



Our STN: BL 125706/0

**MID-CYCLE COMMUNICATION
SUMMARY**
June 17, 2020

Mesoblast, Inc.
Attention: John Picciano
505 Fifth Avenue, 3rd Floor
New York, NY 10017

Dear Mr. Picciano:

Attached is a copy of the summary of your June 1, 2020 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN 125706/0 in your future submissions related to Ex Vivo Cultured Adult Human Mesenchymal Stem Cells.

If you have any questions, please contact Adriane Fisher at (301) 796-9691 or adriane.fisher@fda.hhs.gov.

Sincerely,

Raj K. Puri, MD, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application type and number: BLA 125706/0

Product name: Ex Vivo Cultured Adult Human Mesenchymal Stem Cells

Proposed Indication: Acute Graft versus Host Disease

Applicant: Mesoblast, Inc.

Meeting date & time: June 1, 2020 at 2:00-3:00 pm, EST

Committee Chair: Matthew Klinker, PhD

RPM: Adriane Fisher, MPH, MBA

Attendees:

FDA Attendees:

Ekaterina Allen, PhD, CBER/OCBQ/DMPQ
Rachael Anatol, PhD, CBER/OTAT
Kristin Baird, MD, CBER/OTAT/DCEPT/CHB
Steven Bauer, PhD, CBER/OTAT/DCGT
Kimberly Benton, PhD, CBER/OTAT
Qiao Bobo, PhD, CBER/OCBQ/DMPQ
Wilson Bryan, MD, CBER/OTAT
Heba Degheidy, MD, PhD, CBER/OTAT/DCGT
Melanie Eacho, PhD CBER/OTAT/DCGT
Bindu George, MD CBER/OTAT/DCEPT
Alyssa Kitchel, PhD, CBER/OTAT/DCGT
Matthew Klinker, PhD, CBER/OTAT/DCGT/CTB
Wei Liang, PhD, CBER/OTAT/DCEPT
Anthony Lorenzo, CBER/OCBQ/DMPQ
Bao-Ngoc Nguyen, PhD, CBER/OTAT
Steven Oh, PhD CBER/OTAT/DCGT
Donna Przepiorka, MD, PhD CDER/OND/OOD/DHM1
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Laura Ricles, PhD, CBER/OTAT/DCGT

Mesoblast, Inc. Attendees

Sivliu Itescu, MD, Chief Executive Officer
Fred Grossman, DO, Chief Medical Officer
Mahboob Rahman, MD, Head of Immunology and Pharmacovigilance
Geraldine Storton, Head of Regulatory Affairs and Quality Management
John McMannis, PhD, Head of Manufacturing
Doreen Morgan, PharmD, Global Vice President, Regulatory Affairs
John Picciano, Vice President, Regulatory Affairs
Susan Sukovich, Associate Director, Regulatory Affairs
Evelyn Brandt, Senior Director, Regulatory Affairs
Jack Hayes, Vice President, Biometrics
Fiona See, PhD, Vice President, Translational Development

Justin Horst, Senior Director, Manufacturing
Sujatha Nambiar, Senior Director, Project Management
Stephen DeCrescenzo, Associate Director, Medical Affairs and Drug Safety
Elizabeth Burke, Vice President, Patient Affairs
Karen Segal, PhD, Senior Vice President, Medical Affairs
Catherine DeSombre, Director, Analytical Services
Deepa Patel, MD, Senior Director, Pharmacovigilance
(b) (4), PharmD, Regulatory Consultant
(b) (4), Regulatory Consultant

Agenda:

The Mid Cycle Meeting will primarily consist of Discipline review updates including any issues of concern that warrant a discussion.

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

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1. (b) (4) DCB (b) (4) tested for adventitious viral contaminants at the time of manufacture by *in vitro* assays using MRC-5, VERO, and Hs68 cell lines. However, the protocol used to test (b) (4) DCB (b) (4) indicates that only a (b) (4) assay was performed at the end of the (b) (4)-day observation period. We typically see (b) (4) assays performed at the end of the observation period to detect non-cytopathic viruses, as some viruses cannot be detected by a (b) (4) assay because they do not express glycoproteins that can be found on the plasma membrane. Given the large number of patients who could potentially receive DP derived from a single DCB with an undetected viral contamination, the risks of such an infection could be high. We have requested a consult review from experts in CBER's Office of Vaccine Research and Review (OVR) to better understand these risks and evaluate how effective your overall DCB testing approach is in mitigating these risks.

Meeting Discussion: FDA indicated that a reviewer from OVR had been assigned to the consult request and would provide feedback on both the lack of a (b) (4) assay at the conclusion of *in vitro* viral testing and the adequacy of the overall viral testing approach. The applicant asked when this review would be complete. FDA indicated that the requested due date for the consult was a few weeks after the mid-cycle communication, but that a delay was possible due to the increased workload of reviewers at OVR at this time. The applicant asked to be informed when the review was complete, and FDA agreed to do so.

2. We have concerns that your manufacturing process controls and product specifications may be inadequate to ensure the potency of the remestemcel-L product.

- a) It is not clear that the product attributes you intend to control are related to the effectiveness of the product. In MSB-GVHD001, the potency of DP lots used in initial therapy was not significantly different between subjects who responded to treatment and those who did not respond to treatment. You indicate that one measure of potency (% inhibition of IL-2R α expression) correlated with a reduction in the frequency of activated CD4⁺ T cells in the peripheral blood, however this analysis used data from only (b) (4) subjects, and it is not clear if this correlation would remain significant if corrected for the number of biomarkers analyzed. If the product attributes you control are not related to effectiveness, controlling these attributes may not be adequate to ensure product potency.
- b) Your proposed specifications for the commercial product are below the values observed among DP lots used in MSB-GVHD001 manufactured using the (b) (4) process.

Assay	Proposed Specification	MSB-GVHD001 DP Range	MSB-GVHD001 Average
Viability	(b) (4)	(b) (4)	(b) (4)
TNF R1	(b) (4)	(b) (4)	(b) (4)
% Inhibition of IL-2R α	(b) (4) Inhibition	(b) (4) Inhibition	(b) (4)

If the results from MSB-GVHD001 sufficiently demonstrate product effectiveness, it is not clear that DP lots with potency measures well below those of lots used in MSB-GVHD001 will have similar effectiveness *in vivo*.

- c) Inter-assay variability for both TNF R1 and % inhibition of IL-2R α expression assays is relatively (b) (4), and it is not clear that a single assay performed on a (b) (4) will give a result that reflects the overall potency of the DP lot.
- i) In your process performance qualification (PPQ), you sampled (b) (4). The coefficient of variation (CV) for TNF R1 exceeded (b) (4) DP lots. The CV for % inhibition of IL-2R α expression exceeded (b) (4) DP lots tested.
- ii) The data presented in your validation study for the % inhibition of IL-2R α expression assay suggests that inter-assay variability is inconsistent. While results for (b) (4) of the (b) (4) DP lots tested were relatively consistent (CVs (b) (4)), results for Lot # (b) (4) ranged from (b) (4).

Meeting Discussion: The applicant presented data attempting to show that the TNF R1 potency assay is linked to clinical outcome and the *in vitro* immunomodulatory activity of the product. The data presented included results from TNF R1 knockdown experiments conducted during development, and a reanalysis of manufacturing and clinical data previously submitted to the BLA. The applicant concluded that this reanalysis of clinical data demonstrated that TNF R1 assay results were associated with Day 100 overall survival in a population of subjects pooled from three clinical protocols. Further, the applicant suggested that process improvements leading to increased levels of TNF R1 in the product may be related to the increased survival observed in subjects receiving product lots made after these improvements. The applicant also acknowledged that the IL-2R α inhibition assay was not associated with clinical outcomes in these analyses.

FDA asked for clarification regarding any correlation between TNF R1 results and the IL-2R α inhibition assay, and applicant responded that results from the IL-2R α inhibition assay are too variable and not reliable. FDA asked if the applicant intended to continue use of the IL-2R α inhibition assay for lot release, and the applicant appeared to indicate that they would not and that only the TNF R1 assay would be used to control product potency for lot release.

FDA indicated that the applicant should submit updated specifications and additional information regarding the new analyses presented to the BLA, and that the applicant would receive an information request shortly after the mid-cycle discussion with specific requests.

3. You indicate that process improvements were implemented in the (b) (4) manufacturing process prior to manufacturing PPQ lots in 2019. (b) (4) of the (b) (4) DP lots produced during PPQ were not challenged, however the potency of these lots (as measured by % inhibition of IL-2R α expression) appears reduced relative to DP lots used in MSB-GVHD001 (Avg. = (b) (4) inhibition [range (b) (4)]). This suggests that the changes made to the manufacturing process may have adversely affected product quality.

Meeting Discussion: The applicant reiterated their position that the IL-2R α inhibition assay was not reliable and suggested that the apparent reduction in product potency as measured by this assay was caused by (b) (4) used in this assay rather than a reduction in product quality. FDA indicated that data supporting this suggestion should be submitted to the BLA, and that this request would be included in the information request previously discussed.

Clinical

- Remestemcel-L was evaluated in two previous randomized controlled trials (RCT) in adult and pediatric patients. Of the two RCTs, Study 265 evaluated the efficacy of remestemcel-L compared to placebo in combination with systemic

corticosteroid therapy in 192 patients with newly-diagnosed Grades B-D acute graft vs host disease (aGVHD), and Study 280 evaluated the efficacy of remestemcel compared to placebo in combination with investigators choice of immunosuppression in 244 patients with Grades B-D aGVHD who failed to respond to corticosteroids. Neither study demonstrated an improvement with remestemcel-L over standard care alone.

Meeting Discussion: The applicant requested clarification on the intended discussion for the afternoon clinical session of the upcoming advisory committee meeting, as they had been informed that this would be a non-voting session. The clinical review team indicated that a decision regarding the voting status of the afternoon session had not yet been made. The Chair acknowledged the miscommunication and committed to providing the applicant with an update regarding after discussing the voting status of the afternoon session with the review team.

There are no significant issues/major deficiencies identified at this time in all other disciplines.

2. Information regarding major safety concerns.

Inadequate *in vitro* adventitious viral testing may constitute a safety issue; input from OVRP has been requested.

3. Preliminary Review Committee thinking regarding risk management.

The safety review is ongoing. At this time, the review teams have not identified a need for a REMS.

4. Any information requests sent and responses not received.

N/A

5. Any new information requests to be communicated.

DMPQ IR #21 Due June 23, 2020

6. Proposed dates for the Late-Cycle meeting (LCM).

a. The LCM between you and the Review Committee is currently scheduled for July 23, 2020 1:30-3:00 pm, EST

b. We intend to send the LCM meeting materials to you approximately 10 days in advance of the LCM.

- c. If these timelines change, we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting.

An Advisory Committee meeting is planned for August 13, 2020. Please note that this plan is confidential and not for public release until it posts in the Federal Register. Additional information will be provided to you by your contact in the Division of Advisory Committee and Consultant Management.

The potential topics for discussion at the Advisory Committee Meeting include:

- A general discussion of quality attributes for MSC products and their relation to product efficacy.
- The adequacy of the results of a single-arm trial to establish efficacy in the context of two failed randomized trials.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

There are no changes at this time.