

ANSWERS TO REVIEWERS

December 22, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format with the tracked version followed by the clean version in the same document (file name: 13924_Edited_tracked_and_clean).

Title: Covalently closed-circular hepatitis B virus DNA reduction with entecavir or lamivudine

Authors: Scott Bowden, Stephen Locarnini, Ting-Tsung Chang, You-Chen Chao, Kwang-Hyub Han, Robert G. Gish, Robert A. de Man, Miao Yu, Cyril Llamoso and Hong Tang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13924

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

1 Format has been updated:

Columns: Clinical Trials Study

Author contributions are described in full text.

Comments section at the end of the manuscript has been added.

2 Revision has been made according to the suggestions of the reviewer. Please note that page numbers refer to the tracked version of the manuscript.

Comment	Reply
Reviewer #00068251	
1. There is a confusion in the abstract section. The duration of therapy has been given as 52 weeks and also 48 weeks in the same part however the duration of therapy should be uniform in all parts of the article.	The duration of treatment was for a minimum of 52 weeks (and a maximum of 96 weeks); however, cccDNA and total hepatic HBV DNA were assessed after 48 weeks of treatment (which is also the time point when the primary endpoint [histologic improvement] and other efficacy endpoints were assessed). We have changed the text in the abstract and methods section (page 10) to state 'at Week 48'.
2. In the "core tip" part included a sentence; "However cccDNA was still detectable in most biopsies, suggesting that despite potent viral suppression with entecavir, prolonged treatment may be needed to eradicate cccDNA". This sentence is not appropriate as a consequence of this study, because the	We have deleted this sentence in the core tip section.

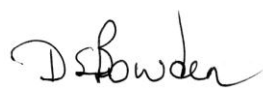
authors should mention their own research result.	
3. This manuscript is too long, which needs to be shortened.	Various sections in the manuscript have been shortened, in particular in the discussion.
Reviewer # 00160603	
Based on this study there are several questions: 1. Could the authors explain the clinical impact of genotype (especially genotype F) since in most Asian countries the genotype distribution are more B and C? Was it only to show the impact of therapy with lower viral load based on genotype?	<p>In our univariate regression analysis we not only tested for an association of cccDNA with HBV genotype F, but also with the other HBV genotypes A, B, C, D, and 'other'; only HBV F showed a significant association (in a negative fashion) with cccDNA levels. We have added this information to the results section on page 14, and have also changed the titles to tables 3 and 4 to indicate that only those associations are shown in the tables that were significant.</p> <p>Regarding the clinical relevance of this finding, we have added a short section in the discussion (page 17) describing the geographic prevalence of HBV F, and speculating that lower baseline cccDNA in HBV genotype F could be related to lower serum HBV DNA levels; however, there are currently no data available to support this hypothesis. Interestingly, genotype F has been linked to one of the highest risks of HCC compared with other HBV genotypes (8 x higher; Ref: Marciano et al; Antivir Ther. 2013;18:485), which we have also mentioned in the discussion. However, we also mention that the results of our HBV genotype regression analysis should be interpreted cautiously due to relatively high number of statistical tests performed)</p>
2. Is there any explanation about the possible impact of antiviral resistance during LAM treatment since we know that after 6 months therapy the risk of resistance is very high and because this cohort study was a small subset of big randomized study?	We agree with the reviewer that development of antiviral resistance during LAM therapy may have been a contributing factor to the lower reduction in cccDNA and total hepatic HBV DNA with LAM. We have added a sentence (pages 15/16) discussing this point and providing the results for virologic breakthrough and emergent resistance among ETV-treated and LAM-treated patients from study ETV-022 [Ref: Chang et al, 2006, NEJM, 354:1001].
3. Some studies showed improvement of	As shown in supplementary Figure 1, within

<p>histology after 1 year therapy, is there any explanation why in this study seemed the liver fibrosis not improved significantly?</p>	<p>this cccDNA biopsy subset of ETV-022 patients, 76% of ETV-treated patients vs 66% of LAM-treated patients achieved histologic improvement, and 43% vs 37% of patients demonstrated an improvement in fibrosis. These results are comparable to those from the overall 1-year primary analysis of study ETV-022 [Ref: Chang et al, 2006, NEJM, 354:1001], where 72% of ETV-treated patients vs 62% of LAM-treated patients achieved histologic improvement, and 39% vs 35% had an improved Ishak fibrosis score. Similar findings to those observed with ETV were also reported in TDF-studies where 72-78% of patients achieved a histologic improvement after 1 year of TDF therapy [Ref: Marcellin et al, 2008, NEJM, 359:2441].</p> <p>We are not aware of any major treatment studies with NUC therapy that actually had fibrosis improvement as a primary endpoint after 1 year of treatment. Usually, this endpoint is assessed with a statistical comparison after several years of treatment. The standard definition of histologic improvement requires improvement in the inflammatory score, but only 'no worsening of fibrosis'.</p>
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3 References and typesetting were corrected

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

Sincerely yours,



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