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Effect of fluticasone propionate/salmeterol (250/50 μg) or salmeterol (50 μg) on COPD exacerbations☆

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Summary
Objectives: COPD exacerbations are associated with significant morbidity and mortality. This randomized, double-blind, parallel-group, multicenter study evaluated the effect of fluticasone propionate/salmeterol 250/50 and salmeterol 50 μg twice daily on moderate to severe exacerbations.
Methods: Patients received standardized treatment with fluticasone propionate/salmeterol 250/50 during a 1-month run-in, followed by randomization to fluticasone propionate/salmeterol 250/50 or salmeterol for 12 months. Moderate to severe exacerbations were defined as worsening symptoms of COPD requiring treatment with oral corticosteroids, antibiotics, or hospitalization.
Results: In 782 patients with COPD (mean $FEV_1 = 0.94 \pm 0.36$ L, 33% predicted normal), treatment with fluticasone propionate/salmeterol 250/50 significantly reduced (1) the annual rate of moderate to severe exacerbations by 30.5% compared with salmeterol (1.06 and 1.53 per subject per year, respectively, $p < 0.001$), (2) the risk of time to first exacerbation by 25% (hazard ratio = 0.750, $p = 0.003$) and (3) the annual rate of exacerbations requiring oral corticosteroids by 40% ($p < 0.001$). Clinical improvements observed during run-in treatment with fluticasone propionate/salmeterol 250/50 were better maintained over 12 months with fluticasone propionate/salmeterol 250/50 than salmeterol. Adverse events were reported for

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FSC, fluticasone propionate/salmeterol combination; FVC, forced vital capacity.

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a similar percentage of subjects across groups. A higher reporting of pneumonia was observed with fluticasone propionate/salmeterol 250/50 than salmeterol (7% vs. 4%).
Conclusions: We conclude that fluticasone propionate/salmeterol 250/50 is more effective than salmeterol at reducing the rate of moderate to severe exacerbations over 1 year. The benefits of this reduction relative to the risk of a higher incidence of reported pneumonia should be considered. This study supports the use of fluticasone propionate/salmeterol 250/50 for the reduction of COPD exacerbations in patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways characterized by progressive airflow limitation that is not fully reversible, with commonly reported symptoms of dyspnea, sputum production and cough.[1] Exacerbations of COPD, although highly variable in clinical presentation, are generally recognized as an acute worsening of symptoms beyond normal day to day variation that warrant a change in disease management.[1,2]

Increasing frequency of COPD exacerbations is associated with greater impairment in quality of life, an increased rate of decline in lung function, and increased mortality.[3–7] More severe airflow obstruction, advanced age, and a history of prior exacerbations are important independent risk factors for both COPD exacerbations and hospitalizations due to exacerbations.[8] Due to the substantial impact that exacerbations have on patients who suffer from them, the prevention and treatment of COPD exacerbations is recognized as a key goal in COPD disease management.[1,2]

Treatment of patients with COPD with fluticasone propionate (FP) 500 μg and salmeterol 50 μg together in a single inhaler (FSC 500/50) twice daily has been shown in several studies to significantly reduce the annualized rate of exacerbations in patients with COPD compared with salmeterol, FP, and placebo.[9–11] Studies of FSC with a lower dose of FP (250 μg) have demonstrated the benefit of FSC 250/50 twice daily on measures of lung obstruction and hyperinflation, symptoms, and exercise endurance time in COPD.[12–15] However, the effect of FSC 250/50 on exacerbations is not well characterized.

This clinical trial was designed to evaluate the effect of FSC 250/50 on moderate to severe exacerbations in patients with COPD and who had a history of prior exacerbations. Salmeterol was chosen as the comparison arm to evaluate the benefit of the FP component of FSC 250/50 over a long-acting bronchodilator alone.

Methods

Patients

Patients were 40 years of age or older with a diagnosis of COPD,[16] a cigarette smoking history of greater than or equal to 10 pack-years, a pre-albuterol FEV_1/FVC of 0.70 or less, a FEV_1 of 50% of predicted normal or less and a history of 1 or more exacerbations of COPD in the year prior to the study that required treatment with oral corticosteroids, antibiotics, or hospitalization. Patients were excluded if they had a diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening.

Study design

This was a randomized, double-blind, parallel-group study (study code SCO40043) conducted at 94 research sites in the United States and Canada. For each site, an institutional review board or ethics committee approved the study and all patients provided written informed consent prior to conduct of study procedures. Patients completed a 4-week run-in period during which they received open-label FP/salmeterol 250/50 via DISKUS® (FSC; Advair, Seretide, GlaxoSmithKline, Research Triangle Park, NC, USA) twice daily. Following run-in, patients were randomized to FSC 250/50 or salmeterol 50 μg (Serevent; GlaxoSmithKline) twice daily via DISKUS for 12 months. Clinic visits were conducted at screening, day 1 (randomization), and after 4, 8, 12, 20, 28, 36, 44, and 52 weeks of treatment. Treatments were assigned in blocks using a center based randomization schedule. Bronchodilator response to FSC DISKUS 250/50 is generally larger in subjects with COPD who demonstrate FEV_1 reversibility to albuterol compared with non-reversible subjects.[12] Therefore, for evaluation of FEV_1, patients were stratified based on FEV_1 response to albuterol at screening to provide a similar distribution of albuterol-responsive and non-responsive patients in each group. Albuterol-responsive was defined as an increase in FEV_1 of $\geq$200 mL and $\geq$12% from baseline following inhalation of four puffs of albuterol. As-needed albuterol was provided for use throughout the study. The use of concurrent inhaled long-acting bronchodilators ($beta_2$-agonist and anticholinergic), ipratropium/albuterol combination products, oral beta-agonists, inhaled corticosteroids, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations.

Measurements

The primary efficacy endpoint was the annual rate of moderate to severe exacerbations. Secondary endpoints were the time to first moderate to severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose FEV_1. Related endpoints were the annual rate of all exacerbations (mild and moderate to severe), duration of moderate to severe exacerbations, time to onset of each moderate to severe exacerbation, exacerbation

recovery time (determined by length of oral corticosteroid and antibiotic courses and hospital stays) and diary records of dyspnea, nighttime awakenings due to COPD, and use of supplemental albuterol. Spirometry was obtained using centralized spirometry services provided by the Compleware Corporation (North Liberty, IA, USA).

Patients recorded daily on diary cards morning peak flow measurements, nighttime awakenings, albuterol use, and symptom ratings of major and minor symptoms. Major symptoms were defined as dyspnea, sputum purulence, and sputum volume, and minor symptoms were defined as cough/wheeze, fever, sore throat, and cold (nasal discharge/congestion).[3,17] Dyspnea, sputum purulence and volume, and cough/wheeze were evaluated relative to their usual state while others were evaluated based on their absence or presence. Dyspnea was rated using a 5 point scale where -2 = much less than usual, -1 = less than usual, 0 = same as usual, 1 = more than usual, and 2 = much more than usual, while sputum purulence and volume, and cough/wheeze were rated using a 2 point scale where 0 = usual level and 1 = increased level.

A COPD exacerbation was defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days.[3,17] Moderate to severe exacerbations were defined as worsening respiratory symptoms as described above requiring treatment with oral corticosteroids, antibiotics, or hospitalization. Mild exacerbations did not require these interventions. Subjects were instructed to contact their study investigator or coordinator if they experienced worsening symptoms of COPD and to report to their study site as required for evaluation. Study investigators assessed the severity of the worsening symptoms to determine the need for additional treatment. If additional treatment beyond blinding study medication or short-acting bronchodilators was required, investigators were instructed to treat the exacerbation with a course of antibiotics and/or oral corticosteroids. Courses of antibiotics were to be 7—14 days in duration with provisions allowed for additional courses if first line treatment failed. Use of antibiotics for treatment of upper or lower respiratory tract infections was not considered an exacerbation unless accompanied by worsening symptoms of COPD. Courses of oral corticosteroids were not to exceed 14 days unless given approval by the study sponsor. Any course of antibiotics or oral corticosteroids starting within 7 days of the stop date for a previous course was considered treatment of a single exacerbation.

Health status was evaluated using the St. George's Respiratory Questionnaire administered at study visits at day 1, and weeks 12, 28, and 52.[18] Safety was assessed by adverse event reporting.

Statistical analysis

Statistical analyses were performed using SAS version 8.2 software in a UNIX reporting environment. The primary analysis of the rate of moderate to severe exacerbations compared treatment groups using a negative binomial regression model. The negative binomial regression model including terms for baseline disease severity, investigator, reversibility stratum, treatment group and time on treatment, incorporated modeling of the variability between subjects in the estimation of exacerbation rates, thereby reducing bias caused by study withdrawals.[19]

The planned enrollment for this study ($N = 740$) provided 90% power to detect a >20% reduction in the rate of moderate/severe exacerbations in the FSC 250/50 treatment group compared with the salmeterol treatment group at the 0.05 significance level using unadjusted annual exacerbation rate estimates of 1.9 and 1.5 for salmeterol and FSC 250/50, respectively. Time to first moderate to severe exacerbation was summarized by treatment group and presented graphically with Kaplan—Meier curves. The hazard ratio for the treatment comparison of time to first moderate to severe exacerbation was derived from a Cox's proportional hazards model with terms for baseline disease severity, investigator, reversibility stratum and treatment group in the model. Time to each moderate to severe exacerbation was compared between treatment groups using an Anderson—Gill model for time to recurrent events.

The primary analysis of pre-dose AM FEV_1 was mean change from baseline compared between treatment groups at endpoint. Endpoint was defined as the last scheduled measurement of pre-dose AM FEV_1 during the 52-week treatment period and baseline was defined as the pre-dose AM FEV_1 measure from day 1 (randomization). An analysis of covariance (ANCOVA) model including terms for treatment group, investigator, reversibility stratum and baseline was used to test statistical differences between treatment groups. An ANCOVA model was also used to test statistical differences in treatment group mean changes from baseline for the overall 52-week treatment period for shortness of breath scores and values for supplemental albuterol use and nighttime awakenings due to COPD.

Results

Patients

Of the 1262 patients screened, 480 were excluded at screening or during run-in, and 782 were randomized of whom 516 (66%) completed the study (Fig. 1). The efficacy and health outcomes data for 6 patients from one investigational site were unevaluable due to poor clinical practices and were excluded from the analysis. Exclusion of these data did not affect the efficacy analyses. A total of 277 of 394 (70%) patients in the FSC 250/50 group completed the study compared with 239 of 388 (62%) patients in the salmeterol group. The probability of subjects withdrawing from the study during the 52-week treatment period is shown in Fig. 2. At week 13, a total of 70 (18%) subjects were withdrawn from the salmeterol group compared with 36 (9%) subjects in the FSC 250/50 group. Thereafter, the difference in the percentage of subjects who were withdrawn from the study was similar between groups. The probability of withdrawing from the study at any time was significantly greater in the salmeterol group compared with FSC 250/50 ($p = 0.003$). The most common reasons for withdrawal in the FSC 250/50 and salmeterol groups were patient decision to withdraw (9% and 10%) and adverse event (7% and 9%). Demographic data, smoking history and baseline lung function values, and prior medication use were similar between groups (Table 1). Patients were predominately white (93%)

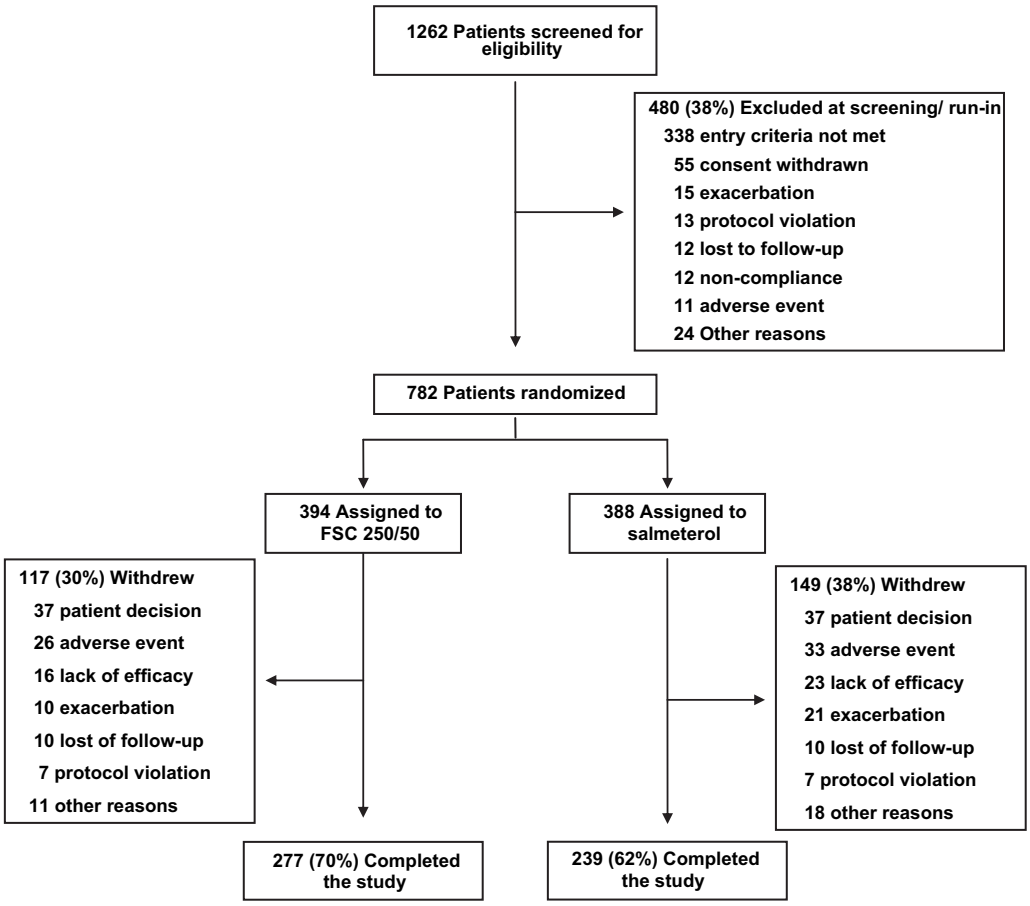

Figure 1 Study flow diagram.

with severe airway obstruction (mean pre-albuterol FEV_1 of 32.8% of predicted normal) and the majority (56%) were using inhaled corticosteroids or an inhaled corticosteroid/long-acting $beta_2$-agonist combination at screening.

COPD exacerbations

The mean annual rate of moderate to severe exacerbations with FSC 250/50 treatment was 1.06 per patient compared

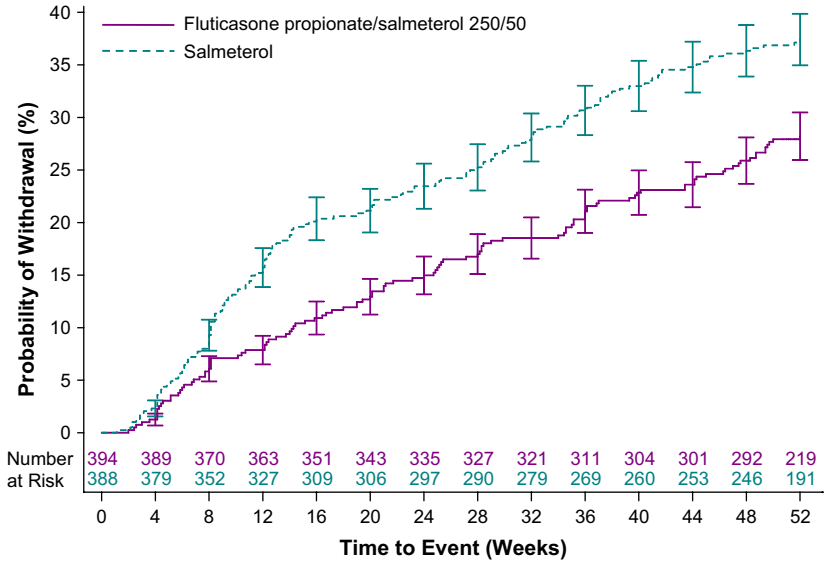

Figure 2 Kaplan–Meier estimates of probability of study withdrawal. Solid line represents FSC 250/50; dashed line represents salmeterol. $p = 0.003$ for comparison of FSC 250/50 with salmeterol.

Table 1 Demography and baseline characteristics

Characteristic	FSC 250/50 ($N = 394$)	Salmeterol ($N = 388$)
Age, years	64.9 ± 9.0	65.0 ± 9.1
Male, %	58	52
Race, %		
White	94	93
Black	4	6
Other	2	1
Body mass index, kg/m^2	27.3 ± 6.2	27.7 ± 7.4
Current smoker, %	40	38
Smoking history, pack-years	58.5 ± 30.6	54.4 ± 25.7
Pre-bronchodilator FEV_1, L	0.95 ± 0.36	0.93 ± 0.35
Pre-bronchodilator FEV_1, % predicted	32.8 ± 11.0	32.8 ± 10.1
Post-bronchodilator FEV_1, L	1.15 ± 0.47	1.15 ± 0.54
Post-bronchodilator FEV_1, % predicted	39.8 ± 13.9	40.6 ± 15.4
Albuterol responsive/non-responsive, %	42/58	41/59
Pre-bronchodilator FVC, L	2.16 ± 0.75	2.14 ± 0.75
Pre-bronchodilator FEV_1/FVC	0.44 ± 0.11	0.44 ± 0.11
Previous medication use, %		
Ipratropium	8	10
Ipratropium/albuterol combination	33	31
Tiotropium	14	10
Short-acting beta$_2$-agonists	48	45
Long-acting beta$_2$-agonists	12	11
Long-acting beta$_2$-agonists/inhaled corticosteroid combination	42	40
Inhaled corticosteroids	15	18
Theophylline	6	8
Anti-leukotrienes	5	4

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; L, liters; FSC 250/50, fluticasone propionate/salmeterol 250/50 twice daily. All values are presented as absolute numbers or means ± SD.

with 1.53 per patient with salmeterol ($p < 0.001$), corresponding to a treatment ratio of 0.695 (95% CI 0.58—0.83) and a 30.5% reduction in the mean annual rate of exacerbations (Table 2). A total of 54% and 60% of patients experienced at least 1 moderate/severe exacerbation over the duration of the study in the FSC 250/50 and salmeterol groups, respectively (Table 2). For the mean annual rate of exacerbations requiring oral corticosteroids, the treatment ratio for FSC 250/50 compared with salmeterol was 0.603, representing a 40% reduction with FSC 250/50 treatment ($p < 0.001$, Table 2). The mean annual rate of all exacerbations (mild plus moderate to severe) was significantly lower with FSC 250/50 treatment (treatment ratio of 0.83, $p = 0.002$, Table 2).

The time to first moderate to severe exacerbation was significantly delayed in patients treated with FSC 250/50 compared with salmeterol, with a hazard ratio of 0.75, corresponding to a risk reduction of 25% (95% CI 0.62—0.91, $p = 0.003$, Fig. 3). FSC 250/50 also significantly lowered the risk of experiencing recurrent exacerbations by 25% compared with salmeterol (hazard ratio 0.75, 95% CI 0.63—0.88, $p < 0.001$).

The mean duration of all moderate to severe exacerbations was similar (23.0 and 21.3 days in the FSC 250/50 and salmeterol groups, respectively) as was the mean recovery time (ranging from 16.2 to 25.7 days for both treatment groups).

The most commonly reported cause of exacerbation, as identified by investigators, was respiratory infection of the upper or lower airways, reported for 49% of all moderate to severe exacerbations. Additional causes were unknown etiology (26%), environmental factors of air pollution, tobacco smoke, and cold air (6%), allergy (5%), use of non-steroidal anti-inflammatory medications (3%), withholding COPD medications (2%), stress/emotions (2%), and other (7%).

Lung function

During run-in, treatment with open-label FSC 250/50 significantly increased mean morning FEV_1 from screening levels (increases of 114 ± 15 mL and 118 ± 16 mL, in patients subsequently randomized to FSC 250/50 and salmeterol, respectively, $p < 0.001$ for within group change from screening, Fig. 4). Following randomization, pre-dose FEV_1 decreased over the 52-week treatment period in both groups. The decrease in FEV_1 was significantly larger in the salmeterol group (−82 ± 17 mL, $p < 0.001$ for within group change from treatment day 1) compared with the FSC 250/50 group (−12 ± 23 mL, $p = 0.592$, for within group change from treatment day 1). Mean differences in pre-dose FEV_1 of

Table 2 COPD exacerbations

	FSC 250/50 ($N = 391$)		Salmeterol ($N = 385$)
Patients with ≥1 moderate/severe exacerbation, *n* (%)	211 (54)		230 (60)
Total number of moderate/severe exacerbations	368		432
Mean annual rate of moderate/severe exacerbations	1.06		1.53
Treatment ratio for FSC 250/50 vs. salmeterol		0.695	
95% confidence interval		0.58, 0.83	
p-value		<0.001	
Patients with ≥1 OCS-treated exacerbation, *n* (%)	150 (38)		166 (43)
Total number of OCS-treated exacerbations	231		289
Mean annual rate of OCS-treated exacerbations	0.66		1.09
Treatment ratio for FSC 250/50 vs. salmeterol		0.603	
95% confidence interval		0.47, 0.77	
p-value		<0.001	
Patients with any exacerbations (mild and moderate/severe)	343 (88)		335 (87)
Total number of all exacerbations	1590		1618
Mean annual rate of all exacerbations	4.82		5.78
Treatment ratio for FSC 250/50 vs. salmeterol		0.833	
95% confidence interval		0.74, 0.94	
p-value		0.002	

OCS, oral corticosteroids; FSC 250/50, fluticasone propionate/salmeterol 250/50 twice daily; moderate/severe exacerbations, worsening symptoms requiring treatment with OCS, antibiotics, and/or hospitalization; mild exacerbations, worsening symptoms that were self-managed by patient and did not require OCS or antibiotic treatment.

47 ± 23 mL and 74 ± 27 mL at endpoint and week 52, respectively, significantly favored FSC 250/50 over salmeterol ($p \leq 0.04$).

Supplemental albuterol use

Mean baseline use of supplemental albuterol was 4.7 ± 0.23 and 5.0 ± 0.24 puffs per day for patients randomized to FSC 250/50 and salmeterol, respectively. Over weeks 1—52, salmeterol-treated patients had a significantly larger mean increase in supplemental albuterol use (0.8 ± 0.13 puffs/day) compared with FSC 250/50 treated patients (0.4 ± 0.12 puffs/day, $p = 0.009$).

Patients' symptoms

Shortness of breath

Increases in dyspnea scores were significantly greater with salmeterol than with FSC 250/50. Diary dyspnea scores increased by 0.12 ± 0.03 and 0.21 ± 0.03 units over weeks 1—52 with FSC 250/50 and salmeterol, respectively, representing a mean difference of 0.10 ± 0.03 units, $p = 0.001$).

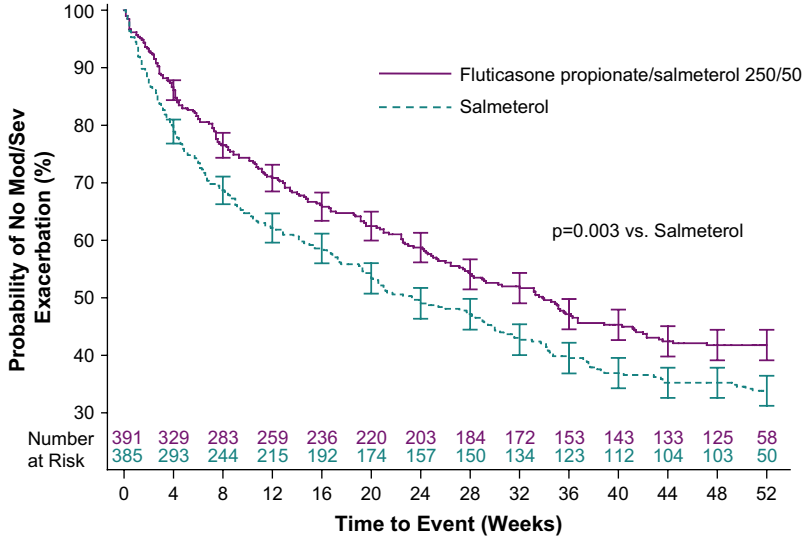

Figure 3 Kaplan—Meier estimates of the time to first moderate to severe COPD exacerbation. Solid line represents FSC 250/50; dashed line represents salmeterol.

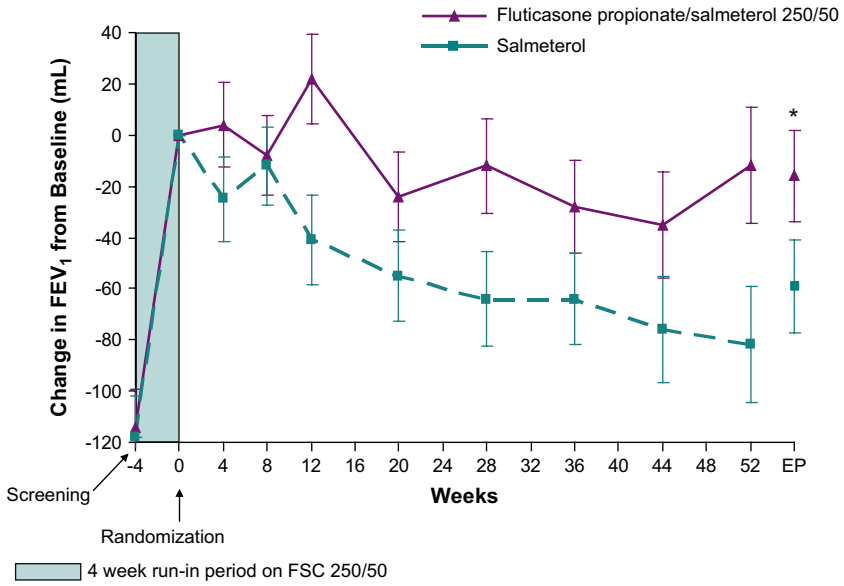

Figure 4 Change from baseline (randomization) for morning pre-dose FEV_1 compared with screening, over the 52-week treatment period, and at endpoint. *$p = 0.04$, FSC 250/50 vs. salmeterol at endpoint. EP, endpoint.

Nighttime awakenings

The *a priori* analysis of nighttime awakenings due to COPD was for the subset of symptomatic subjects that reported at least one nighttime awakening during the 7 days prior to randomization. At baseline, 151 (39%) and 152 (39%) subjects in the FSC 250/50 and salmeterol groups, respectively, reported a nighttime awakening due to COPD with mean values of 6.72 ± 0.49 and 5.95 ± 0.47 awakenings per week. FSC 250/50 treatment significantly decreased the mean number of nighttime awakenings by -1.12 ± 0.35 awakenings per week compared with an increase of 0.42 ± 0.37 awakenings per week in the salmeterol group (mean difference of -1.33 awakenings per week, $p = 0.009$).

Health-related quality of life

In both treatment groups, there was a worsening in mean SGRQ total score from baseline to endpoint with a significantly larger change in the salmeterol group (3.49 units) compared with the FSC 250/50 group (1.86 units, mean difference of -1.86 units, $p = 0.035$). The change from baseline in SGRQ score observed for the treatment groups and the mean difference in score between groups did not meet the threshold of 4 units defined as a clinically meaningful difference.[18] Mean differences between FSC 250/50 and salmeterol for domain scores were -2.8 ± 1.39 for symptoms ($p = 0.045$), -1.96 ± 1.05 for impacts ($p = 0.063$), -1.64 ± 1.01 for activity ($p = 0.104$).

Safety

Adverse events were reported for a similar percentage of subjects in the FSC 250/50 (88%) and salmeterol (86%) groups. The most common adverse events across both groups were nasopharyngitis and pharyngolaryngeal pain which occurred in a similar percentage of subjects in each group (35—38% of subjects). Adverse events that occurred in greater than 5% of subjects in any group are reported in Table 3.

A total of 22% and 20% of patients experienced non-fatal serious adverse events in the FSC 250/50 and salmeterol groups, respectively. The most common serious adverse event was worsening COPD which occurred in 9% and 10% of subjects in the FSC 250/50 and salmeterol groups, respectively. There were 6 deaths in the FSC 250/50 group and 3 deaths in the salmeterol group.

Pneumonias were more commonly reported in the FSC 250/50 group, reported in 29 (7%) subjects treated with FSC

Table 3 Adverse events reported for >5% of patients in either group

Adverse event	FSC 250/50 ($N = 394$)	Salmeterol ($N = 388$)
Any event, *n* (%)	347 (88)	334 (86)
Nasopharyngitis	151 (38)	141 (36)
Pharyngolaryngeal pain	137 (35)	138 (36)
Pyrexia	74 (19)	68 (18)
Headache	45 (11)	46 (12)
COPD	38 (10)	46 (12)
Rhinorrhea	39 (10)	45 (12)
Nasal congestion	34 (9)	36 (9)
Upper respiratory tract infection	31 (8)	31 (8)
Pneumonias	29 (7)	15 (4)
Diarrhea	24 (6)	25 (6)
Back pain	23 (6)	23 (6)
Sinusitis	28 (7)	17 (4)
Cough	14 (4)	25 (6)

FSC 250/50, fluticasone propionate/salmeterol 250/50 twice daily.

250/50 compared with 15 (4%) subjects in the salmeterol group. Serious adverse events of pneumonia were experienced by 19 (5%) and 10 (3%) of subjects in the FSC 250/50 and salmeterol groups, respectively. Adverse events of dysphonia and candidiasis-related events were reported for a larger percentage of subjects in the FSC 250/50 group (4% for each) than in the salmeterol group (<1% and 2%, respectively). The incidence of eye and bone disorders was low (1−3%) and reported for a similar number of subjects in both treatment groups.

Discussion

We found that treatment with FSC 250/50 for 1 year significantly reduced the annual rate of moderate to severe COPD exacerbations by 30.5% compared with salmeterol. This finding was consistent with secondary assessments that showed a significantly lower annual rate of exacerbations requiring oral corticosteroids and a significantly lower risk of time to first moderate to severe exacerbation with FSC 250/50 compared with salmeterol. To account for individual variation in event rate, the negative binomial analysis was used for analysis of exacerbation rate data.[19,20] Finally, pre-dose FEV_1 and symptoms scores for dyspnea were better maintained with FSC 250/50 compared with salmeterol over the 1-year treatment period.

The findings of this study must be evaluated in the context of the study design where the patients enrolled were treated with FSC 250/50 for 4 weeks prior to randomization, resulting in withdrawal of FP for patients randomized to salmeterol. The purpose of the run-in with FSC 250/50 was to standardize treatment prior to randomization in an attempt to minimize the likelihood of exacerbations during run-in related to suboptimal therapy. Additionally, this design was used to emphasize the contribution of FP to the effect of FSC 250/50 on exacerbations by comparison with salmeterol. Previous studies have shown that withdrawal of an inhaled corticosteroid has been associated with an increase in exacerbation rate, a significantly greater risk of time to first and worsening of pulmonary function and symptoms.[21,22] Indeed, the rapid separation between treatment arms for time to first moderate to severe exacerbation occurred early in this study indicating an increased risk of exacerbation following FP withdrawal (Fig. 3). Importantly, the difference between treatments for the probability of experiencing an exacerbation remained consistent throughout the study demonstrating maintenance of effect for FSC 250/50 compared with salmeterol.

Additional analyses indicate that the lower exacerbation rates with FSC 250/50 were not simply due to an inhaled corticosteroid (ICS) withdrawal effect at the start of the study. Indeed, the annual rate of moderate to severe exacerbations was lower with FSC 250/50 compared with salmeterol even when exacerbations which would more likely be due to ICS withdrawal (i.e. those occurring in the first 4 or 8 weeks) were excluded (treatment rate ratios of 0.727, $p < 0.001$ and 0.751, $p = 0.005$, respectively). In addition, exacerbation rate treatment ratios remained significantly in favor of FSC 250/50 for the subset of patients not using inhaled corticosteroids at screening (lower likelihood of exacerbations being due to ICS withdrawal) (0.740, $p = 0.028$) and in those patients using inhaled corticosteroids at screening (higher risk for ICS withdrawal causing exacerbations) (0.648, $p < 0.001$).

Other longer term studies have demonstrated the benefit of FSC at a dose of 500/50 (the higher dose is not currently approved for use in COPD in the US) on exacerbations, each with different study designs.[9−11] For example, in a 3-year study of COPD patients with an FEV_1 of <60% predicted and with no requirement of a history of COPD exacerbations, FSC 500/50 significantly reduced the annual rate of moderate to severe exacerbations compared with placebo, salmeterol, and FP[10] and in a 1-year study of patients of similar severity to the present study (i.e., post-bronchodilator FEV_1 of <50% with a history of exacerbations) the exacerbation rate was 35% lower with FSC 500/50 compared with salmeterol.[11] In two 6-month studies, treatment with FSC 250/50 or 500/50 was not shown to reduce COPD exacerbations[12,23] However, these studies did not enroll patients at higher risk for exacerbation, as they were not required to have a history of exacerbations and exacerbation rates could not be assessed since patients who received systemic steroids for an exacerbation were withdrawn. Comparison of the exacerbation findings from the present study with previous studies, particularly with regard to dose response, is limited due to differences in study design. Additionally, the effect of FSC 250/50 on exacerbations in less severe patients requires future study.

Chronic inflammation in the lung is a well-established characteristic of COPD that is present at all levels of disease severity, leading to disease pathology and progression.[1,2,24] The understanding of COPD-related inflammation has been expanding to include the presence of systemic inflammation and exacerbations are associated with further acute increases in both airway and systemic inflammation.[25,26] Bacterial and viral respiratory tract infections are associated with the majority of COPD exacerbations[27] which is consistent with our study where respiratory infection was identified as the most common cause of moderate to severe exacerbations. Infections of the respiratory tract are thought to be key precipitating events for exacerbations leading to increased airway neutrophils and eosinophils.[27,28] FSC treatment has been shown to have antiinflammatory effects in COPD[29,30] which may provide a potential mechanism for the reduction in exacerbations observed in our study. However, the clinical relevance of any effects of FSC 250/50 on COPD-related inflammation has not been established.

The incidence of pneumonia-related events was higher in the FSC 250/50 group (7%) compared with the salmeterol group (4%). These findings confirm previous studies of 1−3 years showing an increased incidence of pneumonias with use of FSC 500/50 and FP 500 μg twice daily for COPD when compared with salmeterol and placebo.[10,11] Although limited by study design, a recent retrospective population-based cohort study has suggested that, as a class, inhaled corticosteroid use in patients with COPD may be associated with an increased risk of hospitalization for pneumonia.[31,32] The comparative risk of pneumonia between FSC 250/50 and 500/50 is unknown since there are no studies that directly compare the two strengths and due to differences in study design and methodology for determining pneumonia across individual studies. Additional

prospective studies using objective pneumonia definitions and detailed clinical, microbiological, and imaging evaluations are required to further characterize the risk of pneumonia with FSC in COPD.

The overall incidence of adverse events during treatment was high, as expected for a study of 1 year in a severe patient population, and the number of subjects with adverse events was similar between groups. The incidence of known local side effects of inhaled corticosteroids such as oral candidiasis and dysphonia occurred more frequently with FSC 250/50 than salmeterol. Systemic effects of FSC 250/50 were not apparent based on a similar incidence of adverse events related to eye and bone disorders in the FSC 250/50 and salmeterol groups.

In summary, this is the first study specifically designed to evaluate the effect of FSC 250/50 μg twice daily on exacerbations of COPD. Long-term treatment with FSC 250/50 was shown to result in a significantly lower annual rate of moderate to severe exacerbations compared with the long-acting beta-agonist salmeterol in patients with severe COPD with a history of exacerbations. Additionally, a higher incidence of reported pneumonia was observed with fluticasone propionate/salmeterol 250/50 than salmeterol. This study provides further information on the effectiveness and safety of FSC 250/50 for the treatment of COPD.

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Conflict of interest statement

Drs Ferguson, Anzueto and Fei have received research grants from and are speaker bureau members for GlaxoSmithKline. Drs Ferguson and Anzueto are advisory board members for GlaxoSmithKline. A. Emmett, Dr Knobil and Dr Kalberg are employees of GlaxoSmithKline.

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