

## **Reviewer's report**

**Title:** A Natural Mineral Supplement Provides Relief from Knee Osteoarthritis Symptoms: A Randomized Controlled Pilot Trial

**Version:** 1 **Date:** 25 September 2007

**Reviewer:** Lucio Rovati

### **Reviewer's report:**

#### General

This is an interesting (pilot, preliminary and tentative) study on the potential efficacy of a seaweed multimineral supplement on the symptoms of knee OA.

This Reviewer is a strong supporter of the potential benefit (and a careful observer of the potential side effects) of dietary supplements in health and disease. However, I am even more convinced in supporting that the effects should be studied in appropriate high quality clinical trials, before any claims can be made by the authors or inferred by the superficial reader.

This study lacks at least two mainstays of high quality trials, i.e. a sufficient sample size and a sound statistical analysis (the latter is impossible in absence of the former). The fact that this is typical of research in the nutrition field, especially for lack of appropriate resources in performing the expensive clinical trials typical of pharmaceutical research, does not change my opinion. In fact, I am against the publication of otherwise good reports, that do not clearly state repeatedly beforehand (in title, abstract, introduction, methods and results, before making only partial admissions in the discussion as in the present case) that it is just a pilot and preliminary observation from which no claims can be derived, but only further appropriate studies generated.

This is particularly true in this case, where the authors include as an active comparator an unknown, undescribed and previously unstudied formulation of a substance that is also regarded as a prescription drug in Europe and elsewhere (as the authors carefully avoid to mention), as it is the case for what they call glucosamine sulfate (but we do not know what it is since they do not describe how it differs from the reference product). The literature is full of small and inconclusive studies of "glucosamine" that then are included in reviews and meta-analyses, complicating the assessment of the real value of the substance. In this respect, see for example the last discussion in the July issue of *Arthritis & Rheumatism*, where one of such meta-analyses is confronted with its accompanying editorial correctly suggesting to look mainly at pivotal trials for the final assessment of efficacy and safety, rather than concentrating on the confusion introduced by inclusion of any trials that states to have appropriately studied the problem. Since very few authors do this, I suggest that small and inconclusive trials (that on the other hand would deserve publication) are clearly labelled accordingly throughout their manuscript.

This manuscript should therefore completely re-written accordingly.

This review is openly accessible and thus the I do not see any problems in stating that I work in the pharmaceutical company who developed prescription glucosamine sulfate as a prescription drug in OA and participated in several of the relevant studies. If the authors believe that I have an unacceptable conflict of interest, they have the right of asking another reviewer, but I believe this review should be in any case openly accessible.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

This manuscript should be re-written taking into account the comments below and the specific remarks that follow.

Introduction

Second paragraph.

Glucosamine sulfate should be acknowledged as a prescription drug in the countries where it is approved as such. I am not aware of any serious studies showing efficacy of “glucosamine” as a nutraceutical, which has implications also for the validity of the active control in this study.

Methods-Subjects

First paragraph

The restriction in calcium intake limits these preliminary data to subjects with insufficient calcium intake, which should be clearly recognized and makes this study even more preliminary. In addition, the authors should speculate whether the product should be further studied also in patients on a normal calcium diet, which seems unlikely at present.

Second paragraph

A bibliographic reference is not sufficient to justify the sample size. The authors should explain clearly the sample size calculation and explain how it supports the study objectives. The latter needs to be revised, since it is impossible that a study with 15-20 patients/group was designed as such to represent a real proof of efficacy vs comparator treatments.

Methods-Treatments

The authors should give details on the glucosamine sulfate product they used and how it differs from the reference product in terms of active ingredient, pharmaceutical form and pharmacokinetics. Did maltodextrin modify stability and PK behaviour?

I found no reference on how the rescue medication consumption affected the outcomes. If consumption was monitored, data should be reported. If it was not, the study is probably not valid.

### Results-Baseline characteristics

Placebo patients are significantly more severe. This has to be taken into account in the statistics. In any case, this is a major limitation that affects the validity of the study.

There is no description of the reasons for withdrawal.

### Results-WOMAC

There is a general “between groups” significance (limited to pain) which is not clear if it translates into a significant difference between the new treatment and placebo and/or glucosamine. Most likely, given the negligible sample size, none of the differences is significant and thus there is only a trend that should be studied in future studies.

The fact that the combination group shows no efficacy at all is surprising and should be justified.

### Results-6MWD

The absolute changes seem to be irrelevant. The clinical significance of the changes observed should be discussed.

### Results-AEs

The related AEs should be described, similarly to those not belonging to musculoskeletal complaints.

### Discussion

I seriously doubt that the study was designed to test the efficacy of this new treatment and whether it was more or less efficacious than placebo, GS, or the combination with the latter. Please provide all statistical details to support this. Otherwise, please describe clearly and without any claims, the study as extremely preliminary.

The discussion on the “change in the rank of order” has no scientific basis. A statement that the treatment effect may be significant in this study is not acceptable: either it is or it is not significant. Since most likely it is not significant, the interesting preliminary and inconclusive findings should be declared as such, suspend the final judgement and open the way to new trials.

For the rest, the Discussion tries to timidly mention some of the problems, but it is clearly not enough to correct the tone of the rest of the manuscript.

### Abstract

It is completely misleading and should be re-written.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

-It might be useful to add the absolute quantity of the components in Table 1. The

discussion on why these trace elements should be enough to cause a relevant pharmacological effect is insufficient.

-There is a mess when references 17,18, 19 and 20 are quoted. Probably there are mistakes in the text.

-Please justify the cut-off in WOMAC total and describe (and justify) the cut-off in the WOMAC subscales.

-Since the subjects returned to the clinics for further 3 months, it should be recognized as a limitation the lack of assessment of any remnant effect.

-In the Discussion, the trial at ref. n. 19 is reported as a long-term trial, while it is only 4 weeks.

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Reject as not sufficiently sound

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.