

March 21, 2019

Mr. Yan,

Thank you for your comprehensive review of the manuscript entitled, "HEARTLAND: Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir +/- Ribavirin in Real World Hepatitis C Patients" (Manuscript 45668) and for considering this manuscript for publication in *World Journal of Gastroenterology*.

Your comments have been taken into consideration and have been incorporated. Included with this letter are the following:

- A revised copy of the manuscript (file named "45668 HEARTLAND Manuscript Revised"), with all changes highlighted in yellow
- Contract from AbbVie (funding source)
- The Clinical Trials registration information in pdf format
- The completed CONSORT 2010 checklist in pdf format
- The audio core tip
- The first page of the following articles (submitted as Image Files in online submitter), since a PMID and DOI were not available for them:
 - Reference 1: Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144: 705–14. [PMID: 16702586]
 - Reference 7: American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. <http://www.hcvguidelines.org/>. Accessed March 18, 2019.
 - Reference 12: Hispanic Heritage Month 2017 - Census Bureau. <https://www.census.gov/newsroom/facts-for-features/2017/hispanic-heritage.html>. Accessed October 22, 2018.
 - Reference 19: American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV Resistance Primer. <https://www.hcvguidelines.org/evaluate/resistance>. Accessed October 22, 2018.
- A detailed point-to-point response to reviewer comments is included in the pages that follow.

Throughout the Manuscript:

- There are several responses to the comment, “Please reformat your manuscript according to the “Format and Guidelines for clinical trials study””. Changes are detailed throughout this letter by page.

Page 1:

- In response to the comment, “Please don’t include abbreviations in the title”, the title has been changed to “HEARTLAND: Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir +/- Ribavirin in Real World Hepatitis C Patients”.
- In response to the comment, “You need to provide the grant application form(s) or certificate of funding agency for every grant”, a copy of the contract with AbbVie is included showing the funding source.
- The department name and zip code for the corresponding author’s affiliations were added.

Page 2

- In response to the comment, “Please state on the title page” (under Institutional Review Board), the following was added, “The study protocol was approved by the IntegReview Institutional Review Board”.
- In response to the comment, “Authors must provide the registration identification number and the URL for the trial's registry. In addition, the registration information must be provided in a PDF format” the following has been done:
 - The statement was added “Clinical trial registration statement: The study is registered at:
<https://clinicaltrials.gov/ct2/show/NCT03710252?term=heartland&rank=1>. The registration number is NCT03710252.
 - The registration information is attached in pdf format.
- The following was added, per reviewers’ request, “Informed consent statement: All patients provided written informed consent.”
- With regard to the CONSORT 2010 comments:
 - The following was added, “CONSORT 2010 Statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.”
- Under the corresponding author’s information, the department (“Academic and Clinical Affairs”) was added.

Page 3

- An error was noted in the Abstract, Background. The abbreviation for HCV is now spelled out upon first mention (first line).

Page 4

- Keyword abbreviations have been spelled out. They now read, “Keywords: Hepatitis C; Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Genotype 1”.
- The following “Core Tip” was added:

The HCV NS5A inhibitor ABT-267 (ombitasvir, OBV), HCV NS4/4A protease inhibitor ABT-450 (paritaprevir, PTV), CYP3A inhibitor ritonavir (r) and non-nucleoside NS5B polymerase inhibitor ABT-333 (dasabuvir, DSV) (OBV/PTV/r + DSV) with or without ribavirin (RBV) is an approved direct-acting antiviral (DAA) regimen studied in an all-comers population. This study included 100 all-comers; many had comorbidities (44.2% hypertensive, 33.7% obese, 20.2% cirrhotic) and 16% previously failed HCV treatment. In these patients, 12 or 24-weeks of OBV/PTV/r + DSV +/- RBV was highly effective (99% SVR for 12 weeks treatment), tolerable and resulted in better mental and physical health.
- Audio core tip:
- The following was added: Loo N, Lawitz E, Alkhouri N, Wells J, Landaverde C, Coste A, Salcido R, Scott M and Poordad F. Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir +/- Ribavirin in Real World Hepatitis C Patients

Page 7

- In response to the comment, “registration identification number must also be mentioned as a footnote in the manuscript text”, the following footnote was added to the last sentence of the third paragraph: “Registration number NCT03710252”.

Page 10

- An error was noted in paragraph 1, line 2. The word “fibroscan” was changed to “FibroScan®”.

Page 11

- Reviewer 02520359 offered the following comment, “My main concern for this study is that more recently, newer DAAs (like glecaprevir/pibrentasir) have been introduced in treating Gt1 patients, with shorter duration of therapy (e.g. 8 weeks), and the authors have to state how they see the role of the 3D combination plus ribavirin in the new era”. In response to this comment, the following statement was added to the Discussion, Paragraph 1, last sentence:
 - “Although newer DAA regimens with shorter durations have been recently approved, our data on this older regimen remains important; this regimen is an approved treatment option and is still used in some developing countries.”

Pages 14 – 23

- An “Article Highlights” section has been included and was written in accordance with the provided guidelines.

Page 26

- In response to the comment, “Please explain all the abbreviations of each figure/table under each piece of figure/table legends”, abbreviations were explained for table 1 at the bottom of the table.

Page 27

- In response to the comment, “Please explain all the abbreviations of each figure/table under each piece of figure/table legends”, abbreviations were explained for table 2 at the bottom of the table.

Page 28

- The abbreviation for SF36v2 is now spelled out in the title for table 3.

Page 29

- The abbreviation for HCV is now spelled out in the title for figure 1.
- In response to the comment, “Please explain all the abbreviations of each figure/table under each piece of figure/table legends”, abbreviations were explained for figure 1 at the bottom of the figure.

Page 30

- The abbreviation for SVR was spelled out in the title for figure 2.

Page 31 - 34

- In response to the comment “Please check and confirm that there are no repeated references”, all references were checked and none repeat (please note that some author names repeat but the publications are in fact different).
- In response to the comment, “Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list”, all PMID and DOI numbers have been added.
- In response to the comment, “list all authors”, the references have been double checked and all authors were listed in the original version.

- In response to the comment, “The author should provide the first page of the paper without PMID and DOI”, the first pages of references 1, 7, 12 and 19 are included with this submission.

Best regards,
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