Reviewer’s report

Title: The peroxisome proliferator-activated receptor (PPAR) alpha agonist fenofibrate prevents bone loss, while the PPAR gamma agonist pioglitazone exaggerates bone loss, in ovariectomized rats

Version: 1 Date: 22 November 2010

Reviewer: Susan Y Y Smith

Reviewer’s report:

- Major Compulsory Revisions

None

- Minor Essential Revisions

1. The results and conclusions of this study are based on whole body and femur data exclusively from densitometry (DXA), architecture (micro-CT) and strength parameters. It would have been useful to include measurements from other skeletal regions including the spine and possibly the tibia, and to use other densitometry techniques such as pQCT (peripheral quantitative computed tomography) to provide volumetric bone mass and geometry data. Histomorphometry assessments would provide data to support the architecture data derived by micro-CT and (if fluorochrome labels were administered prior to bone harvesting) could also be used to provide dynamic parameters to describe bone turnover which has been assessed in a limited way using biochemical markers.

2. For the biomechanics it would be useful to derive modulus and toughness, and to include peak load and ultimate stress for the femur shaft. It is also important to assess if any of the treatments affected bone quality with respect to the association between bone mass (using densitometry parameters) and bone strength using regression analysis.

3. Materials and Methods: Animals, paragraph 2: Animals were relatively young at the time of OVX, a limitation which should be emphasized, especially when discussing the effects of OVX throughout the manuscript, since OVX control animals did not lose bone but failed to gain.

4. Materials and Methods: Animals, paragraph 2: Explain the rationale for starting dose administration one week after OVX. Why is dose administration referred to as “feeding”?

5. Materials and Methods: uCT Measurements: Need to more clearly identify where scans were acquired anatomically, the description provided is vague.

6. Materials and Methods: uCT Measurements: line 6: typo: metaphysis. Clarification of the term: “endocortical bone volume” is required and how this is derived (threshold used). The reader may also benefit from explanation of the
7. Materials and Methods: Biomechanical testing: Clarify the term: “moment” and how this is derived.

8. Results: General observations and body composition, first paragraph: The fat mass and lean mass should be adjusted relative to body weight.

9. Results: General observations and body composition, paragraph 3: Liver weight should be adjusted relative to body weight. Clarify sentence re liver pathology to indicate no findings were seen on visual inspection. Liver pathology may be detected if tissues were examined microscopically and would provide useful additional information.

10. Results: Whole body and femoral BMC/BMD, first paragraph: Values for area would provide perspective when discussing BMC. This paragraph discusses whole body BMC data which is not presented.

11. Results: Whole body and femoral BMC/BMD: Presenting data in Figure 2 as percent change from baseline would clarify the response among groups since there is some variation between groups at time 0.

12. Results: Bone architecture, last paragraph: Clarify statement is relevant for the femur only.

13. Results: Biomechanical testing, first paragraph: Check accuracy of first sentence: statement is true for the femoral neck but for the shaft the values are also similar to OVX controls, especially for FENO OVX.

14. Discussion: First sentence: For most of the results FENO and WY show similar effects.

15. Discussion: Paragraph 2, first sentence: typo: reduction. This sentence (and the following sentence) only relates to the femur – there is no data presented for whole body BMC. It is a strong statement to say the OVX control data presented in this paper shows impaired bone quality.

16. Discussion: Paragraphs 2, 7 and 14: There is no evidence that bone loss occurred in these OVX control animals, only a failure to gain, therefore statements that treatment (FENO) prevented bone loss and deterioration should be modified.

17. Discussion: paragraph 3: Check accuracy of last sentence: statement is true for the femoral neck but for the shaft the values are also similar to OVX controls, especially for FENO OVX.

18. Discussion: paragraph 5: The authors state that increased osteocalcin levels in the FENO group indicate increased bone formation. What evidence is there to support this? This increase is likely attributed to the effect of OVX rather than FENO. The last sentence in this paragraph is inaccurate and speculative in the absence of supporting data.

19. Discussion: Last paragraph, last sentence: it is highly unlikely FENO would be indicated for the treatment of osteoporosis but it could be emphasized that it may be beneficial for bone in patients on treatment.
20. Figure 4: Add the vehicle control data.

- Discretionary Revisions

1. Introduction, line5: “…broad spectrum of..”

2. Materials and Methods: Animals, paragraph 3: Reword sentence beginning: “Animals were anesthetized....midazolam (1.25 mg/mL) before surgery, for DXA scanning and prior to sacrifice.”

3. Materials and Methods: Animals, paragraph 4: Suggest: “..cardiac puncture under anesthesia. After...or in 4% formalin until analyzed.”

4. Materials and Methods: Bone marrow cell preparation: Clarify if cells were obtained from intact animals. Correct tibias to read tibiae.

5. Results: Whole body and femoral BMC/BMD, first paragraph: Suggest reword: “There were no differences in whole body or femoral BMC or BMD between...”

6. Results: Whole body and femoral BMC/BMD, paragraph 4, line 3: Suggest clarify: “...(Figure 2C) relative to the start of treatment.”

7. Discussion: paragraph 9: Typo line 2: delete “by”. “...in the PIO OVX..”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests