

25th June 2018

World Journal of Gastrointestinal Pharmacology and Therapeutics

Subject: Submission of revised paper

Manuscript NO.: 39914

Dear Editor,

thank you very much for your email dated 19th June 2018.


We like to thank the reviewers for the valuable comments to improve the quality of the manuscript.

We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

Changes to the manuscript are shown in track mode.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,


Jasmin Steudle

Response to Reviewer 1:

Thank you for your review and your comments to our paper. We have answered each of your points below.

1.- How did they recognized and excluded subjects with liver enzymes > 10% above reference range, fasting blood glucose > 100 mg/dL or HbA1c > 5.7 %, total cholesterol > 250 mg/dL or triglycerides > 150 mg/dL, hemoglobin < 11 g/dL (women); < 12.5 g/dL (men)? Were all the mentioned variables assessed at the baseline????

The blood routine parameters were determined in venous blood samples at screening and judged by the investigator according to the exclusion criteria. (Inserted page 8)

2.- *What does it mean "without major protocol deviations". Is there any minor protocol deviations? What were those?*

Just minor protocol deviations occurred. An individually standardized dinner had to be consumed prior to study visits. Furthermore, subjects should drink at least 200 mL of water before they come to study site at the study visits. Reported minor deviations were e.g.: two subjects drank less than 200 mL of water in the morning before the visit; 3 subjects had minor deviations regarding the standardized dinner (cottage cheese instead of spread cheese; 25 % fat or 45 % fat of spread cheese; only 2 slices cucumber instead of 7 slices of cucumber).

A comment about these minor deviations was added in the manuscript on page 11.

3.- *What was the strength of the study? has this study any novelty?*

Inserted page 15:

"This study adds data for currently marketed lactulose products to available data published between 1964 and 1999. For the first time two doses of two lactulose formulations (crystals and liquid) were compared in a cross-over design. Furthermore, older studies included less subjects [7,8] or women only [9]. The study was performed in compliance with ISO 26642:2010."

4.- *Check the abbreviations. You should explain each of your abbreviations the first time it appears in the text. e.g. glycaemic index (GI).*

We checked all abbreviations.

5.- *In discussion section, discuss why this could happen: "Despite the higher concentration of carbohydrate impurities in the used lactulose liquid formulation with 26.45 % in comparison to only 1.5 % in crystals, both formulations showed similar blood glucose curves with no differences when evaluating primary and secondary endpoints".*

Inserted page 15 including new reference:

"This can be explained by the low total amount of sugars in both lactulose products (i.e. 0.3 g in crystals and 5.29 g in liquid formulation in the 20 g dosages). Furthermore, not all sugars may affect blood glucose to the same extent as glucose [15]."

6.- The discussion section should be written more extensively, and focus on previous related studies. Discuss previous related studies.

Data were discussed in more detail with reference to available literature data, see discussion part. (Added at page 14, 15.)

Response to Reviewer 2:

Thank you very much for reviewing and confirming the scientific validity of our manuscript.

Response to Reviewer 3:

Thank you for your review and your comments to our paper. Please refer to the answer below.

1. Taking in consideration the role of exercise in energy expenditure, a more strict design might have been more appropriate especially if we are to consider the expected variation between subjects in regard and how it can influence the blood glucose levels.

This is a very good point, however, outside of the scope of this study. For this study we have chosen a study collective with mixed sportive activities (88 % indicated to perform regular sports which was recorded during screening visit). However sporting activities were restricted 24 hours before the visits including vigorous exercise on the morning of the study days. The study restrictions concerning nutrition, alcohol and sporting activities were in accordance with ISO 26642 “Food products – Determination of the glycaemic index (GI) and recommendation for food classification”.

Furthermore, the study was performed in a cross-over setting for each study part. Thus, the subjects served as their own control and variation between subjects did not have any influence on the relevant treatment comparisons between lactulose doses (crystals), glucose and water on the one hand, and between lactulose doses (liquid), glucose and water on the other.

3rd July 2018

World Journal of Gastrointestinal Pharmacology and Therapeutics

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Manuscript NO.: 39914

Dear Editor,

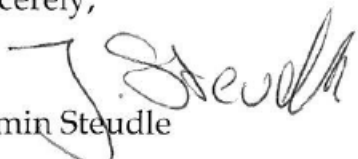
thank you very much for your email dated 29th June 2018.

We have revised the manuscript accordingly to your comments. Unfortunately we were not aware of these comments during our first revision cycle. Sorry for having missed it, but we did not find it in the earlier emails. Thanks for the second chance.

Our responses are given in a point-by-point manner below.

Changes to the manuscript are shown in track mode.

Sincerely,



Jasmin Steudle

Response to Editor:

1 About reviewer 2, the reviewers give the comments: Very minor changes needed: Move core tip (p 4) to be part of conclusion of abstract. Page 5, delete etc line 8, add and in front of excellent (line 8) Page 6, delete etc (last sentence study design) Page 2, line 6, one in place of once, add The in front of majority (line 17) Page 14 replace were kept by being (line 8) . We had send you the comments via my email, but in the answering reviewers file, you did not give the details answer, so please reoffer the answering reviewers file;

All comments were changed accordingly. I hope I changed everything at the correct position. Please let me know if I misunderstood something.

2 Please provide the decomposable figure, whose parts are movable and words can be edited.

I send you the power point file with the figure. I hope this works, otherwise please let us know if you need another electronic format.

3 There are many simiar sentences (highlighted in the crosscheck report) with other articles, please rewrote these sentences.

We rewrote some sentences, mainly in the introduction.

However, the matches with clinical trial gov were not changed as these refer to the registration of the presented study.