



Our STN: BL 125706/0

**LATE-CYCLE
MEETING MEMORANDUM**

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

Dear Mr. Picciano:

Attached is a copy of the memorandum summarizing your July 23, 2020 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Manager, 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

Late-Cycle Meeting Summary

Meeting Date and Time: July 23, 2020 at 13:30-15:00 pm
Meeting Location: WebEx Teleconference
Application Number: BLA 125706/0
Product Name: Ex Vivo Cultured Adult Human Mesenchymal Stem Cells
Proposed Indications: Acute Graft versus Host Disease
Applicant Name: Mesoblast, Inc.
Meeting Chair: Matthew Klinker, PhD
Meeting Recorder: Adriane Fisher MPH, MBA

FDA ATTENDEES

Ekaterina Allen, PhD, CBER/OCBQ/DMPQ
Kristin Baird, MD, CBER/OTAT/DCEPT/CHB
Steven Bauer, PhD, CBER/OTAT/DCGT
Kimberly Benton, PhD, CBER/OTAT
Qiao Bobo, PhD, CBER/OCBQ/DMPQ
Danielle Brooks, PhD, CBER/OTAT/DCEPT
Michael Brony, CBER/OCBQ/DCM/APLB
Wilson Bryan, MD, CBER/OTAT
Nannette Cagungun, MS, PD, RAC, CBER/OTAT/DRPM
Dennis Cato, CBER/OCBQ/DIS
Heba Degheidy, MD, PhD, CBER/OTAT/DCGT
Melanie Eacho, PhD CBER/OTAT/DCGT
Maryna Eichelberger, PhD, CBER/OCBQ/DBSQC
Bindu George, MD CBER/OTAT/DCEPT
James Kenny, D. Sc., CBER/OTAT/DBSQC
Arifa S. Khan, Ph.D., CBER/OVRR/DVP
Alyssa Kitchel, PhD, CBER/OTAT/DCGT
Matthew Klinker, PhD, CBER/OTAT/DCGT/CTB
Carolyn Laurencot, PhD, CBER/OTAT/DCGT
Elizabeth Lessey-Morillon, PhD, CBER/OTAT/DCGT
Wei Liang, PhD, CBER/OTAT/DCEPT
Stan Lin, PhD, CBER/OBE
Ke Liu, MD, PhD, CBER/OTAT/DCEPT
Anthony Lorenzo, CBER/OCBQ/DMPQ
Adamma Mba-Jonas, MD, MPH CBER/OBE/DE/PB
Bao-Ngoc Nguyen, PhD, CBER/OTAT
Steven Oh, PhD CBER/OTAT/DCGT
Most Nahid Parvin, PhD, CBER/OCBQ/DBSQC
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
Hainsworth Shin, PhD, CDRH/OSEL/DBCMS
Archana Siddam, PhD, CBER/OTAT/DCGT
Ramani Sista, PhD, CBER/OTAT/DRPM
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Wenyu (Andy) Sun, MD, PhD, CBER/OBE/DE/PB
Million Tegenge, RPh, PhD, CBER/OTAT/DCEPT
Marc Theoret, MD, OCE
Zehra Tosun, PhD, CBER/OTAT/DCGT
Allen Wensky, PhD, CBER/OTAT/DCEPT
Samanthi Wickramasekara, PhD, CDRH/OSEL/DMCMS

APPLICANT 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
Paul Simmons, PhD, Head of Research & Product Development
Fiona See, PhD, Vice President, Translational Development
Justin Horst, Vice President, Translational Development
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

BACKGROUND

BLA 125706/0 was submitted on May 29, 2019 for Ex Vivo Cultured Adult Human Mesenchymal Stem Cells.

Proposed indication: Acute Graft versus Host Disease

PDUFA goal date: September 30, 2020

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on July 15, 2020, and issued Advisory Committee Briefing Materials on July 24, 2020.

DISCUSSION

1. Discussion of Substantive Review Issues

Chemistry, Manufacturing, and Controls

- a) **Critical Quality Attributes and Product Efficacy.** Prior to the mid-cycle communication, we expressed concerns that your product potency assays do not have a clearly demonstrated relationship to product efficacy or to the product's proposed mode of action. You provided a new analysis of product and clinical efficacy data purporting to show that results of your TNF R1 assay were associated with survival at Day 100 in a pooled dataset of subjects enrolled in three clinical protocols. We requested additional information regarding these new analyses, and you provided this information in amendment 32 dated June 15, 2020.

After reviewing this additional information, we identified several issues with your new analyses that make their results difficult to interpret. First, the pooled analysis dataset used subjects enrolled in three clinical protocols that differed in several important aspects that may confound your results, such as the use of concurrent medications. Secondly, it is not clear that considering only exposure to specific lots rather than the number of doses each subject received from specific lots is an appropriate method for collapsing TNF R1 results for each study subject. Finally, the product administered to subjects under these three protocols was manufactured using multiple versions of your manufacturing process, and you indicate that no significant association is observed when only data from the pivotal study MSB-GVHD001 is considered. The clinical trials from which these data were gathered were not designed with such an analysis in mind, and although the results of these analyses are suggestive, the limitations described above make interpreting your results difficult. We note that a potency assay/critical quality attribute (CQA) with a demonstrated relationship to clinical efficacy may not be required for licensure, however the lack of CQAs relevant to clinical efficacy will likely limit the interpretability of any future comparability exercises you may conduct after implementing changes to the manufacturing process.

Meeting Discussion: FDA summarized the issues, and the applicant acknowledged FDA's concerns and the limitations of the analyses provided but stated that they thought the analyses still provided relevant information. The applicant also indicated that biomarker development would continue and that they intend to collaborate with FDA for future product characterization. The applicant also acknowledged that *in vitro* analyses for product characterization may not be sufficient to show product comparability after future manufacturing changes.

- b) Inhibition of IL-2R α Assay and Product Quality. Prior to the mid-cycle communication, we expressed concerns that the apparent potency of DP lots made during process performance qualification (PPQ) in 2019 showed an apparent reduction in potency relative to DP lots used in study MSB-GVHD001 as measured by your inhibition of IL-2R α assay. At the mid-cycle communication, you indicated that this apparent reduction in potency was due (b) (4) used in this assay and indicated that the inhibition of IL-2R α assay was too variable for use as a release assay. We asked for data to support this conclusion in a follow up information request, and you responded to this request in amendment 32 dated June 15, 2020. In your response you provided data from additional commercial lots from your current manufacturing campaign, and these commercial lots also appear to have a reduced potency relative to clinical DP lots. You now propose to reclassify the inhibition of IL-2R α assay as a qualitative assay for activity with the same specification for release.

While we acknowledge that increased variability due to differences in the (b) (4) could potentially explain this observation, a reduction in the quality of commercial lots due to changes in the manufacturing process or (b) (4) cannot be ruled out with the data provided in your response. Additionally, as several changes have been made to the manufacturing process, this apparent reduction in potency may also indicate that commercial lots made using the revised process are not sufficiently similar to those made using the previous process.

Meeting Discussion: The applicant summarized the manufacturing changes made and restated their position that the post-change product showed increased variability relative to clinical lots rather than overall reduced potency, and that the source of this increased variability is the assay rather than the product. Additional controls for this assay are being developed.

- c) Product Specifications. We noted that several of your proposed product specifications were well below values observed for DP lots used in study MSB-GVHD001 and requested that you revise your specifications. In response, you proposed changes to specifications for residual manufacturing contaminants and the TNF R1 potency assay. These revisions do not, however, ensure that the quality of the commercial product will be consistent with the quality of the product lots used in your pivotal study.

- i. You propose to revise your specification for the TNF R1 potency assay from (b) (4) . As justification for this revised specification you indicate that a “target level” of (b) (4) was determined from your analysis of TNF R1 results and Day 100 OS, and have chosen a specification (b) (4) below this target. It is not clear how you determined this target value or how your choice of a specification below this target is justified. Given the limitations of this analysis discussed above, it is also not clear that using the results of this analysis as a basis for determining specifications for product attributes is appropriate.

Additionally, this specification is still well below the distribution of values observed in DP lots used in MSB-GVHD001, which averaged (b) (4) with a minimum value of (b) (4) and maximum of (b) (4) . Your clinical data, therefore, do not support the use of DP lots with measured values outside of this range. Your specifications should be revised further to include both a minimum and maximum value that together ensure that lots released for commercial use are consistent with the observed values of DP lots used in study MSB-GVHD001.

- ii. You acknowledge that lots used in study MSB-GVHD001 showed more consistent results for inhibition of IL-2R α relative to historical manufacturing data and DP lots made during your current manufacturing campaign. In your response June 15, 2020 you indicated that PPQ and commercial lots made during your current manufacturing campaign average (b) (4) inhibition (range (b) (4)) whereas clinical DP lots averaged (b) (4) inhibition (range (b) (4)). You have proposed reclassifying the inhibition of IL-2R α assay as qualitative, but you have not materially changed this specification or provided a justification supported by data for choosing (b) (4) inhibition as the minimum acceptable level of activity.

Although it may be acceptable to consider this a qualitative assay, your chosen threshold should be supported by manufacturing and clinical data, and should be adequate to ensure that the activity of the commercial DP lots is consistent with DP lots used to demonstrate product efficacy. As discussed above, you have not convincingly demonstrated that the increased variability observed in your commercial product is due to assay variability rather than product variability. We therefore request that you revise the minimum specification for this assay to (b) (4) inhibition so that commercial DP lots will have a level of bioactivity more consistent with DP lots used in the MSB-GVHD001 study.

Meeting Discussion: The applicant agreed to revise the specification for inhibition of IL-2R α to (b) (4) inhibition as recommended by FDA, and proposed to revise the specification for TNFR1 to (b) (4) . FDA asked for clarification on the rationale for the new TNFR1 specification and the applicant confirmed that this value was the lowest value observed for lots used in study MSB-GVHD001. FDA asked the applicant to justify

the lack of an upper limit for this assay, and the applicant indicated that there was not a safety concern associated with high levels of TNFR1. FDA indicated that there is no data to support the safe use of lots with TNFR1 levels exceeding those of lots used in the clinical study, and that lots exceeding values routinely seen may indicate issues with the manufacturing process or assay validity. FDA indicated that this may be acceptable, but a maximum specification may be necessary to provide assurance of consistent manufacturing.

DMPQ

d) GMP Compliance Status of Manufacturing Facilities.

- i. Your DP release testing facility (b) (4) is in Official Action Indicated status based on the outcome of the last US FDA inspection (b) (4)

Meeting Discussion: The applicant indicated that product testing was performed in the chemistry GMP laboratory at this facility, and that this laboratory was under an independent FEI# at the time of the inspection noted. FDA acknowledge the applicant's response and stated that this issue would be investigated further.

- ii. Compliance status of your DP manufacturing facility Lonza Bioscience Singapore Pte. Ltd. (35 Tuas South Ave 6, Singapore, 637377; FEI# 3009725845) cannot be verified at this time.

Meeting Discussion: The applicant asked for clarification on how FDA's inability to conduct an in-person inspection of their manufacturing facility would impact action on this application, and asked FDA if a virtual inspection and document review would be sufficient. FDA stated that an in-person inspection was necessary, but that a decision on how this would impact this application had not yet been made.

e) Sterility Assurance of the Final Product. We are concerned that there is not sufficient sterility assurance of the DP and about the implications it might have on the safety of the product. Specifically:

- i. You indicated during our teleconference on June 18, 2020 that you have no data to support microorganism recovery in release and in-process sterility samples shipped under various conditions to (b) (4) for testing. This issue also applies to in-process solutions/media that are shipped for sterility release testing from LBSS (Singapore) to (b) (4)
- ii. No periodic testing of incoming lots of product contact materials for sterility and endotoxin. Many product contact materials are not tested for endotoxin by supplier.

- iii. CCIT of final container by (b) (4) Test is not capable of detecting holes in the stopper. Stopper is (b) (4) Effectiveness of (b) (4) was not validated by an alternative method.

Meeting discussion: The applicant stated that they were performing studies and implementing testing methods to address the concerns in (i) - (iii) and would be able to submit results no later than mid-September 2020. FDA stated that it would be acceptable.

Clinical

- f) 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.
- g) Study MSB-GVHD001, the primary study intended to support your marketing application is a single arm study. Whether this study represents an adequate and well controlled study to demonstrate efficacy of Remestemcel is a review issue.

2. Discussion of Minor Review Issues

Chemistry, Manufacturing, and Controls

- a) Robustness of the inhibition of IL-2R α assay should include assessing multiple lots of (b) (4) to evaluate the contribution of differences in (b) (4) to the observed assay variability.
- b) The leachables study you performed were not conducted in accordance with FDA recommendations.
- c) Stability data should be re-evaluated considering revisions to product specifications, and shelf-life and in-use hold time should be adjusted accordingly.
- d) *In vitro* adventitious agent testing for DCBs has been reviewed and the methods performed appear to be adequate.

Meeting Discussion: The applicant stated that studies to support the robustness of the inhibition of IL-2R α assay were ongoing and that a protocol for these studies could be provided at FDA's request. The applicant also committed to provide an updated stability assessment. A leachables study plan was submitted to FDA prior to this meeting.

DMPQ

- a) Qualification of following critical equipment submitted for use in licensed manufacturing performed at your contract manufacturer ICS Amerisource Bergen in (b) (4) will not be completed until Q3 2020:
 - i. (b) (4) used for DP visual inspection, as a workbench during packaging, and for transport within ICS facility
 - ii. Serialization equipment is not qualified for use with Mesoblast cartons.

Meeting Discussion: The applicant stated that they were qualifying the equipment in question and would be able to submit results no later than mid-September 2020. FDA stated that it would be acceptable.

3. Additional Applicant Data

At this time, the review teams have not identified a need for a additional applicant data

4. Information Requests

At this time, the review teams have not identified a need for information requests

5. Discussion of Upcoming Advisory Committee 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 topics for discussion at the Advisory Committee Meeting include:

- A discussion of quality attributes for remestemcel-L, their relation to product efficacy, and implications for future manufacturing changes.
- The adequacy of the results of a single-arm trial to establish efficacy in the context of two failed randomized trials.

6. Risk Management Actions (e.g., REMS)

At this time, the review teams have not identified a need for a REMS.

7. Postmarketing Requirements/Postmarketing Commitments

No PMRs/PMCs have been identified at this time, but may be identified later depending on how other review issues are resolved going forward.

8. Major Labeling Issues

There is no anticipation of major labeling issues at this time.

9. Review Plans

Review of the BLA is ongoing.

10. Applicant Questions

Meeting Discussion: The applicant asked for an update as to when they would receive FDA's decision regarding their proposed product suffixes. FDA indicated that review had been completed and that the applicant could expect to receive official notification by the end of the following week.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.