

May 1, 2016

Dr. Ken Brown  
Brandi Scott-Hoy  
Dr. Linda Jennings

Dear Jin-Lei Wang,

Thank you for your email dated March 21, 2016. We appreciate the opportunity to address the reviewer comments for resubmission and formal acceptance of our manuscript (ESPS Manuscript NO: 25119, Now numbered 26481) in the World Journal of Gastrointestinal Pharmacology and Therapeutics. The discussion below outlines the changes which were made to the manuscript to address the reviewer comments.

#### “COMMENTS TO AUTHORS

Overall: This study tests an alternative hypothesis to treat patients with IBS, which is a prevalent disease, with impairment of quality of life, and frequently, the available treatments are not enough. Testing new approaches is of major importance. However, this study included 24 patients from a single centre and a retrospective analysis, where patients were selected according to adherence to medical recommendations was performed. Statistics: paired t-tests. Means and standard deviations are used. Was normality checked? A group of 24 is likely non-normally distributed. Conclusions: The conclusion is too adamant for a retrospective study with 24 patients. To address these issues I suggest to consider this study as a pilot study or preliminary results, and highlight limitations of small retrospective studies where patients are selected in accordance to therapeutic adherence: namely bias and confounders.”

We thank the reviewer for their comments and agree with the changes they suggest. In order to address the comment of the size of the study and whether there is a normal distribution, we have chosen to use a different analysis which makes no assumptions about the shape of the distribution. The test we have used is the sign test. The sign test is a nonparametric statistical method used to test for consistent differences between pairs of observations, in this case differences in visual analogue scores for abdominal pain, bloating and constipation before and after administration of the test product. After calculation, we found that the results were unchanged and still highly statistically significant comparing the results after two weeks to baseline. Therefore, the descriptive statistics in Table 1 have been changed from means and standard deviations to medians utilizing the interquartile range of values which fall between the 25th and 75th percentiles. The middle 50% of the data lies between the 25th and 75<sup>th</sup> percentiles, which gives a better indicator of where the data lie if the distribution happens to be skewed or non-normal as the reviewer rightly pointed out. **The changes in the abstract, methods and Table 1 are highlighted in yellow** to reflect the new, more valid statistical approach. In addition to the changes in statistical analysis, we have **altered language in the conclusion section of the abstract and the Conclusion at the end of the paper** so that our suppositions are not “too adamant for a

retrospective study with 24 patients.” We believe by caveating the results for the paper that we have met the requirements of the reviewer. **These are also highlighted in yellow.**

We wish to again thank the editors and the reviewers for the opportunity to address the comments so that this paper can be formally accepted into WJGPT. We look forward to formal acceptance soon so that the information about this therapy can be read by physicians who are looking for solutions in very difficult to treat IBS-C populations.

Regards,

Ken Brown, MD

Brandi Scott-Hoy

Linda Jennings, PhD