Author’s response to reviews

Title: Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials

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Author’s response to reviews: see over
Dear Editor,

We are submitting our revised manuscript "Safety and efficacy of duloxetine treatment in older and younger patients with osteoarthritis knee pain: a post hoc, subgroup analysis of two randomized, placebo-controlled trials" to be reconsidered for publication in BMC Musculoskeletal Disorders. All authors have read and approved the manuscript for resubmission.

We appreciate the thoughtful appraisal of this paper and the reviewers’ comments were quite helpful. We feel that this revision is more clearly written, and that we have addresses all of the reviewers’ concerns. We sincerely hope that now the paper will be accepted for publication.

Please find our responses to the reviewers’ comments appended to this letter below.

Sincerely,

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Response to Reviewer 1:
1) Thank you for your suggestion. We conducted a sub-group analysis comparing oldest of the old (>75 yrs) with the younger old (65 to <75 yrs) and found no significant effect of age on efficacy with duloxetine treatment. This information was added to page 8, paragraph 2.

2) To determine whether there is a dose-related effect on the rates of TEAEs and SAEs requires a fixed-dose study design. So we were not able to make that assessment due to the flexible-dose design of these 2 studies. However, we added the observations we made regarding the frequency of TEAEs and SAEs occurring after patients were escalated to duloxetine 120 mg. See page 9, paragraphs 2 and 3.

Response to Reviewer 2:
1) Age comparison p values were added to Table 1.

2) Table 2 was deleted and its content was added to paragraph 3, page 8.

3) We re-analyzed the data using an “exact version” of the original analyses, which provided the statistics that we added in the footnote to Table 2 for constipation.

4) In order to report the incidence of treatment-emergent vital sign abnormalities with dosing, we excluded any patient who already had a clinically significant finding prior to dosing at baseline. Treatment-by-age group interaction could not be calculated for diastolic hypertension, PCS weight gain or loss; or for orthostatic tachycardia because there were no patient values for at least one treatment group and the model could not fit these data. This statement was added as a footnote to Table 3.