

Our STN: BL 125706/0

COMPLETE RESPONSE

September 30, 2020

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

Dear Mr. Picciano:

Please refer to your Biologics License Application (BLA) submitted May 29, 2019, received January 31, 2020, for remestemcel-L manufactured at your Singapore location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated August 31, 2020, September 1, 2020, September 14, 2020, and September 18, 2020. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Clinical

1. You provided results from a single-arm study, MSB GVHD 001, as the primary evidence of effectiveness to support this license application for the treatment of steroid-refractory graft versus host disease (sr-GVHD). However, the design of Study MSB GVHD 001 makes the study results highly susceptible to bias, and therefore difficult to interpret. Particularly, we are concerned about the risk of bias in subject selection, baseline assessment, outcome assessment, and selection of the comparator. Therefore, Study MSB GVHD 001 is not a well-controlled study, and your BLA does not meet the statutory requirement for substantial evidence of effectiveness. To meet this requirement, we recommend that you conduct at least one randomized, well-controlled study in adults and/or pediatric subjects to provide evidence of the effectiveness of your product in the treatment of sr-GVHD.

Chemistry, Manufacturing, and Controls

2. Due to the inadequacy of the data submitted to support approval, the agency did not conduct a pre-license inspection of your manufacturing facility. This inspection will need to be performed after the agency receives a complete response with adequate data to address the deficiencies identified in this letter (21 CFR 601.3(a)(2)).

3. All lots of remestemcel-L Drug Product (DP) are tested for potency using an (b) (4) to measure the amount of TNFR1 in the mesenchymal stromal cell (MSC) (b) (4). As this is a non-biological analytical assay for potency, the product attribute measured by this assay should have a demonstrated relationship to a relevant product-specific biological activity. The information you provided in your application was insufficient to establish that your analytical assay for potency measures a product attribute related to the specific ability or capacity of the product per 21 CFR 600.3(s) for the following reasons:
 - a. You provided analyses in Amendment 32 (dated June 15, 2020) purporting to show an association between TNFR1 results and survival outcomes. We do not agree that these analyses adequately support your conclusion, as an association was observed only when analyzing data pooled from multiple clinical studies, where differences in study populations and manufacturing processes for the DP used in these studies severely limit the interpretability of these analyses. You cite manufacturing changes made in 2009 as the source of increased TNFR1 levels and better clinical outcomes, but these changes were not identified in the summary of manufacturing process development you provided in your original submission of this application, and it is not clear how many of these changes were maintained when manufacturing was transferred to the Lonza Singapore facility (LBSS). Furthermore, at the time of implementation, these changes were reported in an annual report to IND 7939 as “minor updates” to the manufacturing process and were reported to have been implemented to simplify the process rather than improve the quality of the product. You also did not provide an explanation supported by data for how this process “optimization” could lead to production of a more consistent product, nor a justification for grouping lots made at LBSS with an updated manufacturing process with lots made at the Lonza Walkersville facility (LWI) in 2009 in this analysis without demonstrating product comparability. As such, the interpretability of these results is severely limited.
 - b. The data provided in your application do not establish a scientific rationale for your assay for product potency, and in fact suggest that the attribute measured by this assay is not related to the immunomodulatory activity of the DP. The basis for selecting TNFR1 as a marker of potency was a series of experiments conducted in 2005 using a previous version of remestemcel-L. These initial experiments showed that knockdown of TNFR1 reduced the capacity of MSCs in the precursor product to inhibit T cell proliferation (Report R-045-05). In Amendment 32 (dated June 15, 2020), you committed to repeating these knockdown experiments using DP made using the current manufacturing process and to provide these results before the late-cycle meeting on July 23, 2020. You stated in this amendment that you anticipated “that the data will show that knockdown or neutralization of TNFR1 will impair the ability of MSC from the current manufacturing process to inhibit T cell proliferation *in vitro*.” The results provided in Amendment 49 (dated August

11, 2020), however, refuted this hypothesis, and in Report MR-128 you stated that these results instead demonstrate that “the immunomodulatory effects of remestemcel-L on activated T cell proliferation *in vitro* are independent of TNFR1 activity and expression.” We agree with this interpretation, and therefore the scientific rationale on which TNFR1 level was selected as an attribute related to product potency does not appear applicable to remestemcel-L made using the proposed commercial manufacturing process.

- c. In light of these results demonstrating that TNFR1 is dispensable for remestemcel-L’s immunomodulatory effect on T cells, at the meeting of the Oncologic Drugs Advisory Committee (ODAC) on August 13, 2020, you proposed an alternative mechanism of action for remestemcel-L. Particularly, you proposed that remestemcel-L exerts immunomodulatory effects on macrophages rather than directly on T cells. The data you provided in Amendment 49 in support of this mechanism show that TNFR1 knockdown reduces the capacity of MSCs to respond to TNF- α , but these results do not adequately demonstrate that TNF- α -dependent factors are required for the purported effect on macrophages, or that a dependence on TNFR1 signaling is relevant in the context of an inflammatory milieu containing multiple cytokines that may activate the immunomodulatory activity of MSCs. Therefore, you have not adequately demonstrated that TNFR1 levels are related to the product’s immunomodulatory activity toward monocytes and/or macrophages.

Because of these deficiencies, you have not demonstrated that TNFR1 levels are relevant to product activity or related to clinical outcomes. Therefore, it is not clear that this test can be considered an appropriate test for potency per 21 CFR 610.10. All biological products regulated under section 351 of the Public Health Service Act must meet prescribed requirements of safety, purity and potency per 21 CFR 601.2. An appropriate assay for potency is necessary to provide assurance of a consistent manufacturing process and establish product stability.

Additionally, you will need to implement a major change to the manufacturing process to continue production of donor cell banks (DCBs) when your current stock of DCB material is depleted. If you intend to leverage previous clinical results to support the safety and/or efficacy of the post-change product, you will need to conduct a convincing comparability exercise. If you have not identified product attributes that are associated with potency, however, it is unlikely that analytical methods alone will be sufficient to demonstrate product comparability to support such a change. Previous clinical results may not be considered relevant to the post-change product if comparability cannot be demonstrated by analytical methods, and therefore new clinical trials may be necessary to support the safety and efficacy of the post-change product.

Please identify all assays that you consider tests for product potency and provide a justification for how controlling the attributes measured by these assays is

adequate to ensure that each lot of remestemcel-L has acceptable levels of product activity. Additionally, please provide data demonstrating that the product attributes measured by potency assays used for lot release testing and establishing stability have a statistically meaningful relationship to clinical outcomes, surrogate markers of *in vivo* activity, or a relevant product activity as measured by an *in vitro* biological assay. If the product attributes measured are related to an *in vitro* activity of the product only, please also include a scientific rationale explaining the relevance of the *in vitro* activity to the clinical effect of the product.

Labeling

4. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.


We acknowledge receipt of your amendments dated August 31, 2020, September 1, 2020, September 14, 2020, and September 18, 2020. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendments dated August 31, 2020, September 1, 2020, September 14, 2020, and September 18, 2020 in your complete response to this letter and we will review those sections as a part of your complete response.

In addition to the deficiencies that were the basis for not granting approval, we have identified the following deficiencies:

Chemistry, Manufacturing, and Controls

1. During review of your application, you agreed to revise the release specifications for TNFR1 and inhibition of IL-2R α assays to reflect the more stringent values observed among DP lots used in Study 001 compared to the initial specifications. Given the distribution of values obtained from vials within a single DP lot as observed in your Process Parameter Qualification (PPQ) multiple sampling analyses, testing a single vial from each lot may not be appropriate because the revised specifications fall within the expected range of values for a given lot, which may result in the rejection of entire lots, if the vial randomly chosen for testing happens to fall on the low end of this distribution. We therefore recommend that you develop a more thorough lot sampling approach that includes testing multiple vials from each lot, and that you revise your specifications for these assays to account for the distribution of values obtained from multiple vials within a lot. For each assay, you should choose a minimum acceptable result for each vial, then perform a statistical analysis to determine how to set your specifications to ensure that the frequency of vials below this minimum value is acceptably low.
2. In Amendment 32 (dated June 15, 2020), you acknowledge that your inhibition of IL-2R α assay is not suitable as a quantitative assay due to variability and attributed this variability to differences in lots of (b) (4). If you intend to continue using this assay for DP lot release, we recommend that you continue to develop this assay and revise the testing procedure as appropriate to improve robustness to (b) (4) variability and provide more consistent results.
3. In the Chemistry, Manufacturing, and Controls Information Request #23, we state that assays established as stability-indicating for the DP may not be stability-indicating for the DCB and recommend that you establish these assays as stability-indicating for the DCBs in addition to the DP. In Amendment 34 (dated June 18, 2020), you indicate that (b) (4). Please note that assays that are not established as stability-indicating specifically for DCB material may not be relevant for use in future comparability exercises performed after changes are made to the DCB manufacturing process.
4. (b) (4)

(b) (4)



5. During validation of the (b) (4) for TNFR1 and IL-2R α that are used for DP lot release testing, you evaluated the effects of (b) (4) different lots of each (b) (4); however, this evaluation was performed using results obtained from different DP lots. We recommend that you characterize variability in performance between lots of (b) (4) by using (b) (4) lots to test the same test article (i.e., the same cell (b) (4)).
6. In Amendment 34 (dated June 18, 2020), you commit to submitting results from additional studies to address deficiencies in the validation of your (b) (4) assays by August 31, 2020. You provided your response in Amendment 52 (dated September 1, 2020) and Amendment 54 (dated September 14, 2020); however, these amendments were not reviewed due to receipt late in the review cycle. Additional information may be requested after review of the materials submitted.
7. In Amendment 45 (dated July 21, 2020), you commit to submitting results from additional extractable and leachable studies to support the use of the 6 mL (b) (4) Vials as container closure for the DP. As these reports were not submitted before the action date for this application, they were not reviewed, and additional information may be needed after the results are reviewed.
8. In your response to FDA late-cycle meeting materials (Amendment 52, dated July 23, 2020), you commit to providing an updated assessment of DP stability using the agreed-upon revised DP specifications, and a final study report supporting microorganism recovery in release and in-process sterility samples shipped under various conditions to the (b) (4) for testing. You provided your responses in Amendment 55 (dated September 18, 2020); however, this amendment was not reviewed due to receipt late in the review cycle. You also committed to providing a written plan for the periodic endotoxin testing of incoming lots of product contact materials; however, this information was not received at the time of this letter issuance. Additional information may be requested after review of these materials.

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

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research