Reviewer's report

Title: No risk for negative effects on cholesterol levels with a commercially available glucosamine product in patients treated with simvastatin or atorvastatin.

Version: 3 Date: 19 January 2012

Reviewer: Andrew Tershakovec

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This is an unblinded cross over design study assessing the potential effect of glucosamine therapy on lipid levels in subjects taking simvastatin or atorvastatin. Specific comments are listed below.

Mandatory comments:
1- If glucosamine therapy did alter lipid levels, it could do it independently, it could interact with statin therapy by altering the metabolism of the statin and thus alter drug levels, or by some other mechanism. The different potential mechanisms should be more clearly described. Is there also the potential that the effect could vary by baseline lipid level (e.g. hypercholesterolemic vs. non-hypercholesterolemic) or other patient characteristics?
2- The metabolism of atorvastatin and simvastatin, and thus the specific potential pathways for drug interactions should be noted.
3- The methods section notes there was a run-in period, but it does not describe what therapy the subjects were getting in the run-in period. I assume they were just on their regular dose of simvastatin or atorvastatin, but this is not defined.
4- There is no washout period between the treatment periods. This is justified by noting the short half life of glucosamine, but the concern here is the timing of a pharmacodynamic effect, not pharmacokinetic. This should be discussed.
5- The statistical section noted that 20 subjects provided adequate power- but the specifics are not provided. For example, was the study powered at 80% or 90%, and to detect what difference in what end points? Also- as the atorvastatin group only has 13 subjects, what the study underpowered for atorvastatin?
6- The statistical analysis should assess for an order of treatment or period effect.
7- The authors make a conclusion on the safety of glucosamine therapy. This is not appropriate. The only conclusion can be based on lipid changes, based upon the actual power of the study. The study is much too small, short term, and not of appropriate design to make such sweeping safety conclusions.

Discretionary comments:
1- Could the brand or formulation of glucosamine have influenced the results?
2- The study assessed glucose and HbA1C, but this is not explained or justified.