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Editors-in-Chief
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RE: Response to Reviewers for *"Cystic Fibrosis Transmembrane Conductance Regulator Modulators Reduce the Development of Cirrhosis in Patients with Cystic Fibrosis"*

Dear Editorial Board,

On behalf of my co-authors, I am pleased to submit a revision of our manuscript. The Reviewers have provided excellent, constructive critiques, and we thank them. We have responded to their suggestions below in a point-by-point manner, re-stating each point before our response.

Again, we thank the reviewers for their careful reading and commentary on our work, and hope that these revisions are satisfactory for publication in *World Journal of Hepatology*.

Kind regards,

Mitchell L. Ramsey, MD

Reviewer Comments:

Reviewer #1:

1. The number of patients is substantial considering the rare condition, and the results of this study are clinically meaningful and can form the basis of future prospective studies, despite the methodological flaws.

- Thank you for this commentary.

2. The main concerns include the decreasing proportion of patients over time, the use of different types of CFTR modulators at different times, the unavailability of many significant data (i.e. LFT), and the substantially shorter follow-up.

- Thank you for these comments. Decreasing proportion of patients with time is common in longitudinal studies. We could limit the study groups to only subjects with full 5 years of follow up, but this would reduce the power at shorter time intervals. Similarly, limiting to specific CFTR modulators would reduce the sample size of the study. We mention the unavailability of LFTs in our limitations section (page 11).

3. The study's main finding, in my opinion, appears to be an increased risk of cirrhosis while using ursodiol versus not using it. Why did UDCA patients develop cirrhosis at a higher rate than untreated patients? The authors have given no explanation for this.

- Thank you for this comment. We discuss this issue in a paragraph on page 11. Briefly, ursodiol is used for patients with CF who have abnormal LFTs or evidence of hepatic dysfunction but it is not effective in treating or reversing the disease. Thus, subjects in our study who received ursodiol were likely to develop cirrhosis in the coming years – representing a selection bias.

Reviewer #2:

1.Please add the diagnostic criteria of Cirrhosis in the part of "METHODS".

- Thank you for this comment. The ICD9 and 10 codes have been added to the Study Sample section of the Methods.

2. In the first column of table 2, it's hard to understand the meaning of "Ursodiol 6 months". "Ursodiol 6 months" is "6 months"?

- This was a typographical error, which has been updated in the revised version of the tables and manuscript.

3. Tables with three lines should be applied in all tables.

- This has been updated in all tables.

Reviewer #3:

1. Though this a retrospective analysis of a cohort of cystic fibrosis patients, the observation made is clinically relevant. Cystic fibrosis is a progressive disease leading to cirrhosis of liver. It would be prudent if a drug can change the natural history of disease. Authors have clearly documented that UDCA group had more incidence of cirrhosis as the drug was started late only after deranged LFTs. And CFTR modulators group had lower incidence of cirrhosis.

- Thank you for the comments.