Paris, July 15th, 2014

Dear Editor,

Please find attached the revised version of our manuscript entitled "**Vitamin D Supplementation in addition to Peg-Interferon-alpha and Ribavirin in Null-Responders Patients with Genotype 1 or 4 Chronic Viral Hepatitis C: ANRS HC25 VITAVIC study**" (ESPS Manuscript NO: 12450), that we are submitting for publication in **World Journal of Gastroenterology**.

We have addressed all of the Reviewer concerns and have made the appropriate changes in the revised text. We think that their pertinent comments have helped us for improving our article and we sincerely thank them.

Changes in the marked version are indicated in red. Our detailed, point-by-point responses to their comments are given below.

Thank you in advance for reconsidering our manuscript and we look forward to hearing from you.

Looking forward to your decision.

Sincerely,

Dr. Benjamin Terrier, MD, PhD, Pr. Patrice Cacoub, MD, PhD

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Responses to Reviewer

This study attempted to answer an important clinical question.

Major comments:

1. However the design was a major problem here as they chose an open-label, uncontrolled study of superiority design of small sample size (40), but in fact only 29 subjects were analyzable for the primary end point. This limitation should be adequately addressed in the Discussion section.

We agree with the Reviewer. We have clarified this point in the Discussion section. **Please** see page 11 lines 21-25 and page 12 lines 1-6: "We must acknowledge the limits of our study. Because we aimed to analyze the efficacy of vitamin D supplementation in the era of new antiviral agents in the more challenging population of patients, i.e. null responder patients, we conducted an open-label, uncontrolled study of superiority design that planned to include 40 patients. Only 32 patients were included before the trial was stopped for futility and 29 patients were analyzable for the primary endpoint. Although it could have been a limitation to draw any conclusion in case of response to vitamin D supplementation, our findings probably demonstrate the absence of interest of vitamin D in previously null-responder patients with chronic genotype 1 or 4 HCV infection".

2. I could not find the reference or justification of the sample size estimation: why EVR rate of 21% with vitamin D in comparison to a hypothesized EVR rate of 7% in the absence of vitamin D? EVR of 21% is really a very ambitious estimation in cohort of null responders.

We totally agree with the Reviewer that an EVR of 21% was very ambitious in a population of null responder patients. This hypothesis was based on the fact that a new therapeutic strategy in chronic HCV infection should improve at least 3 times the baseline EVR rate. According to the PROVE3 [McHutshinson, N Engl J Med, 2010] and REPEAT [Jenssen, Ann Intern Med, 2009] studies, EVR in null responders to previous PegIFN/RBV during a new course of treatment was 7%.

However, in the era of new antiviral agents, such hypothesis was needed in our opinion to demonstrate a potential role of vitamin D supplementation in the therapeutic strategy.

3. Why a weekly dosing of Vit D was chosen? Why not daily dose?

In the present study, we have chosen the following therapeutic protocol, i.e. cholecalciferol 100 000 IU/week for 4 weeks followed by 100 000 IU/per month for 12 months. Supplementation with vitamin D was previously shown to be achieved equally well with daily, weekly, or monthly dosing frequencies [Ish-Shalom, J Clin Endocrin Metab, 2008]. Therefore, our protocol was chosen to optimize adherence of long-term vitamin D supplementation, according to French habits. We have clarified this point in the Discussion section, page 12 lines 6-8.

4. Please discuss the impact of direct acting antiviral (DAA) in relation to vitamin D deficiency.

To our knowledge, there is no published data looking for an impact of vitD deficiency in DAA activities. The role of vitD supplementation to increase SVR rates with future DAA combinations, interferon- or ribavirin-free remains to be defined.