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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 36729

Title: INT-767 improves histopathological features in a diet-induced ob/ob mouse model of biopsy-confirmed non-alcoholic steatohepatitis (NASH)

Reviewer's code: 03648851

Reviewer's country: Japan

Science editor: Ke Chen

Date sent for review: 2017-10-25

Date reviewed: 2017-11-08

Review time: 13 Days

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

COMMENTS TO AUTHORS

Authors indicated the effect of INT-767 on pathological condition in NASH model mice in detail, and INT-767 has more positive effect than OCA on NASH phenotype. The experimental design will be helpful to improve the screening of candidate drugs for NASH in preclinical trials. Thus, it will be suitable for the publication in this journal. There are some minor questions in this manuscript. • It is well known that the lipid droplet size is smaller by the activation of PPAR signaling. In Fig. 3, INT-767 reduced lipid droplet area, and are FXT and TGR5 signaling also involved in the lipid droplet size? • In Fig. 1A, what is the asterisk indicated? • There are some English spelling mistakes.



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Manuscript NO: 36729

Title: INT-767 improves histopathological features in a diet-induced ob/ob mouse model of biopsy-confirmed non-alcoholic steatohepatitis (NASH)

Reviewer’s code: 03022180

Reviewer’s country: Brazil

Science editor: Ke Chen

Date sent for review: 2017-10-25

Date reviewed: 2017-11-11

Review time: 17 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
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<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

This is an interesting and complex study the evaluates INT-767 a FXR and TGR5 agonist improvement on biopsy proven NASH ob/ob mice. In addition it compares INT-767 with OCA and evaluates its genetic and drug levels expression in intestinal and liver setting. Major comments: Abstract: The authors should clarify the three steps of the study in the abstract, it is very confused regarding time of drug use, gourds that are compared and doses. In addition, it is not clear in the abstract that there are different steps in the study. Why time on INT-767 was different between INT -767 only and INT vs OCA? Also, why were the dosis different in the two steps? Would this have any impact on the results? In fact the authors decided to double the time on INT-767 when comparing with OCA. Did they compare eight weeks of INT as well to OCA? They could do this analysis since they have this result. How many mice were lost to the



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experiment? Regarding NASH parameters, NAS scoring system and liver fibrosis , what was considered as improvement by the authors? The authors should better clarify that lean mice were included as controls only for biochemical parameters. Discussion: The authors state that the administration of INT-767 for 16 weeks confirms that INT-767 has durable histological benefits. I don't agree with this conclusion since mice were still under drug use. This should be concluded if those mice had stopped drug use and a liver biopsy was performed to evaluate the permanent improvement in liver histology. This phrase might be excluded or modified.