

September 5, 2019

Jia-Ping Yan, Science Editor

World Journal of Gastroenterology

Re: MS# 49819

Dear Dr. Yan:

On behalf of our co-authors, we thank you and the referees for your review of our paper entitled “**Direct Costs of Carcinoid Syndrome Diarrhea among Adults in the United States.**”

Following please find an itemized response to each of the referees’ comments, with manuscript changes indicated as appropriate.

We have appreciated the thoughtfulness of the review and trust the paper is better from this process.

Thank you for your consideration, we look forward to hearing from you.

Sincerely,

Arvind Dasari, MD and Vijay N. Joish, PhD on behalf of the authors

Corresponding author:

Vijay N. Joish, PhD

Lexicon Pharmaceuticals, Inc.

110 Allen Road, Basking Ridge, NJ 07920

The Woodlands, TX USA

(908) 360-4782

vjoish@lexpharma.com

RESPONSES TO REVIEWERS

Reviewer 1

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

In this retrospective study in adults on the direct costs of carcinoid syndrome diarrhea when compared to those without CSD the results were already expected. The text is well written, but could perform more statistical analysis and thus better understanding the event. The age was higher in those with CSD, and this could be better explored as well as the other identified variables. What are the factors associated with the greatest cost in CSD patients? A regression analysis could be applied in this case.

Author Response: We appreciate the reviewer's comment about the findings and agree that patients with CSD may be expected to incur higher costs, but we have not seen this characterized in as much detail in the existing literature and so we are confident readers will appreciate the specificity offered by this study.

We are aligned with the reviewer's comment regarding factors associated with greater costs and we had conducted multivariate GLM models in this regard. To make this more prominent in the manuscript, we have updated Tables 2 and 3 accordingly. The P values reflect those from the multivariate analysis with accompanying footnotes providing the supporting detail regarding the models and covariates (Table 2, p12; Table 3, p 13).

Reviewer 2

Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Overall well designed and well reported study. Major points Some continuous variables (such as length of stay) are not normally distributed; they are skewed, therefore, non-parametric tests such as the Mann-Whitney U test should be used. The authors need to explain why only 35% of the patients with carcinoid syndrome had diarrhea in this study, when the expected prevalence is 80%. Is this an indication of selection bias?

Author Response: we appreciate the reviewer's comment about the skewness of the data and agree. We used multivariate generalized linear models with Poisson distribution and log link for the count data (healthcare resource use) and with gamma distribution and log link for the cost data. We are confident these methods are appropriate for these data. We have also added the P values for the multivariate analysis to Tables 2 and 3 with supporting detail in the footnotes (p12, 13).

We appreciate the reviewer's comment regarding the proportion of patients with CS who also had evidence of CSD (35%) compared with those who did not. While the expected prevalence of clinical CSD in this population is higher, we suspect the lower prevalence we observed is attributable primarily to the coding of conditions for administrative purposes compared with what might be observed in a medical chart review, for example. That is, CSD may well have been present but not captured in administrative coding. We have added a sentence to the Discussion/limitations paragraph (p15) including the likelihood that this, in turn, makes the incremental resource use and cost estimates similarly conservative. We do believe this is nonetheless an informative finding from the perspective of the population health manager who commonly conducts research in similarly constructed databases.