Journal of Clinical Question

**Decision Letter (JCQ-2026-0033)**

**From:** [redacted]
**To:**
**CC:**
**BCC:**

**Subject:** Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0033

**Body:** 11-Nov-2026

Dear Dr Awadallah:

Manuscript ID JCQ-2026-0033 entitled "Efficacy and Safety of HBV RNA-Targeting Oligonucleotide Therapies in Nucleos(t)ide Analogue-Suppressed Chronic Hepatitis B: A Systematic Review and Meta-analysis of Randomized Controlled Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
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2. Click "Author" at the top left of the screen at "Home" page.
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Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
This is an interesting study. One point that could be added is:
1. A comparison with the APASL study on functional cure using new antiviral agents, as there are significant differences between the two.
2. Severe complications, such as an elevation in ALT levels that necessitates the discontinuation of treatment, should be addressed; furthermore, is there any association between these events and HBsAg loss or low HBsAg levels?
3. Based on your meta-analysis, is it possible to determine which class of new anti-hepatitis B drugs holds greater potential for achieving HBsAg loss or low HBsAg titers?

Reviewer: 2

Comments to the Author
This systematic review and meta-analysis addresses an important clinical question regarding the efficacy and safety of HBV RNA-targeting oligonucleotides in patients with virologically suppressed chronic hepatitis B. The manuscript is generally well structured and incorporates recent randomized controlled trials, including the phase 3 B-Well studies. However, several methodological and reporting issues require clarification to strengthen the reliability and clinical interpretation of the findings.

The handling of the B-Clear trial requires clarification because its crossover design may affect the validity of comparisons between bepirovirsen and placebo. The authors should verify the treatment assignments and assessment time points used in the meta-analysis and ensure that only appropriate randomized comparisons are included. Reanalysis should be performed if post-crossover data were incorporated into placebo-controlled comparisons.

The primary analysis of HBsAg loss combines outcomes assessed at different time points and demonstrates substantial heterogeneity ($I^2 = 97\%$). The authors should clarify the assessment time points and outcome definitions across the included trials. Sensitivity analyses restricted to clinically comparable endpoints should be considered where sufficient data are available.

Several differences in sample sizes between Table 1 and the forest plots require clarification. For example, the reported sample sizes for B-Well 1 and B-Well 2 differ from those included in the HBsAg loss analysis. Although these differences may reflect outcome-specific analysis populations, the authors should verify the extracted data and ensure consistency across the tables, figures, and text. The unresolved verification note concerning quantitative HBsAg reduction in Table 2 should also be addressed.

Functional cure represents a clinically important endpoint but is not included in the quantitative synthesis. The authors should clarify the availability of comparable functional cure outcomes, particularly from the B-Well trials, and consider presenting these results separately. In addition, further information on clinically important safety outcomes, particularly hepatic adverse events and treatment discontinuation, would improve clinical interpretation where such data are available.

The literature search date differs between the Abstract and Methods and should be made consistent throughout the manuscript and supplementary materials. Furthermore, the GRADE certainty assessments require clearer justification, particularly for efficacy outcomes with substantial heterogeneity and varying assessment time points. The authors should ensure that these limitations are appropriately reflected in the interpretation of the pooled results.

**Date Sent:** 11-Nov-2026

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**Author's Response to Decision Letter for (JCQ-2026-0033)**

**Efficacy and Safety of HBV RNA-Targeting Oligonucleotide Therapies in Nucleos(t)ide Analogue-Suppressed Chronic Hepatitis B: A Systematic Review and Meta-analysis of Randomized Controlled Trials**

Dear Editor and Reviewers,
Thank you for your careful evaluation and constructive comments. We have reviewed the original randomized trials, supplementary materials, and analysis dataset and revised the manuscript accordingly. Our point-by-point responses are provided below. Page and line references refer to the revised manuscript.

Reviewer 1
Comment 1. A comparison with the APASL study on functional cure using new antiviral agents, as there are significant differences between the two.
Response. Thank you for this important suggestion. We compared our review with the APASL Viral Elimination Taskforce meta-analysis by Chen et al. (Hepatology International, 2025). The earlier review examined functional cure across a broader range of investigational HBV therapies, whereas our analysis focuses on HBsAg responses in randomized studies of RNA-targeting oligonucleotides in NA-suppressed patients and includes the recent phase 3 B-Well trials. We have briefly clarified this distinction in the Discussion to avoid direct comparison of different endpoints. (Page 17, Lines 300–310)
Comment 2. Severe complications, such as an elevation in ALT levels that necessitates the discontinuation of treatment, should be addressed; furthermore, is there any association between these events and HBsAg loss or low HBsAg levels?
Response. Thank you for highlighting clinically important hepatic safety outcomes. We have added a concise description of ALT elevations (≥3× the upper limit of normal) and adverse-event-related treatment discontinuations observed in the B-Well trials. We also discuss the drug-induced liver injury that led to discontinuation of ALG-020572 development. Although ALT elevations sometimes coincided with marked HBsAg declines, the available aggregate trial data cannot establish whether they independently predict HBsAg loss or low HBsAg levels. We therefore discuss these findings without pooling clinically noncomparable hepatic safety endpoints. (Page 14, Lines 249–255; Pages 17–18, Lines 323–335)
Comment 3. Based on your meta-analysis, is it possible to determine which class of new anti-hepatitis B drugs holds greater potential for achieving HBsAg loss or low HBsAg titers?
Response. Thank you for this question. Our subgroup analyses showed differences in HBsAg loss and achievement of HBsAg <100 IU/mL between ASO and siRNA trials. However, these are indirect, across-trial comparisons rather than randomized head-to-head comparisons of molecular classes. The apparent differences may reflect individual agents, treatment regimens, baseline characteristics, and study size, particularly the large B-Well trials. We have clarified in the Discussion that these findings do not demonstrate intrinsic superiority of ASO over siRNA, especially for durable functional cure. (Page 17, Lines 311–322)
Reviewer 2
Comment 1. The handling of the B-Clear trial requires clarification because its crossover design may affect the validity of comparisons between bepirovirsen and placebo. The authors should verify the treatment assignments and assessment time points used in the meta-analysis and ensure that only appropriate randomized comparisons are included. Reanalysis should be performed if post-crossover data were incorporated into placebo-controlled comparisons.
Response. Thank you for identifying this methodological concern. We rechecked the B-Clear treatment assignments and crossover schedule. For HBsAg loss, the included comparison was bepirovirsen Arm 3 versus placebo Arm 4 at Week 12 (7/68 vs. 0/23), before the placebo group crossed over to active treatment. We have explicitly identified this comparison in the Methods and Results; post-crossover observations were not used as a concurrent placebo-controlled comparison. We also conducted a post hoc sensitivity analysis excluding B-Clear to assess its influence on the pooled primary outcome. (Page 10, Lines 160–175; Page 12, Lines 215–224)
Comment 2. The primary analysis of HBsAg loss combines outcomes assessed at different time points and demonstrates substantial heterogeneity ($I^2$ = 97%). The authors should clarify the assessment time points and outcome definitions across the included trials. Sensitivity analyses restricted to clinically comparable endpoints should be considered where sufficient data are available.
Response. We agree that differences in HBsAg-loss assessment times limit interpretation of the pooled effect, particularly given the substantial heterogeneity ($I^2$=97%). The manuscript now clarifies that trial-reported on-treatment or post-treatment assessment times were used, rather than a single uniform end-of-treatment time point. In a post hoc sensitivity analysis excluding B-Clear, the pooled effect remained statistically significant (RD, 0.22; 95% CI, 0.03–0.42; $I^2$=97%; eight comparisons), indicating that this trial alone did not explain the heterogeneity. We have retained a cautious interpretation because sufficiently comparable time-specific outcomes were not available across all agents to support a robust class-wide time-restricted synthesis. (Page 12, Lines 215–224; Page 18, Lines 336–347)
Comment 3. Several differences in sample sizes between Table 1 and the forest plots require clarification.

For example, the reported sample sizes for B-Well 1 and B-Well 2 differ from those included in the HBsAg loss analysis. Although these differences may reflect outcome-specific analysis populations, the authors should verify the extracted data and ensure consistency across the tables, figures, and text. The unresolved verification note concerning quantitative HBsAg reduction in Table 2 should also be addressed.
Response. Thank you for pointing out these discrepancies. We rechecked the study characteristics against the trial reports and the outcome-specific analysis data. Table 1 summarizes trial-level participant numbers, whereas the forest plots use the populations assessed for individual endpoints; these denominators need not be identical. We also reconciled the quantitative HBsAg reduction reporting: the synthesis includes nine estimable comparisons involving 230 participants, as consistently reported in the Results and Table 2. The provisional verification note has been removed from Table 2. We have not changed the pooled estimates merely to make trial-level and outcome-specific denominators match. (Page 13, Lines 232–238; Page 25, Lines 461–465)
Comment 4. Functional cure represents a clinically important endpoint but is not included in the quantitative synthesis. The authors should clarify the availability of comparable functional cure outcomes, particularly from the B-Well trials, and consider presenting these results separately. In addition, further information on clinically important safety outcomes, particularly hepatic adverse events and treatment discontinuation, would improve clinical interpretation where such data are available.
Response. Thank you for this valuable suggestion. We now report the phase 3 B-Well functional-cure outcomes descriptively and distinguish the Week 72 sustained response from HBsAg loss assessed at other time points. Functional cure occurred in approximately 20% and 19% of bepirovirsen-treated participants in B-Well 1 and B-Well 2, respectively, compared with none in the placebo groups. We have also added a concise account of clinically important ALT elevations and adverse-event-related treatment discontinuations. We did not add a separate class-wide meta-analysis because comparable off-treatment functional-cure outcomes and safety definitions were unavailable across most other agents; this limitation is acknowledged in the Discussion. (Page 14, Lines 249–255; Page 18, Lines 336–345)
Comment 5. The literature search date differs between the Abstract and Methods and should be made consistent throughout the manuscript and supplementary materials. Furthermore, the GRADE certainty assessments require clearer justification, particularly for efficacy outcomes with substantial heterogeneity and varying assessment time points. The authors should ensure that these limitations are appropriately reflected in the interpretation of the pooled results.
Response. Thank you for these comments. We have standardized the final literature-search date to September 20, 2026, in the Abstract and Methods, consistent with Supplementary Table S1. We also reviewed the GRADE judgments and their explanations. HBsAg loss is now rated as moderate certainty, downgraded one level for inconsistency; quantitative HBsAg reduction remains low certainty, and the other key outcomes are rated moderate. The reasons for downgrading are summarized in the Results and Table 2. The Discussion continues to emphasize the substantial heterogeneity and differences in assessment times when interpreting pooled efficacy estimates. (Pages 3 and 9, Lines 35–36 and 136–140; Page 14, Lines 268–275)
We appreciate the reviewers' constructive comments, which have strengthened the methodological transparency and clinical interpretation of this review.

Sincerely,
Salma Mohamed Awadallah

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