

## Format for ANSWERING REVIEWERS



January 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7198-review.doc).

**Title: I.31, A NEW COMBINATION OF PROBIOTICS, IMPROVES IRRITABLE BOWEL SYNDROME-RELATED QUALITY OF LIFE. A PILOT, DOSE-FINDING, MULTICENTER, DOUBLE BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL.**

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 7198

The manuscript has been improved according to the suggestions of the editor and the reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers:

(1) If the subjects fulfilled all the inclusion and exclusion criteria, they were randomized immediately, without a run-in period.

(2) Consumption of PPI was not allowed during the study. Added in the text.

(3) The study was adhered to the CONSORT 2010 statement. The method for randomization was computer-generated random list, both patients and physicians were blinded to the actual treatment given to each patient.

(4) Results were expressed as mean $\pm$ SE. IBSQoL data did not follow a normal distribution, so we used non-parametric ANOVA (Kruskall-Wallis test). A linear mixed model with repeated measures, adjusted for age, BMI and sex, obtained a P=0.024. Data on the statistical test used has been included in the text.

(5) The discussion has been modified following the suggestions of the reviewer: "The most relevant finding of the present study is that a new combination of 3 different probiotic bacteria (I.31 probiotics), taken daily for 6 weeks, had a positive impact on IBS-related quality of life, and this effect was not related to the dose of probiotics".

(6) Data from table 2 has been included in the text, and the table 2 has been erased

(7) We have changed "each" to "this"

(8) The method for randomization was a computer-generated random list, and identical capsules and blisters were produced by AB-biotics, so that both patients and physicians were blinded to the actual treatment given to each patient.

(9) Inflammatory bowel disease and celiac disease were excluded with clinical and analytical data, including blood chemistry, CRP and tisuilar antitransglutaminase antibodies

(10) Visceral sensitivity index (VSI) was used to assess gut-related anxiety. Even though no significant changes were observed between the groups after 3 weeks of treatment, there was a significant change in VSI after 6 weeks probiotic consumption both in patients receiving the high dose

and in those receiving the low dose of bacteria.

(11) As stated in the title, this is a pilot, dose-finding study, specifically powered to detect effects of probiotics on IBSQoL. To detect significant differences in other abdominal symptoms, like pain, bloating or bowel habits, at least 100 subjects per arm should be included. For this reason, these specific parameters were not analyzed. Instead, we analysed a global symptom relief using a 5-point scale. As expected, it showed a greater symptom relief in patients treated with probiotics, but the difference was not statistically significant.

(11) "Figura" was changed to figure

(12) The empty blisters delivered by patients were counted to confirm treatment compliance. No analysis of fecal samples was performed.

(13) Concentration of viable cells was measured from probiotic preparation at the beginning and at the end of the study.

(14) We agree with the reviewer that the terms tendency or trends can only be used when p-values are smaller than 0.1. The text has been corrected accordingly

(15) The abstract and the results section have been modified, and the correlation data have been removed following the reviewers suggestions. We have modified the results in IBSQoL, VSI and relief of symptoms

(16) Figure 2b and 3 has been modified, and figure 4 has been erased

(17) Discussion has been shortened and modified following the reviewers suggestions.

3 References and typesetting were corrected

We hope the changes introduced in the manuscript match all the suggestions raised by the reviewers and that you find now the manuscript acceptable for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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