Decision Letter (JCQ-2025-0028)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0028

Body: 5-Sep-2025

Dear Dr Zhao:

Manuscript ID JCQ-2025-0028 entitled "Comparative Therapeutic Strategies for Secondary Progressive Multiple Sclerosis: A Systematic Review and Network Meta-Analysis" 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.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

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,
Professor Richard Isaacs
Editor in Chief, Journal of Clinical Question
jcqeic@gleampub.com

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

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
This systematic review and NMA provide an informative synthesis of therapeutic strategies in SPMS. The focus on siponimod, tolebrutinib, and interferon beta-1b is clinically relevant, but several methodological and interpretive issues should be addressed before publication.
Major Concerns
1. Statistical analyses: While frequentist NMA methods are appropriate, the authors should clarify how they addressed potential small-study effects, especially since only seven RCTs were included. Did they conduct sensitivity analyses excluding smaller trials?
2. Safety outcomes: The conclusions regarding tolebrutinib's adverse events are based on limited data (one RCT with 2-year follow-up). The discussion should acknowledge the restricted evidence base more explicitly.
3. Bias assessment: Four studies were rated as having "some concerns." The impact of these methodological limitations on pooled results should be discussed more fully.
4. Clinical interpretation: The recommendation that siponimod offers the "most favorable balance" may overstate the certainty given the modest differences between SUCRA rankings. A more cautious phrasing is warranted.

Reviewer: 2

Comments to the Author
This manuscript addresses an important clinical question on therapeutic options for secondary progressive multiple sclerosis (SPMS). The systematic review and network meta-analysis (NMA) are timely given the growing number of disease-modifying therapies (DMTs). The methodology is broadly sound, and the findings are clinically meaningful, particularly the comparative insights into siponimod, tolebrutinib, and interferon beta-1b. The manuscript is well-structured, with clear tables and figures that aid interpretation.
Major Comments
1. Scope of interventions: While the rationale for excluding mitoxantrone from the NMA is appropriate (due to toxicity), it may be useful to emphasize its role in historical context more clearly in the introduction and discussion.
2. Heterogeneity: The manuscript notes low statistical heterogeneity, but clinical heterogeneity (e.g., inclusion of active vs. non-active SPMS, differences in baseline EDSS, trial durations) warrants more discussion regarding generalizability.
3. Long-term outcomes: The discussion highlights limitations of short follow-up, especially for tolebrutinib. It would strengthen the manuscript to suggest how real-world evidence could complement trial data.
4. Certainty of evidence: Although GRADE is applied, the "moderate" certainty rating should be elaborated on—what were the key downgrading factors?
Minor Comments
1. Ensure consistency in reporting sample sizes across text and tables (e.g., "5,872" vs. study-level totals).
2. Correct a minor typographical error: "Departmet" (p.1, line 10).
3. Consider a brief limitations paragraph at the end of the abstract for balance.

Date Sent: 5-Sep-2025

Author's Response to Decision Letter for (JCQ-2025-0028)

Comparative Therapeutic Strategies for Secondary Progressive Multiple Sclerosis: A Systematic Review and Network Meta-Analysis

Response Letter

Dear Reviewers,
We would like to sincerely thank you for your careful review of our manuscript and for the constructive feedback you have provided. Your thoughtful comments have been invaluable in helping us improve the clarity, rigor, and balance of our work. We have carefully considered each point raised and provide our detailed responses below, together with the corresponding revisions that will be incorporated into the manuscript.

Reviewer 1
Reviewer's comment: While the rationale for excluding mitoxantrone from the NMA is appropriate (due to toxicity), it may be useful to emphasize its role in historical context more clearly in the introduction and discussion.
Reply: Thank you for your suggestion. We agree with the reviewer's suggestion. We have added the contents in discussion as follows: "Mitoxantrone demonstrated the most pronounced short-term efficacy among the evaluated agents; however, its clinical utility is severely limited by a well-documented toxicity profile. Notably, the risks of cumulative dose-dependent cardiotoxicity and therapy-related secondary acute myeloid leukemia significantly outweigh its benefits in most settings, thereby precluding its routine use in long-term disease management."

Reviewer's comment: The manuscript notes low statistical heterogeneity, but clinical heterogeneity (e.g., inclusion of active vs. non-active SPMS, differences in baseline EDSS, trial durations) warrants more discussion regarding generalizability.
Reply: We appreciate this important point. We have expanded the discussion to explicitly address clinical heterogeneity in the limitation as follows "While statistical heterogeneity was low, clinical heterogeneity, including differences in disease activity status, baseline EDSS, and trial durations, should be considered when interpreting the generalizability of these findings."

Reviewer's comment: The discussion highlights limitations of short follow-up, especially for tolebrutinib. It would strengthen the manuscript to suggest how real-world evidence could complement trial data.
Reply:Thank you for your comment on this point. We added contnets in the discussion as follows "Nevertheless, concerns remain due to the higher risk of SAEs and the short follow up, which limits understanding of its long-term safety and efficacy. Real world evidence from observational cohorts, registries, and post marketing surveillance will be valuable in assessing durability of benefit, safety, and treatment persistence in broader patient populations. Furthermore, the inclusion of participants without active relapses in several trials may restrict generalizability. Despite these limitations, the findings highlight tolebrutinib's potential and underscore the need for longer term studies."

Reviewer's comment: Although GRADE is applied, the "moderate" certainty rating should be elaborated on: what were the key downgrading factors?
Reply: Thank you for your comment on this point. We have modified the certainty of evidence section as follows: "Risk of bias assessments (Figure S5) showed that four studies were rated as having some concerns, while the remaining three were judged to have a low risk of bias. The evaluated outcomes included CDP at 3 and 6 months. Overall, the risk of bias was considered to be of some concern. The certainty of evidence for the treatment rankings was rated as moderate, downgraded due to risk of bias."

Reviewer's comment: Ensure consistency in reporting sample sizes across text and tables (e.g., "5,872" vs. study-level totals).
Reply: We appreciate your comment. We carefully reviewed all sample size reporting and ensure consistency between the text and tables as 5872.

Reviewer's comment: Correct a minor typographical error: "Departmet" (p.1, line 10).
Reply: We appreciate your comment We correct this typographical error.

Reviewer's comment: Consider a brief limitations paragraph at the end of the abstract for balance.
Reply: We agree and add a concise limitations paragraph at the end of the abstract to provide a balanced summary as follows "This NMA found that tolebrutinib, IFN-β-1b, and siponimod delay disability progression in SPMS, with IFN-β-1b and siponimod remaining the most practical options. The conclusions should be interpreted cautiously given bias risk, moderate evidence certainty, limited safety data, and clinical heterogeneity."

Reviewer 2
Reviewer's comment: While frequentist NMA methods are appropriate, the authors should clarify how they addressed potential small-study effects, especially since only seven RCTs were included. Did they conduct sensitivity analyses excluding smaller trials?
Reply: We appreciate this observation. Due to the limited number of studies and the use of multiple agents, conducting a sensitivity analysis in the NMA was not feasible. Although heterogeneity was low, we have added the following statement: "The small sample size and inclusion of multiple agents limited safety comparisons and precluded sensitivity analyses."

Reviewer's comment: The conclusions regarding tolebrutinib's adverse events are based on limited data (one RCT with 2-year follow-up). The discussion should acknowledge the restricted evidence base more explicitly.
Reply: We appreicate the reviwer's comment on this point. We have added the following statement to the discussion section to address this concern: "Nevertheless, concerns remain due to the higher risk of SAEs and the short follow up, which limits understanding of its long-term safety and efficacy."

Reviewer's comment: Four studies were rated as having "some concerns." The impact of these methodological limitations on pooled results should be discussed more fully.
Reply: Thank you for pointing this out. As Reviewer 1 noted, the GRADE assessment was downgraded to moderate due to concerns regarding risk of bias. We have revised the text as follows: "Risk of bias assessments (Figure S5) showed that four studies were rated as having some concerns, while the remaining three were judged to have a low risk of bias. The evaluated outcomes included CDP at 3 and 6 months. Overall, the risk of bias was considered to be of some concern. The certainty of evidence for the treatment rankings was rated as moderate, downgraded due to risk of bias."

Reviewer's comment: The recommendation that siponimod offers the "most favorable balance" may overstate the certainty given the modest differences between SUCRA rankings. A more cautious phrasing is warranted.
Reply: Thank you for pointing this out. We agree and revised the contents as follows "Moderate-certainty evidence suggests that siponimod may offer a favorable balance of efficacy and safety for delaying disability progression. Tolebrutinib appears promising but requires further investigation due to safety concerns."

Reviewer's comment: Clarify whether the analysis included both active and non-active SPMS populations, and whether subgroup analyses were feasible.
Reply: Reply: We thank the reviewer for this insightful comment. We have clarified in the Methods and Results that both active and non-active SPMS populations were included. However, subgroup analyses were not feasible, as the included trials did not report outcomes stratified by disease activity, and the proportion of non-active SPMS patients was fewer than 50%. As follows "Studies were excluded if they (1) presented only subgroup analyses without new, relevant data; (2) had non-extractable or insufficient outcome data; (3) included fewer than 50% SPMS participants;"

Reviewer's comment: The abstract could better reflect the study's limitations.
Reply: Reply: We appreciate the reviewer's comment on this point. As Reviewer 1 noted, we have added the following limitation to the abstract: "This NMA found that tolebrutinib, IFN-β-1b, and siponimod delay disability progression in SPMS, with IFN-β-1b and siponimod remaining the most practical options. The conclusions should be interpreted cautiously given bias risk, moderate evidence certainty, limited safety data, and clinical heterogeneity."

Reviewer's comment: References are comprehensive but could be shortened in places to focus on the most relevant works.
Reply: We appreciate the reviewer's comment. We have modified the reference list to focus on the most directly relevant sources.

We are deeply grateful for the time and expertise both reviewers dedicated to evaluating our work. Your insights have strengthened the manuscript substantially, and we are confident that the revisions will enhance its clarity, methodological transparency, and interpretive balance. We look forward to your continued feedback and hope that the revised version meets your expectations.

Sincerely,
Danyu Zhao
School of Basic Medical Sciences, Liaoning University of Traditional Chinese Medicine
Email: zhaody781107@163.com