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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 84337

Title: Safety evaluation of human umbilical cord-mesenchymal stem cells in type 2 diabetes mellitus treatment: A phase 2 clinical trial

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03490943
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Assistant Professor, Doctor, Postdoc
Reviewer's Country/Territory: Serbia
Author's Country/Territory: China

Manuscript submission date: 2023-03-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-03-17 05:07

Reviewer performed review: 2023-03-27 18:23

Review time: 10 Days and 13 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The topic of this paper is very interesting. Introduction provides sufficient background information, materials and methods are thoroughly described. Results are correctly presented, discussion puts the findings in an appropriate context, but conclusion should be stated more firmly. My greatest objection goes for language quality and the technical preparation of manuscript in general (a lot of misuse of lower/upper case, grammatical inaccuracies, failing to mention table in the text, etc.). Authors must greatly improve this aspect of manuscript before its potential acceptance for publication.

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Reviewer's code: 05671495
Position: Peer Reviewer
Academic degree: BSc, DPhil, MPhil, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

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Reviewer accepted review: 2023-03-28 16:21

Reviewer performed review: 2023-03-28 18:07

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No novelty
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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1. The authors should significantly improve the description of the materials and methods related to the manufacturing and storage of the cells, as well as to the formulation of the final infusion product. Of the 2 references (18-19) cited by the authors, only ref. 19 provides minimal, yet insufficient, information on the manufacturing process. Important details are missing, such as the cryopreservation conditions, the composition of the cryopreservation medium, and the formulation of the final infusion product (FIP), including the detailed composition of the FIP solution that the cells are suspended in. 2. Is the composition of the placebo identical to the FIP solution with the exception of the absence of the cells? 3. The authors tend to refer to generic QC testing, instead of clearly specifying exactly what QC testing is carried out, and when, during the manufacturing of the cells and the formulation of the FIP. Authors refer to a generic paper describing ISCT minimal criteria for MSCs. However, such criteria only relate to cell identity and were NOT described for hUC/Wharton's Jelly MSCs. ALL release criteria (Viability, Sterility, Purity, Potency) should be clearly defined. I think the authors tried to do that in Table I, but did not use conventional terminology (e.g., do they mean

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viability with "cell survival rate"? What does "0.5 EU/tube" mean?). Did they only use Gram stains to test for sterility? 4. How was the stability study conducted? Based on what parameters was the 12 hour infusion limit defined? 5. The authors refer only to the passage number at which cells are harvested, but that information is pretty much useless unless we know the corresponding population doublings. The authors should clearly define the corresponding PDL at harvest. 6. What post-infusion parameters were monitored that would allow to specifically identify infusion-related toxicity? That needs to be clearly specified. 7. Have the authors looked for expression of tissue factor on these cells, and how it compares to MSCs derived from other sources? if not, they should and at the very least, discuss it in the discussion. 8. Fig. 1 needs to be drastically improved. I'm sure the figure is only clear to their manufacturing staff, but it's uncomprehensible to all other readers. For example, what does "Peel to obtain Wadi adhesive" mean? What does "P0 replacement of full quantity and half quantity" mean? What does "P0/P1 generation harvest transmission P1/P2" mean? 9. Fig. 2 legend states that the qualified cells are transported to the requesting hospital "for a second QC test". WHAT TEST? AUTHORS NEED TO BE SPECIFIC! 10. The authors use Wharton's Jelly (WJ) MSCs and yet, nowhere in the manuscript is WJ mentioned, while the generic "MSC" term is widely used interchangeably. This is confusing and tends to mislead the reader. 11. The english should be significantly improved throughout the manuscript by having it revised by a native english speaker with familiarity with conventional terminology used in the field.