

January 22, 2024

Dear Editor:

Thank you for the opportunity to submit this invited manuscript in revised form for possible publication in the *World Journal of Hepatology*. The reviewer comments were helpful and have resulted in meaningful improvements in the manuscript. A point-by-point response is provided below and a fully revised manuscript addressing all issues raised in peer review has been submitted for consideration. We hope the editors will find this manuscript acceptable for publication. Thank you again for your kind consideration.

Best regards,

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Director, Clinical Hepatology  
Vice-Chief, Section of Digestive Diseases  
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**Reviewer #1:**

**Specific Comments to Authors:**

The manuscript is written in a very unclear way. Editing in English is required. It does not advance the scientific field.

The entire manuscript text was carefully proofread and edited to address grammatical and formatting errors.

**Reviewer #2:**

**Specific Comments to Authors:**

Title. - I suggest rephrasing the title - not phase II and III agents, but "Advances in Novel Investigational Agents for Functional Cure of Chronic Hepatitis B: A Comprehensive Review of the results of Phase II and III trials"

Title was renamed to include the requested words, "results" and "phase II and III trials", while meeting the World Journal of Hepatology requirement for a maximum title length of 18 words.

Title changed to: "Novel Therapies for Functional Cure of Chronic Hepatitis B: A Comprehensive Review of Phase II/III Trial Results".

Methods. The relevancy of this type of manuscript greatly depends on the sources of data. I suggest briefly describing the process of search and acquisition of data (authors experience, authors involvement in the research, database search, drug pipeline overview by specialised company, market research etc. This goes particularly for the agents without published results of the studies (table 2)

Our paper is a narrative review. Per request, we have now included a brief description of our data acquisition process:

"This paper is a narrative review. Investigational agents for treatment of chronic HBV under active phase II and III development were identified using the National Institutes of Health Clinical Trials directory<sup>[24]</sup>. This directory includes details regarding the study design, study population, treatment arms, and sponsoring pharmaceutical company for all publicly supported clinical studies. Information from this website was also used to develop Table 2 which summarizes information about investigational agents without published study results. A PubMed search was conducted for each investigational agent under active phase II and II development. Data was retrieved from published original research articles and conference abstracts. The website of the sponsoring pharmaceutical company website for each investigational agent was reviewed for published presentation slides from international liver meetings."

Results. - the coverage of agents and the description of trials is adequate. However I suggest to be more specific when reporting the results of the trials - e.g. in the example below write the exact proportion of patients who achieved endpoint, not 9-10%

" B-Clear Trial was a phase 2b, randomized controlled study investigating the efficacy and safety of Bepirovirsen in 457 enrolled patients with chronic HBV when used for 12 and 24 weeks. Results revealed that 9-10% ..."

Recommendation to specify the exact proportion of patients in the results of the trials has been applied to all applicable reported results of the manuscript.

For example, our revised manuscript now reads: "The B-Clear Trial was a phase IIb, randomized controlled study investigating the efficacy and safety of Bepirovirsen in 457 enrolled participants with chronic HBV when used for 12 and 24 weeks. Results revealed that 6/68 participants and 7/70 participants who received 24 weeks of Bepirovirsen once weekly with and without NA therapy respectively achieved HBsAg and HBV DNA loss that persisted for 24 weeks following the end of the treatment period."

Is the style, language and grammar accurate and appropriate? - not a native english speaker

As mentioned above, the entire manuscript was carefully proofread and edited for grammatical and formatting accuracy.

Specific comments - check spelling - tenofovir disoproxil (not disoproximal), HBsAg, HbSAg consistency, abbreviations explanation (e.g. LLOQ)

Spelling error for tenofovir disoproxil noted in the Introduction.

Sentence now reads: "NA currently used in clinical practice, namely Tenofovir disoproxil fumarate (TDF) and Entecavir (ETV), have potent antiviral activity and a high barrier to resistance"

Correct abbreviation for HBsAg is now used consistently throughout the manuscript.

LLOQ throughout the body of the manuscript is now changed to lower limit of quantification. Abbreviation of "LLOQ" in Table 2 includes an explanation of the abbreviation at the bottom of the table.

I suggest expanding the conclusions section with authors own opinion on the most promising candidates, the potential avenues of research with highest likelihood of success, and maybe timeframe required to develop a cure along with the biggest scientific obstacles .

Manuscript now includes an updated conclusion synthesizing our own views on the novel therapeutics and clinical implications.

#### **Science Editor:**

The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

The entire manuscript text was carefully proofread and edited to address grammatical and formatting errors.

Specific comments: (1) Please provide the filled conflict-of-interest disclosure form. (2) Title: The article title cannot exceed 18 words.

Conflict of interest disclosure form completed.

Title has been changed so that it is 17 words in length.

“Novel Therapies for Functional Cure of Chronic Hepatitis B: A Comprehensive Review of Phase II/III Trial Results”

(3) Please add the Core tip section. The number of words should be controlled between 50-100 words.

Thank you for this instruction. We have now included a Core tip section to the manuscript.

(4) Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Table 1 and 2 revised to World Journal of Hepatology requirements. Both tables are now formatted as standard three-line tables. Italics are omitted.