Author's response to reviews

Title: Safety of phosphatidylserine containing omega-3 fatty acids in non-demented elderly: a double-blind placebo-controlled Trial followed by an open-label extension

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Author's response to reviews: see over
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Eric M Wassermann
Associate editor

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Dear Dr. Wassermann,

Thank you for the reviews of our manuscript No. 2122710483517470: “Safety of phosphatidylserine containing ω-3 fatty acids in non-demented elderly: a double-blind placebo-controlled trial followed by an open-label extension”

We have addressed the reviewers’ comments and revised the manuscript accordingly and hope that you will find it now suitable for publication in BMC Neurology

Enclosed please find our response to the reviewers' comments, listing the changes we have made in our manuscript, and the revised manuscript with changes highlighted.

Sincerely,

Prof. Amos D. Korczyn

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Reviewer 1
1. It is important to know how many in each study group were diagnosed with hypertension, diabetes and hyperlipidemia and taking medications for these conditions since this may affect the physiologic response to the PS formulation. There were no significant differences between treatment groups in the incidence of any existing disorder including cardiovascular disease and endocrine or metabolic disorders. This information is now included in page 6 lines 20-22.
2. While reading the background, I became confused about whether the formulation tested is soy derived or from a different source. Soy derived PS was mentioned first, then safe-sourced PS was mentioned next. Safe-sourced is not defined in the manuscript. Consistent use of soy-derived (if that is the correct source) and avoiding the term safe-sourced is preferred.
   The source of the PS (marine source) is now defined in page 2 line 6 and in page 3 line 23
3. In the hematological parameters, basophils were also significantly different in females before correction for multiple comparisons but this is not mentioned in the manuscript text.
   As shown in table 5 the basophils did not differ between treatment groups. The only hematological parameter that did differ between groups was neutrophils count of the female population and this is already mentioned in the text (page 7 lines 24-25).
4. In the statistical analysis section, Bonferroni correction for multiple comparisons was listed, but later in the manuscript Bonferroni_Holm (I believe this is misspelled Bonferroni-Holme) was listed. If Bonferroni-Holm correction was used, this should be stated in the statistical analysis section.
   In the statistical analysis we have used Bonferroni correction for multiple comparisons. The mistake was corrected in page 6 line 10 and page 7 lines 8, 18 and 25.

Reviewer 2
Major compulsory revisions:
A similar paper was also recently published entitled “Phosphatidylserine Containing omega-3 Fatty Acids May Improve Memory Abilities in Non-Demented Elderly with Memory Complaints: A Double-Blind Placebo-Controlled Trial.” focusing on the cognitive effects of such therapy.
Since the usefulness of PS treating conditions with cognitive impairment is not fully proven the authors should mention their previous/and other results in a more detailed way with also underlining the novelty of the present study compared to the earlier one(s)
Additional relevant information was introduced to page 4 lines 6-12.
Minor essential revisions:
1. The authors should present some pharmacokinetic data about the PS-DHA in the introduction.
   There is no available pharmacokinetic data about PS-DHA.
2. The authors should also briefly describe the possible mechanism of action of PS-DHA.
The possible mechanism of action of PS with omega 3 fatty acids attached to its backbone was added to Page 9 lines 18-23.

3. Were the subjects verified if there was any other medical/pharmacological condition which would modify the effect of PS-DHA (absorption, action)?
Subjects were excluded if they had renal, respiratory, cardiac, and hepatic disease, diabetes mellitus, endocrine, metabolic or hematological disturbances unless well controlled. This information is now included in the manuscript in page 4 lines 20-23.

Reviewer 3
My main criticism of this paper is that I believe that it does not warrant a separate publication from the publication on efficacy. Rather the data from this paper should have been summarized in the paper on efficacy. Given that they conclude that there were not significant changes in biochemical and clinical parameters, it does not seem worth publishing 9 pages of tables of negative results of every laboratory study they performed in the study. This information could either have been summarized in the text, or made accessible to readers as supplemental on-line information associated with the efficacy study. There are other aspects of this study that suggest that it should have been included as part of the efficacy study. The subjects are not characterized, only described as “non-demented with memory complaints” and the reader is referred to the efficacy paper. Much of the Discussion is devoted to discussing the parameters that differed significantly on t-tests between the groups. But then the authors conclude that these differences are not actually significant when corrected for multiple comparisons.

Although the efficacy results of 15 administration weeks were already published, we find it of great importance to publish also the 30 weeks safety results, not only due to the fact that the novel compound (PS-DHA) was not tested previously, but also because the studied population consisted of elderly participants. Elderly are known as a vulnerable population in which certain medications are associated with increased risk of side-effects and may pose a safety concern. Although PS-DHA is based on natural ingredients, it is well known that natural products are not always necessarily safe.