Reviewer's report

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

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Reviewer: Christopher Ryerson

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Loveman et al report their findings of a network meta-analysis, with the primary purpose being the comparison of pirfenidone to nintedanib. The authors conclude that nintedanib may be superior to pirfenidone with respect to the common primary outcome of change in FVC, however pirfenidone may have other benefits compared to nintedanib. This is a provocative study that will surely generate significant debate. The manuscript is well written.

The authors do not appear to have a significant conflict of interest in favor of either medication, although the authors are not entirely clear of conflicts with respect to these medications.

MAJOR COMMENTS

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.

MINOR COMMENTS

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.

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?

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.

5. Consider adding subheadings to the Results section, corresponding to the outcomes of importance.

6. Throughout the results, it would be 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?

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

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have participated in advisory boards, received speaking honoraria, and received research funding from both InterMune Inc. and Boehringer Ingelheim.