Journal of Clinical Question

Decision Letter (JCQ-2025-0022)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0022

Body: 06-Aug-2025

Dear Dr Tagami:

Manuscript ID JCQ-2025-0022 entitled "Oral Antifibrotic Agents for the Treatment of Progressive Pulmonary Fibrosis: A Systematic Review and Network 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.
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,
Richard Isaacs
Editor in Chief,
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
1. Check grammar and flow for minor errors.
2. Ensure all abbreviations are defined on first use in both abstract and main text.
3. Add ORCID IDs for authors if available

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
The utility of this systematic review is unclear considering nintedanib and nerandomilast are already approved for PPF based on their respective phase 3 clinical trials (which are all that is included in this review). I worry about the quality of combining a small number of small trials that use 3 different medications in very different patient populations. I also worry that the result of this review would be clinicians using these results like a head-to-head comparison for effectiveness.

Reviewer: 2

Comments to the Author
This manuscript presents a well-structured, timely, and clinically relevant systematic review and network meta-analysis (NMA) evaluating the comparative efficacy and safety of oral antifibrotic agents in progressive pulmonary fibrosis (PPF). The study adheres to PRISMA-NMA guidelines and employs appropriate statistical methodologies. However, several areas require clarification and strengthening to improve the manuscript's rigor and interpretability. Specifically:

Abstract: Clarify in the results section that Pirfenidone did not achieve statistical significance despite ranking well in SUCRA, and revise the conclusion to briefly acknowledge the lack of significant mortality benefit.

Introduction: Expand the rationale by explaining how PPF differs clinically and pathologically from idiopathic pulmonary fibrosis (IPF) to support the applicability of IPF treatments to PPF.

Methods: Clearly define the primary outcome (change in FVC at 52 weeks) and justify the inclusion of a 42-week trial. Replace the placeholder "OO" for reviewer initials with distinct identifiers for clarity. Specify whether Nerandomilast dose groupings were pre-specified or derived post hoc.

Results: Reiterate when differences between treatments are not statistically significant, especially regarding Pirfenidone and mortality outcomes, to avoid overinterpretation.

Discussion: Expand on why improvements in FVC did not translate into significant reductions in mortality or serious adverse events (SAEs)—consider discussing the limitations of FVC as a surrogate endpoint. Additionally, clarify the clinical relevance of SUCRA rankings when statistical differences are not present to guide evidence-based decision-making.

Figures and Tables: Ensure all abbreviations are defined within figure legends (e.g., NRD_LN) and add footnotes to tables indicating clinical significance thresholds, such as the minimal clinically important difference (MCID) in FVC.

Date Sent: 06-Aug-2025

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Author's Response to Decision Letter for (JCQ-2025-0022)

Oral Antifibrotic Agents for the Treatment of Progressive Pulmonary Fibrosis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Dear Editor and Reviewers,

We sincerely thank you and the reviewers for your time, constructive feedback, and valuable suggestions on our manuscript titled "Oral Antifibrotic Agents for the Treatment of Progressive Pulmonary Fibrosis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials." We have carefully considered each comment and made the necessary revisions to improve the clarity, accuracy, and overall quality of the work. Below, we provide a detailed, point-by-point response to all comments. Changes in the manuscript are highlighted for ease of reference.

Responses to Editor's Comments
1. Check grammar and flow for minor errors.
Response: We thank the editor's comment on this point. We have thoroughly reviewed the manuscript to correct minor grammatical issues and improve the overall flow.

2. Ensure all abbreviations are defined on first use in both abstract and main text.
Response: We thank the reviwer's comment on this point. All abbreviations have now been defined upon first use in both the abstract and the main text.

3. Add ORCID IDs for authors if available
Response: We thank the editor's comment on this point. We have added ORCID IDs for all authors where available.

Responses to Reviewer 1
Comment: The utility of this systematic review is unclear considering nintedanib and nerandomilast are already approved for PPF based on their respective phase 3 clinical trials (which are all that is included in this review). I worry about the quality of combining a small number of small trials that use 3 different medications in very different patient populations. I also worry that the result of this review would be clinicians using these results like a head-to-head comparison for effectiveness.
Response: Thank you for your thoughtful feedback. We agree that both nintedanib and nerandomilast are already approved for PPF on the basis of their respective phase 3 trials, and that these trials form part of our review. Our intent, however, was not to imply a head-to-head comparison or to supplant individual trial conclusions, but rather to provide a structured synthesis of all available randomized evidence in PPF, including studies of other agents, to contextualize the breadth of therapeutic investigation in this space.
We acknowledge that the included studies differ in patient populations, interventions, and trial sizes, and have explicitly discussed these limitations in our manuscript. Our meta-analytic approach was chosen to offer a consolidated evidence overview, highlight consistencies and differences across trials, and identify gaps where future research could focus (e.g., comparative effectiveness studies or trials in underrepresented subgroups).
To reduce the risk of misinterpretation as a direct comparison, we strengthen our discussion to emphasize the heterogeneity of included studies, clarify that no indirect or direct comparative conclusions should be drawn, and reiterate that treatment decisions should remain guided by the individual phase 3 trial evidence and clinical judgment. We have modified our limiatiation section as follows to emphasis this weakpoint "The analysis was limited by the small number of eligible RCTs, with only four studies meeting the inclusion criteria. These trials differed in patient populations, interventions, and sample sizes, reducing the precision of pooled estimates and the scope for meaningful comparisons. Furthermore, most had relatively short follow-up periods (24–52 weeks), which may not adequately capture longer-term outcomes such as mortality, disease exacerbations, or sustained safety signals. Additionally, one trial was identified as having a high risk of bias, and the certainty of evidence for most outcomes was downgraded due to imprecision. The reliance on indirect comparisons and the absence of head-to-head trials between specific regimens further limit the strength of comparative inferences."

Responses to Reviewer 2
Comment 1: Clarify in the results section that Pirfenidone did not achieve statistical significance despite ranking well in SUCRA, and revise the conclusion to briefly acknowledge the lack of significant mortality benefit.
Response: Thank you for your thoughtful feedback. We have revised the Results section to clarify this point as follows: "Pirfenidone demonstrated the lowest odds ratios for mortality (OR = 0.29; 95% CI, 0.03–2.30) and serious adverse events (OR = 0.69; 95% CI, 0.35–1.40), although these differences were not statistically significant." This change aims to present the findings more clearly and avoid any potential misinterpretation.

Comment 2: : Expand the rationale by explaining how PPF differs clinically and pathologically from IPF to support the applicability of IPF treatments to PPF.
Response: Thank you for your thoughtful feedback. We have added content highlighting the similarities between IPF and PPF to support the applicability of IPF treatment to PPF, as follows: "Both IPF and many cases of PPF exhibit the histologic and radiologic hallmarks of UIP, including patchwork fibrosis, fibroblastic foci, and honeycomb changes. Both conditions are characterized by relentless progression of fibrosis with a generally poor prognosis if left untreated."

Comment 3: Clearly define the primary outcome (change in FVC at 52 weeks) and justify the inclusion of the 42-week trial. The primary outcome, change in FVC at 52 weeks, is now clearly defined, and a justification for including the 42-week trial has been provided.
Response: Thank you for your comment. We have clearly defined the primary outcome as the change in FVC at 52 weeks and have provided a justification for the inclusion of the 42-week trial in the revised manuscript.We modified the mansucript as follows "The primary outcome was initially defined as the absolute change in FVC (in milliliters) from baseline at 52 weeks. However, a study of pirfenidone with a maximum follow-up of 42 weeks was also included, as it was the only study eligible for inclusion in the network meta-analysis."

Comment 4: Replace the placeholder "OO" for reviewer initials with distinct identifiers for clarity.
Response: Thank you for your thoughtful feedback. We have clarified the reviewer information as follows: "Two independent reviewers (Y.T. and M.K.) screened the titles and abstracts of the retrieved articles, followed by a full-text review of potentially eligible studies. Any discrepancies were resolved through discussion or, if necessary, consultation with a third reviewer (H.K.).

Comment 5: Specify whether Nerandomilast dose groupings were pre-specified or derived post hoc.
Response: Thank you for your thoughtful feedback. We have specified the pre-specification status of the nerandomilast dose groupings as follows: "Nerandomilast dose groupings were pre-specified."

Comment 6: Expand on why improvements in FVC did not translate into significant reductions in mortality or serious adverse events (SAEs), consider discussing the limitations of FVC as a surrogate endpoint. Additionally, clarify the clinical relevance of SUCRA rankings when statistical differences are not present to guide evidence-based decision-making.
Response: Thank you for your insightful comment. We have expanded the discussion to address why improvements in FVC did not translate into significant reductions in mortality or serious adverse events (SAEs), including a consideration of the limitations of FVC as a surrogate endpoint. Additionally, we have clarified the clinical relevance of SUCRA rankings in the absence of statistically significant differences, highlighting their potential role in guiding evidence-based decision-making as follows "FVC, while a standard endpoint in interstitial lung disease trials, has limitations as a surrogate marker. It reflects changes in lung volume but may not fully capture outcomes such as quality of life, symptom burden, or extrapulmonary complications. Improvements in FVC over the short-to-medium term may not directly translate into long-term survival benefits if disease mechanisms persist. SUCRA rankings offer a probabilistic comparison of treatments and can inform clinical decision-making when interpreted alongside safety, tolerability, and patient context. However, in the absence of statistically significant pairwise differences, these rankings should be viewed cautiously, as they reflect both effect magnitude and precision rather than definitive superiority."

Comment 7: Ensure all abbreviations are defined within figure legends (e.g., NRD_LN) and add footnotes to tables indicating clinical significance thresholds, such as the minimal clinically important difference (MCID) in FVC.
Response: Thank you for your comment. We have ensured that all abbreviations, including NRD_LN, are defined within the figure legends. Regarding the MCID, the treatment effects observed reflected a reduction in the rate of FVC decline rather than an improvement in FVC, making it inappropriate to establish a threshold for MCID in this context.

We trust that these revisions address all the concerns raised and that the revised manuscript meets the journal's standards for publication. We are grateful for the opportunity to improve our work through your and the reviewers' insightful feedback.

Sincerely,
Hideya Kitamura
Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center,
Email: kitamura.19056@kanagawa-pho.jp

1. Response Letter.pdf PDF

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