

## **Author's response to reviews**

**Title:** A Natural Seaweed Derived Mineral Supplement (Aquamin F) for Knee Osteoarthritis: A Randomised, Placebo Controlled Pilot Study

### **Authors:**

Joy L Frestedt PhD, RAC, CCTI ([jf@frestedt.com](mailto:jf@frestedt.com))  
Michael A Kuskowski PhD ([mike@james.psych.umn.edu](mailto:mike@james.psych.umn.edu))  
John L Zenk MD ([jzenk@humaneticscorp.com](mailto:jzenk@humaneticscorp.com))

**Version:** 2 **Date:** 18 December 2008

### **Author's response to reviews:**

Response to Reviewers Comments Letter

December 18, 2008

Nutrition Journal Editorial Team

RE: MS: 1480054083224650

A Natural Seaweed Derived Mineral Supplement Improved Range of Motion and Walking Distance Following a 50% Reduction in NSAID Dose: A Randomised, Placebo Controlled Pilot Study Joy L Frestedt PhD, RAC, CCTI, Michael A Kuskowski PhD and John L Zenk MD

Dear Nutrition Journal Editorial Team: (or put a contact person's name here)

We are grateful to the Reviewers of our manuscript #1480054083224650 for their insightful comments and suggestions and we are pleased to provide them with the following responses.

#### Reviewer #1

1. How were the subjects randomized? Centralized vs. independent

All subjects were randomized by our independent statistician, Dr. Kuskowski using a centralized computer-generated randomization list.

2. Please list AE's

All of the AE's occurring in this study are listed in the now Table 4.

3. Was ROM difference at V6 statistically significant?

No. Passive and active extension ROM was only statistically significant at V4. Please see ROM details in the "Results" section of the manuscript.

#### Reviewer #2

1. Please use and report data as recommended in the CONSORT statement when writing a paper following a RCT.

The paper has been revised to comply with the CONSORT statement.

2. I'm very concerned about the number of participants (randomly?) allocated to each of the groups ( $N_c=14$  and  $N_e=8$ ); the authors state that they used an ITT approach (?). How come data is allocated like this? Was it a 1:2 allocation with a preference to Placebo?

The randomization was a 1:1 allocation performed by our independent statistician. The reason the number of subjects in the two groups is not equal or nearly equal is because initially 29 subjects were consented, screened and assigned blindly to one of two treatment groups according the randomization code in the order of their enrollment at the time of their screening when they started keeping track of their NSAID pain medication use for 2 weeks prior to their baseline visit for the active treatment. At the baseline visit, 7 subjects no longer met the selection criteria and were discontinued from the trial. Of the initial 29 subjects enrolled, 13 were assigned to the Aquamin group and 15 were assigned to the Placebo group, one of the initial 29 subjects had not yet been randomized to a group assignment. Of the 7 subjects who were initially discontinued, 5 were assigned to the Aquamin group and 1 was assigned to the Placebo group one of the seven subjects was not yet randomized to a group assignment. This resulted in the 22 reported subjects who were ITT treated after screening into this trial during the two week screening period, 8 assigned to the Aquamin group and 14 assigned to the Placebo group.

3. It is not OK to introduce the use of a total  $N=29$  in the Abstract when that isn't the ITT population.

The statement in the Abstract is correct. 29 subjects were initially randomized to each of the two treatment groups during the screening phase (see response to #2 above). Additional language has been added to the Abstract to clarify that only 22 subjects actually went on to treatment and an ITT analysis.

4. When looking at CLINICALTRIALS.GOV it looks like the WOMAC index was the (most) primary outcome as I would expect a priori. Please do not downplay the importance of a primary outcome. I wouldn't hesitate to report non-significant results as the first one in the Abstract.

The Abstract has been revised in response to this reviewer comment.

5. Please provide a Table with the Efficacy data; e.g. N, Mean (SE) for each group and a column with group mean differences.

Please see new Table 3 added to the manuscript in response to this comment.

#### ABSTRACT

6. I would suggest the following title: A Natural Seaweed Derived Mineral Supplement (Aquamin F) for Knee Osteoarthritis: A Randomised, Placebo Controlled Pilot Study

The title has been changed in response to this reviewer comment.

7. Please correct the ABSTRACT according to the number of patients included.

Done. See response to #3 above

8. Refer to WOMAC (e.g. pain, disability and global) as the co-primary outcome. The Abstract has been revised to reflect this. See response to #4 above.

9. When referring to the number of patients being randomly allocated, please provide those numbers. (e.g. Ne=8 & Nc=14).

Done. Please see response to #2 and #3 above.

10. The number of patients included in each (ITT) group would be considered a results (i.e. CONSORT)

The number of patients in the ITT statistical analysis (n=22) has been added to the "Results" section of the Abstract.

11. Although not significant – state the Primary outcomes before ROM and 6MWD.

Done. Please see response to #4 and #8 above.

12. When reporting ROM and 6MWD, I would also like to see the group mean differences (with 95% confidence intervals)

The Abstract has been revised to include the group mean differences with 95% confidence limits.

## METHODS

13. On Page 5, the authors report specifics on the patients enrolled in the study; this should be in the results section. Please correct.

Corrected as requested.

14. I am concerned about how the patients were randomized: Please state!

The explanation of the randomization is already included in the manuscript at the bottom of the paragraph entitled "Study Visits and "Treatment" in the "Methods" section. To further clarify the numerical differences in the number of subjects in the treatment groups, additional detailed language has been added to the "Subject Enrollment" and "Disposition" section of the "Results" section of now revised manuscript.

15. I am concerned about the allocation concealment: how was the result of the randomization implemented (i.e. Describe whether there was a Concealed Allocation)

Every effort was made to conceal the allocation. We used a third party statistician to create a computer generated randomization table and then another third party who correctly labeled either the test article or placebo according to this randomization table and its group code assignments and subject numbers. Additional language has been added to the "Study Visits and" Treatment" paragraph in the "Methods" section to better illustrate this process.

16. In the statistics section please be more explicit on how/when/why the authors used the different tests.

We have specified, in a more detailed manner, the choice of statistical tests in the “Statistical Analyses” section.

17. I approve the ITT note for robustness; however, it is important for the ITT approach that the authors state which patients were considered eligible for this “population”. The ITT population should be all the individuals being randomized-independent of whether they received any therapy etc.

The only subjects we intended to treat were those given test article at baseline after maintaining their eligibility during the screening period. The problem in the execution of this design was that we should not have assigned their treatment/randomization number at the screening visit. We should have waited until we actually intended to treat them. We did not complete baseline measurements nor provide any test article treatment for those who were not qualified after the two-week screening period. Some of these patients who “screened out” did not record daily pain and some did not take any of the NSAIDs during the screening period, etc. so they were not eligible for the trial treatment.

18. Again: Move all the patient specific data (including Baseline Characteristics) to the results section (As recommended in the CONSORT statement). The idea is that until the results section you only include prior knowledge; and in the results section you show “what happened”.

These sections were moved to the “Results” section in response to this comment.

19. I am happy with FIGURE 1 (although it should be presented in the Results section) – however, I’m concerned about the allocation scheme (1:2?)

Figure 1 will be placed in the “Results” section and please see responses #2, 3, 14 & 15 above.

## RESULTS

20. Minor note: When referring to the patients’ body weight I would prefer kilograms instead of pound (use SI units)

The weight figures have been changed to kilograms instead of pounds in response to this comment.

21. In Table 2 – a minor correction; it is incorrect to report SE’s when referring to descriptive statistics – it should be SD’s.

Table 2 has been revised to include SD’s rather than SE’s.

22. When reporting efficacy data – on the other hand – it is “elegant” to provide the Mean values with the SE’s (applicable to hypothesis tests).

In the new Table 3 we have included SE’s for this efficacy data.

Thank you for the opportunity to make these revisions and we look forward to

your favorable review of these responses to the Reviewers Comments.

Respectfully,

Joy L. Frestedt, PhD, RAC, CCTI

Principal Investigator