We appreciate the time and effort of the reviewers and editors in reading and considering our manuscript. Our responses to the individual reviewers are outlined below.

Reviewer *00187937:*

"Dear Editor, In this review Bambha and Yuan addressed the topic of bile acids and bile acid receptors in NASH pathogenesis and treatment. It is well designed and prepared review, but there are just two spelling issues that should be taken care. 1. In the 5th sentence of the section of 'Bile acid recycling' 'In' should be written by the lower case, as 'in'. 2. In the 5th sentence of the section of 'Bile acid synthesis' 'Bile' should be written by the lower case, as 'bile'."

Author Reply:

Thank you for your very kind comments. We have made changes per your recommendation.

Reviewer *00068723:*

"This review described INT-777 for the treatment of NAFLD/NASH. INT-777 was interesting due to dual effects to FXR and TGR5. Before application of INT-777 to clinics, were there any limitations to improvement of life-style, control of diabetes mellitus, and hyperlipidemia? Otherwise the rationale of INT-777 was not clear. Were there any literatures on clinical trial regarding modulation of bile acid metabolism for the treatment of NAFLD/NASH? This information would also affect the rationality of INT-777. INT-777 was interesting. Were there any proposed mechanism of dual antagonism to FXR and TGR5?"

Author Reply:

Thank you for your comments. Although improvement of lifestyle can improve some features of NAFLD/NASH, this has only been accomplished in dedicated lifestyle-intensive clinical trials with close participant follow up and education. As practiced in real-life (daily life) and as practiced in clinical trials whose main factors of interest are not intensive lifestyle modifications, lifestyle modifications, control of diabetes mellitus, and hyperlipidemia are not, in and of themselves, quite sufficient to result in substantial improvements in NAFLD/NASH. The TGR5 antagonist, INT-777, not only improves metabolic features, it has also been shown to ameliorate inflammation in cellular models and animal models. A recent study (Jourdainne V et al., Dig Dis. 2015;33(3):319-26) showed TGR5 signaling plays a crucial role in protecting liver regeneration from bile acid overload. TGR5 signaling remains to be explored. INT-777 is a TGR5-specific antagonist. INT-767 is a dual antagonist to FXR and TGR5. Many clinical trials led by Intercept are ongoing to assess the therapeutic effects of FXR antagonists, such as obeticholic acid, on NASH, PBC, PSC and bile acid diarrhea.

Reviewer *3388397*:
“In this manuscript Yuan and Bambha focus on the topic of bile acid receptors in NASH pathogenesis and treatment. Unfortunately the manuscript provides little new information on the issue addressed in relation to the data found in the literature: Biochemical Pharmacology 86 (2013) 1517–152; Nature Reviews Gastroenterology & Hepatology 11, 55–67 (2014); World J Gastroenterol 2014 October 7; 0(37): 13493-13500. J Lipid Res. 2012 Sep; 53(9): 1723–1737.”

Author Reply:
Thank you for your comments. We have made some revision and polished the review.