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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36349
Title: Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis
Reviewer's code: 02444760
Reviewer's country: China
Science editor: Li Ma
Date sent for review: 2017-09-25
Date reviewed: 2017-10-01
Review time: 5 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript of 'Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis' presents some informative and interesting findings about the therapeutic efficacy of liraglutide, obeticholic acid and elafibranor in rodent nonalcoholic steatohepatitis, such as the improvements in hepatic steatosis, inflammation, and liver firbosis. Because of the limited approach to clinical interference, these achievements could be valuable to both pharmaceutical research and clinical application. Major comments 1. According to the results obtained from present study, liraglutide, obeticholic acid and elafibranor demonstrate therapeutic effects in different pathological characteristics of nonalcoholic steatohepatitis. For example, elafibranor and OCA reduce hepatic steatosis and inflammation in both DIO-NASH and ob/ob-NASH. Elafibranor

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attenuates liver fibrosis. Liraglutide improves scores of steatosis, fibrosis and inflammation. However, there is weak evidence for the drug comparison. Revision in this aspect is then suggested. 2. The effects of liraglutide are reported to be 'Liraglutide improves steatosis scores in DIO-NASH mice only, but reduces total steatosis, fibrosis and inflammation levels in both models'. Is there any conflict? 3. It's unclear whether liraglutide, obeticholic acid and elafibranor exert their effect in a dose-dependent manner. Therefore, the rationality of dose selection should be clarified, at least be discussed carefully. 4. The Abstract draw a conclusion of 'Diet-induced mouse models of biopsy-confirmed NASH show distinct treatment effects of liraglutide, OCA, and elafibranor, being in general agreement with corresponding findings in clinical trials for NASH'. Then, what's the novelty for these findings? Minor comments 1. Limited information has been exhibited in the result of Abstract. It will be appreciated for authors to revise it, if possible, with more numerical details.

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Manuscript NO: 36349
Title: Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis
Reviewer's code: 03648851
Reviewer's country: Japan
Science editor: Li Ma
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Authors indicated time course of changes in metabolic parameters and histopathological findings in liver in detail, and that effect of three drugs on those phenotypes in two types NASH model mice. The findings will contribute to understanding of pathophysiological alterations in NASH model mice, and the experimental design will be helpful to improve thescreening of candidate drugs for NASH in preclinical trials. Thus, it will be suitable for the publication in this journal. However, author should answer the following two points. ・Can the NASH score adapted to human disease be used to NASH model mice? Author used Kleiner's NASH score, which is produced for diagnosis of human NASH, in this study. However, histopathological findings in NASH model mice is inconsistent with that in human, especially low-grade fibrosis. If you modified the scoring method, it should be described in method section. ・Steatosis in

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vehicle group of ob/ob-NASH mice was more severe than that in other groups. Did individual mice randomly divide to four groups? ・Fig.6 was not looked. The display in figure legends get corrupted.

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Name of journal: World Journal of Gastroenterology
Manuscript NO: 36349
Title: Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis
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Science editor: Li Ma
Date sent for review: 2017-10-10
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Tølbøl KS and colleagues provided evidences about the therapeutic effects of three different drugs (liraglutide, OCA and elafibranor) in the context of biopsy-proven experimental non-alcoholic steatohepatitis (NASH). They evaluated the efficacy of the above-mentioned compounds in two different strains of high-fat fed mice namely wild type (C57BL/6J) and genetically obese (ob/ob) mice. They analyzed the metabolic effects of the drugs (body weight, lipid profile) as well as the liver damage both from a biochemical (ALT, AST) and histological point of view (steatosis, inflammation and fibrosis). Moreover, they corroborated their findings by analyzing the hepatic transcriptome. As expected, they found that all three drugs ameliorated somehow the different pathological aspects (metabolic and/or histological) involved in NASH evolution. The present manuscript is potentially interesting taking in account the

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urgent need to define an efficient therapeutic regimen for a successful treatment of human NASH. Presently, one of the most important goal within the liver research field is to find a therapy aiming to avoid the progression of NASH toward advanced phases such as cirrhosis and hepatocellular carcinoma (HCC). Major Comments: In my opinion, to allow an easier reading of the paper, the authors should insert in the introduction section some hints concerning the molecular mechanisms/pathways targeted by the different drugs classes. Otherwise, it is quite difficult for the reader to clearly understand the experimental results provided in the following sections. The inflammation plays a crucial role in the pathogenesis of NASH and on the same vein a growing body of evidences suggested as immune responses may drive the worsening of the hepatic injury during the evolution of NAFLD. On the base of these premises, I believe that for an overall understanding of the data presented in the manuscript (for example transcriptome profile), the authors should give just a quick overview about the critical role of the immunity (see for instance World J Hepatol. 2015 Jul 8;7(13):1725-9 "Is there a role for adaptive immunity in nonalcoholic steatohepatitis?" and Immune Netw. 2016 Jun;16(3):147-58 "The Immune Landscape in Nonalcoholic Steatohepatitis."). Even if, it is not the target of the present manuscript, however this aspect is quite important considering the strict connection between FXR signaling and immune system function. In fact, as the authors mentioned, it is well established the anti-inflammatory action mediated by FXR agonist (see for instance Curr Pharmacol Rep. 2017 Apr;3(2):92-100). I guess that the impact of the pharmacological treatment on the systemic inflammation should be evaluated. For instance, they could measure by ELISA the circulating levels of pro-inflammatory cyto/chemokines such as TNF-α and MCP-1. I guess it could be also relevant for clinical purposes. Minor Comments: I would use the same nomenclature for the genes in the transcriptome analysis images: Figure 1I, the authors reported MCP-1 instead in Figure 5E they used CCl2 (please choose only one). Moreover, I guess in figure 1I Ccr should be replaced by Ccr2. Why they did not use the same order and the same genes to display? It would be much easier to compare the figures. In figure 1I there is showed Mac-2 while in figure 5E appears Lgals3. Please add both.

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Manuscript NO: 36349
Title: Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis
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Reviewer's country: Turkey
Science editor: Li Ma
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Date reviewed: 2017-10-23
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Authors analyzed the effects of liraglutide, OCA, and elafibranor in 2 different NASH models, namely DIO-NASH and ob/ob-NASH mice. it seems that the manuscript data is taken from a thesis. therefore there are too many unnecessary data. if authors want to emphasize the differential effect of drugs on 2 different model result and discussion must be organized accordingly. if authors want to compare the 3 drugs in different animal models, then they must give relevant data and make conclusions about the dugs. the results an conclusions should be clearly stated by omitting unrelevant data. i.e data reveals that elafibranor improves weight, biochemical marker, inflammation and fibrosis in both model, while other 2 drugs has partial effects on these parameter.

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Title: Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Tølbøl et al. demonstrated the efficacy of liraglutide, obeticholic acid and elafibranor using C56 and ob/ob mice fed AMLN diet, showing histology of NASH. Basically, experimentations are well-done and data interpretation is adequate. However, results and discussion sections are too long and need improvement. 1. Discussion sections: The authors need to state the discussion more clearly. For example, I recommend to state the efficacy of drugs according to histological components of NASH, such as steatosis, inflammation, and fibrosis. 2. The authors should add the data of diet intake amount and mention whether it was basically similar or matched between the groups. 3. There are some discrepancies between biochemical/histological data and mRNA expression. For example, elafibranor attenuated fibrosis score but the expression of collagen 1a1 and galectin 3 was unchanged. The authors should comment this point. 4. Also, serum ALT

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was unchanged or increased but NAS improved (Figure 1,2 elafibranor; Figure 7 OCA). The authors should mention the reason of this discrepancy or the validity of ALT measurement. 5. Figure 4C and 4E, Figure 7F and 7G: How did you measure collagen 1a1 and galectin contents (g)?