

Dear Editor,

We submit a revised version of our invited editorial titled “The role of cenicriviroc in the management of nonalcoholic fatty liver disease” for consideration for publication in the World Journal of Gastroenterology. We thank the Reviewers for their comments, which improved our paper. We modified the text according to these comments. All changes are shown in red in the revised text.

Response to Reviewers' comments

Reviewer's code: 03647461

The emphasis of this short communication seems to be on the anti-fibrotic effect of cenicriviroc (CVC) in curtailing the progression of NAFLD to cirrhosis. It was also related in this manuscript that CVC, an oral CCR2/CCR5 antagonist, averts macrophage trafficking and hepatic infiltration by CCR2+ MoMFs, thus blocking the fibrotic process enhanced by CCR2 and CCR5 activation. The increase in CCL-2 and -4 in CVC - treated patients is also another testament to its effect. However, it is not evident that CVC can reverse cirrhosis, which is an advanced stage of fibrosis (stage 4). This in contrast to the statement made in the manuscript, which states that “Preclinical studies and a phase 2b study in humans suggest that this agent might hold promise in the management of NAFLD, particularly in patients with advanced fibrosis.” Some of the studies conducted in human patients do not have statistically significant results. Although the manuscript details NAFLD treatment regimen with CVC, in large part, the impact on NASH could also be important according to the CENTAUR study. Therefore, the efficacy of CVC is high as this is also a multinational study. However, it remains that patients in the initial stages of fibrosis can still reverse it without the need for CVC with lifestyle changes in diet and exercise. Nevertheless, this report adds value to pharmacotherapeutic options such as CVC suggested by ongoing clinical phase studies. This is especially significant if

taking 150 mg once daily does not interfere with the safety and tolerability of CVC as reported by Friedman S. [Placebo-Controlled Trial of Cenicrivitoc for Treatment of Nonalcoholic Steatohepatitis With Fibrosis. Hepatology 2018; 67: 1754-1767]. The authors do acknowledge, however, that larger studies are required to accurately determine the safety and efficacy of the drug.

We thank this Reviewer for these positive comments. We removed the statement that cenicriviroc might be more effective in patients with advanced fibrosis.

Reviewer's code: 03388095

The manuscript entitled "The role of cenicriviroc in the management of nonalcoholic fatty liver disease" was an informative review regarding cenicriviroc and its phase 2b study in patients with NAFLD. However, the scope of the manuscript was somewhat narrow as a review. The manuscript was an optimal one as an editorial.

We thank this reviewer for stating that our manuscript is informative and that "The manuscript was an optimal one as an editorial." We apologize for the misunderstanding. Our manuscript is an invited editorial and this is why it is focused on cenicriviroc. We inadvertently mentioned in our submission that it is a review. We corrected this mistake.

Reviewer's code: 00034151

This is a well-written, quite focused review on the role of Cenicriviroc in fatty liver disease, particularly in patients with advanced fibrosis. The review detailed the molecular pathway, animal studies, and on-going clinical trials. It will be nice if the authors can provide some diagram to illustrate the molecular pathway so readers can better understand it.

We thank this Reviewer for these positive comments. We added a diagram showing the molecular pathway through which cenicriviroc acts.

We look forward to your decision.

Best regards,

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