Professor Lian-Sheng Ma
President and Editor-in-Chief
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Dear Professor Ma,

ESPS Manuscript NO: 9389

Thank you for your letter dated 20th March, 2014, regarding the above article entitled "**Otilonium bromide in patients with irritable bowel syndrome: a dose-ranging randomized double-blind placebo-controlled trial**".

We would like to thank the editor and the 2 reviewers for their critical reading of the manuscript and their helpful comments.

Our point-by-point response to the reviewers' comments is listed below. Also attached is the revised manuscript. Each change made to the manuscript is detailed in the response. We believe the manuscript has improved because of the opportunity to revise it as suggested. If you, or the reviewers, require further elaboration on any points, we would be happy to provide this.

The manuscript, or part of it, neither has been published nor is currently under consideration for publication by any other journal. I declare that the co-authors and I have read the revised manuscript and approved its submission to Drug Design, Development and Therapy.

Thank you again for considering this revised manuscript. I look forward to hearing from you soon.

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RESPONSE TO EDITORIAL COMMENTS

1. The BPG's Revision Policies for Research Reports has been carefully examined and followed it detail.

2. All changes made to the manuscript have been made using Microsoft Word track changes option.

3. The title has now been shortened to 12 words.

4. Since the manuscript has been written by a native English speaker (CGE), a language certificate is not necessary. Regardless, the entire manuscript has been carefully checked again for English language.

5. The BPG copyright assignment forms have now been completed and signed by all authors and are included as a single pdf file.

6. PMID and DOI numbers have been added at the end of each reference where it was possible to obtain. Three of the older cited studies did not have PMID or DOI numbers.

7. A section entitled "comments" has now been added at the end of the manuscript - including Background, Background, Research frontiers, Innovations and breakthroughs, Applications, Terminology and Peer review.

8. The figures have now been included as modifiable figures as Microsoft Powerpoint files.

RESPONSE TO REVIEWERS
We thank the reviewers for their thorough assessment of our manuscript, and for the appreciative remarks. We answer their various comments as follows:

REVIEWER 1

This is well done randomized, double-blind, placebo controlled clinical investigating efficacy and tolerability of oiliniu Otiloniumm bromide in IBS. Only some minor points should be considered.

Minor points:

1) Please close parenthesis in the line 3 of Study design.
2) In Efficacy measurements: This sentence is not meaningful: Regular intestinal habits were also recorded and defined as: "all conditions not present such as constipation or diarrhoea or more then 2 evacuations per week". Please resentence it.
3) In method section, please discuss the dosage form of Otilonium and its placebo.

We thank the reviewer for these positive comments.

1) In line 3 of Study design, parentheses have now been closed (page 8).
2) The definition of "regular intestinal habits" has now been fully described in the Methods section; Efficacy measurements (lines 8-14) according to Ref 16 (Glende et al 2002).
3) The dosage and mode of administration of active medication and placebo have now been described in detail in the Methods section (Study design, page 8, line 8).

REVIEWER 2

This a dose ranging trial for OB in IBS. The authors should be congratulated on performing this study in a rigorous manner.

1)I have several issues with the presentation. The statistical section indicate that pain and 'evacuation capacity' were the primary endpoints yet the results section and abstract are not so clear. What is evacuation capacity? If these were your primary endpoint then this is a negative study for the key endpoints associated with IBS. In addition, several other key endpoints were also negative (discomfort, bloating, etc..). This should be clearly stated in the abstract, results and discussion.

The reviewer makes an excellent point. The primary efficacy variables were incorrectly described in the statistical methods section and have now been modified to "abdominal discomfort or pain and stool/defecation (evacuation) frequency" (Statistical analysis, page 10, lines 2-3). The negative results of these primary endpoints have been clearly presented in the Abstract (page 3, lines 11-14), Results (page 11) and Discussion sections (page 14, paragraph 3, page 15 paragraph 1)

2) What does 'regular intestinal habits' mean? The definition given in the Methods section ('all conditions not present such as constipation and diarrhea or more then 2 evacuation per week' is not clear so it is impossible for me to understand these results.

The definition of "regular intestinal habits" has now been fully described in the Methods section; Efficacy measurements (lines 8-14) according to Ref 16 (Glende et al 2002),

3) Figure 3 and 4 are identical. Since there is a paucity of data in the results section I can not comment on the results that should be in Figure 4.

There was an error performed during the upload process during submission and the correct Figure 3 has now been included.

4) Was the discomfort index prespecified? Is there precedent for its use (i.e. published elsewhere?). What components of this index were driving the results?

The Global discomfort index as used in this study has not been previously published. However, a similar global index (termed "global efficacy") has been previously used by Clave et al. (ref 15: 2011) in the OBIS trial. It was designed in order to assess the clinical efficacy of the drug in a complex pathology such as IBS where each single symptom (that is recognized to wax and wane) can be integrated into a statistical algorithm in order to facilitate a global assessment of drug efficacy.

5) The study was completed in 2008 have parts of these results been published elsewhere? Why the long delay?

This study has not been published elsewhere. Frequent turnover in the people managing the product in the sponsor company is responsible of this delay.

6) The distention results at the end of the study should be presented.

While some ano-rectal distention parameters were measured in the present trial, the large degree of experimental variability did not allow the applicability of inferential test appropriate for the evaluation of this data and results were inconclusive. These data were therefore omitted from the present manuscript. However, these results have now been briefly acknowledged in the Discussion section (page 14, paragraph 2, lines 9-11).

7) I don't follow the arguments in the 2nd paragraph of the discussion.

The main points made in the second paragraph of the Discussion highlight that in a longer and larger trial such as OBIS (Clavè et al., 2011) the drug was able to affect the single main symptoms of IBS such as abdominal pain frequency and bloating while others were unaffected. In the final part of the paragraph it is discussed that the OBIS trial has used inclusion criteria of Rome II (like the present study) that exclude people with transient symptoms. This paragraph has now been revised for clarity.

8) Does the current study really address the limitations of this large study of longer duration?

No. The present study is obviously limited by the much smaller sample size. In order to overcame this limitation, we have built the algorithm "global discomfort index" able to integrate the symptoms and to gathered a more precise information on the status of the IBS patient (see point 4).

9) Does this study include a population different from the OBIS study? If so I would emphasize this.

The inclusion criteria used in the present study were the same as those used in OBIS. Differences between the 2 studies are mainly specific to the supportive effect of being entered into a long-term trial; frequent (weekly vs monthly) visits are well known to lead to patient expectation as well as the patient-practitioner relationship, both potential contributing factors in the improvement of the symptoms. This has already been addressed in the final 2 paragraphs of the Discussion.

10) What dose of OB do you recommend for patients.

This study confirms that 40 mg tid of OB is the recommended dose. Due to lack of adverse effect 80 mg tid of OB can be used as well. This has now been clearly stated in the conclusion of the Abstract and at the start of the Discussion section (page 14).

11) Do any of the authors have any conflict of interest?

None of the authors has a conflict of interest.