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Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients

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Lung function

Summary
Background: Fluticasone furoate/vilanterol (FF/VI) is an inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA), recently approved as once-daily maintenance therapy for COPD. We compared the lung function effects of FF/VI with those of twice-daily fluticasone propionate/salmeterol (FP/SAL).
Methods: Three 12 week studies comparing FF/VI and FP/SAL were conducted. Patients aged ≥40 years with moderate-to-very severe COPD were randomized to receive double-blind, double-dummy FF/VI 100/25 mcg once-daily, or FP/SAL 250/50 mcg twice-daily for 12 weeks following a 2 week placebo run-in period. The primary endpoint of each study was change from baseline trough in 0–24 h weighted mean FEV_1 ($wmFEV_1$) on Day 84. Safety was also assessed.
Results: In Study 1 (HZC113109) (intent-to-treat *n*: FF/VI = 260; FP/SAL = 259), the increase from baseline in 0–24 h $wmFEV_1$ was significantly greater with FF/VI than FP/SAL (Δ80 mL, $P < 0.001$). In Study 2 (HZC112352) (intent-to-treat *n*: FF/VI = 259; FP/SAL = 252) and Study 3 (RLV116974) (intent-to-treat *n*: FF/VI = 412; FP/SAL = 416), the increase from baseline in 0

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−24 h wmFEV$_1$ was not significantly greater with FF/VI than FP/SAL (Δ29 mL, $P = 0.267$; Δ25 mL, $P = 0.137$). The treatment difference was statistically but not clinically significant in a pooled analysis (Δ41 mL, $P < 0.001$). Pooled adverse events (FF/VI 27%; FP/SAL 28%) and serious adverse events (FF/VI 2%; FP/SAL 3%) were similar between treatments.
Conclusions: Our data suggest that once-daily FF/VI 100/25 mcg provides FEV$_1$ improvement in COPD that is at least comparable with that conferred by twice-daily FP/SAL 250/50 mcg, although interpretation is limited by differences in individual study outcomes. The safety profiles of FF/VI 100/25 mcg and FP/SAL 250/50 mcg are similar.
Clinical trial registration: clinicaltrials.gov: NCT01323634; NCT01323621; NCT01706328. GlaxoSmithKline study codes: HZC113109; HZC112352; RLV116974.

Introduction

The 2014 update of the Global Initiative for Obstructive Lung Disease (GOLD) strategy document recommends combined inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) as possible maintenance therapy for COPD patients with severe or very severe airflow limitation (% FEV$_1$ < 50%) and for those with ≥2 exacerbations (or ≥1 exacerbation requiring hospitalization) in the prior year [1]. These recommendations are informed by numerous studies demonstrating the benefits of ICS/LABA versus LABA alone on exacerbation rate and lung function in moderate-to-very severe COPD [2–4].

Previously, ICS/LABA combination therapies were all dosed twice-daily, as compared with long-acting muscarinic antagonist and LABA monotherapy, which are available as once-daily or twice-daily therapies. Dosing frequency has been suggested to influence adherence to therapy [5], though it is not the sole factor [6]. It is also known that poor adherence (even in the setting of a clinical trial) is associated with adverse outcomes [7].

Fluticasone furoate/vilanterol (FF/VI) is a new ICS/LABA combination with a once-daily dosing profile. The steroid component (FF) has greater *in vitro* anti-inflammatory activity than fluticasone propionate (FP) [8], while VI has superior selectivity for the β_2-receptor than other once-daily LABAs [9]. Once-daily FF/VI at the 100/25 mcg strength was recently approved in the United States, Canada and Europe for the long-term maintenance treatment of patients with COPD. FF/VI 100/25 has previously been shown to improve lung function versus placebo, FF alone and VI alone over 24 weeks of treatment [10,11]. In addition, FF/VI 100/25 improves lung function and reduces exacerbations versus VI alone over 52 weeks [12]. The present analysis describes the results of three 12 week studies that compared the lung function effects of once-daily FF/VI 100/25 mcg and twice-daily FP/salmeterol (SAL) 250/50 mcg, in patients with moderate-to-very severe COPD. Though the approved dose of FP/SAL in the EU is 500/50 mcg, the 250/50 mcg dose used in these trials represents the only approved strength for the treatment of COPD in the United States and Canada.

We hypothesized that the 0–24 h weighted mean (wm) for FEV$_1$ would be greater with FF/VI 100/25 mcg than with FP/SAL 250/50 mcg.

Methods

Further methodological details are provided in the Online Supplemental Material.

Patients and ethics

The studies were similar in design and conduct. At screening, patients (male or female) were ≥40 years of age with a clinical history of COPD as defined by ATS/ERS criteria [13], post-albuterol FEV$_1$/forced vital capacity (FVC) ratio of ≤0.70 and FEV$_1$ ≤70% of that predicted using NHANES III equations [14] and had a ≥10 pack-year history of cigarette smoking. Exacerbation frequency was not a study entry criterion. Patients with a current diagnosis of asthma were excluded. All patients provided informed consent. The studies were approved by local or central ethics review committees, and were conducted in accordance with the Declaration of Helsinki [15] and Good Clinical Practice [16] guidelines.

Study design

These were 12 week, randomized, multi-center, double-blind, double-dummy, parallel-group, comparative studies. Study 1 was conducted between March 18 and December 14 2011 at 51 centers in six countries (Czech Republic, Germany, Poland, Romania, Russia, United States). Study 2 was conducted between March 18 2011 and January 26 2012 at 48 centers in five countries (Italy, South Africa, Spain, Ukraine, United States). Study 3 was conducted between October 15 2012 and June 17 2013 at 68 centers in five countries (Germany, Romania, Russia, Ukraine, United States).

In each study, eligible patients entered a 2 week, single-blind, placebo run-in period and, providing they met the continuation criteria, were randomized (1:1) to FF/VI 100/25 mcg once-daily in the morning via the ELLIPTA® dry powder inhaler[1] (the strength of 100/25 mcg represents an emitted dose from the dry powder inhaler of 92 mcg of FF

[1] ELLIPTA® is a trademark of the GSK group of companies.

and 22 mcg of VI), or FP/SAL 250/50 mcg twice-daily via Diskus/Accuhaler™ for 12 weeks. Patients were stratified by reversibility (increase in FEV_1 of $\geq$12% and $\geq$200 mL of the pre-dose value 10–15 min after four inhalations of albuterol) and assigned to study treatment – in accordance with a randomization schedule generated by the sponsor using a validated computerised system (RandAll; GlaxoSmithKline, UK) – using the Registration and Medication Ordering System (RAMOS; GlaxoSmithKline, UK), an automated, interactive telephone-based system. Compliance with study treatment was assessed by reviewing the dose counters on the inhalers.

Open-label albuterol was supplied to patients for symptomatic relief during the study. Stable-dose ipratropium and mucolytics were permitted, as was oxygen therapy for $\leq$12 h per day.

Efficacy assessment

The primary efficacy endpoint was the difference between treatment groups in change from baseline trough in 0–24 h weighted mean FEV_1. This weighted mean FEV_1 is determined by calculating the area under the curve (AUC) during the 24 h post-dose interval and then dividing that value by 24 h. While results for FEV_1 AUC are typically described in L*hr or mL*hr, this weighted mean approach allows the results to be presented as a single FEV_1 value. Baseline trough FEV_1 was the mean of two assessments of FEV_1 made 30 min and 5 min pre-dose on Day 1 (i.e., at the end of the run-in period). On Day 84, $wmFEV_1$ was calculated from measures taken 5 min pre-dose then 5, 15, 30, 60 min and 2, 4, 6, 8, 12, 13, 14, 16, 20 and 24 h post-dose. The secondary efficacy endpoint was time to onset of action on Day 1 (defined as the time to an increase in FEV_1 of 100 mL from baseline over the first 4 h post-dose). An additional secondary endpoint of change from baseline trough FEV_1 after 12 weeks was included for Study 3. Other efficacy endpoints were change from baseline in FVC on Day 84, the proportion of patients demonstrating a 100 mL increase in FEV_1, and (in Studies 1 and 2 only) pre-dose inspiratory capacity (IC) at Day 84 and rescue (albuterol) use.

Safety assessment

Safety and tolerability were assessed by the incidence of adverse events (AEs) and serious AEs (SAEs), coded using the Medical Dictionary for Regulatory Activities. AEs of special interest were pre-defined as those often associated with either ICS or LABA therapy. COPD exacerbations, pneumonias, oropharyngeal examinations, clinical chemistry and hematology assessments, vital signs and electrocardiogram measurements were also recorded.

Statistical analysis

The primary endpoint of 0–24 h $wmFEV_1$ was analyzed in each study using an analysis of covariance, with baseline pre-bronchodilator FEV_1, reversibility, smoking status, country, and treatment as covariates. The secondary endpoint of time to onset was analyzed by log-rank analysis, stratified by reversibility. A P-value <0.05 for the primary endpoint was required in order to allow statistical significance to be inferred for secondary and other endpoints. For this reason, P-values are presented only for comparisons from which statistical significance can be inferred; otherwise, point estimates and 95% confidence intervals (CI) are presented. No such procedure was employed in the post-hoc analysis of the pooled data.

Sample size calculations for all three studies were based on the primary endpoint. Based on prior studies of VI [17] and a putative minimal clinically important difference for trough FEV_1 of 100 mL [18], each study was designed to test for a 60 mL difference in 0–24 h $wmFEV_1$ between FF/VI and FP/SAL using a two-sided 5% significance level, assuming a standard deviation (SD) of 190 mL for Studies 1 and 2. The observed SD for those studies was approximately 240 mL, which was therefore used as the assumed SD for Study 3. To provide 90% power to detect a 60 mL treatment difference (see Supplemental Material), assuming a drop-out rate of 15%, 250 patients per treatment arm were planned to be randomized in Studies 1 and 2 to achieve a sample size of 212 evaluable patients in each arm, and 400 patients per treatment arm were planned to be randomized in Study 3 to achieve a sample size of 338 evaluable patients per arm.

Results

Patient characteristics

Of 2465 patients screened across the three studies, 1858 were randomized (Fig. 1; Fig. E1). Patients were well matched between studies and study arms (Table E1). Lung function at screening and baseline demonstrated, on average, severely impaired airflow (Table 1). Ninety-one percent of randomized patients completed treatment; the primary reasons for withdrawal in both treatment arms were adverse event and withdrawal of consent. Mean compliance with treatment was $\geq$97% in both treatment arms in all three studies.

Efficacy: primary outcome

Improvements in 0–24 h $wmFEV_1$ were seen with both FF/VI 100/25 mcg and FP/SAL 250/50 mcg compared with baseline trough in all three studies and in the pooled analysis (Table 2). In Study 1, the treatment difference between FF/VI and FP/SAL was statistically significant (80 mL; $P < 0.001$). In Studies 2 and 3, respectively, the difference (29 mL; 25 mL) were not significant ($P = 0.267$; $P = 0.137$; Table E2). In the pooled analysis of all three studies, a small but statistically significant treatment difference of 41 mL ($P < 0.001$) was found (Table 2). The absence of significance for the primary treatment comparison in Studies 2 and 3 meant that significance could not be inferred for the other endpoints in these studies (analysis of pooled data was performed post hoc and was not subject to any testing hierarchy). $wmFEV_1$ over 0–4 h, 0–12 h and 12–24 h post-dose on Day 84 showed significant differences between FF/VI and FP/SAL on all measures in Study 1, and at 0–4 h and 0–12 h in the pooled analysis. Data obtained from the comparison of FEV_1 measures recorded over all three

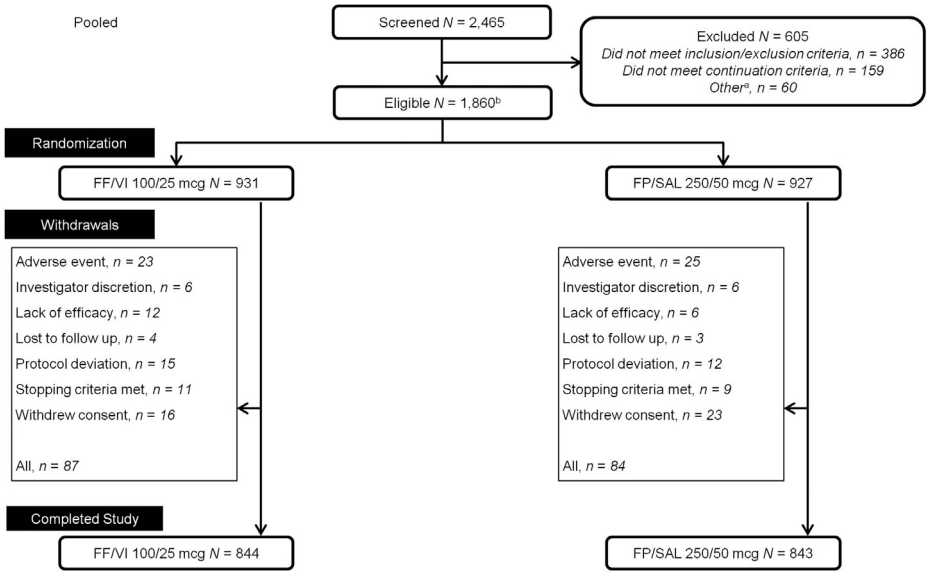

Figure 1 CONSORT flowchart for pooled data. Flowcharts for individual Studies 1–3 are provided in Online Supplement. [a]Comprised: withdrew consent ($n = 34$), investigator discretion ($n = 16$), adverse event ($n = 5$), lost to follow-up ($n = 3$), protocol deviation ($n = 2$). [b]Two patients in Study 1 were randomized but did not receive any double-blind study medication and were therefore not included in the ITT population. FF = fluticasone furoate; FP = fluticasone propionate; ITT = intent-to-treat; SAL = salmeterol; VI = vilanterol.

studies over 24 h on Day 84 suggest that FF/VI is at a minimum comparable with FP/SAL on lung function (Fig. 2; Fig. E2).

Efficacy: secondary endpoints

Median time to onset (≥100 mL from baseline) ranged from 15 to 16 min for FF/VI and 15–30 min for FP/SAL across the three studies. For the pooled data, median time to onset was 15 min for FF/VI and 19 min for FP/SAL (Fig. 3). Differences in time to onset were statistically significant in Study 1 ($P = 0.012$) and the pooled data ($P = 0.018$) only.

In Study 3, there was no statistically significant improvement in trough FEV_1 between the FF/VI treatment group and the FP/SAL treatment group ($P = 0.089$) after 12 weeks of treatment (Table 2).

Table 1 Demographic and clinical characteristics of the pooled intent-to-treat population.

	Pooled data	
	FF/VI 100/25 mcg $n = 931$	FP/SAL 250/50 mcg $n = 927$
Demographics		
Age, years: mean (SD)	61 (9)	61 (9)
Sex, *n* (%): male	646 (69)	630 (68)
Race, *n* (%): white	899 (97)	898 (97)
BMI, kg/m^2: mean (SD)	27 (6)	27 (6)
COPD duration < 10 yrs, *n* (%)	663 (71)	673 (73)
Current smoker, *n* (%)	496 (53)	522 (56)
Pack-years, mean (SD)	42 (23)	42 (23)
Screening lung function (before 2 week placebo run-in)		
Post-bronchodilator FEV_1, L mean (SD)	1.49 (0.49)	1.48 (0.47)
Post-bronchodilator FEV_1, % mean (SD)	48 (12)	48 (12)
Post-bronchodilator FEV_1 reversibility, % mean (SD)	11 (13)	12 (13)
Reversible to albuterol, *n* (%)	246 (26)	261 (28)
Post-bronchodilator FEV_1/FVC, L mean (SD)	0.51 (0.10)	0.50 (0.10)
Baseline lung function (pre-dose on Day 1 of randomization)		
Pre-bronchodilator FEV_1, L mean (SD)	1.35 (0.50)	1.33 (0.48)
Pre-bronchodilator FEV_1, % mean (SD)	44 (14)	43 (13)

Data for individual Studies 1–3 are provided in the Online Supplement.
BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FF = fluticasone furoate; FP = fluticasone propionate; FVC = forced vital capacity; SAL = salmeterol; SD = standard deviation; VI = vilanterol.

Table 2 Efficacy assessments in individual studies and pooled analysis (intent-to-treat population). FF/VI dosed at 100/25 mcg; FP/SAL dosed at 250/50 mcg.

	Study 1		Study 2		Study 3		Pooled data	
	FF/VI $n = 260$	FP/SAL $n = 259$	FF/VI $n = 259$	FP/SAL $n = 252$	FF/VI $n = 412$	FP/SAL $n = 416$	FF/VI $n = 931$	FP/SAL $n = 927$
Wm (0–24 h) FEV_1, mL on Day 84								
LS mean change from baseline (SE)	174 (15)	94 (16)	142 (18)	114 (18)	168 (12)	142 (12)	162 (9)	122 (9)
LS mean treatment difference (95% CI)	80 (37, 124)	$P < 0.001$	29 (−22, 80)	$P = 0.267$[a]	25 (−8, 59)	$P = 0.137$[a]	41 (17, 65)	$P < 0.001$
Wm (0–4 h) FEV_1, mL on Day 84								
LS mean change from baseline (SE)	235 (16)	162 (16)	208 (17)	167 (17)	230 (12)	201 (12)	225 (8)	181 (8)
LS mean treatment difference (95% CI)	73 (30, 117)	$P < 0.001$	42 (−7, 90)		29 (−4, 62)		44 (21, 67)	$P < 0.001$
Wm (0–12 h) FEV_1, mL on Day 84								
LS mean change from baseline (SE)	217 (16)	121 (16)	181 (18)	128 (18)	206 (12)	161 (12)	202 (9)	141 (9)
LS mean treatment difference (95% CI)	96 (51, 141)	$P < 0.001$	53 (2, 104)		46 (12, 79)		61 (37, 85)	$P < 0.001$
Wm (12–24 h) FEV_1, mL on Day 84								
LS mean change from baseline (SE)	131 (16)	66 (16)	104 (19)	101 (19)	129 (13)	123 (13)	122 (9)	102 (9)
LS mean treatment difference (95% CI)	65 (21, 109)	$P = 0.004$	3 (−50, 56)		6 (−29, 41)		21 (−4, 45)	$P = 0.101$
Log-rank analysis of time to onset of action, Day 1								
Median time to onset, min	15	30	16	30	15	15	15	19
p-value of treatment difference	$P = 0.012$						$P = 0.018$	
Change from baseline trough FEV_1, mL on Day 85								
LS mean change from baseline (SE)	143 (16)	72 (16)	120 (19)	96 (19)	151 (13)	121 (13)	140 (9)	101 (9)
LS mean treatment difference (95% CI)	70 (26, 115)	$P = 0.002$	24 (−29, 77)		30 (−5, 65)		39 (14, 64)	$P = 0.002$

CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; SAL = salmeterol; SE = standard error; VI = vilanterol; wm = weighted mean.
[a] No inferences (*P*-values) provided for secondary/other endpoints in Study 2, as primary endpoint did not show an effect.

Outcomes of other efficacy analyses are reported in Table E2. In Studies 1 and 2, no difference was observed between FF/VI and FP/SAL for occasions of rescue use per 24 h period, 24 h periods free from rescue use over 12 weeks, or pre-dose IC on Day 84.

Safety

Pooled safety data are presented below and summarized in Table 3, while individual study data are provided in Table E3. The frequency of AEs was similar between the treatment arms (FF/VI: 27%; FP/SAL: 28%). Headache and nasopharyngitis were the most frequent events, occurring in 4–5% of patients in either treatment group. Patients in the FF/VI and FP/SAL groups experienced 19 and 27 SAEs, respectively. Across the three studies, two fatal AEs occurred in patients receiving FF/VI (gastrointestinal hemorrhage; myocardial infarction with cardiac and respiratory failure) and four occurred in patients receiving FP/SAL (cardiac failure [two patients]; small cell lung cancer; cardio-respiratory arrest). None of the fatal events were deemed by the applicable study investigator to be related to study treatment. In Study 1, one SAE of atrial fibrillation in the FP/SAL arm was considered related to study treatment. In Study 2, one SAE of bronchitis in the FF/VI arm was considered related to study treatment. In Study 3, one SAE of convulsion and mouth injury in the FF/VI arm and one SAE of COPD in the FP/SAL arm were considered related to study treatment.

AEs of special interest, defined as those often associated with either ICS or LABA therapy, were also assessed (Table E4). The most prevalent AEs of special interest were local steroid effects (primarily candidiasis which occurred in 2% of patients treated with FF/VI and 3% of those who received FP/SAL) and potential LABA-related cardiovascular effects (FF/VI: 2%; FP/SAL: 2%).

Six exacerbations occurred in Study 1 (FF/VI: 2; FP/SAL: 4), 15 occurred in Study 2 (FF/VI: 11; FP/SAL: 4), and 40 occurred in Study 3 (FF/VI: 21; FP/SAL: 19). All of these resolved without sequelae and accounted for five, 13 and 37 withdrawals, respectively. A pneumonia-associated term was reported in one patient (FF/VI arm) in Study 1 as a

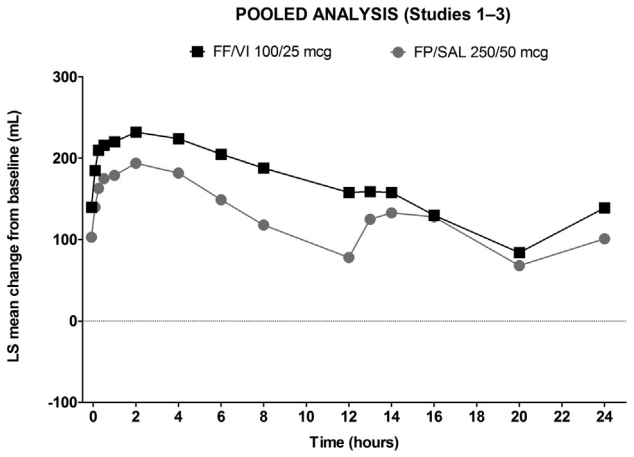

Figure 2 LS mean FEV_1 Day 84 change from baseline (pooled intent-to-treat population). Figures for individual Studies 1–3 are provided in the Online Supplement. FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; SAL = salmeterol; VI = vilanterol.

result of tuberculosis. In Study 2 there were two AEs of pneumonia in the FF/VI arm (none in the FP/SAL arm); neither was defined as a SAE, both showed infiltrates on chest X-ray, and one was deemed potentially related to study drug by the blinded investigator. In Study 3 there were four on-treatment AEs of pneumonia in the FF/VI arm and four in the FP/SAL arm; one pneumonia in the FF/VI arm and four in the FP/SAL arm were defined as SAEs, and none were considered related to study treatment. A chest X-ray was performed on all but one of the patients with recorded AEs of pneumonia; all of the chest X-rays showed infiltrates.

No clinically relevant abnormalities were demonstrated for any laboratory or electrocardiogram assessment, or urinary cortisol measurement, in any of the studies. In Study 1 a significant difference in 0–4 h wm pulse rate (bpm) was observed at Week 12 between FF/VI and FP/SAL

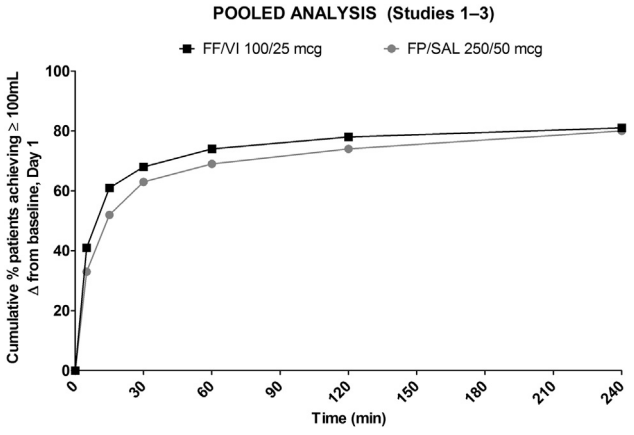

Figure 3 Cumulative proportions of patients reaching an increase in FEV_1 ≥100 mL from 0 to 4 h on Day 1 (pooled intent-to-treat population). Figures for individual Studies 1–3 are provided in the Online Supplement. BD = twice-daily; FF = fluticasone furoate; FP = fluticasone propionate; OD = once-daily; SAL = salmeterol; VI = vilanterol.

Table 3 Number (and %) of on-treatment AEs and events of special interest by treatment arm (intent-to-treat population).

	Pooled data	
	FF/VI 100/25 mcg n = 931	FP/SAL 250/50 mcg n = 927
On-treatment AEs		
Any AE	250 (27)	261 (28)
Headache[a]	46 (5)	50 (5)
Nasopharyngitis[a]	44 (5)	38 (4)
Oral candidiasis[a]	8 (<1)	19 (2)
Back pain	11 (1)	11 (1)
Oropharyngeal candidiasis[a]	7 (<1)	11 (1)
Any non-fatal serious AE	19 (2)	27 (3)
Any fatal AE	2 (<1)	4 (<1)
Treatment-related AEs[b]	28 (3)	43 (5)
AEs leading to study withdrawal	23 (2)	24 (3)

Data for individual Studies 1–3, and for adverse events of special interest, are provided in the Online Supplement.
AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; SAL = salmeterol; VI = vilanterol.
[a] Preferred terms listed where incidence was ≥3% of patients in either treatment group for either study.
[b] As determined by the investigator.

(−1.9 [95% CI: −3.3, −0.5], P = 0.009); no significant difference was observed in Study 2 (−0.8 [95% CI: −2.1, 0.6], P = 0.267) or Study 3 (0.1 [95% CI: −1.1, 1.2]; P = 0.901).

Discussion

The results of these three studies, which directly compared once-daily FF/VI with twice-daily FP/SAL, demonstrate that once-daily FF/VI 100/25 mcg improves lung function at least as much as does twice-daily FP/SAL 250/50 mcg. The improvement in 24 h lung function observed in Study 1 and favoring FF/VI 100/25 mcg was both clinically and statistically significant and was accompanied by a more rapid increase in FEV_1. Treatment differences observed in Study 2 and Study 3 numerically favored FF/VI 100/25 mcg over FP/SAL 250/50 mcg but did not reach clinical or statistical significance. Although the treatment effect of FF/VI 100/25 mcg achieved statistical significance in the pooled analysis, we consider it likely that this is a result of the increased sample size as the point estimate of the difference was not felt to be clinically relevant. Both treatments were well tolerated with generally similar safety profiles.

A careful analysis of all data collected in the three studies did not reveal any differences between the study populations, either as a whole or by treatment arm that could readily explain the differences in outcomes of the primary endpoint analysis between the studies. The differing outcomes were also not the result of poor patient adherence as this was assessed by dose counter and was excellent in all three studies. It is our conclusion that the most plausible explanation for the observed differences is natural study-to-study variability.

Adherence during clinical trials is typically high and this was suggested by the dose counter data from these three studies. However, it is also well established that adherence to inhaled therapies in the real-world setting continues to be sub-optimal though it can be positively influenced by multiple factors [6], including dosing frequency [19]. Our findings suggest two related mechanisms through which once-daily FF/VI may encourage adherence. First, though a difference in time to onset as assessed by FEV_1 was only observed in Study 1 and in the pooled data, and the difference between FF/VI and FP/SAL only 4 min, it is possible that some patients may perceive more rapid lung function improvement with FF/VI. This is uncertain as there is no established minimal clinically important difference for this outcome. However, this possibility is important as the rapid relief of early morning symptoms of COPD is known to lead to greater daytime activity levels [20] and in a pan-European survey of 719 COPD patients 65.8% of patients felt that "*regular therapy with immediate results gives me reasons for taking regular therapy*" [21]. Second, as the peak bronchodilator effect of FF/VI occurs 4 h after dosing and because both FF/VI and FP/SAL are impacted by circadian changes in lung function, the majority of the additional FEV_1 benefit gained with FF/VI was obtained in the first 12 h which may have potential benefits on activities of daily living.

Our safety findings indicate similarities between FF/VI and FP/SAL in terms of overall incidence of AEs across the three studies, and a low overall rate of SAEs. While the incidence of cardiovascular AEs of special interest (possibly related to the LABA) did not differ between treatment groups, we did observe a higher incidence of local steroid effects (primarily candidiasis) in patients treated with FP/SAL compared with FF/VI. Both fluticasone propionate and fluticasone furoate have been associated with an increased risk of pneumonia in COPD patients when compared to treatment with LABA therapy alone [2,3,12]. Though there were numerically more pneumonias in the FF/VI arms as compared to the FP/SAL arms (7 vs. 4), the overall rate was quite low and definitive conclusions about their comparative risk cannot be drawn. It should be noted that the populations recruited for these trials were not enriched for exacerbation risk, and as the risks for exacerbation are similar to those for pneumonia the current trials were not well suited to address this issue [22].

Determining dose equivalence for FF and FP is a complex issue as clinical efficacy and toxicity relate to multiple factors including steroid potency, binding time, and likely, the pathobiological processes occurring in the underlying disease (i.e. asthma as opposed to COPD). Although equivalent data in patients with COPD are lacking, FF is four times more potent than FP in improving lung function in subjects with asthma [23,24].

The studies have limitations including the divergent primary analysis outcomes, which mean definitive conclusions cannot be drawn regarding the lung function advantage conferred by FF/VI relative to FP/SAL. While the *post-hoc* pooled analysis showed a statistically significant treatment difference over the large patient sample, the observed treatment difference (41 mL) is below the suggested minimal clinically important difference for lung function [18]. In addition, there was no difference between treatment groups in rescue albuterol use, suggesting that acute episodes of dyspnea were not differentially reduced in those receiving FF/VI, despite improvements in FEV_1. Due to the lack of patient-reported outcomes, it was not possible to determine the impact of FF/VI on overall symptoms and health status, which correlate poorly with lung function [25]. In addition, the studies were only 12 weeks in duration, and as discussed above did not enroll a population at high risk for exacerbations, and thus inferences about the relative effects of FF/VI and FP/SAL on these events and the rates of important AEs (such as pneumonia) cannot be made.

In conclusion, our findings suggest that once-daily FF/VI 100/25 mcg is at least comparable with and may provide a greater improvement in lung function than twice-daily FP/SAL 250/50 mcg, with a comparable safety profile over 12 weeks.

Conflict of interest

MTD has served as a consultant for GlaxoSmithKline (GSK), Boehringer Ingelheim (BI), and Ikaria. His institution has received research grant funding from the NHLBI, GSK and Forest and has received contracted support for enrollment in clinical trials from Aeris, BI, Boston Scientific, Centocor, Forest, GSK, Otsuka, Pfizer, and Pulmonx.

GF has served as a consultant for GSK. He is a Medical Director for S. Carolina Pharmaceutical Research that contracted research funding for participation in this study, and has served as Principal Investigator for that site.

PK has served as a consultant for Novartis and Targacept. He has received lecture fees from Novartis and has received research funding from Actelion, Amgen, Alphastar, Biota, BI, Cephalon, Circassia, Dey, Electrocore, Forest, Genentech, GSK, MedImmune, Merck, Novartis, Pearl Pharmaceuticals, Pfizer, Sanofi-Aventis, Shionogi, Sunovion, TEVA and Watson. His spouse owns stock or stock options in Dendreon, Johnson & Johnson, GSK, and Stereotaxis Inc.

CFL has served as a consultant for GSK, Novartis, Alcon and Sunovion. He has received research fees from GSK, Novartis, BI, Teva, Ono, Mylan, Roxane, Meda Alcon, Forest, Pfizer, Merck, AstraZeneca and others.

MP has served as a consultant for Nycomed, GSK, and Almirall. He has received funding from the European Community and the Ministry of Health for COPD-related research and research funding, travel reimbursements and fees for lectures from GSK, Novartis, Nycomed, BI, Merck, Menarini, Chiesi and Pfizer.

FJM has participated in advisory boards about development of therapeutics for COPD for Actelion, Almirall, American Institutes for Research, AstraZeneca, Bayer, BoomComm, Forest, GSK, Ikaria, Janssen, MedImmune, Merck, Novartis, Nycomed/Takeda, Pearl, Pfizer, and Schering; been a member of the steering committee for COPD studies sponsored by Actelion, GSK, Forest, MPex, and Nycomed/Takeda; participated in US Food and Drug Administration mock panels for BI and Forest; served on speaker bureaux or in continuing medical education activities sponsored by the American College of Chest Physicians, the American Lung Association, Almirall, AstraZeneca, Beaumont, BI, the Center for Health Care

Education, CME Incite, ePocrates, Forest, the France Foundation, GSK, Lovelace, MedEd, NACE, Nycomed, Potomac, Prescott, Projects in Knowledge, Sanofi-Aventis, St Luke's, and UpToDate; and received royalties from Associates in Medical Marketing and Castle Connolly. His institute (University of Michigan) has received funds from BI for a COPD study.

NL, **MLW** and **CC** are employees of and hold stock in GSK.

Other contributions

We thank all patients and investigators involved in the three studies.

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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.2014.05.008.

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