Author's response to reviews

Title: Choline-stabilized orthosilicic acid supplementation as an adjunct to Calcium/Vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial.

Authors:

Tim D. Spector (tim.spector@kcl.ac.uk)
Mario R. Calomme (mario.calomme@biominerals.be)
Simon H. Anderson (simon.anderson@gstt.nhs.uk)
Gail Clement (Gail.Clement@gstt.nhs.uk)
Liisa Bevan (Liisa.Bevan@gstt.nhs.uk)
Nathalie Demeester (nathalie.demeester@biominerals.be)
Rami Swaminathan (R.Swaminathan@gstt.nhs.uk)
Ravin Jugdaohsingh (ravin.jugdaohsingh@kcl.ac.uk)
Dirk A. Vanden Berghe (Dirk.VandenBerghe@ua.ac.be)
Jonathan J. Powell (Jonathan.Powell@mrc-hnr.cam.ac.uk)

Version: 2 Date: 5 March 2008

Author's response to reviews: see over
Title: Choline-stabilized orthosilicic acid supplementation as an adjunct to Calcium/Vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial.


Answers to Reviewer 1 comments:

- It should be emphasized in the abstract, and equally so in the discussion, that treatment efficacy only was found in some sites and not in other, with no clear dose response.

  Please see abstract (page 2, paragraph 3) and discussion (pages 13 and 14) in revised manuscript.

- Three bone formation markers are measured, osteocalcin, PINP and ALP. There seems to be no real correlation between these otherwise similar measurements of bone formation. This needs to be explained and discussed.

  Based on the present findings (i.e. significant effect on PINP) and previous studies (see references 27, 28, 30 and 31) we are in the opinion that ch-OSA stimulates specifically collagen metabolism in bone without an effect on non-collagenous proteins. This would explain why no clear effect was obtained on bone markers in general and only on PINP. This rationale is explained in the discussion (page 14) of the revised manuscript.
Answers to Reviewer 2 comments:

- **The key question is, whether ch-OSA is not very effective, or is there a lack of power?**

  Based on the present findings (i.e. significant effect on PINP) and previous studies (see references 27, 28, 30 and 31) we are in the opinion that ch-OSA stimulates specifically collagen metabolism in bone without an effect on non-collagenous proteins. This would explain why no clear effect was obtained on bone markers in general and only on PINP. This rationale is explained in the discussion (page 14) of the revised manuscript.

- **Is silica the effective compound, or choline?**

  ch-OSA is a specific complex of orthosilicic acid and choline. Please see revised manuscript – background section page 4.

- **Why is there an effect on PINP, and not on other markers of bone formation? (osteocalcin, BAP)**

  Please see comments above.

- **Abstract – Conclusion: why the comment “combined therapy of ch-OSA and Ca/Vit D3 is a safe”? This is not mentioned in the results?**

  Please see pages 10 and 11 of the Results section and tables 2+ 3 for the biochemical safety parameters analysed in serum and urine.

- **Discussion: High urinary magnesium/creatinine ratio due to low muscle mass in osteopenic women: please insert a reference**

  Please see new reference by Dominiguez L.J. et al.

- **Discussion: The relatively high dropout rate is not related to the medication itself? (Some (n?) decided not to take further part in the study).**

  Please see ‘Subject Flow Chart’ which was submitted as an additional file. The number of drop-outs is comparable for the placebo group and the ch-OSA group i.e. 27% for placebo (14 on 51 subjects), 25% for ‘3 mg Si’ (11 on 44 subjects), 28% for ‘6 mg Si’ (13 on 46 subjects) and 23% for ‘12 mg Si’ (10 on 43 subjects). Consequently we do not think that the drop-out rate was related to ch-OSA. Please note that both the placebo and the ch-OSA have an identical fishy taste: this “bad” taste may have causing drop-outs in both the placebo and the ch-OSA groups.
• Conclusion: Please remove reference 31 out of the conclusion

Reference 31 is omitted from the conclusion.