

16th November 2014

The Editor in Chief
World Journal of Gastroenterology

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13968-review.doc).

Title: Boceprevir Early-Access For Advanced Fibrosis/Cirrhosis In Asia-Pacific HCV
Genotype 1 Non-Responders/Relapser Patients (Beacon Study)

Author: Wattana Sukeepaisarnjaroen, Tri Pham, Tewesak Tanwandee, Saroja Nazareth, Sam Galhenage, Lindsay Mollison, Leanne Totten, Alan Wigg, Rosalie Altus, Anton Colman, Brenda Morales, Sue Mason, Tracey Jones, Nadine Leembruggen, Vince Fragomelli, Cheryl Sendall, Richard Guan, Dede Sutedia, Soek Siam Tan, Yock Young Dan, Yin Mei Lee, Widjaja Luman, Eng Keong Teo, Yin Min Than, Teerha Piratvisuth, Seng Gee Lim, on behalf of the BEACON investigators

Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

A. Format has been updated

B. Revision has been made according to the suggestions of the reviewers

(1) Stopping rules are not defined in 'Methods'.

Reply: The stopping rule was based on the BNPP criteria, HCV RNA > 100IU/ml at week 12 or HCV RNA detectable at week 24. We have included this in the methods section:

Stopping Rules

The stopping rule was based on the BNPP criteria, HCV RNA > 100IU/ml at week 12 or HCV RNA detectable at week 24.

(2) Taking into account that cirrhotics are the most difficult to treat, it would be interesting to describe SVR results taking into account previous response.

Reply: We included a new graph Fig 4B showing the SVR rates in cirrhosis patients based on their prior response. We also added a sentence in the results section under SVR12 in cirrhosis:

There was a significant difference in SVR12 when comparing cirrhotic relapsers (81%) to non-responders (40%) (figure 4B, p=0.005).

(3) 150 patients were enrolled but "86 (Asians)+63 (Caucasians) =149".

Reply: One patient had missing data on ethnic background hence could not be classified as Asian or Caucasian. We have made a footnote in the legend of table 1b. In addition, table 1A SVR (+)=91, SVR(-)=55, which adds up to 146 (total reads 150). We have amended this total =146. There were 4 patients who did not have HCV RNA tested for SVR hence this is considered missing data and we have made a footnote in the legend to table 1A.

Table 1A *Four patients did not have HCV RNA test for SVR at followup week 12, hence could not be classified.

Table 1B * one patient had missing data on ethnic background hence could not be classified as Asian or Caucasian.

- (4) The "conclusion" section reports results, which is not the aim of this section. Please reformulate.

Reply: Thank you for your comment. The conclusion of the abstract as been reworded as follows:

Conclusions: Boceprevir can be used successfully in PR treatment failures with SVR12 >80% if they have good on treatment responses but discontinuations occurred in 30% due to virological failure or adverse events.

- (5) Introduction - "but in Asia, SVR>70% due to the high prevalence of the IL28B good-responder genotype [4]." Please reformulate and be more accurate.

Reply: Thank you for your comments, and we have put more specific percentages into the introduction.

Introduction

In many Asian countries, Standard-of-care (SOC) still remains a combination of pegylated-interferon and ribavirin (PR), which achieves sustained virological response (SVR) in approximately 50% of Caucasian HCV genotype 1-infected subjects [3], but in Asia, the largest randomised control study showed 74% SVR with 48 weeks of PR due to the prevalence of the IL28B good-responder (CC) genotype in 80% of their patients [4], the most common genotype in Asians [5].

- (6) Material and Methods - the authors mentioned SVR24 data but these are not reported in the "results" section.

Reply: Thank you for notifying us of this result. We have removed SVR24 from the list of variables collected in the methods section.

- (7) Results - the number of weeks for the treatment is unclear, since all patients receive a lead-in phase with PR for 4 weeks. W4 of therapy means W4 of triple therapy (W8 since the beginning of treatment) or W4 of therapy since the beginning ? Because rapid viral response (RVR) is commonly defined as undetectable virus at 4 weeks of

boceprevir treatment and not at the end of the lead-in phase as considered in this paper. Please use the right terminology for virological responses

Reply: Thank you for your comments. We have made a clarification of the meaning of the weeks in the methods section to avoid confusion.

On-Treatment Response

HCV RNA was measured at regular intervals after starting PR therapy, week 4 (also known as RVR), week 8 (4 weeks after starting boceprevir), and week 12 (week 8 after starting boceprevir), week 24 (week 20 of boceprevir) and week 48 (week 44 of boceprevir).

- (8) One paper with updated results concerning virological responses was published since the references used in this manuscript. Please update Hezode et al. "Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis", Gastroenterology, Jul 2014

Reply: Thank you. We have updated the reference.

- (9) Kindly change all figure legends; there should be one legend for all panels in figure 1, i.e. 1A, 1B and 1C, likewise one legend for Figure 2 (2A, 2B), one legend for 3 (3A, 3B, 3C, 3D), one legend for 4 (4A, 4B) and one legend for Table 1 (1A, 1B). 2. Kindly remove the results from Figure legends, e.g. Figure 2B and 4B legends.

Reply: We have changed the figure legends as requested.

- (10) Kindly apply the statistical analysis for Table 1B as is applied for Table 1A.

Reply: Thank you for your comments. We have changed this accordingly and shown the significant p values in table 1B. We have also included a paragraph in the section on safety to reflect these findings:

Differences between Asians and Caucasians

Significant differences were found in SAE, AE and discontinuations between Asians and Caucasians (table 1C). Caucasians had significantly higher level of sepsis, neutropenia, skin rash, weight loss, dysgusia, diarrhoea and higher discontinuations than Asians.

We also included a short sentence in the discussion section to reflect this finding:

We did find however that Caucasian patients had significantly higher rate of AEs and higher discontinuations than Asians.

- (11) In results section "Multivariate analysis of baseline and on-treatment predictors of SVR12", there is a statement "Notably, IL28B CC genotype was not a significant predictor of SVR in this population of prior treatment failures", (Kindly mention figure/table no/data not shown for this statement).

Reply: Thank you for your comments. We have added this comment - (No figure or table shown).

(12) In results section “Serious Adverse Events (SAE)” there is a statement “Multivariate analysis showed that only older age was a significant protective factor for SAEs (RR =0.895, 95% CI 0.809-0.991)”, (Kindly mention figure/table no/data not shown for this statement).

Reply: Thank you for your comments. We have added this comment - (No figure or table shown).

C. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Yours sincerely



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