Itemized Response to Reviewers’ and Editorial Comments

Comment 1. Page 9. Eligibility: Is there a reason the authors limited their analysis to Phase II studies? I can see limiting the study to clinical trials, or even Phase II and III clinical trials, but is there a reason for just Phase II?

Author’s response: The decision to focus on phase II studies was not arbitrary, but a result of a meticulous research process. We aimed to maintain uniformity in the data for analysis, considering the fundamental changes between phases I and III vs. phase II. These changes include the sample size, endpoints, and duration. Phase II data, being decisive for starting phase III trials, was our primary focus. We also find that compiling the available data from one phase is more reasonable considering all these differences. Therefore, we decided to stick to phase II, which is only a randomized controlled trial study without variations in the endpoints.

Comment 2. Title. I recommend adding “Phase II” before RCTs in the manuscript title.

Author’s response: We greatly appreciate the reviewer's suggestion and have promptly modified the title as recommended.

Comment 3. Page 11. Results and Figure 1: The authors state they narrowed their literature search down to 35 studies, then eliminated 24 to come up with 12 studies to analyze; this is somewhat picky, but 35 - 24 = 11, not 12. The authors analysed 12 Phase II studies; do the authors mean 36 studies?

Author’s response: We appreciate the reviewer’s keen observation. To clarify, we initially screened the full text of 35 articles and included 11 for analysis. However, during our full-text screening, we also conducted a thorough review of the references of those articles (a process known as snowballing). This led us to identify an additional article that met our inclusion criteria. As a result, this article has been added to the PRISMA flowchart under the snowballing box, and it has been properly screened for our analysis.

Comment 4. Page 14, last 3 lines: The authors say the IM subgroup significantly decreased 6MWD, but the p value is 0.29, which is not significant.

Author’s response: We revised this version and corrected the mistake.

Comment 5. Page 15, Discussion: I would recommend caution in using the terms “engraftment” and “stemness” unless the studies analyzed specifically examined these. There is a paucity of evidence for long term engraftment of MSC, and many researchers
believe that the benefits of MSC are due to paracrine stimulation of tissue stem/progenitor cells, or anti-inflammatory effects, and not due to MSC engraftment.

Author’s response: We agree with the worthy reviewer. The reported cell-based therapy mechanisms include engraftment and paracrine activity of the donor cells. The literature does contain evidence for both. We ourselves have published in this regard. However, we have taken care of the worthy reviewer's suggestion to tone it down by removing the word engraftment, as these clinical studies have not attempted to provide evidence of cell engraftment.

Comment 6. Page 15, last line: Several times the authors say “reduction in SAEs”. Since SAEs would probably only increase with an intervention (MSC delivery) it may be better to say something like “change in SAE incidence” or the like.

Author’s response: The text was revised accordingly throughout the paper.

Comment 7. Page 16: The term “most favored” is used; perhaps most common, or most utilized would be better. Once abbreviations are defined, please use them consistently.

Author’s response: Change applied accordingly to tone down the expression.

Comment 8. In the Core Tip, please define HF.

Author’s response: The point was added accordingly.

Editorial Office’s Comments

Comment 1. The language classification is Grade B. Please visit the following website for the professional English language editing companies that we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Author’s response: The manuscript has been extensively revised language-wise, and minor language mistakes have been updated, taking help from our Sulaiman Rajhi English Department Faculty.
Comment 2. Figure and Table Legends: Please do not add figures, figure legends, or tables to the “Edit Revision” …

Author’s response: The figures and tables have been submitted in a separate file and decomposable version of the Figures have been included as required.

Comment 3. Abbreviations other than special types of words such as COVID-19 and SARS-CoV-2 are not allowed in the article title.

Author’s response: The title was revised accordingly.

Comment 4. The title is too long and should be no more than 18 words.

Author’s response: The title has been revised accordingly to be with the required word limit.

Comment 5. References. Please edit the references in step 3 “References” of "INTELLIGENT MANUSCRIPT FORM EDITOR". The specific steps for editing references by Auto-Analyser are:…

Author’s response: Done and completed per instructions.