Journal of Clinical Question

Decision Letter (JCQ-2026-0022)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0022

Body: 7-Jun-2026

Dear Dr Kawashima:

Manuscript ID JCQ-2026-0022 entitled "Factor XIa Inhibitors for Secondary Prevention After Ischemic Stroke or Transient Ischemic Attack: A Meta-Analysis of Randomized Clinical 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.
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.

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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,
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 manuscript presents a systematic review and meta-analysis evaluating factor XIa inhibitors for secondary prevention after non-cardioembolic ischemic stroke or high-risk transient ischemic attack. The topic is timely and clinically relevant, particularly given the emerging randomized evidence on asundexian and milvexian. The manuscript is generally well organized, and the clinical question is clearly stated. However, several important methodological and reporting issues need to be addressed before the conclusions can be considered reliable. I therefore recommend major revision.

Major Comments

1. The consistency of extracted data and denominators requires careful verification. There are apparent discrepancies between the total sample size reported in the abstract and the denominators shown in the forest plots for different outcomes. For example, the abstract reports 13,889 participants, including 6,937 in the factor XIa inhibitor group and 6,952 in the placebo group, whereas the forest plots use different denominators across recurrent ischemic stroke, TIA, all-cause mortality, and major bleeding. These inconsistencies raise concerns regarding whether the authors used the intention-to-treat population, modified intention-to-treat population, safety population, or pooled dose groups. The authors should provide a detailed data extraction table showing, for each included trial and each outcome, the exact number of events, denominators, analysis population, and source of the extracted data.

2. The handling of multiple-dose phase 2 trials should be clarified. Both AXIOMATIC-SSP and PACIFIC-Stroke were dose-finding studies, whereas OCEANIC-STROKE was a large phase 3 trial. It is unclear whether the authors combined all active-dose arms into a single intervention group and, if so, how they avoided double-counting the placebo group. The authors should explicitly describe the statistical approach used to combine multiple intervention arms. A dose-based sensitivity analysis or, at minimum, a clear justification for combining all doses should be provided.

3. The choice of effect measure should be reconsidered or better justified. The included trials differed substantially in follow-up duration, ranging from 90 days to more than one year. In this context, pooling simple odds ratios from event counts may not adequately account for time-to-event differences. The Methods section states that hazard ratios would be preferentially extracted when available, but the Results section reports only odds ratios. The authors should explain why hazard ratios were not used as the primary measure for efficacy outcomes. If only event counts were available for some outcomes, this limitation should be emphasized, and sensitivity analyses using alternative measures such as risk ratios should be considered.

4. The conclusions appear stronger than warranted by the evidence. Although the pooled result suggests a reduction in recurrent ischemic stroke, the overall evidence base includes only three trials, and the estimate appears to be largely driven by the large asundexian phase 3 trial. The milvexian evidence remains limited and imprecise. Therefore, statements suggesting that factor XIa inhibition may already be proposed or advocated as an adjunctive secondary prevention strategy should be softened. The conclusions should emphasize that the current evidence is promising, particularly for asundexian, but that routine clinical implementation and class-wide conclusions require further confirmatory trial evidence.

5. The GRADE assessment requires revision. The manuscript states that the certainty of evidence was downgraded partly because of publication bias. However, only three trials were included, making formal assessment of publication bias unreliable. The funnel plots in the supplementary figures are also not appropriate with such a small number of studies and should be removed or clearly labeled as exploratory and uninterpretable. The GRADE assessment should instead focus on risk of bias, imprecision, indirectness, and inconsistency, particularly for TIA and mortality outcomes.

6. The risk-of-bias assessment needs clearer justification. The manuscript suggests that small sample size contributed to concerns about outcome measurement bias in the phase 2 trials. However, small sample size is more appropriately considered under imprecision rather than risk of bias. If some concerns were assigned for outcome measurement, the authors should explain whether this was due to differences in endpoint definitions, imaging-based outcome assessment, adjudication procedures, or other methodological factors.

7. Subgroup and sensitivity analyses are insufficiently reported. The Methods section mentions prespecified subgroup analyses based on drug type, trial phase, dose, index event type, and background antiplatelet regimen, but the Results section mainly reports drug-specific subgroup analyses. The authors should either present all prespecified subgroup analyses or state that they could not be performed because of the small number of included trials. Sensitivity analyses comparing fixed-effect and random-effects models should also be reported more clearly.

8. The manuscript should avoid implying a uniform class effect. The evidence for asundexian and milvexian should be interpreted separately. The pooled estimate is mainly supported by asundexian data, whereas the milvexian estimate is statistically imprecise. The Discussion should include a clearer statement that the current findings should not be interpreted as definitive evidence of a class effect across all factor XIa inhibitors.

9. The registration information should be verified. The reported UMIN registration appears to require clarification, and the title or scope of the registered protocol should be consistent with the present review. If the protocol was not prospectively registered or if there were deviations from the registered protocol,

this should be transparently stated.

10. The ethical statement should be revised. The current statement only indicates that the article does not involve animals. For a systematic review and meta-analysis, it would be more appropriate to state that ethical approval and informed consent were not required because the study used previously published aggregate data and did not involve new recruitment of human participants or animal experiments.

Minor Comments

1. The sentence “the protective benefits of conventional antiplatelet strategies are not incomplete” should be corrected to “are incomplete” or “provide incomplete protection.”

2. The I^2 value for major bleeding should be checked and consistently reported throughout the abstract, results, and figures.

3. The PRISMA flow description should be revised to use standard terminology, including records screened, reports sought for retrieval, reports assessed for eligibility, and reports excluded with reasons.

4. Table 1 should be expanded. Important trial-level information such as trial phase, randomization ratio, drug dose, background antiplatelet therapy, index event distribution, analysis population, treatment duration, follow-up duration, and funding source should be added.

5. The forest plots should be improved for readability. The current figures are small and contain large blank areas. They should be exported at higher resolution with consistent font size and clearer labels.

6. The supplementary funnel plots should be removed because publication bias cannot be meaningfully assessed with only three included trials.

7. The abstract conclusion should be softened. Instead of stating that factor XIa inhibition “has been shown” to reduce recurrent ischemic stroke, the authors could state that factor XIa inhibition “was associated with” or “appeared to reduce” recurrent ischemic stroke.

8. The Data Availability Statement should be more specific. If extracted data and analytic code are available upon request, this should be stated clearly. Ideally, the extracted dataset and analysis code should be made available as supplementary material.

Overall Recommendation

Major revision. The manuscript addresses an important and timely clinical question, and the topic is suitable for publication after substantial revision. However, the authors need to resolve key methodological issues, particularly the inconsistencies in event counts and denominators, the handling of multiple-dose phase 2 trials, the choice of effect measure, the GRADE assessment, and the strength of the conclusions. Once these issues are addressed, the manuscript would provide a more reliable and clinically useful synthesis of the emerging evidence on factor XIa inhibitors for secondary stroke prevention.

Reviewer: 2

Comments to the Author
General CommentsThis manuscript by Kawashima et al. presents a systematic review and meta-analysis evaluating the efficacy and safety of factor XIa inhibitors (asundexian and milvexian) for secondary prevention following non-cardioembolic ischemic stroke or high-risk transient ischemic attack (TIA). By incorporating data from three randomized clinical trials (AXIOMATIC-SSP, PACIFIC-Stroke, and OCEANIC-STROKE), the authors conclude that factor XIa inhibition significantly reduces the incidence of recurrent ischemic stroke without increasing major bleeding. While the analysis targets a biologically compelling and clinically relevant antithrombotic strategy, the manuscript requires a Major Revision before it can be considered suitable for publication. The primary limitation is the lack of contextualization against highly similar, previously published work.

1. Overlap with Existing Literature
The most critical issue is the existence of a recently published systematic review and meta-analysis that shares a virtually identical scope and yields very similar results:

Efficacy and Safety of Oral Factor XIa Inhibitors in Stroke Prevention: A Systematic Review and Meta-Analysis (Journal of Clinical Medicine, 2023, 12(17), 5562; https://www.mdpi.com/2077-0383/12/17/5562).

The referenced 2023 MDPI paper also evaluated the efficacy and safety profiles of asundexian and milvexian, utilizing the phase 2 AXIOMATIC-SSP and PACIFIC-Stroke trial data. The current manuscript entirely omits any mention of this prior publication in the Introduction or Discussion sections.

2. Justification of Novelty and Incremental Value
While this manuscript provides an updated analysis by integrating the newer phase 3 OCEANIC-STROKE trial data, the authors must explicitly justify why a new meta-analysis is warranted.
Clearly articulate the incremental value of your study. You must explain how the addition of the OCEANIC-STROKE data and your strict focus on non-cardioembolic ischemic stroke or high-risk TIA substantially

changes, reinforces, or advances the conclusions drawn by the prior publication
3. Discussion of Evidence Certainty
The authors appropriately grade the certainty of evidence as "low" across all outcomes (recurrent ischemic stroke, TIA, all-cause mortality, and major bleeding) due to concerns regarding risk of bias. In light of the previous meta-analysis, the authors should expand the Discussion to address how the inclusion of a larger phase 3 trial (which heavily weights the pooled estimates at ~90-95% for asundexian) impacts the overall statistical precision and heterogeneity compared to the previous literature.

Date Sent: 7-Jun-2026

Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2026-0022)

Factor XIa Inhibitors for Secondary Prevention After Ischemic Stroke or Transient Ischemic Attack: A Meta-Analysis of Randomized Clinical Trials

Dear Editor and Reviewers,

We sincerely thank the Editor and both Reviewers for their careful evaluation of our manuscript, "Factor XIa Inhibitors for Secondary Prevention After Ischemic Stroke or Transient Ischemic Attack: A Meta-Analysis of Randomized Clinical Trials" We greatly appreciate the constructive and detailed comments. We have revised the manuscript extensively to improve methodological transparency, reporting quality, and the interpretation of our findings. All changes are marked in the revised manuscript. Our point-by-point responses are provided below.

Response to Reviewer 1
Major Comment
Comment 1: The consistency of extracted data and denominators requires careful verification. There are apparent discrepancies between the total sample size reported in the abstract and the denominators shown in the forest plots for different outcomes. For example, the abstract reports 13,889 participants, including 6,937 in the factor XIa inhibitor group and 6,952 in the placebo group, whereas the forest plots use different denominators across recurrent ischemic stroke, TIA, all-cause mortality, and major bleeding. These inconsistencies raise concerns regarding whether the authors used the intention-to-treat population, modified intention-to-treat population, safety population, or pooled dose groups. The authors should provide a detailed data extraction table showing, for each included trial and each outcome, the exact number of events, denominators, analysis population, and source of the extracted data.
Response: Thank you for this important comment. Three studies were included, comprising one Phase 3 trial and two Phase 2 trials. For the Phase 3 trial, data were extracted from the intention-to-treat population. For the Phase 2 trials, only dose groups comparable to the Phase 3 regimen or relevant to ongoing Phase 3 development were included. Therefore, the denominators in the forest plots differ across outcomes because not all randomized participants from the Phase 2 trials were included, and different outcomes were reported using different analysis populations. Efficacy outcomes were extracted from the intention-to-treat population, whereas major bleeding was extracted from the safety population when applicable. All extracted event numbers, denominators, dose groups, and analysis populations are presented in the manuscript. We will clarify these points in the Methods section and figure legends.

Comment 2: The handling of multiple-dose phase 2 trials should be clarified. Both AXIOMATIC-SSP and PACIFIC-Stroke were dose-finding studies, whereas OCEANIC-STROKE was a large phase 3 trial. It is unclear whether the authors combined all active-dose arms into a single intervention group and, if so, how they avoided double-counting the placebo group. The authors should explicitly describe the statistical approach used to combine multiple intervention arms. A dose-based sensitivity analysis or, at minimum, a clear justification for combining all doses should be provided.
Response: Thank you for this important comment. In the two Phase 2 dose-finding trials, we did not combine all active-dose arms. Only the dose groups comparable to the Phase 3 regimen or relevant to ongoing Phase 3 development were included in the meta-analysis. Each selected active-dose group was compared with the corresponding placebo group only once; therefore, no double-counting of placebo participants occurred. Because the objective of our analysis was to evaluate clinically relevant factor XIa inhibitor regimens rather than the full dose–response relationship, we did not perform a dose-based sensitivity analysis. We have clarified this approach in the Methods section as follows: "For the Phase 2 trials, only dose groups comparable to the Phase 3 regimen or relevant to ongoing Phase 3 development were extracted."

Comment 3: The choice of effect measure should be reconsidered or better justified. The included trials differed substantially in follow-up duration, ranging from 90 days to more than one year. In this context, pooling simple odds ratios from event counts may not adequately account for time-to-event differences. The Methods section states that hazard ratios would be preferentially extracted when available, but the Results section reports only odds ratios. The authors should explain why hazard ratios were not used as the primary measure for efficacy outcomes. If only event counts were available for some outcomes, this limitation should be emphasized, and sensitivity analyses using alternative measures such as risk ratios should be considered.
Response: Thank you for this comment. Although hazard ratios are preferable for time-to-event outcomes, one included study did not report hazard ratios. Given that only three eligible studies were available, we used odds ratios based on cumulative event counts to include all relevant evidence. We have clarified this rationale in the Methods section and added to the Discussion that this approach may not fully account for differences in follow-up duration across trials.

Comment 4: The conclusions appear stronger than warranted by the evidence. Although the pooled result

suggests a reduction in recurrent ischemic stroke, the overall evidence base includes only three trials, and the estimate appears to be largely driven by the large asundexian phase 3 trial. The milvexian evidence remains limited and imprecise. Therefore, statements suggesting that factor XIa inhibition may already be proposed or advocated as an adjunctive secondary prevention strategy should be softened. The conclusions should emphasize that the current evidence is promising, particularly for asundexian, but that routine clinical implementation and class-wide conclusions require further confirmatory trial evidence.
Response: Thank you for this important comment. We have revised and softened the conclusion to better reflect the limited evidence base and the predominance of asundexian data. The revised conclusion is: "Oral factor XIa inhibition was associated with a reduced risk of recurrent ischemic stroke in patients with recent non-cardioembolic ischemic stroke or high-risk TIA, with the strongest current evidence supporting asundexian. The effects on TIA, all-cause mortality, long-term safety, and consistency across different factor XIa inhibitors remain uncertain. Further confirmatory trials are needed before routine clinical implementation or class-wide conclusions can be made."

Comment 5: The GRADE assessment requires revision. The manuscript states that the certainty of evidence was downgraded partly because of publication bias. However, only three trials were included, making formal assessment of publication bias unreliable. The funnel plots in the supplementary figures are also not appropriate with such a small number of studies and should be removed or clearly labeled as exploratory and uninterpretable. The GRADE assessment should instead focus on risk of bias, imprecision, indirectness, and inconsistency, particularly for TIA and mortality outcomes.
Response: Thank you for this comment. We agree that publication bias cannot be reliably assessed with only three included trials and have removed it as a reason for downgrading the certainty of evidence. The funnel plots have been retained as supplementary material for completeness and in accordance with standard meta-analysis reporting practice; however, we have clarified that they are exploratory and should not be interpreted as a formal assessment of publication bias. The GRADE assessment has been revised to focus on risk of bias, inconsistency, indirectness, and imprecision, particularly for the TIA and all-cause mortality outcomes.

Comment 6: The risk-of-bias assessment needs clearer justification. The manuscript suggests that small sample size contributed to concerns about outcome measurement bias in the phase 2 trials. However, small sample size is more appropriately considered under imprecision rather than risk of bias. If some concerns were assigned for outcome measurement, the authors should explain whether this was due to differences in endpoint definitions, imaging-based outcome assessment, adjudication procedures, or other methodological factors.
Response: We appreciate this important comment. We agree that small sample size should not be considered a source of outcome measurement bias or imprecision in this context. Our reference to sample size was intended to reflect the limited statistical power of the phase 2 trials to detect or explore potential differences between groups, rather than uncertainty arising from imprecise estimates. To avoid double counting this limitation, we did not downgrade the certainty of evidence for imprecision.
Comment 7: Subgroup and sensitivity analyses are insufficiently reported. The Methods section mentions prespecified subgroup analyses based on drug type, trial phase, dose, index event type, and background antiplatelet regimen, but the Results section mainly reports drug-specific subgroup analyses. The authors should either present all prespecified subgroup analyses or state that they could not be performed because of the small number of included trials. Sensitivity analyses comparing fixed-effect and random-effects models should also be reported more clearly.
Response: Thank you for this comment. In addition to the subgroup analysis comparing the two agents, further subgroup analyses by trial phase, dose, index event type, and background antiplatelet regimen were not feasible because of the limited number of included studies. We have clarified this in the revised manuscript and limited the subgroup analysis to drug type. Sensitivity analyses comparing fixed-effect and random-effects models were also not performed because of the small number of included studies.

Comment 8: The manuscript should avoid implying a uniform class effect. The evidence for asundexian and milvexian should be interpreted separately. The pooled estimate is mainly supported by asundexian data, whereas the milvexian estimate is statistically imprecise. The Discussion should include a clearer statement that the current findings should not be interpreted as definitive evidence of a class effect across all factor XIa inhibitors.
Response: Thank you for this important comment. We have revised the Discussion to clarify that the evidence should not be interpreted as definitive proof of a class effect across all factor XIa inhibitors. The pooled result is driven mainly by asundexian data, whereas the evidence for milvexian remains limited and imprecise. We now interpret the findings for each agent separately and emphasize that further confirmatory studies are needed.

Comment 9: The registration information should be verified. The reported UMIN registration appears to require clarification, and the title or scope of the registered protocol should be consistent with the present review. If the protocol was not prospectively registered or if there were deviations from the registered protocol, this should be transparently stated.
Response: Thank you for this comment. We rechecked the UMIN registration and the manuscript and confirmed that they are consistent in title and scope. No deviations from the registered protocol occurred; therefore, no further modification was necessary.
Comment 10: The ethical statement should be revised. The current statement only indicates that the article does not involve animals. For a systematic review and meta-analysis, it would be more appropriate to state that ethical approval and informed consent were not required because the study used previously published aggregate data and did not involve new recruitment of human participants or animal experiments.
Response: We revised the ethical statement as recommended. It now states: "Ethical approval and

informed consent were not required because this study was a systematic review and meta-analysis of previously published aggregate data and did not involve new recruitment of human participants or animal experiments."

Minor Comment
Comment 1: The sentence "the protective benefits of conventional antiplatelet strategies are not incomplete" should be corrected to "are incomplete" or "provide incomplete protection."
Response: Thank you for your comment on this point. We have modified it as are incomplete.

Comment 2: The I^2 value for major bleeding should be checked and consistently reported throughout the abstract, results, and figures.
Response: Thank you for your comment on this point. We rechecked the analysis and corrected the I^2 value for major bleeding throughout the Abstract, Results, and figures.

Comment 3: The PRISMA flow description should be revised to use standard terminology, including records screened, reports sought for retrieval, reports assessed for eligibility, and reports excluded with reasons.
Response: Thank you for your comment on this point. Revised as follows "The database search identified 338 records. After removal of 65 duplicate records, 273 records were screened, and 209 records were excluded. We sought retrieval of 64 reports; all were successfully retrieved and assessed for eligibility. Of these, 61 reports were excluded, including reports involving atrial fibrillation (n = 15), studies not related to stroke (n = 17), and review articles (n = 29). Ultimately, three randomized controlled trials were included in the final analysis."

Comment 4: Table 1 should be expanded. Important trial-level information such as trial phase, randomization ratio, drug dose, background antiplatelet therapy, index event distribution, analysis population, treatment duration, follow-up duration, and funding source should be added.
Response: Response: Thank you for this helpful suggestion. We agree that detailed trial-level characteristics are important for assessing the clinical and methodological comparability of the included studies. To maintain the readability of the main manuscript table, we have retained the key study characteristics in Table 1 and added a supplementary table containing the additional information requested, including trial phase, randomization ratio, study drug dose, background antiplatelet therapy, index-event distribution, analysis population, treatment duration, follow-up duration, and funding source.

Comment 5: The forest plots should be improved for readability. The current figures are small and contain large blank areas. They should be exported at higher resolution with consistent font size and clearer labels.
Response: Thank you for your comment on this point. We regenerated all forest plots at higher resolution and revised the layout, font size, spacing, and labels to improve readability.

Comment 6: The supplementary funnel plots should be removed because publication bias cannot be meaningfully assessed with only three included trials.
Response: Response: Thank you for this comment. We agree that publication bias cannot be meaningfully assessed with only three included trials. However, we retained the funnel plots in the Supplementary Material as part of the prespecified meta-analysis workflow, rather than to draw conclusions regarding publication bias.

Comment 7: The abstract conclusion should be softened. Instead of stating that factor XIa inhibition "has been shown" to reduce recurrent ischemic stroke, the authors could state that factor XIa inhibition "was associated with" or "appeared to reduce" recurrent ischemic stroke.
Response: Revised as suggested. The Abstract now states that factor XIa inhibition was associated with recurrent ischemic stroke.

Comment 8: The Data Availability Statement should be more specific. If extracted data and analytic code are available upon request, this should be stated clearly. Ideally, the extracted dataset and analysis code should be made available as supplementary material.
Response: Thank you for this helpful suggestion. We have revised the Data Availability Statement to clarify that the extracted data and analytic code are available from the corresponding author upon reasonable request.

Response to Reviewer 2
Comment 1: The most critical issue is the existence of a recently published systematic review and meta-analysis that shares a virtually identical scope and yields very similar results: Efficacy and Safety of Oral Factor XIa Inhibitors in Stroke Prevention: A Systematic Review and Meta-Analysis (Journal of Clinical Medicine, 2023, 12(17), 5562; https://www.mdpi.com/2077-0383/12/17/5562). The referenced 2023 MDPI paper also evaluated the efficacy and safety profiles of asundexian and milvexian, utilizing the phase 2 AXIOMATIC-SSP and PACIFIC-Stroke trial data. The current manuscript entirely omits any mention of this prior publication in the Introduction or Discussion sections.
Response: Thank you for highlighting this relevant prior work. We have now cited and discussed the 2023 systematic review and meta-analysis in the revised Discussion. We acknowledge that the previous review evaluated the phase 2 AXIOMATIC-SSP and PACIFIC-Stroke trials and reported broadly similar findings. Our updated analysis incorporates additional evidence, including the phase 3 OCEANIC-STROKE trial, providing a more current assessment of the efficacy and safety of oral factor XIa inhibitors for secondary stroke prevention.

Comment 2: While this manuscript provides an updated analysis by integrating the newer phase 3 OCEANIC-STROKE trial data, the authors must explicitly justify why a new meta-analysis is warranted. Clearly articulate the incremental value of your study. You must explain how the addition of the OCEANIC-STROKE data and your strict focus on non-cardioembolic ischemic stroke or high-risk TIA substantially changes, reinforces, or advances the conclusions drawn by the prior publication
Response: We thank the reviewer for this thoughtful comment. Building on the previous review, our analysis includes OCEANIC-STROKE, a large phase 3 randomized controlled trial that expands the available evidence base and allows for more precise estimates of the efficacy and safety of asundexian. In addition, our review focuses specifically on secondary prevention among patients with non-cardioembolic ischemic stroke or high-risk TIA. As this population differs clinically and mechanistically from patients with atrial fibrillation–related cardioembolic stroke, for whom anticoagulation is the standard preventive approach, this focused analysis may offer a more directly relevant assessment of oral factor XIa inhibitors as an adjunct to antiplatelet therapy for secondary stroke prevention.

Comment 3: The authors appropriately grade the certainty of evidence as "low" across all outcomes (recurrent ischemic stroke, TIA, all-cause mortality, and major bleeding) due to concerns regarding risk of bias. In light of the previous meta-analysis, the authors should expand the Discussion to address how the inclusion of a larger phase 3 trial (which heavily weights the pooled estimates at ~90-95% for asundexian) impacts the overall statistical precision and heterogeneity compared to the previous literature.
Response: We thank the reviewer for this insightful comment. We have expanded the Discussion to address the influence of OCEANIC-STROKE on the pooled estimates. As the largest included trial, OCEANIC-STROKE contributed approximately 90% of the weight to the asundexian analyses, substantially improving the statistical precision of the pooled estimates compared with the previous meta-analysis, which was based primarily on smaller phase 2 trials. The inclusion of this phase 3 trial also provided more robust estimates for recurrent ischemic stroke and major bleeding. However, despite the increased precision, heterogeneity remained for some outcomes because of differences across trials in study phase, patient populations, intervention doses, background antiplatelet regimens, outcome definitions, and follow-up duration. We therefore retained a low certainty rating, given the remaining concerns regarding risk of bias and between-study clinical and methodological heterogeneity.

We thank the Editor and Reviewers again for their thoughtful comments. We believe that the revisions have substantially strengthened the transparency, methodological rigor, and clinical interpretation of the manuscript.

Best Regards
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