The response to each of the issues raised in the peer review report.

Reviewer #1:

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.

Reply: Thanks for the expert's correction. I have added the following part of the text in "hUC-MSC preparation" (page 6) and added Table 1.

The added contents are:

The isolation process involved Wharton's jelly, a gelatinous tissue around umbilical vessels, from donated hUCs. First, the primary cells were obtained by tissue block adherent culture method, followed by inoculation with 5000 cells/cm2 and harvesting when the fusion degree reached 85%~90%. After continuous expansion, the fourth passage (P4) of hUC-MSCs was suspended in a 10% DMSO cryopreservation solution and stored in liquid nitrogen (-196 °C)[20] (Figure 1). In their future use as a cell stock material, the samples were thawed at 37 °C, washed to remove the DMSO cryopreservation solution, and resuspended in a compound electrolyte preservation solution (containing 5% albumin) before testing of the "final frozen product" for clinical applicability and safety (Table 1).

Table 1 Quality control standards of human umbilical cord-mesenchymal stem cells

Test	Final frozen product	Final infusion product
Visual inspection	NA	Absence of visible particle
Morphology	Fibroblastic	NA
Viability	≥ 90%	≥ 85%
Cell count	4.5~6 × 10^7	According to clinical needs
Pathogen tests		
Sterility	Negative	Negative
Mycoplasma	Negative	Negative
Endotoxin	< 0.5 EU/mL	< 0.5 EU/mL
Cell surface markers		
CD73	≥ 95%	－－
CD90	≥ 95%	－－
CD105	≥ 95%	－－
CD29	≥ 95%	－－
CD34	≤ 2%	－－
CD45	≤ 2%	－－
CD79a	≤ 2%	－－
CD14	≤ 2%	－－
HLA-DR	≤ 2%	－－

NA: Not applicable.

2. Is the composition of the placebo identical to the FIP solution with the exception of the absence of the cells?

Reply: The composition of the placebo is the same with the FIP, the compound electrolyte preserving solution (containing 5% albumin) without hUCMSCs. I add it in the page 6 in the part " Study design"

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 viability with "cell survival rate"? What does "0.5 EU/tube" mean?). Did they only use Gram stains to test for sterility?

Reply: The word "cell survival rate" mentioned on page 6 of the original text is wrong, I have amended it to viability. For the part of cell quality such as QC testing, we deleted the original table 1 and replaced it with a new one in order to better display the relevant properties of cells.

4. How was the stability study conducted? Based on what parameters was the 12 hour infusion limit defined?

Reply: The transport stability of the FFP has been verified. 6 batches of FFP were stored at 2℃, 4℃, 10℃, 25℃, and sampled at 0, 6, 12, and 18 hours. Cell count, viability, sterility, and cell surface markers were detected according to the Quality control standards (Table 1). The results: the quality of FFP met the standards when the cells were stored at 4 ~ 10℃ for 18 hours. Therefore, the FIP transport preservation conditions were set to be stored at 4-10 ℃ and used within 12 hours after thawed.

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.

Reply: The PDL of each passage is about 3~4 times, so the total PDL of P4 is about 12~16 times.

6. What post-infusion parameters were monitored that would allow to specifically identify infusion-related toxicity? That needs to be clearly specified.

Reply: Human umbilical cord mesenchymal stem cells were defined in accordance with the ISCT criteria. I have added the following part of the text in " INTRODUCTION" (page 3-4).The added contents are: Among the different types of MSCs, those from the human umbilical cord (hUC) have been widely applied in the treatment of different diseases[8]. The hUC-MSCs are a group of more primitive cells derived from neonates and express original stem cell-specific surface markers such as embryonic stem cell stage-specific surface antigen 4 (SSEA4) and tumor rejection antigen 1-60 (TAR-1-60). Compared with MSCs derived from other tissues such as bone marrow and fat, the hUC-MSCs have a more abundant content, stronger proliferation ability, and lower immunogenicity[7]. Moreover, hUC-MSCs can be sampled conveniently without damage to the health of the donor, and they do not present any ethical challenges. As such, they are attractive and preferred for clinical applications.

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.

Reply: We have looked for expression of tissue factor on these cells, and add new table 1 in this time. As to compares to MSCs derived from other sources, we have added some attends in " INTRODUCTION" (page 3-4).

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?

Reply: "Peel to obtain Wadi adhesive" was the translation error ，UC-MSCs are isolated from Wharton's Jelly, a gelatinous tissue around umbilical vessels. We have modified Figure 1 after communicating with Shenzhen Beke Company. The revised picture is as follows:

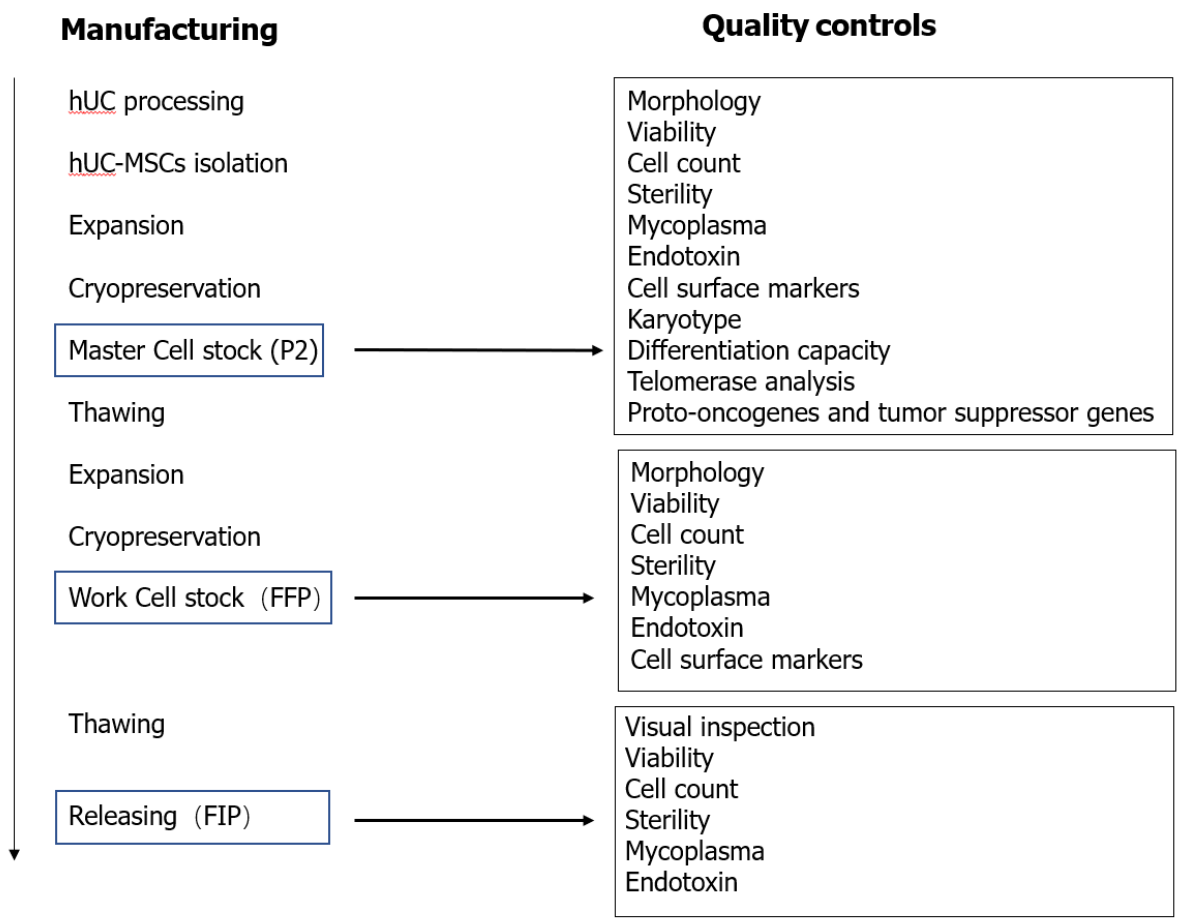

Figure 1 Stem cell manufacturing and quality control processes. FFP: Final frozen product; FIP: Final infusion product; hUC: Human umbilical cord; MSCs: Mesenchymal stem cells; P2: Second passage.

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!

Reply: For the correction of Figure 2, we modified and integrated Figure 1 and deleted Figure 2.

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.

Reply: Thanks for the editor's correction, we added some we have added some attends in " INTRODUCTION" (page 3-4) to describe WJ.

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.

Reply: For the revised article and the original article language modification, we have send our revised manuscript to the professional English language editing company (Filipodia Publishing, LLC: http://www.filipodia.com/), and the company had provided a language certificate along with the manuscript. We submit the language certificate again this time, please check

Reviewer #2:

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.

Reply: For the revised article and the original article language modification, we have send our revised manuscript to the professional English language editing company (Filipodia Publishing, LLC: http://www.filipodia.com/), and the

company had provided a language certificate along with the manuscript. We submit the language certificate again this time, please check