April 25, 2014

Dear editor,

Please find enclosed the edited manuscript in Word format (file name: 9585-edited_revision_Def.docx).

Title: Telaprevir and boceprevir-based tritherapies in real practice for F3-F4 pretreated HCV patients.
(Please note that accordingly to the reviewers answer, the title has been changed to fit into the 12 words instruction. The older title was: "Efficacy and tolerance of Telaprevir and Boceprevir triple therapies in nonresponder HCV genenotype 1 patients with a severe liver fibrosis: results in real life practice").

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Delphine Bonnet, Matthieu Guivarch equally contributed to the work.

Name of Journal: World Journal of Hepatology.

ESPS Manuscript NO: 9585

We read with great interest the comments of the 2 reviewers and the editor, and according to their suggestions we modified the manuscript as follows; the significant changes in the main manuscript have been highlighted in yellow:

1. Formats have been updated, with:
- A precision about the **Columns scope**: the **Retrospective study** subgroup seems to suit the best.
- The **highlighted contents** and the **core tip** (72 words) have been fulfilled inside the main manuscript.
- The **title** has been shortened and has a 12-words length now.
- We fulfilled **postcodes and cities** for all co-authors.
- The **abstract** has been slightly modified to best fit the format's requirements.
- We completed the **legend of the Figure 1** by specifying the meanings of abbreviations and hope that you will find that the legend meets now the Journal standards.

2. In response to corresponding comments of reviewer 1 (reviewer NO: 02861401), revisions of the manuscript were made:
- (Minor point 1) We changed the title word "nonresponder" to "pretreated", to best describe our population which includes null-responders and relapsers.
- (Minor point 2) We agree with the comment about the comparison between both arms of treatment that is questionable because treatment arms were not randomly assigned. To avoid any confusion we suppressed the statistical comparison in the

abstract. However, as specified in the Characteristics of patients at baseline Subsection on page 10, the groups were compared for all significant clinical and biological variables and we found that their were well balanced. Consequently, we used univariate analysis to compare the results of the two treatments, and discussed extensively on page 14 that this findings should be interpreted with caution.
- (Minor point 3) We agree with the notion that RVR is undoubtedly associated with some baseline factors. For this reason, as described in the Statistical analysis subsection, our multivariate model was adjusted to all baseline factors that were associated with SVR in univariate analysis (with a P value<0.20), which were the type of treatment, gender, prior response to treatment and liver stiffness, together with RVR.
- (Minor point 4) We modified the Statistical analysis subsection to describe with better accuracy how we defined the liver stiffness cut-off value, and added the following sentence: "We assessed accuracy of liver stiffness to predict SVR according to ROC-curve (plotting sensitivity versus 1-specificty, at various cut-off settings) and we defined the optimal liver stiffness cut-off value of 21.3KPa according to the best rate of correctly classified subjects (((true positives+true negatives)/total); 69.2%)".
- (Minor point 5) We clarified the sentence that was confused in the discussion because an error has been made in the numbers: the sentence "Our 54 patients included null-responder to PR had an SVR of 44%, higher than that found in studies like REALIZE" has been replaced by this one: "We observed an unexpected high SVR (54,9%) with TPV triple therapy in our previous null-responders. This rate is about twice higher than the SVR found in the REALIZE study in the same population of null-responders with severe liver fibrosis".

We agree with the comment of reviewer 1 concerning the better results of Sofosbuvir-based therapies than triples therapies with first generation HCV antiproteases, i.e. Telaprevir and Boceprevir. Of course the results of controlled trials with Sofosbuvir give us hope that greater than 90% HCV patients will experience viral clearance. However, data on the difficult-to-treat patients with Sofosbuvir are still limited. Up to date we do not dispose of any data on the use of Sofosbuvir in real clinical practice. Moreover, Sofosbuvir and other second-generation PI will not be available for all around the world, and in many regions their use are restricted to patients without any other alternative treatment. Consequently, it seems important to continue collecting results on the efficacy and the safety of the first protease inhibitors-based treatments, which place in the therapeutic arsenal would be defined in the coming years.

We read with interest the comment about our unexpected good results with the Telaprevir-based triple therapy, particularly in the subgroup of null-responders with cirrhosis. We could not provide any explanation of these results, as the two population has not been compared. However, this point has been discussed on page 14.

3. In response to reviewer 1 (reviewer NO: 00181443) comments, revisions of the manuscript were made:

- (Point 1): We decided to exclude partial responders to previous PR therapy because it was difficult to retrospectively check if these patients were true partial responders or inobservant patients. As it was unclear in our text, we modified the main manuscript and changed "non-responders" to "null-responders".
- (Point 2): We did not show any results about the relationship between the liver stiffness value and the incidence of SAE because no statistical association was found between both variables.

We thank you for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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