Reviewer’s report

Title: Bone Mineral Density (BMD) Changes in a Bone Health Plan Using Two Versions of a Bone Health Supplement: A Comparative Effectiveness Research (CER) Study

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Reviewer: Bo Rud

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Major Compulsory Revisions

Abstract: The authors state ‘Conclusions: Following the Plan for six months with either version of the bone health supplement was associated with significant increases in BMD’.

This conclusion is not supported by the results. In AlgaeCal 1 the MAPC BMD change from baseline is 0.5%, which is non-significant (p=0.14) (Column 2, Figure 2). The conclusion should not be based on MAPC BMD change over expected because this estimate constitutes an artificially inflated BMD increase based on assumptions rather than empirical facts.

p. 7: ‘Total bone density phantoms’ should be ‘bone density phantom’ or just ‘phantom’. There is no such thing as total bone density phantoms and hopefully, longitudinal stability was monitored by using a single phantom.

p. 8: The description of compliance assessment is confusing and insufficient.
- Does compliance only relate to the intake of the health supplements or does the term also include QOL recordings and recordings of daily activity as measured by the pedometer?
- What does compliance level 1-5 signify?
- There are two compliance assessments, the 5-point scale and the subjective overall assessment. Which of the two was used for the analyses presented in the results section?

Finally, it remains inconcise that the authors define the terms ‘compliant’ and ‘partially compliant’ in the methods section, whereas they use the term ‘highly compliant’ in Figure 2. Is the group of ‘highly compliant’ participants identical to the group of ‘compliant’ participants? Or is the term ‘highly compliant’ a category in the subjective evaluation of compliance made by the study technician and the investigator?

p. 8: It should be stated if the academic statistician took part in the planning of the study. An academic statistician is no safeguard to prevent biased results if she only takes part in the analysis phase of the study.
p.9-10: The authors state that ‘...while the difference was significant between the two partially compliant sub-groups (3 vs. 8, p=0.01).’ To achieve a balanced reporting the authors should state that this result was partly driven by the unexpected BMD decline in partially compliant AlgeCal 1 participants. As stated in the previous review of the manuscript this finding influences the comparative analyses, and therefore it must be mentioned in the results section.

p.10: The first sentence in the discussion section states ‘This CER study was designed to compare the safety and efficacy of two bone health plans’. But on p. 5 it is stated that ‘During the study, new information became available suggesting that the plan might be enhanced by making changes in the nutritional composition of the bone-health supplement. Upon receipt of the ending data, a second study was commissioned to retain the physical activity and health literacy component’. Hence, it appears to be an exaggeration to state that the study was ‘designed to compare safety and efficacy’ - design precedes data collection. This also explains why the study was not conducted as a randomised trial.

p. 10: The authors state that ‘Support for the safety of the AlgaeCal 1 Plan is provided by the absence of adverse events or changes from baseline in the QOL, daily tracking reports and the 43-chemistry blood panel.’. Furthermore, the authors state ‘The most parsimonious explanation for the absence of any change in BMD for the partially compliant sub-group taking AlgaeCal 1, is that this bone-health plan had no effect on BMD when subjects only partially adhered to the plan,

An alternative explanation is confounding. Did partially compliant participants in AlgaeCal 1 for instance use glucocorticoids, did they loose weight, did they smoke more than compliant AlgaeCal 1 participants?

It would also be relevant for the reader to know the number of participants with a BMD decline above expected.

Finally, what is the reason why a BMD decline above expected in partially compliant AlgaeCal 1 participants is not considered an adverse event?

A more elaborate discussion of the BMD decline in partially compliant AlgaeCal 1 participants is needed to before it can be concluded that the results support the safety of the AlgaeCal 1 plan.

p. 10-11: The authors state ‘Although the sequential design, as opposed to an RCT, posed difficulties in interpreting the data, the consistency of changes in BMD with the AlgaeCal 2 plan supports the plan’s efficacy and safety and superiority over the AlgaeCal 1 plan.’

The authors report three analyses to support the superiority AlgaeCal 2 over AlgaeCal 1:

1) ‘The between-groups MAPC in BMD for all subjects in each group was significantly
greater in AlgaeCal 2 than in AlgaeCal 1 (2 vs. 7, p=0.005)'. However, the significant outcome of this analysis is related to the low BMD increase in AlgaeCal 1 overall (column 2 in Figure 2), which again is related to the unexpected BMD decline in partially compliant AlgaeCal 1 participants (column 3 in Figure 2). Hence, the outcome of this analysis appears to be driven to some extent by the BMD decline in partially compliant AlgaeCal 1 participants.

2) ‘A comparison between compliant sub-groups in AlgaeCal 1 and AlgaeCal 2 revealed that the increase failed to reach statistical significance (4 vs. 9, p=0.12)’. The significance level is defined as 5% (two sided), hence this analysis does not support the superiority of AlgaeCal 2 over AlgaeCal 1.

3) ‘The difference was significant between the two partially compliant sub-groups (3 vs. 8, p=0.01)’. The result of this analysis is directly influenced by the BMD decline in partially compliant AlgaeCal 1 participants.

It appears that the analyses supporting the superiority claim of AlgaeCal 2 over AlgaeCal 1 are partly driven by the BMD decline observed in partially compliant AlgaeCal 1 participants. This fact should be explicitly mentioned as part of the discussion on p. 11.

p. 12. The discussion of a possible placebo effect remains irrelevant, irrespective of the grantors considerations. If the grantor wished to assess the effect of AlgaeCal over placebo the study should have been designed accordingly.

p. 13: The authors state ‘No attempt was made to partition the effects of the three components of the Plan since the goal of the study was to examine the effectiveness of the Plans, not the individual components in the Plans. This part should be left out. The present study gives no information about the efficacy of health literacy and physical activity parts of the plan. The authors have previously agreed to this. Possible interactions between the components of the plans remain speculative.

p. 12: The authors state ‘Taken together, these similarities provide considerable evidence that the two groups were reasonably equivalent.’ Considerable evidence of reasonable equivalence is vague. A more concise and realistic wording would be ‘Taken together, these similarities suggest that the two groups were equivalent’.

p. 13: The authors state ‘….the study also underscores the importance of assessing compliance and using compliance as an outcome measure of efficacy.’ This is incorrect, the authors have not used compliance as a measure of efficacy. Instead, the authors have explored if levels of compliance could explain variations in efficacy. Hence, compliance is used only as an explanatory variable.

p. 14: In the conclusion the authors state ‘Notwithstanding the absence of a
placebo group, the unusual finding of the magnitude of the increases in BMD in both study groups is a marked departure from previous studies in which the decline in BMD was slowed or, at best, maintained, warrants further study.’

The wording is inconsistent with the observed BMD decline in partially compliant participants in AlgaeCal 1, as well as the discussion of this finding. This part should preferably be omitted. Otherwise, it must be stated that the increase was only observed in compliant participants.

**Level of interest:** An article of limited interest

**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