Author's response to reviews

Title: Efficacy and tolerability of PEG-only laxative on faecal impaction and chronic constipation in children: a randomized controlled study vs a standard PEG-electrolyte laxative.

Authors:

Francesco Savino (francesco.savino@unito.it)
Serena Viola (viola.serena@libero.it)
Erasmo Miullari (erasmo.miullari@oirmsantanna.piemonte.it)
Giovanni Di Nardo (giovanni.dinardo@uniroma1.it)
Salvatore Oliva (salvatore.oliva@uniroma1.it)
Salvatore Cucchiara (salvatore.cucchiara@uniroma1.it)

Version: 5 Date: 18 September 2012

Author's response to reviews: see over
Efficacy and tolerability of PEG-only laxative on faecal impaction and chronic constipation in children: a randomized controlled study vs a standard PEG-electrolyte laxative

We thank the reviewers for their thoughtful suggestions. Please find below an itemized response to all the reviewer comments:

Response to Reviewer 1 (Hannah Ladenhauf)

Conflict of interest, funding

The following phrase has been added to the section Competing interests: “The study was partially funded through a grant from Promefarm to our Institutions. The funding sources had no role in the study design, data collection, data interpretation, data analysis, or writing the manuscript”.

Enrollment of Patients:

1) Age

We agree with the Reviewer that this point needs clarification and change. We confirm that, according to the study protocol, eligibility for entry was limited to children between 2 and 16 years. We also checked the data of patients demographics in Table 1 and confirm that they are correct. The inconsistency is therefore in the phrase included in the discussion which has been accordingly modified. In table 1 we have added the age range for each study group.

Study Program

2) Faecal Impaction:

For children with faecal impaction we actually overlook the GCP rule that leave parents a period of 24 hours to provide consent. The Ethical Committee did not raise any objection to the protocol requirements. However it must be considered that both products were already available in the market. As a matter of fact, the study did not evaluate new investigational drugs but was intended to gather new knowledge relevant for clinical practice.

As reported in the Methods, treatment for faecal impaction lasted until resolution or for a max of 6 days for PEG-only group or 7 days for PEG-EL in accordance with the respective product labelling.

At visit 2, children resumed treatment for constipation at the scheduled doses and were followed up for treatment response according to the study protocol.

3) Follow-up

No, children were not followed-up after visit 3 (end-of treatment).

4) Analysis (major)

We agree with the Reviewer that two different study groups were evaluated in our study – children with faecal impaction and children with chronic constipation. We maintain the position that it is not appropriate to make statistical comparison for patients with faecaloma due to the limited size of the sample. In order to be consistent with that, we have revised the phrase in the discussion, as follows:

“The small sample of children with faecal impaction did not allow a proper statistical comparison; however PEG-only appeared to be slightly faster than PEG-EL in disimpaction”.

In our opinion it is appropriate to maintain children after disimpaction in the constipation group for two reasons:
- All our children with faecal impaction had a history of chronic constipation (faecal impaction may be considered an additional condition, related to chronic constipation)
- After disimpaction children require treatment for constipation (also to avoid the recurrence of faecal impaction).

In order to evaluate the robustness of our results, we have made an additional efficacy analysis excluding children previously treated for faecal impaction and the results are confirmed.

We have accordingly changed the text of the manuscript.

5) Exclusion from analysis (major)
In our opinion our procedure for analysis is appropriate and in line with the Consort Statement for parallel group randomised trials. We excluded from efficacy analysis the children (n=4) who discontinued treatment. Children receiving medication influencing GI motility at baseline did not meet the inclusion criteria and did not enter the study. The inclusion/exclusion criteria were therefore implemented correctly. This differs from use of laxative stimulants (rescue therapy) during the study which was considered as a secondary efficacy analysis. We hope this clarify this point.

There is no need to change the text of the manuscript

6) Power analysis (major)
Enrolled children were 96. ITT population 91 and after exclusion of drop-outs the PP population was 87 (see Figure 1). According to our statistician, the power analysis indicates the population to be recruited, not the actual population completing the study which is unknown at the study planning. We therefore confirm the power analysis with 44 patients per group. With regard to children with faecal impaction, we refer to the response 4).

There is no need to change the text of the manuscript

Discussion

7) Safety statement (major)
Actually, the primary endpoint of the study was efficacy. However we also collected data to evaluate tolerability, acceptance and compliance between the two formulations. We did not perform lab evaluations so our investigation on safety is limited. We collected data on clinical tolerability and suspected ADRs which are part of safety. We agree eliminate the word “safe” from the text of the manuscript (section Discussion).

The text of the manuscript has been changed accordingly

8) Efficacy statement (major)
Actually the statistically analysis does not allow to make a comparison and conclude for a difference between the two formulations. However by considering the rate of disimpaction after 3 days of treatment we can reasonably conclude that both formulations are effective for faecal impaction.

There is no need to change the text of the manuscript
Response to Reviewer 2 (Mike Geraint)

1) Dose of the two products (major)
As reported clearly in the paper, the study aim was to compare the efficacy, tolerability, acceptance and compliance of two PEG-based laxatives having different features.
Both products were already available in the market and we used in accordance to product information.
This is clearly described in the Methods. In the Discussion it is reported that the dose recommendation for PEG only is based on body weight and for PEG-EL is based on the child age.
The interpretation of “the better efficacy of the PEG-only formulation” observed in our study “is that it contains a higher amount of PEG as compared to PEG plus electrolytes” is duly reported in the discussion.
We agree with the reviewer about his comment for Abstract.
We change the abstract as follows:
“At doses recommended by the manufacturers, children in the PEG-only group had higher and more regular soft stool frequency than PEG-EL.”
The text of the Abstract has been accordingly changed.

2) Treatment of faecal impaction (major)
We agree with the reviewer that it is not appropriate to make statistical comparison for patients with faecaloma due to the limited size of the sample. We have consequently removed the phrase in the discussion which improperly reported the success rate in the faecaloma treatment for both products.
The text has been accordingly changed.

3) Non-equivalence (major)
A better explanation has been added in the discussion reporting the PEG-only formulation contains a higher amount of PEG as compared to PEG plus electrolytes
We agree to include a phrase about the clinical significance and value of stool frequency for evaluation of constipation.
“Stool frequency alone is not necessarily a measure of the clinical efficacy and other variables are sometimes considered (stool consistency, difficult or painful defecation), especially for adults”.
The text has been accordingly changed.

4) Acceptability and compliance (major)
We accept the point. The term tastless has been deleted.
Again the comparison was made according to prescribing information. The fact that PEG-only can be taken with many fluids and drinks explains its better taste/palatability. As a consequence, the taste of PEG-only does not have a significant value.
The text has been accordingly changed.

5) Tolerability, preference (major)
The evaluation of tolerability has been well defined (episodes of nausea and abdominal discomfort as well as acceptability (difficulty in administration and taste/palatability). We removed the word “preference”. Ease of administration is simply the reverse of difficulty administration.

**Minor revisions**

1. The dose of PEG only has been clarified in the text.

2. Correct. All children entered formally at visit 2.

3. Correct. The text has been revised

4. Correct. The phrase “when they are dissolved in 125 ml of water” has been added.

5. References have been added.

6. References have been added.

7. The definition of responder was “children with at least one daily painless defecation of soft stools without stimulant laxative”.

**Discretionary revisions**

1. The text has been corrected

2. The ITT and PP are shown in the trial flow chart