Author's response to reviews

Title: Effect of a Proprietary Magnolia and Phellodendron Extract on Stress Levels in Healthy Women: a pilot, double-blind, placebo-controlled clinical trial

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Thank you for accepting our study “Effect of Relora® on Stress Levels in Healthy Women: a pilot, double-blind, placebo-controlled clinical trial”. We appreciate the Reviewers comments and respond as noted below to each of the comments.

Since the reviews were not numbered, but rather the name of the reviewer was given, our reply is personalized so that the editor and reviewers know the responses to the review.

**Reviewer: Jerry Cott.**

1. Honokiol and berberine are marker compounds in the test product. Both compounds have both been reported to have relevant activity and this is the reason why minimum amounts were selected as a quality control measures. Comments on the activity of berberine have been added to the Background section.

2. Psychiatric disorders were determined by medical history, rechecked by the Principal Investigator (a medical doctor) and upon questionnaires given by trained professionals.

3. We asked all study subjects to follow the following: If subject already was taking a multivitamin/mineral supplement, they were allowed to continue doing so in the study (although no supplements that are or were purported to affect mood states were allowed). Study subjects were also not allowed to start any new supplements to be allowed throughout this clinical trial. To ensure compliance, a dichotomous questionnaire was used by the coordinator at each visit.

4. Thank you, we have changed the p=0.0068 to 0.006 per your recommendation.

5. The results or conclusions from prior studies have been removed from the Results section.

**Reviewer: Uwe Koetter**

**Major Revisions:**

1. The Intent to Treat Population in this current study was defined as follows: The intent-to-treat population was defined as all validly-enrolled subjects (i.e.: those who met the inclusion/exclusion criteria and provided informed consent) who received product, and for whom any efficacy evaluations are available (including
baseline evaluations). If a subject was non-compliant, or withdrew early, or was lost to follow-up, the last available efficacy results were carried forward to be used in place of the missing results. This is referred to as last observation carried forward (or “LOCF”) imputation. LOCF imputation was not used for safety variables, only for efficacy variables. In terms of why there were 40 subjects in the ITT Efficacy and only 39 in the Safety analysis, the reasoning was as follows: The safety population consists of randomized subjects, excluding three who were lost to follow-up with no evaluable post-dosing information (#27, #35, and #47). Therefore the safety population has 39 subjects. The intent-to-treat population consists of all randomized subjects, excluding the two subjects who were found not to have met the protocol’s inclusion/exclusion criteria, and were classified as protocol violators (#6 and #22). These subjects should not have been in the study in the first place. Therefore the intent-to-treat population has 40 subjects.

2. Last-observation-carried-forward (LOCF) imputation was performed for missing efficacy variables in the intent-to-treat and per-protocol analyses. As described in Section 5.1, no imputation was done for missing safety variables.

3. We thank the reviewer for astutely spotting the discrepancies in the placebo column of Tables 2 and 3, Upon investigation, we found that there had been an error in the LOCF imputations for one subject (who received placebo). This error has been corrected, and the descriptive statistics and significance tests have been recalculated for these two tables. The related text in the Results – Efficacy section has also been updated accordingly. The correction and recalculation did not change any conclusions from the study.

**Minor Revisions:**

1. All abbreviations are now spelled out prior to the first time that they have been noted in the revised text in their abbreviated form.

2. Page 7, 2nd paragraph, 2nd line has been corrected

Sincerely,

Douglas Kalman PhD, RD
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