Author's response to reviews

Title: No changes on cholesterol levels with a commercially available glucosamine product in patients treated with simvastatin or atorvastatin: a controlled, randomised, open cross-over trial

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Author's response to reviews:

Cover letter to manuscript MS: 2537355160657648
Thank you for valuable comments which we have followed and made specific changes in the manuscript:

Rew 1 AT:
1. The metabolism of glucosamine is not known. This was an explanatory study to investigate if there was a signal that could verify clinical observations of a possible interaction. If a signal had been detected then further studies on possible mechanisms would have been justified. (In discussion)
2. Simvastatin and atorvastatin are to a large extent metabolized by cytochrome P450 3A4. The hypothesis for our study was that glucosamine could interfere with this major metabolic pathway, causing a deterioration in lipid control as was reported for three cases in Denmark. (Background)
3. The patients were on their regular dose of simvastatin or atorvastatin (Methods)
4. We consider that the treatment period of four weeks is adequate for possible glucosamine effects to vanish and thus no further wash out period was considered mandatory. (Methods)
5. The study was powered to detect a difference of 0.48 mmol/L with a power of 81.2 % with a significance level of 0.05 (two sided) and a standard deviation within the groups of 0.52. A sample size of 20 subjects was considered adequate. We can not with this sample size exclude that there may be a type 2 error and thus we would like to change the title of our paper to “No changes of cholesterol levels” (Title and discussion)
6. The treatment order was randomized and half of the patients started with glucosamine and the other half started with control. Thus any effect of an “order of treatment or period effect” has been considered and eliminated by the design of the study.
7. We agree with the reviewer that the conclusions should be more restricted and
we also have changed this (Abstract and discussion).

Discretionary comments

1. We selected the product that was the market leader in Sweden. We do not consider that the choice of product was of major importance for the outcome.
2. Glucosamine could have an effect on glucose homeostasis as stated in the SPC of the product. In order to exclude negative effects on this variable HbA1c was followed as a safety measure. (methods and results)

Rev 2 A-L G-O:
1. Answered in point 5 above
2. Table 2 is presented more clearly with new headings.
3. This was not the purpose with our study.

Abstract: Spelling is revised
Background: The two different sentences are corrected
Methods: Headings are added as suggested.
Results: Simvastatingroup is splitted
References: Halling A is splitted in the third reference.

Discretionary Revisions:
We could not find this in a graphic presentation.