September 13th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **NO: 13027 revised**).

Title: Oral mixture of autologous colon-extracted proteins for the Crohn's disease: A double-blind trial

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The manuscript has been improved according to the suggestions of reviewers

Sincerely yours,

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Reponses to reviewers:

Reviewer 1:

a. *The paper is quite of interest and also original in design, even if the sample size is small. The Author should better describe how they prepared the colon-specific antigen-containing extract.*

A detailed description was added to the Method section as suggested.

b. *Furthermore if the extract can be administered at meal or fasting.*

An explanation that the drug was administered on an empty stomach was added to the Methods section.

Reviewer 2:

c. *Take an important role of biological treatment in Crohn`s disease, but I pay attention on that there is no CRP protein value, which is very simple and sensitive parameter.*

We accept this comment. CRP data was not available in this study, and is subject for testing in ongoing trials.

d. *The Authors should estimate endoscopic evaluation of mucosal healing, because at the moment it is the most important goal with IBD treatment.*

We accept the comment. Mucosal healing was not evaluated in this trial and will be tested in future studies.

e. *I think that p value should be also used in statistical analysis.*

The number of patients per group was too small to reach significance. As suggested by the reviewer, we have highlighted this point in the Methods and the Results section of the revised version.

f. *Change reference – numbers should be on the opposite site.*

Corrected.

Reviewer 3:

g. *This manuscript bears very similar resemblance to a phase 2 study evaluating Alequel which was published in American Journal Gastroenterology 2006 by the same group (Margalit et al, Am J Gastroenterol 2006;101:561–568). Thus I am confused why the authors would re-do(?) this study in a rather inferior way to the study above, and clearly with insufficient power to detect what should have been anticipated to be a fairly mild benefit (if any) with Alequel over placebo, given the previous study's results. This has culminated in a negative study which does not add to the current literature, given the almost identical study was already done in 2006.*

We thank the reviewer for his comments.

- The aim of the phase II study reported here was to further evaluate the safety and efficacy of oral administration of this personalized drug in a more diverse cohort of CD patients in a randomized, double-blind, placebo-controlled format. Part of the previous trials were uncontrolled proof of concepts studies, or trials on highly selected group of patients. Some of the patients enrolled in the present study had previously failed standard therapy (such as anti-TNF-α and/or thiopurines).
- Furthermore, in this study we evaluated several markers that could be used to construct an immune profile to predict which of these individuals would be likely to respond to the administration of Alequel™. These were not studied before. The data suggests a significant difference in the immune profile of subjects who respond to treatment. The data presented here show an increased ratio of CD4+/CD8+ T lymphocytes in subjects with a significant clinical response, compared with a decrease in the ratio in non-responders.

Reviewer 4:

h. *This paper addresses an important and widely-investigated area dealing with the pharmacological treatment of Crohn's disease. In their article, the Authors describe the results of a controlled double-blind trial of oral administration of the autologous colonic extract that was shown to be effective for the treatment of patients with moderate to severe CD. The Authors well describe all the diagnostic procedures they adopted and the methods for the Study Drug Preparation and Administration However, there are some issues that need to be reviewed to make the paper suitable for publication on WJG 1) The authors should include some inflammatory parameters (i.e., mean CRP and ESR levels) at enrollment and during follow up (6-9-12 weeks) in the drug and placebo group in order to help evaluating clinical response or remission.*

As stated above, CRP and ESR were not followed in the present study and will be tested in future studies.

i. *Provide an endoscopic assessment at enrollment and during follow up, at least for patients with a colonic localization of the disease, in order to evaluate mucosal healing that is today considered the main goal of any IBD-treatment.*

We accept the comment. Mucosal healing was not evaluated in this trial and will be tested in future studies. Enrollment was not based on endoscopy. In light of the comment we have revised the inclusion criteria paragraph in the Methods section.

j. Provide data regarding the steroid sparing-effect of the drug respect to placebo.

In the present study subjects receiving oral steroid therapy at the time of enrollment were required to be on a stable dose regimen of less than 10 mg of prednisone per day for four weeks prior to enrollment. One subject in the drug group and three subjects in the placebo group were on a regimen of corticosteroids (less than or equal to a dose of 10 mg of prednisone) at initiation of treatment. Two patients in the drug group and four patients in the placebo group were receiving azathiopurine at initiation of treatment. These were highlighted in the Results section and in Table 1. No changes in steroid treatment occurred in all evaluable subjects throughout the study period.

k. Improve the statistical analysis using p evaluation (put the numbers)

In light of the remark we have revised the relevant section in the Methods section. As the group was too small, no significant differences were noted between the two groups. The relevant paragraphs in the Results section were revised accordingly.

l. Modify reference paragraph (it's written according Hebrew order from right to left)

Corrected.

m. Improve the figures and figures legend including p values (even if there is not statistically difference among groups).

Figures and figure legends were corrected as suggested.