Reviewer's report

Title: Combination therapy with alfacalcidol and risedronate improves the mechanical property by ameliorating the biological apatite c-axis orientation of bone in ovariectomized rat model of osteoporosis.

Version: 2 Date: 28 January 2009

Reviewer: Matthew Allen

Reviewer's report:

The authors are commended on their significant revision of the manuscript. Although the majority of concerns have been addressed, a few remain which lessen my enthusiasm for the paper. This is a nice study which provides interesting data and thus I encourage the authors to carefully consider the comments below.

Major Revisions

1. The method by which the authors determine the ‘addative’ nature of ALF and RIS, although better than the original version, still does not seem appropriate. Specifically, the authors state that an effect was determined to be additive if the combination of RIS and ALF was significantly higher than ‘EITHER’ of the individual effects. This should be changed to be significantly higher than ‘BOTH’ of the individual effects. For example, in the mechanical properties of the vertebra, the ultimate load of the combination treatment is significantly higher than the low dose of RIS, but not versus the low dose of ALF. As such, it does not seem appropriate to conclude that treatment with RIS + ALF is additive when adding RIS to the ALF does not produce a significantly higher value compared to ALF alone. The text should be revised accordingly, not only with respect to this variable, but to all variables for which additive effects are being addressed. Certainlly some parameters such as DPD do show additive effects and should remain termed as such.

2. The discussion related to the BAP c-axis states that the changes in this variable are a ‘cause’ of the mechanical changes. There is no data presented to show ‘cause’; at best the study shows an association. The text should be modified accordingly (pay particular attention to the conclusions in the abstract and discussion).

Minor revisions

1. The introduction paragraph concerning the BAP c-axis is much improved although the last sentence is a bit strong. I’m not sure there is sufficient information (at least it isn’t presented) to say that the BAP orientation is ‘one of the most important’ factors in these outcome assessments.

2. The introduction text concerning bisphosphonates remains misleading. The
authors are simply referencing a few papers that show the effect is on mineralization. There are plenty of papers showing bisphosphonates prevent the loss of bone volume in high turnover settings. Please consider altering this text to provide a more balanced view of the literature.

3. It would be extremely helpful if a figure could be included to show regions of BAP c-axis and pQCT BMD measures. Although the authors have greatly improved the text concerning how these measures were made, a figure would provide even greater clarity.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have received research funding from Amgen, Eli Lilly, and Procter & Gamble and served as a consultant for Merck and Procter & Gamble.