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Effect of once-daily fluticasone furoate/vilanterol *versus* vilanterol alone on bone mineral density in patients with COPD: a randomized, controlled trial

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Abstract

Background: The relationship between inhaled corticosteroids and bone mineral density (BMD) remains uncertain despite extensive research.

Methods: This was an international, multicenter, randomized, double-blind, parallel-group, 3-year noninferiority study. Patients with chronic obstructive pulmonary disease (COPD) (⩾40 years of age; smoking history ⩾10 pack years) and at least one native hip evaluable for BMD were enrolled and randomized 1:1, stratified by sex, to treatment with vilanterol (VI) 25 µg or fluticasone furoate/vilanterol (FF/VI) 100 µg/25 µg. BMD measurements were taken *via* dual-energy X-ray absorptiometry every 6 months. The primary endpoint was assessment of the noninferiority of change from baseline in total hip BMD per year at the −1% noninferiority level. Change from baseline in BMD at the lumbar spine and BMD measurements by sex were secondary endpoints. Incidences of COPD exacerbations and bone fractures throughout the study were also recorded.

Results: Of 283 randomized patients, 170 (60%) completed the study. Noninferiority was demonstrated for FF/VI *versus* VI with regards to change from baseline in total hip BMD per year, with changes of −0.27% and 0.18%, respectively, and a treatment difference of −0.46% per year [95% confidence interval (CI) −0.97 to 0.06]. The treatment difference for FF/VI *versus* VI regarding lumbar spine BMD was −0.51% per year (95% CI −1.11 to 0.10). COPD exacerbations and bone fracture rates were similar between treatment groups.

Conclusion: FF/VI showed noninferiority to VI for change from baseline in total hip BMD per year, when assessed at the −1% noninferiority margin in a combined sample of men and women with COPD.

The reviews of this paper are available via the supplemental material section.

Keywords: bone density, chronic obstructive pulmonary disease, fractures, inhaled corticosteroids, lumbar spine

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation, arising from inflammatory and structural changes in the airways and/or lung parenchyma.[1] Populations of patients with COPD often comprise individuals of advanced age with a smoking history, sedentary lifestyle, and dietary deficiencies,[2] all of which are risk factors for reduced bone mineral density (BMD).[3,4] BMD could be further affected by long-term inhaled corticosteroid (ICS) use[5] if prescribed for COPD treatment.

Combination treatment with an ICS and long-acting β_2-agonist (LABA) is an option for patients

with COPD who, despite long-term, long-acting bronchodilator therapy, continue to experience exacerbations.[1] ICS/LABA combinations are more effective than treatment with an ICS or LABA alone in reducing exacerbations and improving lung function in patients with COPD.[6–9] Some evidence suggests that long-term corticosteroid use may lead to reduced BMD and increased fracture risk,[5,10,11] and that reductions in BMD may be less with an ICS *versus* oral corticosteroids due to lower levels of systemic exposure.[12] However, a more complete understanding of the relationship between ICS use and BMD, which also accounts for lifestyle factors associated with both COPD and osteoporosis, is required to better assess the potential risks of ICS use in COPD treatment.

In the present study, we hypothesized that, owing to the low systemic corticosteroid exposure of an inhaled product, the effect of fluticasone furoate/vilanterol (FF/VI) on BMD would be noninferior to that of VI alone; that is, the addition of FF to VI would not accelerate bone demineralization beyond the 1% preset margin of noninferiority at the total hip.

Methods

Study design

This was a multicenter, randomized, double-blind, parallel-group, noninferiority study conducted across 44 sites, that is, USA ($n=17$), The Netherlands ($n=8$), Germany ($n=7$), Spain ($n=7$), and Canada ($n=5$), between January 2014 and March 2018 [ClinicalTrials.gov identifier: NCT01957150]. Patients were randomized (1:1) to receive either FF/VI (100/25 µg) or VI (25 µg) once daily for 3 years, and attend 12 on-treatment clinic visits (one every 3 months; BMD measurements were taken every 6 months) following a 3-week run-in period between screening (Visit 1) and randomization (Visit 2). A safety follow up was conducted by telephone 7 days after receipt of the last study treatment. Patients used a placebo ELLIPTA inhaler and could continue their usual COPD medications during the run-in period; baseline BMD measurements were taken at this time. Randomization was stratified 50:50 by sex due to the frequently reduced BMD of postmenopausal women *versus* men of a similar age.[13]

Inclusion and exclusion criteria

Eligible patients were current or former smokers (age ⩾40 years; smoking history ⩾10 pack years) with a COPD diagnosis (according to the American Thoracic Society/European Respiratory Society guidelines),[14] and who had ⩾1 native hip evaluable for BMD. Patients were required to have a postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio of <0.70 and a postbronchodilator FEV_1 of 50–70% predicted normal at screening (calculated using the National Health and Nutrition Examination Survey III reference equations[15]), with ⩽1 moderate/severe COPD exacerbation in the 12 months prior to screening. The nature of the inclusion criteria minimized the likelihood of patients experiencing an exacerbation requiring the use of systemic corticosteroids, which could potentially confound any effects of ICS on BMD; however, eligible patients who experienced an exacerbation or required treatment with systemic corticosteroids during the study were not required to withdraw. Patients receiving medications to treat low BMD at screening, such as bisphosphonates, could continue treatment as required throughout the study.

Patients who failed to demonstrate ⩾80% compliance with a placebo ELLIPTA inhaler during the run-in period were excluded from the study. Additional key exclusion criteria included: a current diagnosis of asthma; COPD due to α1-antitrypsin deficiency; lung resection ⩽12 months prior to screening; acute worsening of COPD ⩽12 weeks prior to screening; or >1 moderate/severe COPD exacerbations and/or lower respiratory tract infection ⩽12 months prior to screening. Patients with bone disorders and/or conditions that might affect their BMD, such as bone cancer or rheumatoid arthritis, or removal of vertebrae between L1 and L4 of the lumbar spine, were excluded at screening.

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization/Good Clinical Practice, and all applicable regulatory requirements. The study protocol and informed consent form were reviewed and approved by the appropriate independent ethics committee or institutional review board. Patients provided written, informed consent prior to screening.

Study endpoints

The primary endpoint was assessment of the noninferiority of change from baseline in total hip BMD per year. Further details relating to the noninferiority testing are provided in the online supplemental data. Noninferiority was not assessed at the lumbar spine.

BMD at the lumbar spine (L1–L4) and BMD measurements (total hip and lumbar spine) by sex were assessed as secondary endpoints. Other endpoints included adverse event (AE) and serious adverse event (SAE) reporting, as well as the incidence of bone fractures, pneumonia, and COPD exacerbations.

BMD assessment

BMD was measured using BMD dual-energy X-ray absorptiometry (BMD DEXA) every 6 months post randomization. BMD DEXA images were assessed in a blinded fashion by a central laboratory (Bioclinica, Princeton, NJ, USA). All analyses of BMD used corrected BMD values only, as these could be considered standardized given potential machine variability. Estimates of percentage change in BMD, percentage change per year by treatment arm, and the difference between treatment arms, were calculated. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates, along with the difference between treatment arms, which were used for the primary test of noninferiority. T-scores and Z-scores were also assessed for BMD evaluation: further details are provided in the online supplemental data.

Statistical analysis

Estimands were used for analysis of all endpoints; an explanation of the estimands used in this study is provided in the online supplemental data.

Baseline information and primary and secondary endpoints were analyzed in the safety population (all randomized patients who received $\geq$1 dose of study drug) using a repeated measures model, including baseline body mass index (BMI) and age as continuous variables, over a period of 3 years. While previous analyses have focused on a final time point for such comparisons, we chose to evaluate change in BMD per year over 3 years in order to ensure that all time point estimates were handled equally before inclusion in the final noninferiority assessment.

The noninferiority margin of −1% per year change in BMD was employed for the assessment of BMD at the total hip only. This margin of −1% was within the expected range for decline in BMD when compared with the rate of decline observed in patients not using ICS.[12,16]

Additional safety assessments: AEs, exacerbations, pneumonia, and bone fractures

AEs and SAEs were monitored for the duration of the study; post-treatment safety findings were recorded by the investigator during the follow-up phone call at Visit 15. Further details of AE and SAE assessments are provided in the online supplemental data.

Results

Study population

Of 283 patients randomized to receive treatment, 170 (60%) completed the study (Figure 1).

Demographics were generally similar between treatment groups (Table 1): 50% were men (n=142) per the study design (Figure 2). Mean baseline BMD was 0.891 g/cm^2 at the total hip and 1.045 g/cm^2 at the lumbar spine. Overall, 7% (n=19) of patients had a T-score at the total hip of $\leq$−2.5, indicating osteoporosis, and 4% (n=10) had a Z-score at the total hip lower than normal for a patient of the same age. Mean treatment exposure was similar: FF/VI, 2.29 years; VI, 2.26 years.

Change from baseline per year in mean BMD at the total hip

A small mean percentage decrease from baseline in BMD at the total hip was observed for the FF/VI group over the course of the study (primary endpoint), while the mean change from baseline in the VI group was closer to zero (Figure 3(a)). However, the 95% confidence intervals (CIs) overlapped and the mean treatment difference in the annual percentage change from baseline calculated for each time point was similar over the course of the study: −0.13% to −0.78% (Table 2).

There was a small decrease in yearly rate of change in total hip BMD from baseline for the

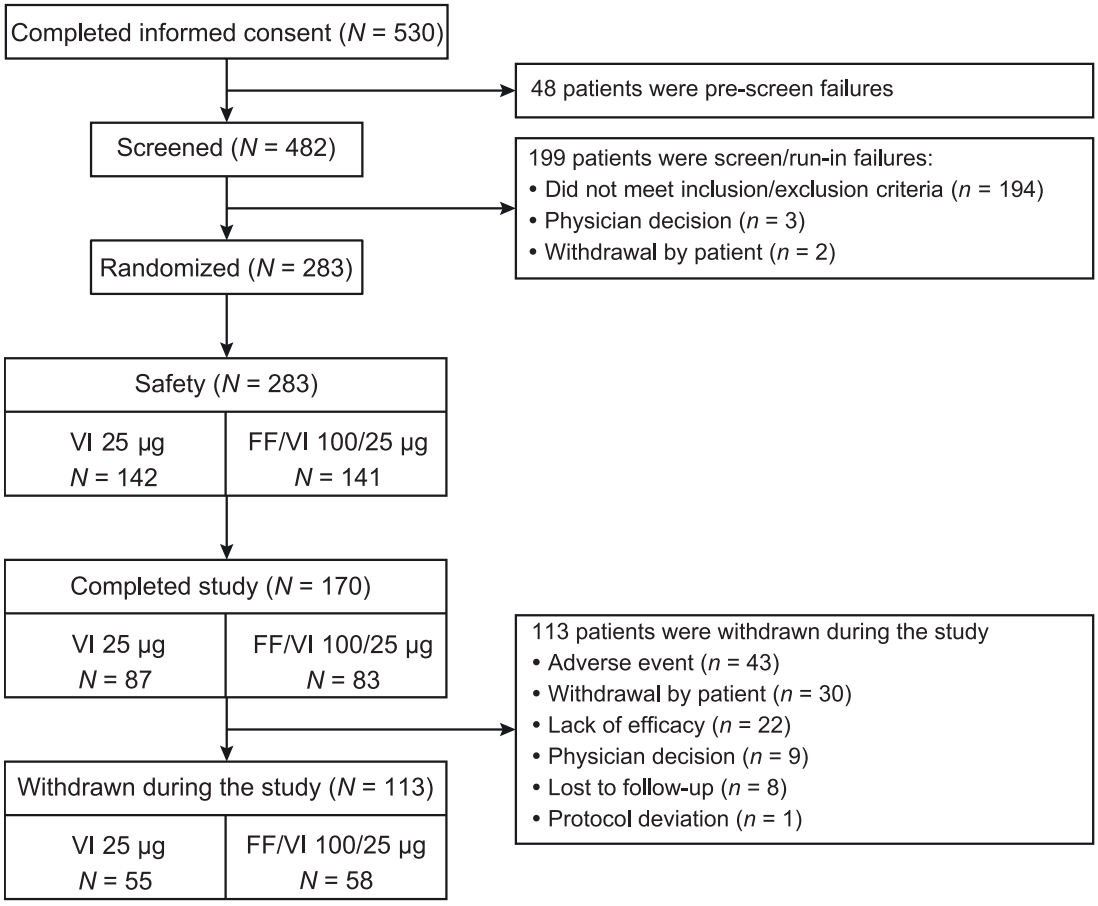

Figure 1. Flow diagram of patient disposition.
FF/VI, fluticasone furoate/vilanterol; VI, vilanterol.

FF/VI group (−0.27% per year) and a small increase for the VI group (0.18% per year). The overall treatment difference for FF/VI *versus* VI was −0.46% per year (95% CI −0.97 to 0.06) for total hip BMD (Figure 3(b)). The lower limit of the 95% CI was within the prespecified noninferiority margin of −1.0% per year.

There was no evidence of a statistically significant interaction with treatment for the covariates included in the analysis of the primary endpoint (sex, age, baseline BMI, and smoking status) when tested at the 10% significance level.

For the yearly rate of change in BMD at the total hip by sex (secondary endpoint), treatment differences for FF/VI *versus* VI were −0.47% per year (95% CI −1.17 to 0.24) for men, and −0.40% per year (95% CI −1.16 to 0.36) for women. These were consistent with the safety population analysis, but noninferiority could not be determined because of the reduced sample size involved, leading to wide CIs that exceeded the noninferiority margin of −1% per year.

Change from baseline per year in mean BMD at the lumbar spine

The yearly rate of change from baseline in BMD at the lumbar spine was small in both treatment groups, but was higher with VI (0.79% per year) than with FF/VI (0.28% per year) with an overall treatment difference of −0.51% per year (95% CI −1.11 to 0.10) (secondary endpoint) (Figure 4).

For the yearly rate of change from baseline in BMD at the lumbar spine by sex, treatment differences for FF/VI *versus* VI were −1.02% per year (95% CI −1.90 to −0.13) for men, and −0.05% per year (95% CI −0.87 to 0.78) for women. There was no evidence of a statistically significant interaction between treatment and sex.

Table 1. Demographics and baseline characteristics.

Population	VI *n* = 142	FF/VI *n* = 141	Total *n* = 283
Sex, *n* (%)			
Male	72 (51)	70 (50)	142 (50)
Female	70 (49)	71 (50)	141 (50)
Age, mean (SD) years	66.0 (8.2)	64.4 (9.0)	65.2 (8.7)
BMI, mean (SD) kg/m^2	29.1 (5.8)	28.3 (5.5)	28.7 (5.6)
Duration of COPD			
⩾1 to <5 years	43 (30)	60 (43)	103 (36)
⩾5 to <15 years	81 (57)	70 (50)	151 (53)
⩾15 to <25 years	15 (11)	9 (7)	24 (8)
⩾25 years	3 (2)	2 (1)	5 (2)
Overall BMD medication use during the study, *n* (%)			
Male (*n* = 142)	6 (8)	4 (6)	10 (7)
Female (*n* = 141)	14 (20)	14 (20)	28 (20)
Postbronchodilator FEV_1, mean (SD), L	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)
Postbronchodilator FEV_1, mean (SD), % predicted	59.5 (6.1)	58.9 (5.9)	59.2 (6.0)
Postbronchodilator FVC, mean (SD), L	3.0 (0.8)	3.1 (0.8)	3.0 (0.8)
Postbronchodilator FEV_1/FVC, mean (SD), %	55.7 (8.4)	55.1 (9.1)	55.4 (8.7)
Total hip			
n	139	140	279
DEXA BMD, g/cm^2, mean (SD)	0.902 (0.165)	0.879 (0.162)	0.891 (0.164)
T-score, mean (SD)	−0.89 (1.147)	−1.06 (1.070)	−0.97 (1.111)
Z-score, mean (SD)	0.07 (1.221)	−0.16 (1.065)	−0.04 (1.149)
Lumbar spine			
n	142	141	283
DEXA BMD, g/cm^2, mean (SD)	1.059 (0.222)	1.032 (0.199)	1.045 (0.211)
T-score, mean (SD)	−0.60 (1.757)	−0.81 (1.584)	−0.70 (1.674)
Z-score, mean (SD)	0.52 (1.793)	0.26 (1.629)	0.39 (1.715)

BMD, bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DEXA, dual-energy X-ray absorptiometry; FEV_1, forced expiratory volume in 1 s; FF/VI, fluticasone furoate/vilanterol; FVC, forced vital capacity; SD, standard deviation; VI, vilanterol.

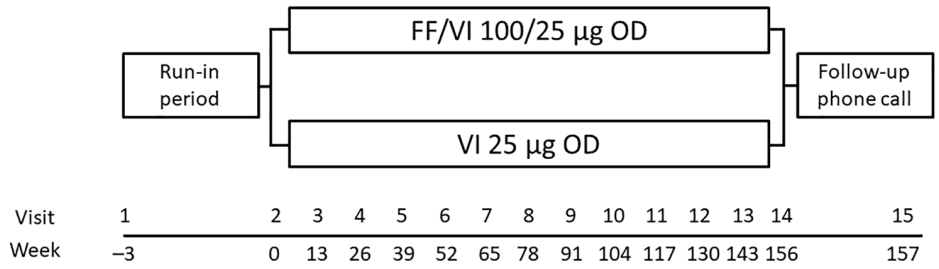

Figure 2. Study design.
FF/VI, fluticasone furoate/vilanterol; OD, once daily; VI, vilanterol.

Table 2. Percentage change from baseline in BMD at the total hip by study visit (primary endpoint, safety population).

Visit	VI *n* = 142	FF/VI *n* = 141
Visit 4 (week 26)		
N	130	130
Percentage change from baseline (95% CI)	0.37 (–0.07 to 0.82)	0.31 (–0.31 to 0.76)
FF/VI *versus* VI percentage change per year (95% CI)		–0.13 (–1.37 to 1.13)
Visit 6 (week 52)		
n	104	121
Percentage change from baseline (95% CI)	0.35 (–0.21 to 0.91)	–0.43 (–0.96 to 0.10)
FF/VI *versus* VI percentage change per year (95% CI)		–0.78 (–1.54 to 0.01)
Visit 8 (week 78)		
n	97	102
Percentage change from baseline (95% CI)	0.22 (–0.41 to 0.85)	–0.68 (–1.29 to 0.07)
FF/VI *versus* VI percentage change per year (95% CI)		–0.60 (–1.18 to –0.02)
Visit 10 (week 104)		
n	94	96
Percentage change from baseline (95% CI)	–0.16 (–0.84 to 0.52)	–1.02 (–1.68 to –0.36)
FF/VI *versus* VI percentage change per year		–0.43 (–0.90 to 0.05)
Visit 12 (week 130)		
n	88	84
Percentage change from baseline (95% CI)	0.00 (–0.73 to 0.75)	–1.02 (–1.75 to –0.29)
FF/VI *versus* VI percentage change per year (95% CI)		–0.41 (–0.83 to 0.01)
Visit 14 (week 156)		
n	76	75
Percentage change from baseline (95% CI)	–0.16 (–1.02 to 0.71)	–1.29 (–2.13 to –0.45)
FF/VI *versus* VI percentage change per year (95% CI)		–0.38 (–0.78 to 0.03)
Overall		
*N**	130	132
Yearly rate (%) of change from baseline (95% CI)	0.18 (–0.18 to 0.55)	–0.27 (–0.63 to 0.09)

*Subjects with analyzable data for baseline and one or more postbaseline time points.
BMD, bone mineral density; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; VI, vilanterol.

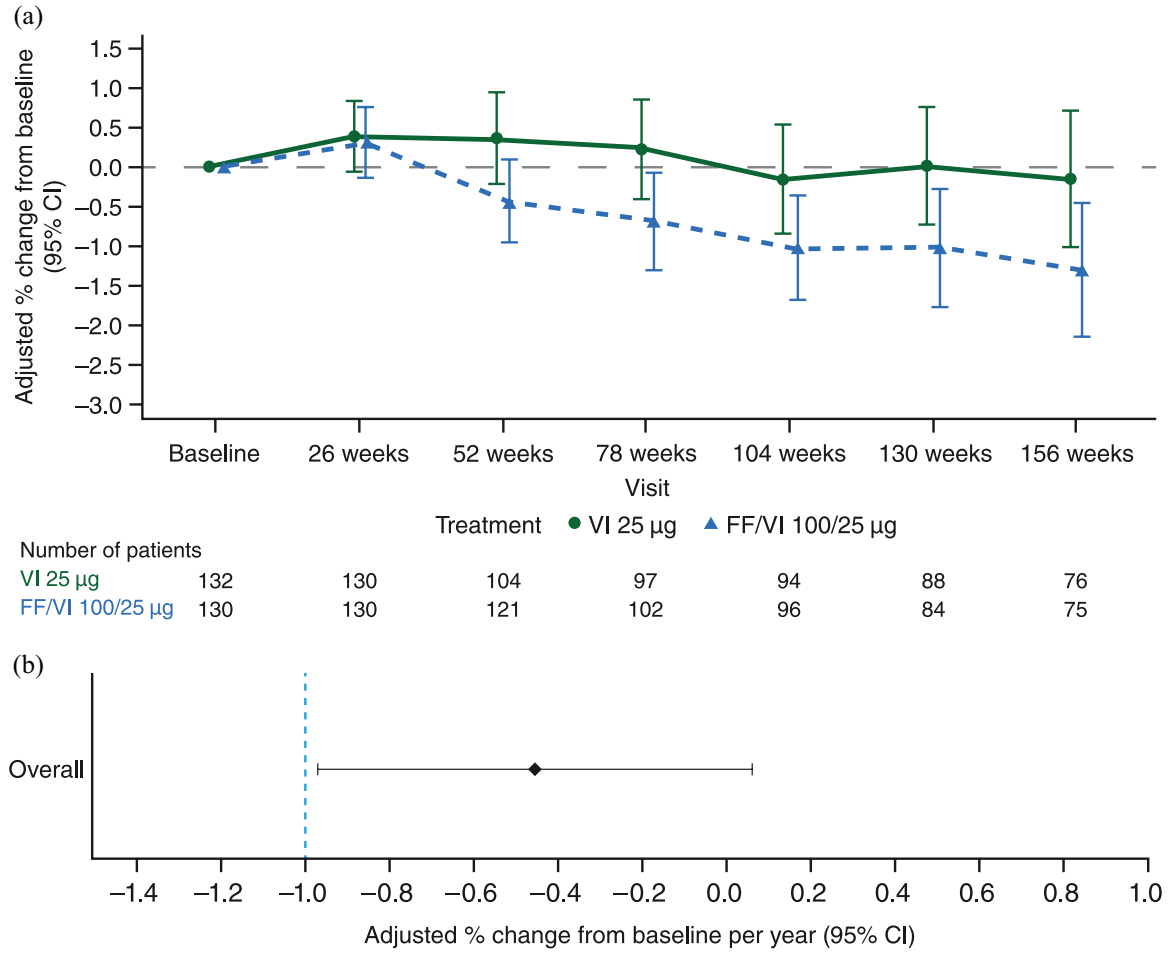

Figure 3. (a) Adjusted percentage change from baseline in on-treatment bone mineral density (g/cm^2) at the total hip over time (primary endpoint, safety population); (b) adjusted yearly rate of change from baseline between FF/VI and VI in on-treatment bone mineral density (g/cm^2) at the total hip. The prespecified noninferiority margin of –1% is indicated by the dotted blue line. Any values to the right of this line are noninferior.
CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; VI, vilanterol.

Additional safety assessments: AEs, exacerbations, pneumonia, and bone fractures

The overall incidence of drug-related and on-treatment AEs and SAEs, including those leading to study withdrawal, were similar between the two treatment groups (e-Table 1). Both treatments were well tolerated. SAEs resulted in 10 deaths during the study (4 in patients on FF/VI and 6 in patients on VI), none of which were considered by the investigator to be treatment related.

The overall annual exacerbation rate for moderate/severe exacerbations was similar in the FF/VI and VI groups (mean number of exacerbations per year per patient 0.47 and 0.46, respectively), and approximately half of patients in both treatment groups experienced ⩾1 COPD exacerbation during the study. In total, 104 patients (37%) required systemic corticosteroid treatment for a COPD exacerbation during the study; this proportion was similar between the two study arms (35% of patients in the VI arm; 38% of patients in the FF/VI arm). Pneumonia incidence was higher in the FF/VI group (19 events for 14 patients) than in the VI group (10 events for 10 patients). There were no pneumonia events with a fatal outcome in either treatment group.

The overall incidence of on-treatment bone fractures was low in both the FF/VI group ($n=12$) and the VI group ($n=7$). The incidence of on-treatment non-traumatic fractures was very low in both groups; four fractures reported for four patients in the FF/VI group and three fractures

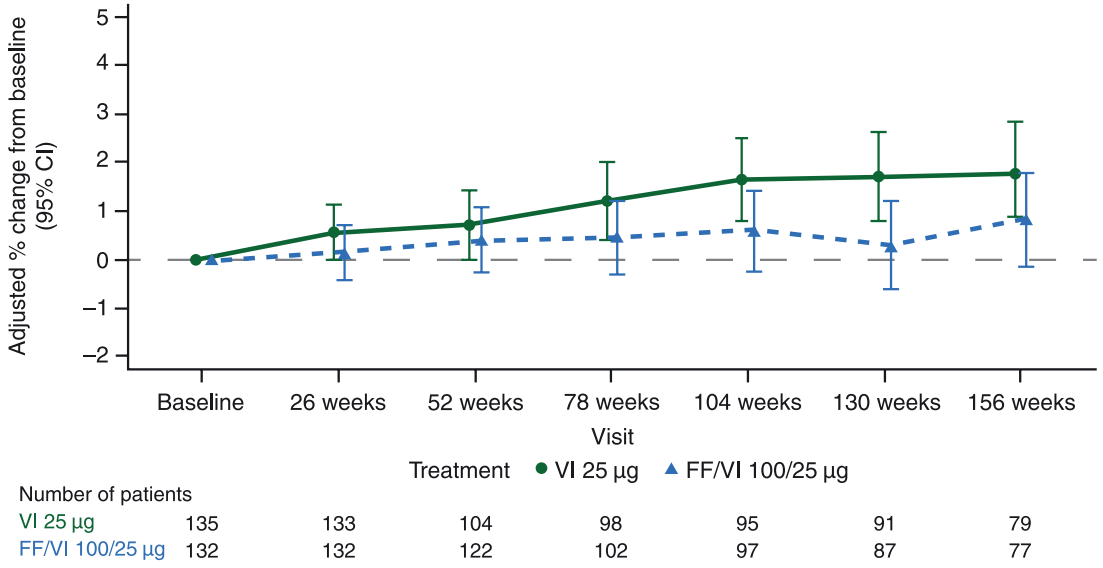

Figure 4. Adjusted percentage change from baseline in on-treatment bone mineral density (g/cm^2) at the lumbar spine over time (secondary endpoint, safety population).
CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; VI, vilanterol.

for two patients in the VI group. In total eight patients (6%) in the VI group, who were not previously taking BMD medications, were started on BMD concomitant medications during treatment, compared with five patients (4%) in the FF/VI group.

Discussion

The addition of FF to VI was noninferior to VI at the total hip for the whole study population of men and women combined (primary endpoint), but noninferiority was not achieved at the total hip when patients were stratified by sex (secondary endpoint).

The potential relationship between ICS use and BMD is difficult to characterize due to an abundance of conflicting results, which could be due to differing study designs, study drugs, and patient populations.[5] However, ICSs are known to exert a number of metabolic effects that may lead to subsequent reductions in BMD, including the disruption of bone homeostasis by limiting osteogenesis,[17] and the induction of osteoblast apoptosis by reactive oxygen species.[18] This could be particularly important when, for instance, considering the most appropriate treatment option for patients with COPD, who may experience an increased prevalence of osteoporosis compared with the general population.[19,20]

To our knowledge, our study was the first to evaluate the BMD effects of FF/VI using DEXA, and did so in prospective settings. In this study, patients with moderate COPD experienced noninferior changes in BMD at the total hip following treatment with FF/VI compared with VI alone at the −1% noninferiority margin, that is, the addition of FF to VI did not reduce BMD at the total hip by any more than 1% per year *versus* treatment with VI alone. The mean treatment difference between FF/VI and VI in both male and female patients was consistent with the overall population; however, with the reduced sample size of each subgroup, the CIs were wider and noninferiority was not demonstrable.

Change in BMD at the lumbar spine by sex showed greater variation than changes in BMD at the total hip by sex. At the lumbar spine, the CIs of the yearly rate of change from baseline for men lay entirely below zero, indicating that BMD was lower in men receiving FF/VI *versus* VI. However, it is important to highlight that, in the context of our study, this related to BMD increasing over time in both the FF/VI and VI arms, and there was no statistically significant interaction between treatment and sex at the lumbar spine.

Results from BMD measured at the total hip and at the lumbar spine, observed using an active control, support outcomes previously observed in the

TOwards a Revolution in COPD Health (TORCH) study,[21] in which changes in BMD at both the hip and lumbar spine were not significantly different between patients receiving placebo (−3.1%), salmeterol (−1.7%), fluticasone propionate (−2.9%), or salmeterol/fluticasone propionate (−3.2%).[21] In the present study, the treatment difference in BMD at the lumbar spine was significant in men but not in women for FF/VI *versus* VI alone. Although within sexes, the proportion of patients receiving BMD medications was equal between treatment arms, an overall greater proportion of women (20%) than men (7%) were receiving BMD medication during the study, potentially as a result of sex-specific differences in BMD[22] and an increased fracture risk in women *versus* men. Subsequently, this could have counteracted the effects of ICS on BMD.

Meta-analyses of the relationship between ICS use and BMD have suggested that treating patients with ICS may increase fracture risk.[10,11] A potentially increased fracture risk with ICS use is also highlighted by the results of replicate, 12-month trials in 3255 patients with COPD, in which 2% of patients receiving FF/VI experienced bone fractures *versus* <1% of patients receiving VI alone.[23] A cohort of 7799 patients with COPD who received ⩾1000 µg of ICS with a follow up of >4 years in Québec (relative risk 1.10 *versus* controls; 95% CI 1.02 to 1.18) also may have experienced an increased fracture risk, but these results should be regarded with caution as patients in this database did not have a well-validated diagnosis of COPD.[24] Results from the TORCH study[21] demonstrated a low incidence of bone fractures across treatment groups (5.1–6.3%). Our study also had low fracture risks between groups, which was higher for FF/VI (8.5%; $n=12$) than VI (3.5%; $n=5$). This may indicate an increased fracture risk with the addition of ICS, but these results must be interpreted in context with the low number of patients on which they are based, and also because patients were not stratified by sex. In addition, prospective studies of ICS use are rarely designed with enough statistical power to explore fully the relationship, and so may not reliably reflect the fracture risks (including non-traumatic fractures) in patients with COPD receiving ICS treatment.

A small proportion of patients in our study had osteoporosis, shown by T-scores ⩽−2.5 ($n=19$) and Z-scores less than normal for a given age group ($n=10$) at the total hip, which is consistent with our findings that ICS use did not significantly impact BMD. Extending this study over a longer duration and in a larger patient population could be useful for further investigating the potential relationship between FF/VI and BMD, and thus its safety profile for treating patients with COPD who may have comorbidities including osteoporosis. Although other studies have considered T- and Z-scores at the total hip, and have identified greater proportions of patients with osteoporosis compared with the present study,[25,26] their overall study designs have differences that make comparison with our results difficult to interpret.

For the additional safety endpoints monitored (AEs, exacerbations, and pneumonia), results were largely similar between patients receiving FF/VI and VI, with a slightly higher incidence of pneumonia events in the former. In contrast to Dransfield *et al.*,[23] we observed no reduction in exacerbation rate with the addition of FF to VI. This discrepancy between the two studies is likely related to differences in study population; Dransfield *et al.*[23] only randomized patients with ⩾1 moderate-to-severe exacerbation in the previous year, whereas this was not a prerequisite for participation in the present study.

A particular strength of our study was its prospective design, allowing BMD data to be collected from patients with COPD specifically to study its association with ICS use. Stratification of randomization by sex enabled an equal representation of differences in BMD between men and women. A further strength of this study is that it contained longitudinal follow-up data collected over a long (3-year) time period.

In contrast, the 3-year study duration allowed for a high withdrawal rate (40%) among patients, representing a possible limitation of the study. This was similar to withdrawal rates seen in another study of BMD in patients with COPD receiving treatment with fluticasone propionate/salmeterol or salmeterol alone [SCO40041 (NCT00355342)]. BMD data collected after permanent discontinuation was not used in the analyses. The presence of comorbid conditions, which can be common in patients with COPD[27] and which could have affected BMD in addition to ICS use, was a further potential limitation. To represent a population of patients with COPD, individuals receiving anti-osteoporosis medications were not excluded and were allowed to continue these medications during the study; in

total, 20% of female patients and 7% of male patients were receiving ⩾1 anti-osteoporosis medication, which may have counteracted any possible effects of corticosteroids on BMD. In addition, 37% of the patients overall experienced an exacerbation during the study that was treated with systemic corticosteroids. Patients who were treated with systemic corticosteroids during the study were not required to withdraw, and so exposure to systemic corticosteroids could, in theory, have confounded the effects of ICS on BMD. To minimize this possibility, patients with severe COPD were excluded to minimize the occurrence of exacerbations and requirement for subsequent systemic corticosteroid treatment. This study design explains the relatively low exacerbation rate observed in the trial (0.4 exacerbation/patient/year). Furthermore, the proportion of patients treated with systemic corticosteroids was similar in each study arm (35% of patients in the VI group and 38% in the FF/VI group), suggesting that exposure to systemic corticosteroids was unlikely to be a major confounder of the study results. Nevertheless, a future study including patients at high exacerbation risk and at greater likelihood of being exposed to systemic corticosteroids could be of value in further assessing the benefit/risk profile of ICS treatment.

Conclusion

FF/VI was noninferior to VI at the −1% per year margin of noninferiority regarding the primary endpoint of percentage change from baseline in total hip BMD per year for men and women combined. There were no new or unexpected safety findings. The study helps to support the favorable benefit/risk profile of FF/VI on BMD in patients with COPD who are receiving ICS treatment.

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Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Author contribution(s)

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Conflict of interest statement

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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