Reviewer's report

Title: Different Skeletal Effects of the Peroxisome Proliferator Activated Receptor (PPAR)Alpha Agonist Fenofibrate and the PPAR Gamma Agonist Pioglitazone

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Reviewer: Guenter Klaus

Reviewer's report:

In their manuscript entitled „Differential skeletal effects of the PPAR## agonist fenofibrate and the PPAR# agonist Pioglitazone” Syversen and colleagues analyze the effects of synthetic PPAR ligands with selectivity for either PPAR # or # in vivo on bone mineral density and bone mineral content, and biomechanical properties of the rat femur. The in vivo studies are extended by measurements of various signaling molecules involved in bone metabolism. The effects of the selective agonists on osteoblast differentiation and proliferation are analyzed in vitro using MC3T3-E1 cells. The key finding of this study is that rats treated with fenofibrate for 4 months exhibit an increased femoral bone mineral density while exposure to pioglitazone decreased it. In vitro fenofibrate is shown to stimulate differentiation, proliferation and OPG release from the preosteoblastic cell line MC3T3-E1. The effects of pioglitazone are largely confirmatory.

Comments:

Discretionary Revisions:

1. The key finding of this study: a 10% increase in femoral BMD with fenofibrate would be significantly substantiated if they could also be induced using another PPAR # agonist such as Wyeth 14643. This would place PPAR # centerstage and reduces the possibility of off target effects of fenofibrate causing the increase in femoral BMD.

2. 10 µm feno – in contrast to lower concentrations- does not promote osteoblast proliferation, why?

Major Compulsory Revisions:

3. Lean body mass and BMD was influenced by the treatment. The authors correctly state, that bone strength is also determined by muscle mass. To strengthen this argument, it is suggested to be analysed, whether there was a correlation between lean body mass and cortical bone volume or thickness.

4. Methods: The gender of the mice used is not given in this section. This might be important, because osteopenia is mainly induced by pioglitazone in female humans. In the pioglitatone group 4 animals (25%) died, whereas no animal was lost in the other groups. Was any specific reason identified for this discrepancy?

Minor Essential Revisions:
5. The data from the human cells should be mentioned in the discussion.

6. Pioglitazone (as fenofibrate) leads to a significant induction of osteoblastic markers yet only fenofibrate increases BMD while pioglitazone does the opposite. This finding needs to be discussed.

7. The discussion contains detailed repetitions of leptin and adiponectin data which are difficult to understand for the reader unfamiliar with this system. Maybe a graph would be more informative to illustrate the current ideas.

**Level of interest:** An article of importance in its field

**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