

Reviewer 1.

The present study addresses a key issue for the daily intestinal constipation gastroenterology clinic. However, it should be regarded as a pilot study. I suggest that some points should be emphasized in the text:

1. The title should emphasize the primary goal of the manuscript as a tolerance study of the drug.

A: As the primary goal of the study was to evaluate the resolution of straining and lumpy or hard stools in subjects taking PEG 3350 as compared to placebo, and not to assess tolerance to PEG 3350, mentioning as such in the title would be incorrect. Moreover, title word-count limitations (<12 words) preclude the addition of text without deleting important text already there.

2. How precisely define occasional constipation? It is possible? The text would need to better explain this clinical condition.

A: We thank the editor and reviewers for this point because the definition of occasional constipation is crucial to interpretation of the results. There is no validated definition for occasional constipation. Neither the original FDA monograph proposal published in 1975 nor subsequent revisions provided a definition for 'occasional constipation' based on symptoms or differentiation from physician-diagnosed and treated constipation (e.g., chronic constipation or idiopathic constipation). The only possible differentiator for occasional vs. chronic constipation is that symptoms respond to self-directed treatment within one week.

The term occasional constipation was suggested as the label indication for OTC laxatives by an expert panel in their proposal for the initial FDA OTC laxative monograph published in 1975. The panel recommended the term occasional constipation, but did not define the term in any objective or subjective means by which it would distinguish constipation symptoms appropriate for self-diagnosis and treatment versus symptoms that could be termed chronic constipation or idiopathic constipation. The expert panel cited a 1965 publication by Connell et al which defined a stool frequency of less than 3 bowel movements per week as indicative of constipation. The FDA defines occasional constipation not defined by specific symptoms, but by frequency. The protocol attempts to define occasional constipation based on symptoms using modification to the Rome criteria, and also relied on frequency of bowel movements.

Based on this, we have added further text to the manuscript in the introduction that clarifies some aspects of the definition of occasional constipation as follows:

Although there is no validated, agreed-upon definition of occasional constipation, this study evaluated occasional constipation sufferers as being those with constipation (straining with lumpy or hard stools, or the inability to produce a BM in the last 48 hours) that does not resolve on its own with time, as opposed to chronic sufferers who need prescription medication and/or medical intervention to resolve their problem.

Additionally, in the Methods, in the inclusion criteria section, we added the following (shown here in boldface):

Subjects had to be users of OTC laxatives for the treatment of occasional constipation (**defined as using a nonprescription laxative to treat < 3 episodes of constipation within the last 12 months prior to randomization**).

批注 [Cactus1]: Please suggest if this way of representing of changes is acceptable.

#### References:

- i. Proposal to establish monographs for OTC laxative, antidiarrheal, emetic, and anti-emetic products. Fed. Reg. 40(56): 12902 – 12944, 1975.
- ii. Laxative drug products for over-the-counter human use; tentative final monograph. Fed. Reg. 50(10): 2124- 2158, 1985.
- iii. A.M. Connell, et al. Variation of bowel habit in two population samples. Br. Med. J. 2: 1095 – 1099, 1965.
- iv. G. F. Longstreth, et al. Functional bowel disorders. Gastroenterology 130 : 1480 – 1491, 2006.

3. The conclusion is adequate, but needs to be emphasized in the title. We conducted a similar study in Brazil in 2003. It was titled "Subjective Global Assessment (SGA) of the symptoms of the Gastrointestinal Tract (GIT) of patients with Constipation after 2 weeks of treatment with Tegaserod (Novartis)

A: Thank you for this point; we agree that including the trial duration in the title provides important information. The title has accordingly been revised to the following: Polyethylene glycol 3350 in occasional constipation: A one-week, randomized, placebo-controlled, double-blind trial

#### Reviewer 2.

Since PEG 3350 has been shown to be effective in chronic constipation, it is not surprising, nor unexpected, that it also helped relieve occasional constipation. The second part of the conclusion, ie, it is more effective and better tolerated by patients than other laxatives is, however, questionable. Thus I suggest that the latter part of the conclusion be toned down and this limitation of dependence on patient's perception be mentioned in the discussion.

A: Thank you for pointing this out. The conclusion has been revised to indicate that PEG 3350 *may* be preferred by subjects over other laxatives; the conclusion does not draw comparisons with other laxatives regarding efficacy or tolerability but simply states that it is safe, effective, and well tolerated. The discussion has been revised to indicate the important limitation pointed out by the reviewer of the dependence on patients' perceptions, as indicated by the following new text:

The self-limiting nature of occasional constipation may sometimes result in spontaneous improvement, which could be perceived by the subjects as a drug-related effect, especially over the short one-week treatment duration. This could also have had an effect on the global assessment of the impact of constipation on the subjects' daily lives and their laxative preferences, which were based on the subjects' perceptions of symptom alleviation.

#### Reviewer 3.

An interesting paper, facing a scarcely investigated topic (occasional constipation). My comments are detailed below.

1. Page 8. the author states that the study was a multicenter one, yet no affiliations/multiple authorship/investigation sites were given. Please amend this point.

A: Details of the study sites and primary investigators have been added as a new table, Table 5.

2. It would be useful to have a better definition of occasional constipation.

A: Please see response to Reviewer 1's second point.

3. The discussion should go a little more in depth on the possibility that occasional constipation could spontaneously improve, and a one-week treatment could be considered as a placebo.

A: Thank you for this excellent point, also pointed out by Reviewer 2. The discussion has been revised accordingly, as indicated by the following new text:

The self-limiting nature of occasional constipation may sometimes result in spontaneous improvement, which could be perceived by the subjects as a drug-related effect, especially over the short one-week treatment duration. This could also have had an effect on the global assessment of the impact of constipation on the subjects' daily lives and their laxative preferences, which were based on the subjects' perceptions of symptom alleviation.