number of night-time awakenings requiring rescue medication. The percentage of symptom-free 24-h periods over the 12-week treatment period was slightly lower in the FF/VI 100/25 μg group, compared with VI 25 μg. A 12-week study of budesonide/formoterol compared with formoterol alone, that had a similar design to the present study, also showed a significant difference in breathlessness and no significant difference in cough [4]. The symptom results in the current study were also consistent with the results for the comparison of FF/VI 100/25 versus VI 25 alone in the 6-month studies of FF/VI [13,14].

The adjusted mean change from baseline in SGRQ total score exceeded the MCID of −4 points or lower in both treatment groups; however, participants in the FF/VI 100/25 μg group were more likely to be a responder than a non-responder on the SGRQ total score, compared with participants in the VI 25 μg group (nominally significant). Both treatment groups exceeded the estimated MCID of −2 points or lower in adjusted mean change from baseline in CAT score; the difference between the groups was not significant. At treatment day 84, there was a nominally significant difference in favour of the VI 25 μg group for both sputum symptoms and sputum impact CASA-Q domains. There was no significant difference between the groups for cough symptoms and cough impact domains.

No new safety concerns were identified during this study for FF/VI 100/25 μg or VI 25 μg. The incidence of AEs, SAEs, and AEs of special interest, including local steroid effects, was similar between the treatment groups. Previous studies have reported an association with FF/VI and an increased risk of pneumonia, compared with VI alone [12,28]. In this study, the incidence of pneumonia was the same in both treatment groups (n = 7 [<1%] in each group; none fatal), although the 12-week treatment period used in this study is too short to elucidate whether there was any increased risk of pneumonia as observed in longer trials. The SUMMIT trial also found no increased risk of pneumonia in patients taking FF/VI [9].

A strength of this study was the large sample size, which provided a robust point estimate of the lung function effect attributable to FF. A limitation of this study is that lung volume measurements were not performed, which might partly explain the lack of appreciable differences between treatments on symptomatic endpoints, particularly breathlessness.

5. Conclusion

This study confirmed the contribution on lung function of FF 100 μg in the FF/VI 100/25 μg combination, and reinforced the important clinical benefit of FF/VI 100/25 μg compared with VI 25 μg alone in reducing the time to first moderate/severe COPD exacerbation. There was also a nominally significant reduction in breathlessness and a nominally significant increase in SGRQ responders in the FF/VI 100/25 μg group, compared with the VI 25 μg group. The percentage of rescue-free 24-h periods, symptoms of cough and sputum production, and CAT scores were similar

between treatment groups. No new safety concerns were identified for FF/VI 100/25 μg or VI 25 μg. The reported AEs in the study do not alter the established safety profile for FF/VI 100/25 μg and provide further evidence that this treatment is well tolerated over a 12-week treatment period in patients with COPD.

Contributors

All authors contributed to the conception and design of this study, were involved in the interpretation of the data, and the development and approval of the manuscript. The data analysis was conducted by D Midwinter.

Declaration of interests

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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.2016.12.001.

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