Author's response to reviews

Title: Comparing New Treatments for Idiopathic Pulmonary Fibrosis - a network meta-analysis

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Author's response to reviews: see over
<table>
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<th>Reviewer 1 comments</th>
<th>Author responses</th>
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<td>1. The manuscript appears methodologically sound, however given the topic of study it is imperative to ensure that the methods are beyond reproach. This manuscript should therefore be reviewed by an expert in meta-analysis methodology. Aside from this comment, I do not have any major concerns.</td>
<td>No action at present, we would welcome comments from a methodologist in this area.</td>
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<td>2. Some additional detail is required to fully explain the methods of the meta-analysis. Is it correct that all placebo groups were pooled in the analysis? This is my assumption from Figure 2, although I cannot see this figure referenced in the text.</td>
<td>Placebo groups were not pooled as such but were a common comparator to connect the network in the analysis. As such our fixed effects model assumes homogeneity between the placebo groups between trials. Text added into line 100 on page 4: “In circumstances where randomised evidence between all relevant comparators is unavailable, network meta-analysis combines evidence from trials comparing different sets of treatments that form a connected evidence network through common comparators, in this case placebo. It retains within trial randomisation, allowing direct and indirect evidence to inform estimates of relative treatment effect in a single analysis.”</td>
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<td>3. There is substantial debate about whether there was something different about the placebo group in the CAPACITY-2 study. Does exclusion of this group impact the results? Similarly, does this suggested difference in CAPACITY-2 impact the decision to use a fixed-effects model?</td>
<td>The reviewer raises an important point and we agree there is considerable debate about why the results of CAPACITY-2 vary from CAPACITY-1. We would not consider excluding this trial from the meta-analysis on the basis of it showing a different result from the other CAPACITY trial (or the other included trials) as this is the strength of a meta-analysis. If there were differences in the study populations we would have considered a sensitivity analysis but there were no significant differences in characteristics of the populations in the two CAPACITY trials. As there was no a priori justification for treating Capacity 2 differently we propose no action is required. We don’t have enough information in the network to robustly estimate a random effects model</td>
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<td>4. Suggest adding a brief statement to the abstract that pirfenidone tended to prevent exacerbation and mortality compared to nintedanib, or that there was no significant difference between these medications with respect to these outcomes.</td>
<td>Added: ‘… between nintedanib and pirfenidone to line 45-46 of the abstract.</td>
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<td>5. Consider adding subheadings to the Results section, corresponding to the outcomes of importance.</td>
<td>Sub-headings for the outcomes are now inserted into the results section.</td>
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<td>6. Throughout the results, it would be</td>
<td>We agree that this would aid interpretation of</td>
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preferable to structure each statement similarly, putting the drug with relative benefit first. For example, the statement on page 7, line 171 should be modified to state that “pirfenidone is associated with slightly lower odds of a decline in FVC%....” Such consistency would improve interpretability of these multiple comparisons. There are some other examples of this throughout the results section.

7. It is surprising to me that pirfenidone was associated with lower odds of AE-IPF compared to nintedanib and I have concern that this result is related to the analysis methods rather than a difference between medications. For preventing AE-IPF, how is it possible that nintedanib is superior to placebo, pirfenidone is similar to placebo (non-significant), and yet pirfenidone is superior to nintedanib? (page 7, lines 188-193) Does this relate to the background rates of acute exacerbation in studies of nintedanib versus pirfenidone? If that is the case, is it appropriate to pool these studies in a meta-analysis?

This is a good question which we have considered carefully. Although we state in the text that these analyses are non-significant, underpowered and should be interpreted cautiously, and the point estimate is associated with a wide credible interval, we feel that these caveats may not be appreciated fully by the average reader and the results could be misleading. In addition, as the background rates of acute exacerbation were low, and the nintedanib estimate is based on bigger, more recent trials but the pirfenidone two smaller, older trials (AE rates not reported in the newer pirfenidone trials) overall we feel that there is too much uncertainty and have therefore removed the results of this analysis from the manuscript. We have resubmitted the additional file with the updated efigure 2.

8. Page 9, line 227-229: The wording of these sentences should be improved. What is meant by “drop” on line 227?

We have amended the text in line with the reviewers comment.

Reviewer 2 comments

I would like to congratulate authors for providing this valuable and useful analysis. I do not have any comments or concerns, to my mind the manuscript is well written and includes interesting and clinically relevant data.

No action