Reviewer 1:

Comments to the Author

1. Well designed study to assess BMD in patients with moderate COPD. The high drop out rate may compromise the results but this was commented on by the authors. The study only included patients with moderate COPD. The inclusion of more severe patients most likely would have yielded a higher level of bone density deficiency at baseline and it would be on interest to see if this would have altered the results. A comment in the discussion would be suggested to explain the rationale of excluding more severe patients. The similar exacerbation rate between the 2 groups is also interesting as one would expect a lower rate in the ICS group although the population recruited was intentionally a group with a low exacerbation rate. I think this study adds useful information to the literature concerning this important co-morbidity in this group of patients.

Many thanks to the reviewer for this feedback. Regarding your comment on the study rationale, we wanted to focus specifically on the effects of ICS on BMD and so we chose patients with moderate COPD who were less prone to exacerbations than patients with more severe disease, and who were thus at a lower risk of requiring (systemic) corticosteroid treatment for an exacerbation. We have moved some information from the supplementary methods to the main manuscript to clarify our rationale for including patients with moderate COPD rather than severe COPD, and have also added a sentence to the discussion to acknowledge that including patients with severe COPD could be of use in further evaluating the benefit/risk profile of FF/VI in COPD.

Methods (lines 83–96):

“No 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), and who had ≥1 native hip evaluable for BMD. Patients were required to have a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio of <0.70 and a post-bronchodilator FEV1 of 50–70% predicted normal at screening (calculated using the National Health and Nutrition Examination Survey III reference equations), with ≤1 moderate/severe COPD exacerbation in the 12 months prior to screening. Further details relating to the inclusion and exclusion criteria are provided in the online supplementary data. 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.”

Discussion (lines 310–325):

“Additionally, approximately half 37% of the patients in each treatment arm overall experienced an exacerbation during the study, but were not required to withdraw if their exacerbation that was treated with systemic corticosteroids. Thus, differing exposure to 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 affected confounded the effects of ICS on BMD. during the study, which 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 similarly low in each study arm, (37%) 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 have impacted BMD in a way that ICS did not be of value in further assessing the benefit/risk profile of ICS treatment.”
Reviewer: 2

Comments to the Author

1. Well designed, well written.

Many thanks to the reviewer for this kind feedback.

2. You said how many males and females were on BMD meds, but I could not find the number in each study arm on BMD meds. Please add to table 1 and comment in discussion.

Thank you for raising this important point. We have added the numbers of males and females receiving BMD medications in each study arm to Table 1. Additionally, to clarify that the text in the discussion refers to the overall percentages per sex (including both treatment arms) we have made a minor adjustment to the sentence.

Table 1. Demographics and baseline characteristics (p11–12):

| 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 (5.0) | 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 | | | |
| \( \geq 1 \) to <5 years | 43 (30) | 60 (43) | 103 (36) |
| \( \geq 5 \) to <15 years | 81 (57) | 70 (50) | 151 (53) |
| \( \geq 15 \) to <25 years | 15 (11) | 9 (7) | 24 (8) |
| \( \geq 25 \) years | 3 (2) | 2 (1) | 5 (2) |

Overall BMD medication use during the study, \( n (\%) \):

| | Male \( N=142 \) | Female \( N=141 \) |
|---|---|---|
| Post-bronchodilator FEV\(_1\), mean (SD), L | 1.6 (0.4) | 1.6 (0.4) |
| Post-bronchodilator FEV\(_1\), mean (SD), % predicted | 59.5 (6.1) | 58.9 (5.9) |
| Post-bronchodilator FVC, mean (SD), L | 3.0 (0.8) | 3.1 (0.8) |
| Post-bronchodilator FEV\(_1\)/FVC, mean (SD), % | 55.7 (8.4) | 55.1 (9.1) |

Total hip:

| | VI | FF/VI | Total |
|---|---|---|---|
| \( N \) | 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:

| | VI | FF/VI | Total |
|---|---|---|---|
| \( N \) | 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) |
Discussion (p18, lines 258–262):

“A Although within sexes, the proportion of patients receiving BMD medications was equal between treatment arms, an overall, greater proportion of females (20%) than males (20% versus 7%, respectively) were receiving BMD medication during the study, potentially as a result of sex-specific differences in BMD (Nieves et al. J Bone Miner Res 2005; 20:529–535) and an increased fracture risk in females versus males. Subsequently, this could have counteracted the effects of ICS on BMD.”

3. Were any subjects started on BMD meds over the course of the study?

Yes, some patients in both treatment groups were started on BMD medications over the course of the study. We have added some text to the Results to clarify this (p16, lines 223–225):

“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 nontraumatic fractures was very low in both groups; four fractures reported for four patients in the FF/VI group and three fractures for two patients in the VI group. In total, 8 patients (6%) in the VI group, who were not previously taking BMD medications, were started on BMD concomitant medications during treatment, compared with 5 patients (4%) in the FF/VI group.”

4. Knowing cumulative SCS exposure over the course of the study would also have been helpful. Was this evaluated?

In total, 104 patients (37%) required corticosteroid treatment for a COPD exacerbation during the study. Although we did not monitor the total dose of systemic corticosteroids to which each study participant was exposed during the trial, the proportion of patients treated with systemic corticosteroids in each study arm was similar (35% of patients in the VI arm; 38% of patients in the FF/VI arm). Furthermore, we did not evaluate cumulative SCS exposure in the study, although we did select our patient population to minimise the risk of patients requiring SCS treatment for an exacerbation in order to avoid this confounding our results as much as possible. This study design explains the relatively low exacerbation rate observed in the trial (0.4 exacerbation/patient/year). Altogether, this suggests that exposure to systemic corticosteroids was not a major influence on the study results. For clarification of this point, we have added some explanatory text in the Results section. Per our response to Reviewer 1, comment 1, we have also amended the text in the Discussion.

Results (p16, lines 214–216):

“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).”

Discussion (p20, lines 310–325):

“Additionally, approximately half 37% of the patients in each treatment arm overall experienced an exacerbation during the study, but were not required to withdraw if their exacerbation 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 affected confounded the effects of ICS on BMD. during the study, which 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 similarly low in each study arm, (37%) 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 have impacted BMD in a way that ICS did not be of value in further assessing the benefit/risk profile of ICS treatment.”