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: Barbara D Boyan

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Different Skeletal Effects of the Peroxisome Proliferator Activated Receptor (PPAR)a Agonist Fenofibrate and the PPARg Agonist Pioglitazone
Syversen et al.

General Comments

This is a thorough assessment of the effects of two compounds, one of which is a PPARa agonist and one of which is a PPARg agonist, in bone. The manuscript addresses these compounds as if they are representatives of their entire class, but the actual justification for picking these two specific compounds is never provided. Presumably they are experimental compounds under development by Eli Lilly, but if so, the authors should include information that provides specific data about each one, not the least of which is their chemical name and structural properties. Without this information, it really isn’t possible to go beyond what is written to consider mechanisms involved and the reader is forced to accept that these compounds function as agonists of their respective putative receptors as indicated. If this is the first report on the compounds, what is their LD50, and if it is not the first report, where can the reader go to find out. What is the specificity of each compound for its putative receptor? The Discussion should include a paragraph (at the very least, a few sentences) on how the molecular mechanism might account for the results reported.

Specific Comments

Page 3
Moreover, TZDs have been associated...

Page 6
BMD and BMC should be defined.
The location for Hologic should be provided.
Was the histology decalcified or undecalcified?
How many reviewers graded the histology?

Page 7
“the neck” should be described using the anatomic term.
“...by protein isolation...”

Page 8
R&D Systems

Page 9
“...manufacturer’s protocol. Analyses..”

Page 10
Commercially available human...

Page 11
Was FixDenat part of the kit?
DEPC should be defined.
The authors used beta-actin as the reference gene. However, numerous investigators have shown that there are marked changes in beta-actin expression as osteoblasts differentiate due to the shape change that occurs. Most investigators use GAPDH or 18S mRNA. The authors should discuss the potential for changes in beta-actin affecting their observations.

Page 12
M-CSF should be defined.
What do the authors mean by six parallels?

Page 13
Was the osteolyse assay a kit?
What was the source of the primary human osteoclasts? Were these actually purified osteoclasts?
“...two-tailed Student’s t-test..”

Page 14
BMC tended to be...

Page 18
“...on either differentiation...

Page 19...
The authors should see General Comments. The description of fenofibrate as a PPARα agonist should be referenced as should the description of pioglitazone as a PPARγ agonist. The data suggest but do not indicate that the entire class of each compound acts in the way that these two compounds act.

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.