PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and Tertiary Centers: The Alpine study
AUTHORS	Pohl, Daniel; Fried, Michael; Lawrance, Dominic; Beck, Elmar; Hammer, Heinz

VERSION 1 – REVIEW

REVIEWER	Lucinda AHarris Mayo Clinic Scottsdale, Division of Gastro & Hepatology
REVIEW RETURNED	05-Dec-2018

GENERAL COMMENTS	This is an open label multi-center observational study (N=138 pts) involving adult pts in Austria and Germany that were assigned to receive 290ug of linaclotide for the treatment of moderate to severe IBS-C for 4 weeks in Austria (2 visits) and 16 weeks in Switzerland (3 visits). It is unclear which diagnostic criteria if any were used to make a diagnosis of moderate to severe IBS (Rome 3 or 4) or just clinical impression. Was any scale administered to the pts to determine severity? The study was performed to determine the real world tolerability of Linaclotide.. Indeed there seemed to be a statistically significant improvement in abdominal pain, bloating and constipation. There was however no placebo grp. Having the following questions/comments 1. Was the dose of drug ever adjusted or the drug held by the clinician? 2. Page 4 of the PDF – would the authors be so kind to define their terminology as there is no abbreviations guide so I am clear as to the intent under Resutls & gt p&it 3. Was compliance to taking the medication assessed in any way? 4. What is the basis of this 11 point scale that was used ? Has it been validated? Information as to the nature of this scale and validation should be discussed. 5. There is much room for bias in this study as this is physician assessed outcome. The discussion should include the fact that efficacy in pts was not a composite endpoint as it was in the clinical trials so in one sense the efficacy may seem somewhat inflated as compared to the trials. 6. Although mostly excellent there should be some review of the English, e.g. page 8 line 123. The decision to treat a pt with linaclotide was “taken” probably would be more correctly said was made.

	7. Was lubiprostone used by any of the patients? The observation that concomitant laxatives decreased the efficacy of the medications is an interesting one but reading this paper one is not clear on what percentage of the pts used concomitant laxatives as this data is missing from Table 3. It might be interesting to also spell out the laxative type that was used i.e. osmotic,etc. 8. Are you able to figure out what % of pts got relief of both increase in BMs and improvement in abdominal pain, that would also be a good “real world “ analysis, although it would need to be clearly spelled out that this was not equal to the clinical trials because different criteria were used. 9. Despite the significant potential for bias, I do feel this study does have value in describing the “real world “ experience of the drug.

REVIEWER	Tadayuki Oshima M.D., Ph.D. Hyogo College of Medicine, Japan
REVIEW RETURNED	02-Jan-2019

GENERAL COMMENTS	In the manuscript by Pohl et al., the authors evaluated the effectiveness and safety of linaclotide for the treatment of IBS-C in a real-world setting. The results must be important to know the treatment effectiveness of linaclotide on IBS-C in countries. However, there are some concerns in the study. Major 1. The reasons why the treatment courses were different in two countries were not clear. Although the authors stated the rate of discontinuation of linaclotide over the course of the study, when did the actually discontinued. Did they all happen over 4 weeks treatment? 2. They should show the data of the frequency of bowel movements even in Figures 2 and 3. It is good to know how pre- and concomitant laxative treatment affect the outcome with linaclotide. Furthermore, they should clearly state what laxatives were used. 3. What was the definition of “improvement” in general symptom, abdominal pain, bloating, and constipation? Although the improving rates were high in this study, the most important point of the outcome must be the satisfaction for the treatment. Just the improvement of the value of scores does not always introduce the satisfaction of patients. Minor 1. Introduction. Although the prevalence of IBS must be high, the prevalence of IBS-C is not high when they are defined by the Rome III criteria (PMID: 26095436). As the definition easily affect the prevalence of IBS-C/IBS, it is better to state the prevalence of IBS-C defined by the Rome III/IV criteria and by other definitions. 2. How did the authors define moderate-to-severe IBS-C in this study? If it is not defined clearly, selection bias must exist. 3. Figures 1 and 2. Does “visit 2” always mean at 4 weeks in this study? Please state this point clearly. 4. It is better to show the data of Figure 2 with the median and 95th percentile as the data must be skewed. 5. Lines 193 to 195. They should not state this without statistical significance. As the employees of the company are included in the authors, they should be careful to state the results of linaclotide. 6. Lines 306 to 309. Did they perform statistical analyses for these differences? These should be stated in the results and should be discussed.

	7. Lines 309 to 312. The reference 21 did not show that PEG exacerbates abdominal pain and bloating at least. As far as they state these important issues, they should refer appropriate references. They should also state how the data were inconsistent in previous reports. 8. Line 386. If the published data with the real-world setting using linaclotide from other countries including Germany, they should refer those articles.

REVIEWER	Apoorva Chandar Case Western Reserve University Cleveland, Ohio United States of America
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	The authors should be commended for their efforts in conducting a well done non-randomized study to see the real world effectiveness of linaclotide in the Alpine region. There are a few concerns that need to be addressed: 1. Did the included participants meet Rome II/III/IV diagnosis for IBS-C? 2. Being a real world study, it is not expected that the inclusion and exclusion criteria for linaclotide be as strict as the original RCTs. However, a small, but not insignificant proportion of patients were on psychoanaleptics or psycholeptics. Did these include anticholinergics which could potentially cause constipation? 3. About a quarter of patients in both study populations were on laxatives at baseline. These were presumably allowed to continue during the study. Specifically, in the original RCTs of linaclotide, patients on a stable, continuous regimen of fiber, bulk laxatives, or stool softeners in the previous 30 days prior to start of the study were allowed to continue taking the medications. What process/procedure was followed in your study? Were all laxatives allowed to be continued? Did certain laxatives have to be stopped prior to starting linaclotide? Can the authors comment? 4. While the outcome time points for the 2 study populations are different, could the authors have reported on the composite EMA or FDA endpoint for the Swiss population? 5. What would have been interesting is if the same satisfaction scale comprising (0 to 10 scale) that was used to measure physician satisfaction with linaclotide therapy could also have been administered to patients to see what their level of satisfaction was and then comparisons could have been made. 6. Quality of life is an important outcome measure in IBS-C sufferers. Clearly, from the study, it seems that there was noticeable and substantial improvement in symptoms. It would have been useful if the authors had used a scale like IBS-QOL (or even other scales like SF-36, etc.) to see the impact of their study on quality of life. 7. I think the biggest shortcoming (which the authors acknowledge to an extent) is that the study had a very small sample size and much more sophisticated analyses could not be undertaken. The other shortcoming is the different outcome time points for the 2 populations. While the patients in Austria started seeing meaningful improvements by week 4, it may be too premature to see sustained improvement and hence, the Swiss population's outcome data is more robust.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Reviewer Name: Lucinda A Harris
Institution and Country: Associate Professor, Mayo Clinic School of Medicine, Scottsdale, AZ, USA

1. It is unclear which diagnostic criteria if any were used to make a diagnosis of moderate to severe IBS (Rome 3 or 4) or just clinical impression. Was any scale administered to the pts to determine severity?

Response: In keeping with the real-world study design, IBS-C diagnosis and severity grading were at the discretion of the treating physician. New wording has been added to paragraph 1 of the 'Participants' section of the Methods to clarify this.

2. Was the dose of drug ever adjusted or the drug held by the clinician?

Response: Dose reductions were reported due to an adverse event in two patients in the Austria study. This information has now been added to the 'Safety and Tolerability' section of the Results.

3. Page 4 of the PDF – would the authors be so kind to define their terminology as there is no abbreviations guide so I am clear as to the intent under Results & gt p&it

Response: We have reviewed the terminology used in the manuscript and have provided the abbreviations at first mention.

4. Was compliance to taking the medication assessed in any way?

Response: Monitoring of compliance was at the discretion of the treating physician. Lack of compliance was reported for one patient who discontinued treatment in the Austrian study, as noted in Table 2.

5. What is the basis of this 11-point scale that was used? Has it been validated? Information as to the nature of this scale and validation should be discussed

Response: Thank you for your comment. New text has been added to the second paragraph of the Discussion where previous validation of the scale in patients with chronic pain and IBS is now discussed.

6. There is much room for bias in this study as this is physician-assessed outcome. The discussion should include the fact that efficacy in pts was not a composite endpoint as it was in the clinical trials so in one sense the efficacy may seem somewhat inflated as compared to the trials.

Response: New text has been added to the final paragraph of the Discussion to highlight the possibility of inflated efficacy results when compared to the clinical trials due to the lack of a composite endpoint. Text has also been added to this paragraph to note that satisfaction with linaclotide was a physician-measured outcome, as compared to a patient-measured outcome in the clinical trials, which may lead to potential bias.

7. Although mostly excellent there should be some review of the English, e.g. page 8 line 123.

The decision to treat a pt with linaclotide was “taken” probably would be more correctly said was made.

Response: An editorial review for English grammar has been completed.

8. Was lubiprostone used by any of the patients? The observation that concomitant laxatives decreased the efficacy of the medications is an interesting one but reading this paper one is not clear on what percentage of the pts used concomitant laxatives as this data is missing from Table 3. It might be interesting to also spell out the laxative type that was used i.e. osmotic,etc

Response: Lubiprostone use was not reported for any patient in the study. Additional lines have been added to Table 1 listing the laxative types used by patients in the study.

9. Are you able to figure out what % of pts got relief of both increase in BMs and improvement in abdominal pain, that would also be a good “real world “ analysis, although it would need to be clearly spelled out that this was not equal to the clinical trials because different criteria were used

Response: We agree that this analysis would be interesting; however, as mentioned, the results would not be comparable to the clinical trials due to the utilization of different criteria. Thus, there is no basis to evaluate the effect of linaclotide on the combined endpoint. Additionally, the subset of patients with both results would further reduce the patient numbers in an already small population producing insubstantial evidence.

10. Despite the significant potential for bias, I do feel this study does have value in describing the “real world” experience of the drug

Response: We thank the reviewer for this response.

Reviewer 2
Reviewer Name: Tadayuki Oshima M.D., Ph.D.
Institution and Country: Hyogo College of Medicine, Japan

Major
1. The reasons why the treatment courses were different in two countries were not clear

Response: The study treatment in each country was largely driven by the investigator’s routine clinical practices, leading to some variability between the two countries.

2. Although the authors stated the rate of discontinuation of linaclotide over the course of the study, when did the actually discontinued. Did they all happen over 4 weeks treatment?

Response: We have added text to paragraph 2 of the ‘Patient characteristics’ section of the Results to clarify that these discontinuations occurred throughout the study, including the follow-up period.

3. They should show the data of the frequency of bowel movements even in Figures 2 and 3. It is good to know how pre- and concomitant laxative treatment affect the outcome with linaclotide. Furthermore, they should clearly state what laxatives were used

Response: We thank the reviewer for this comment. While the mean frequency of bowel movements is presented in Figure 1, Figures 2 and 3 present abdominal pain and bloating

data, in order to investigate the effect of pre-treatment or concomitant treatment with laxatives on other symptoms of IBS-C besides bowel movement frequency. A list of laxatives used by patients during the treatment period has been added to Table 1.

4. What was the definition of “improvement” in general symptom, abdominal pain, bloating, and constipation? Although the improving rates were high in this study, the most important point of the outcome must be the satisfaction for the treatment. Just the improvement of the value of scores does not always introduce the satisfaction of patients

Response: Thank you for your comment. Improvement in symptoms were patient-reported. This was measured by patient responses to simple yes/no questions asked by the physicians, such as whether general symptoms had improved, with additional individual responses for abdominal pain, bloating, and constipation. New text has been added to paragraph 2 of the ‘Study assessments’ section of the Methods to clarify this.

Improvement in abdominal pain and bloating was measured by improvement in the 11-point NRS score compared to prior to therapy start. Improvement was defined as a statistically significant difference in the 11-point NRS. The improvements found in this study are consistent with those determined to represent a clinically significant change in pain in previous studies using similar numerical rating scales for pain and IBS. Please see new text in paragraph 2 of the Discussion.

Minor
1. Introduction. Although the prevalence of IBS must be high, the prevalence of IBS-C is not high when they are defined by the Rome III criteria (PMID: 26095436). As the definition easily affect the prevalence of IBS-C/IBS, it is better to state the prevalence of IBS-C defined by the Rome III/IV criteria and by other definitions.

Response: A new sentence has been added to paragraph 1 of the Introduction to state the prevalence of IBS-C measured by Rome III criteria.

2. How did the authors define moderate-to-severe IBS-C in this study? If it is not defined clearly, selection bias must exist

Response: In keeping with the real-world study design, IBS-C diagnosis and severity grading were at the discretion of the treating physician. New wording has been added to paragraph 1 of the ‘Participants’ section of the Methods to clarify this. Additional text has also been added to the final paragraph of the Discussion to state that this could lead to possible selection bias.

3. Figures 1 and 2. Does “visit 2” always mean at 4 weeks in this study? Please state this point clearly

Response: Yes, visit 2 is referring to week 4 in the study. The figure legends for Figures 1-3 have been amended to clarify this.

4. It is better to show the data of Figure 2 with the median and 95th percentile as the data must be skewed

Response: We thank the reviewer for this comment. However, mean intensity scores have been retained for consistency throughout the manuscript. Moreover, the mean value was presented for the combined data from both studies.

5. Lines 193 to 195. They should not state this without statistical significance. As the employees of the company are included in the authors, they should be careful to state the results of linaclotide

Response: This text has now been removed from the Results.

6. Lines 306 to 309. Did they perform statistical analyses for these differences? These should be stated in the results and should be discussed

Response: Thank you for your comment. The p numbers for these analyses are located in paragraph 2 of the 'Effectiveness outcomes' of the Results and in Figure 3.

7. Lines 309 to 312. The reference 21 did not show that PEG exacerbates abdominal pain and bloating at least. As far as they state these important issues, they should refer appropriate references. They should also state how the data were inconsistent in previous reports

Response: Referring to the following sentence: 'Laxatives such as polyethylene glycol are often used as first-line therapy for patients with IBS-C; however, their effect on improvements in abdominal pain or bloating are inconsistent and may lead to exacerbation of bloating, gas, and loose stools.' A reference has been added to further support this statement.

8. Line 386. If the published data with the real-world setting using linaclotide from other countries including Germany, they should refer those articles

Response: We thank the reviewer for this comment. Additional citations have been added to the final paragraph of the Discussion section on page 18.

Reviewer 3
Reviewer Name: Apoorva Chandar
Institution and Country: Case Western Reserve University, Cleveland, Ohio, United States of America

1. Did the included participants meet Rome II/III/IV diagnosis for IBS-C?

Response: In keeping with the real-world study design, IBS-C diagnosis and severity grading were at the discretion of the treating physician. New wording has been added to paragraph 1 of the 'Participants' section of the Methods to clarify this.

2. Being a real world study, it is not expected that the inclusion and exclusion criteria for linaclotide be as strict as the original RCTs. However, a small, but not insignificant proportion of patients were on psychoanaleptics or psycholeptics. Did these include anticholinergics which could potentially cause constipation?

Response: Thank you for your question. No patients in the study were receiving anticholinergic psychoanaleptics or psycholeptics.

3. About a quarter of patients in both study populations were on laxatives at baseline. These were presumably allowed to continue during the study. Specifically, in the original RCTs of linaclotide, patients on a stable, continuous regimen of fiber, bulk laxatives, or stool softeners in the previous 30 days prior to start of the study were allowed to continue taking

the medications. What process/procedure was followed in your study? Were all laxatives allowed to be continued? Did certain laxatives have to be stopped prior to starting linaclotide? Can the authors comment?

Response: We thank the reviewer for their comment. However, as a non-interventional study, there were few exclusion criteria and therefore there was no overarching process or procedure regarding laxative use other than routine clinical practices.

4. While the outcome time points for the 2 study populations are different, could the authors have reported on the composite EMA or FDA endpoint for the Swiss population?

Response: While the components of the FDA composite response were collected as endpoints in this study, the percentage of responders was not reported in this way to be able to conduct this type of analysis. Additionally, as mentioned by the reviewer, the two studies also had two different time points, which would complicate a composite responder analysis.

5. What would have been interesting is if the same satisfaction scale comprising (0 to 10 scale) that was used to measure physician satisfaction with linaclotide therapy could also have been administered to patients to see what their level of satisfaction was and then comparisons could have been made

Response: Although this would be interesting, the study did not collect patient satisfaction information.

6. Quality of life is an important outcome measure in IBS-C sufferers. Clearly, from the study, it seems that there was noticeable and substantial improvement in symptoms. It would have been useful if the authors had used a scale like IBS-QOL (or even other scales like SF-36, etc.) to see the impact of their study on quality of life

Response: Although quality of life is an important aspect of chronic illnesses such as IBS-C, this study reflected only the routine information collected at physician visits.

7. I think the biggest shortcoming (which the authors acknowledge to an extent) is that the study had a very small sample size and much more sophisticated analyses could not be undertaken. The other shortcoming is the different outcome time points for the 2 populations. While the patients in Austria started seeing meaningful improvements by week 4, it may be too premature to see sustained improvement and hence, the Swiss population's outcome data is more robust

Response: Thank you for your observation. We agree with this assessment and therefore have presented the two studies together for a stronger evidence base.

VERSION 2 – REVIEW

REVIEWER	Tadayuki Oshima Hyogo College of Medicine
REVIEW RETURNED	18-Sep-2019

GENERAL COMMENTS	The authors well responded to my queries and the quality of this manuscript has been much improved. However, I still have a comment on the manuscript.

	As I mentioned in the original comment (Minor 7), the reference 23 in the revised manuscript did not show that PEG exacerbated abdominal pain and bloating at least. The reference just showed that PEG improved bowel complaints, including stool frequency and consistency, but did not reliably improved abdominal pain or bloating. The authors statements cannot be introduced from the indicated references. Furthermore, the other indicated reference was a review and was not an original article. The review did state some without indicating original articles. If the authors want to state as they did, they should refer direct evidence that showed “inconsistency” and “exacerbation”.

REVIEWER	Apoorva Chandar Case Western Reserve University, Cleveland, Ohio
REVIEW RETURNED	01-Oct-2019

GENERAL COMMENTS	The authors have satisfactorily answered all of my questions. The discussion section is a bit too long, but it doesn't necessarily have to be shortened as the authors have covered all the necessary sections (such as strengths, limitations, comparison to other studies, etc.) adequately.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Reviewer Name: Tadayuki Oshima M.D., Ph.D.

Institution and Country: Hyogo College of Medicine, Japan

1. The authors well responded to my queries and the quality of this manuscript has been much improved. However, I still have a comment on the manuscript.

As I mentioned in the original comment (Minor 7), the reference 23 in the revised manuscript did not show that PEG exacerbated abdominal pain and bloating at least. The reference just showed that PEG improved bowel complaints, including stool frequency and consistency, but did not reliably improved abdominal pain or bloating. The authors statements cannot be introduced from the indicated references. Furthermore, the other indicated reference was a review and was not an original article. The review did state some without indicating original articles. If the authors want to state as they did, they should refer direct evidence that showed “inconsistency” and “exacerbation”.

Response: This statement has been amended so that it more accurately reflects the cited studies (Discussion, page 15, paragraph 2, lines 340–341).

Reviewer 3

Reviewer Name: Apoorva Chandar

Institution and Country: Case Western Reserve University, Cleveland, Ohio, United States of America

1. The authors have satisfactorily answered all of my questions. The discussion section is a bit too long, but it doesn't necessarily have to be shortened as the authors have covered all the necessary sections (such as strengths, limitations, comparison to other studies, etc.) adequately.

Response: We thank the reviewer for this comment. Some deletions have been made in the Discussion to reduce redundancy and decrease the overall length.