

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14668

Title: Irsogladine maleate and rabeprazole in non-erosive reflux disease – a double-blind, placebo- controlled study

Reviewer's code: 00029540

Reviewer's country: Italy

Science editor: Jing Yu

Date sent for review: 2014-10-21 17:48

Date reviewed: 2014-10-31 01:09

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed 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
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Summary The article entitled "Irsogladine Maleate and Rabeprazole in NERD – A Double-Blind, Placebo-Controlled Study" by Suzuki T et al. is a prospective, double-blind, placebo-controlled trial designed to evaluate the efficacy of adding irsogladine maleate (IM) to proton-pump inhibitor (PPI) therapy in endoscopy-negative Japanese patients with reflux symptoms. The main result was that no statistically significant difference between the FSSG scores in group I (IM+PPI) and those in group P (placebo+PPI). Moreover, a subgroup analysis showed that significant improvements in the FSSG scores had occurred in the patients in group I who had NERD grade N according to endoscopic assessment. The study is well written and clear. However, there are some limitations: Major comments. 1. Introduction section. The following sentence "NERD patients administered proton pump inhibitors (PPIs), which are the first-line therapy for GERD, show a low symptom improvement rate, and almost 50% of NERD patients fails to respond to standard acid-suppression therapy" is questionable. A Recent meta-analysis (Neurogastroenterol Motil 2012; 24: 747–e350)

underlined that well defined patients with NERD (in case of abnormal distal esophageal acid exposure and/or positive symptom association) have a similar response to PPI therapy than patients with Erosive Esophagitis. In keeping, the main limitation of previous studies/trials assessing the efficacy of PPIs in NERD was that NERD was diagnosed only on the basis of endoscopic findings. This led to include in the NERD subgroup a high number of patients without reflux disease (functional heartburn) who, by definition, do not respond to PPI therapy. Please, include this information (and related references) in the introduction section and also comment among the limitations of the study the lack of a correct definition of NERD according to medical literature (Nat Rev Gastroenterol Hepatol. 2013 Jun;10(6):371-80). 2. Introduction section. The diagnostic and clinical relevance of the modified Los Angeles Classification for NERD is controversial. Indeed, it is used almost only in Japan. Please, comment on that among the limitations of the study 3. Discussion section. There is no mention about the role of non-acid reflux in the manuscript although its relevance in NERD is well-established (Am J Gastroenterol. 2008 Nov;103(11):2685-93 and J Gastroenterol. 2012 Feb;47(2):159-68). Please, included this information in the discussion section. Moreover, are there any data on the role of this new drug “Irsogladine Maleate” in patients with hypersensitive esophagus to non-acid reflux in whom a major role of DIS has been suspected (J Gastroenterol. 2013 Apr;48(4):473-82)? You could speculate on that

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Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14668

Title: Irsogladine maleate and rabeprazole in non-erosive reflux disease – a double-blind, placebo- controlled study

Reviewer's code: 01803905

Reviewer's country: Japan

Science editor: Jing Yu

Date sent for review: 2014-10-21 17:48

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed 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 checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This report is a prospective controlled trial with the PPI+ placebo group and the PPI+irusogladine group for NERD. I read this report with fascination. I have several questions. Major comments 1. Is the diagnosis of NERD accurate? I think there not being mucosal injury and the criteria of FSSG to be insufficient as a diagnosis of NERD. Because functional heartburn is not excluded, I think that I am not found whether a reflux occurs truly. 2. Which doctor determined endoscopic findings of NERD? Does not your diagnosis have the bias? 3. There was not a significant difference in GroupI and GroupP in GradeM. However, it is difficult for it to be understood why you were significantly different in GradeN. GradeM is thought to be stronger in inflammation than GradeN. From a point of view called the anti-inflammatory action in Irsogladine, may an effect be expected towards GradeM? 4. When was endoscopy performed? At endoscopy, were the patients no treatment? Minor comments 1. Is Helsinki Declaration observed? 2. Is this study registered with UMIN? 3. What is the medication compliance of this study?

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Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 14668

Title: Irsogladine maleate and rabeprazole in non-erosive reflux disease – a double-blind, placebo- controlled study

Reviewer's code: 02286315

Reviewer's country: China

Science editor: Jing Yu

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input checked="" type="checkbox"/> [Y] Accept
<input checked="" type="checkbox"/> [Y] Grade B: Very good	<input checked="" 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		[Y] No	<input type="checkbox"/> [] Major revision
		BPG Search:	
		<input type="checkbox"/> [] The same title	
		<input type="checkbox"/> [] Duplicate publication	
		<input type="checkbox"/> [] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This work was a prospective, randomized, double-blind, placebo-controlled trial and evaluated clinical efficacy of rabeprazole alone or in combination with irsogladine maleate in patients with non-erosive reflux disease. The following comments are worth consideration. 1. A difference in the levels of gastric acid is an objective index, whereas the symptoms are a subjective index. In the Discussion section, gastric acid secretion was mentioned in many paragraphs. Was there gastric acid measure in each group before and after treatment? 2. Was there any difference in the FSSG scores between grade N and M in either group I or group P? 3. As shown in Table 2, there was no significant difference in the distribution of grade N and grade M between group I and group P. How to reasonably explain a significant difference in the FSSG scores between group I and group P only for grade N, but not for grade M? 4. Add the units for height, weight, and BMI, respectively, into Table 1. 5. Were there any other diseases and drugs known to affect the evaluation of treatment outcomes that should be included in the exclusion criteria? 6. Add the drug safety data on drug treatment into the manuscript. 7. Add some further relevant discussion about the factors that could



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affect the metabolism of and response to each study drug and their drug-drug interactions.