Author’s response to reviews

Title: The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole (EME-TIPAC): : study protocol for a randomized controlled trial.

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Reviewer #1: -Please specify the term unplanned hospitalization-free survival (abstract). This needs to be explicit to facilitate understanding. WE HAVE NOW UPDATED THIS TO CLARIFY WHAT WE MEAN BY THE TERM.

And please change the following paragraph Page 2, lines 34 to 43. Precise the outcomes, e.g. "The primary outcome is a composite endpoint consisting of the time to death, transplant or first non-elective hospital admission. Secondary outcomes include the individual components of the composite outcome, respiratory related events, quality of life assessment…” THIS HAS BEEN UPDATED ACCORDINGLY.
- When do patients receive folic acid and why? THE DOSE REGIMEN AND REASON FOR FOLIC ACID NIMP (TO REDUCE BONE MARROW DEPRESSION) HAS BEEN ADDED

- Please clearly state for how long patients will receive the investigational product/placebo. This needs to be explicit to be facilitated. THE MEDIAN TREATMENT PERIOD OF 27 MONTHS (PLUS THE RANGE 12-42 MONTHS) HAS BEEN ADDED

- The 50 patients receiving bronchoscopy, at what time point of the study will those patients be included? At the beginning, at the end, or whenever the patients agree to this procedure? - THE BRONCHOSCOPY SUBSTUDY HAS BEEN TERMINATED SINCE THE ORIGINAL SUBMISSION OF THE PAPER. AS A RESULT REFERENCES HAVE BEEN REMOVED THROUGHOUT THE MANUSCRIPT AND A NOTE ADDED TO THE AMENDMENT SECTION.

- Please include an additional table demonstrating the participating centers. Moreover, include an additional table with the members of the TMG, TSC and DMC. - THIS HAS BEEN ADDED AS TABLE 1

- Page 4, line 43: precise "classical IPF" - NOW REWORDED TO JUST "IPF"

- The authors need to precisely describe the standard therapy. REFERENCE TO THE NICE GUIDELINES ON TREATMENT OF IPF HAS BEEN ADDED.

- I assume that patients' data will be documented pseudonymously /anonymously, correct? If yes, please include this statement. YES, THIS IS CORRECT AND HAS BEEN ADDED TO THE TEXT

- Inclusion criteria: is there a defined max time point since diagnosis of moderate/severe IPF? Maybe the authors need to precise the screening and inclusion process more precisely. Do I get it right, that hospitalized as well as non-hospitalized patients are included in the trial? THERE IS NO MAX TIME POINT AND THE TEXT HAS BEEN UPDATED ACCORDINGLY TO STATE THIS. PATIENTS WHO HAVE BEEN HOSPITALISED PREVIOUSLY FOR IPF RELATED REASONS WILL BE ELIGIBLE ASSUMING THEY MEET THE OTHER CRITERIA.

- Please precise the MRC dyspnoea score. THIS HAS BEEN FURTHER EXPLAINED IN THE TEXT AND A REFERENCE TO THE SCORE ADDED.

- How do the authors deal with non-compliance with regard to the final analysis? Please explain. THE USE OF CACE ANALYSIS HAS BEEN ADDED AND EXPLAINED.

- Page 15, line 19: is the sensitivity analysis of patients from TIPAC based only on IPF patients or on the overall cohort? THE OVERALL COHORT (SO ALL PATIENTS) WERE USED. TEXT UPDATED.
Are the analyses stratified (e.g. center, gender, severity of IPF) - YES CLARIFICATION ADDED THAT THEY ARE ADJUSTED FOR SITE AND USE OF BASELINE IPF MEDICATION.

Discretionary revisions:

- The keywords include the word septrin. However, I cannot find it in the text. Is it really a keyword? - THIS HAS NOW BEEN REMOVED.
- Page 4, line 24: please add "TIPAC trial" in brackets and describe precisely the results of the TIPAC trial in patients with classical IPF (with numbers) - DONE
- Page 4, line 38: please include the p-value. - ADDED
- Page 4, line 60: the role of infection is becoming more evident. Please include a reference. REFERENCE TO RELEVANT PAPER HAS BEEN ADDED.
- Page 6, line 34: Figures 1 and change the term schematic representation to study flowchart - WORDING UPDATED AS REQUESTED.
- Page 6, line 10: participants will remain in the trial. Please change to "participants receive cotrimoxazole or placebo until they meet a primary endpoint…" - WORDING UPDATED AS REQUESTED
- Page 7, line 36 "…characteristic feature of on a thoracic high resolution…" - CORRECTED
- Page 9, line 19: change to "Following consent, patients meeting all inclusion and non of the exclusion criteria…" - WORDING UPDATED AS REQUESTED