FDA Briefing Document

Oncologic Drugs Advisory Committee (ODAC) Meeting

Session on Product Characterization (AM Session)

August 13, 2020

BLA 125706
Remestemcel-L
Applicant: Mesoblast, Inc

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the remestemcel-L BLA to this Advisory Committee in order to gain the Committee's insights and opinions regarding the characterization and quality attributes of the proposed drug product for the proposed oncologic indication. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the FDA for discussion by the advisory committee in the morning session of this meeting. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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ABBREVIATIONS

CQA	Critical quality attribute
DCB	Donor cell bank
DP	Drug product (final product)
DS	Drug substance (bulk before vialing)
GvHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
IL-2	Interleukin 2
IL-2Rα	Receptor for IL-2
ISCT	International Society for Cellular Therapy
MSC	Mesenchymal stromal cell
PBMCs	Peripheral blood mononuclear cells
QA	Quality attribute
TNF-α	Tumor necrosis factor alpha
TNFR1	Receptor for TNF-α

1. INTRODUCTION

1.1 Product Background

Mesoblast, Inc. ("the Applicant") has submitted biologics license application (BLA) 125706 seeking to market remestemcel-L, a cellular therapy product composed of allogeneic culture-expanded mesenchymal stromal cells (MSCs) that have been isolated from bone marrow aspirate collected from healthy human donors. The proposed indication is the treatment of pediatric patients with steroid-refractory acute graft-vs.-host disease (SR-aGVHD), a life-threatening complication of hematopoietic stem cell transplantation (HSCT) characterized by immune-mediated damage to multiple tissues, including the skin, liver, and gastrointestinal tract. The tissue-damaging inflammation associated with SR-aGVHD is thought to be initiated by alloreactive immune cells present in the HSCT allograft material that target recipient tissues as foreign, which leads to sustained and systemic immune activation. The proposed mode of action for remestemcel-L is a reduction of this pathogenic immune activation mediated by the immunomodulatory bioactivity of MSCs present in the product.

Remestemcel-L development began more than 20 years ago, and the product has been tested in multiple clinical trials for a variety of conditions thought to have an inflammatory component, yet the product is not approved in the US for any indication. The Applicant acquired the rights to the remestemcel-L development program in 2013, and initiated manufacturing of the remestemcel-L drug product (DP) using an updated manufacturing process to support new clinical studies. Product made with this updated process was used to conduct study MSB-GVHD001, the results of which are included in this application as the primary evidence of effectiveness of remestemcel-L in treating the proposed indication.

1.2 Topics of Discussion

The purpose of the morning session of this Advisory Committee meeting is to discuss the product attributes of remestemcel-L and their relation to product quality and effectiveness. The Applicant has defined critical quality attributes (CQAs) for remestemcel-L that are proposed to be related to the potency and activity of the product (see Section 5.1 *Critical Quality Attributes* in the Applicant's briefing document). FDA's position is that the product attributes the Applicant has identified as related to potency and activity, however, do not have a demonstrated relationship to the clinical performance of specific DP lots, and that the product's proposed immunomodulatory mechanism of action has not been demonstrated *in vivo* in study subjects receiving remestemcel-L. Without a demonstrated relationship with clinical effectiveness and/or *in vivo* potency/activity, controlling these CQAs may not be sufficient to ensure the manufacturing process consistently produces remestemcel-L lots of acceptable quality.

We ask the committee to consider the product attributes identified by the Applicant as CQAs and discuss whether they are adequate to ensure that the manufacturing process will continue to

produce lots of consistent quality. Additionally, given the limitations of the current CQAs, we ask that the committee discuss other product characteristics not previously identified as CQAs for remestemcel-L that might provide more meaningful measures of product quality and potency and therefore provide better assurance of product quality from lot-to-lot.

2. REGULATORY PERSPECTIVE ON POTENCY FOR CELL THERAPY PRODUCTS

A biologics license application may be approved on the basis of a demonstration that the biological product that is the subject of the application is "safe, pure, and potent" (42 USC 262(a)(2)(c)(i)(I). Federal regulations provide the following definitions of potency that apply to cell-based drug products:

- Biological Products: "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result" (21 CFR 600.3(s)).
- Drugs in General: "the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data" (21 CFR 210.3(b)(16)(ii))

These definitions allow for the use of laboratory tests or clinical data to demonstrate the potency of a drug product. Well-controlled clinical data can be used to demonstrate that the manufacturing process is capable of producing a potent product, and laboratory tests can be used to ensure that product potency is consistent from lot-to-lot. Laboratory tests to be used as product potency assays are most effective if they measure product attributes that are linked to a clearly-defined mechanism of action, and/or attributes that have a demonstrated relationship with clinical efficacy.

Development of adequate potency assays, however, can be particularly challenging for MSC-based products. The *in vivo* activity of cell-based products can be multimodal and difficult to characterize, and as a result the mechanism of action may not be clearly established. Characterization of cell-based products in general is complicated by the complex nature of cells relative to other types of drugs, as well as heterogeneity among cells comprising the active ingredient. Defining product quality attributes that relate to the product's clinical effectiveness, therefore, may require more extensive product characterization for cell therapy products than for other biological products. Additionally, because of the complex nature of cell therapy products, clinical trials designed with efficacy endpoints in mind may not be adequately powered to detect association of clinical outcomes with relevant product attributes.

Despite these challenges, FDA has suggested that developers of cell-based products may progress in two relevant ways. The first is that potency assays based on reasonable hypotheses about mechanisms of action rather than a clearly demonstrated mechanism of action may be adequate in some circumstances. FDA has provided guidance on potency assay development that allows a matrix approach for complex biological products, including cell therapies. This matrix

approach relies on at least one quantitative bioassay and one qualitative bioassay, which together are sufficiently related to the proposed mechanisms of action. As for other assays for quality attributes, potency assays used under these conditions must be sufficiently robust in terms of reproducibility and as indicators of product quality and product stability.

The second approach is to use clinical performance to demonstrate potency. For instance, if a product meets the primary clinical outcomes, has been extensively characterized during product development, and is produced by a well-controlled manufacturing process, these clinical data may be considered to demonstrate potency even if the mechanism of action is not completely understood. In this scenario, assays purporting to measure product attributes thought to be related to product potency must be sufficiently robust in terms of reproducibility and as indicators of product quality and stability. This approach can allow novel therapies with clearly demonstrated efficacy and well-controlled manufacturing processes to progress to licensure even if the mechanism of action and its relationship to the relevant potency assay are not completely understood.

3. REMESTEMCEL-L PRODUCT ATTRIBUTES AND CLINICAL EFFECTIVENESS

All lots of remestemcel-L are subject to specifications designed to assure a high frequency of cells possessing a specific surface phenotype based on expression of the markers CD166, CD105, and CD45, and product purity is consistently high with little variability between product lots[1]. These identity markers are consistent with, but not identical to, a widely-accepted consensus phenotype for MSCs (> 95% positive for CD73, CD90, and CD105 [2]).

The proposed mechanism of action for remestemcel-L is a reduction in pathogenic inflammation mediated through the immunomodulatory activity of the MSC active ingredient. Given this mode of action, controlling the immunomodulatory bioactivity is critical to maintaining consistent product quality. To control the immunomodulatory bioactivity of remestemcel-L, the Applicant has implemented a matrix approach as discussed above. This approach uses two assays to measure product attributes purported to be related to the potency and activity of the product:

(1) Expression of TNF receptor 1 (TNFR1) protein in the MSC active ingredient: TNFR1 is a receptor for tumor necrosis factor alpha (TNF-α), a cytokine commonly secreted in inflammatory circumstances. In *in vitro* experiments, exposure to inflammatory cytokines such as TNF-α can stimulate MSCs to produce immunomodulatory molecules.

(2) Inhibition of IL-2Rα expression in activated T lymphocytes: In this *in vitro* bioassay, peripheral blood mononuclear cells (PBMCs) are cultured in the presence or absence of the MSC active ingredient. PBMCs contain T cells which when activated increase expression of IL-2Rα. T cells are activated in both conditions, and the amount of IL-2Rα is measured for each. A reduction of IL-2Rα expression in the presence of the MSC active ingredient is interpreted as inhibition of T cell activation. The Applicant considers this assay to be a measure of the *in vitro* immunomodulatory activity of the MSC active ingredient.

Although these assays are consistent with the hypothesized mechanism of action of immunomodulatory activity, this mechanism of action has not been demonstrated in the clinical

trials submitted to support licensure. While remestemcel-L and other MSC-based investigational products have demonstrated apparent immunomodulatory effects in *in vitro* experiments, the ability of remestemcel-L to reduce inflammation as measured by inflammatory biomarkers in humans receiving the product has not been demonstrated. SR-aGVHD is thought to be an immune-mediated disorder but its etiology is complex and many cell types are likely to be involved in its pathogenesis. Therefore, any efficacy remestemcel-L might have in treating this disease is not sufficient to demonstrate the product's mechanism of action.

A relationship between these *in vitro* lot release assays and the clinical effectiveness of the product has also not been demonstrated. Using data from the clinical study MSB-GVHD001, there were no apparent differences in the mean value of product lots given to responders or non-responders for either the potency or immunomodulatory activity assays. The Applicant presents an analysis using data pooled from multiple clinical studies purporting to show that TNFR1 results are associated with survival on Day 100 post-treatment (see Section 5.4 *Remestemcel-L Potency and Efficacy Results* in the Applicant's briefing document). This analysis, however, is confounded by differences in the study populations and outcomes measured, and the association between TNFR1 and survival on Day 100 is not observed when the analysis is limited to data from MSB-GVHD001. Additionally, the fact that most subjects received product from multiple lots further dilutes the power of these studies to detect an association between lot release *in vitro* potency or activity and clinical outcomes.

The Applicant has also provided data that they interpret as showing a relationship between TNFR1 results and *in vitro* immunomodulatory activity by showing that experimental reduction of TNFR1 by shRNA/siRNA knockdown leads to a corresponding reduction in the capacity of MSCs to inhibit T cell proliferation (see Section 2 *Mechanism of Action*, CMC Figures 6-11, in the Applicant's briefing document). These experiments, however, do not necessarily reflect the biological variation of TNFR1 expression observed among lots of remestemcel-L. When unmanipulated lots of remestemcel-L (i.e., lots not treated with siRNA/shRNA to reduce TNFR1) are used in similar experiments, TNFR1 levels do not correlate with *in vitro* inhibition of T cell proliferation. It is therefore not clear that TNFR1 levels in remestemcel-L are related to lot-specific *in vitro* bioactivity.

Considering the available data, FDA's position is that while the CQAs identified by the Applicant and controlled in the product by *in vitro* lot release assays may have some value in assuring a consistent manufacturing process, these CQAs do not have a demonstrated relationship with clinical potency, and may therefore not by themselves ensure adequate control of clinical effectiveness of individual lots of product.

4. PRODUCT ATTRIBUTES AND CHALLENGES FOR QUALITY ASSURANCE FOR MSC-BASED PRODUCTS

In 2016, the International Society for Cellular Therapy (ISCT) published a perspective paper on immune functional assays for mesenchymal stromal cells as potency tests [3]. The paper described a consensus that human MSC-like cell products likely share fundamental mechanisms of action mediating their anti-inflammatory function and that identification of functional markers

that could be used as standardized, easily deployable methods for potency measurements would benefit the field. The paper describes a workshop in which participants identified three preferred analytic methods that could inform a matrix assay approach: quantitative RNA analysis of selected gene products; flow cytometry analysis of functionally relevant surface markers, and protein-based assays of the secretome.

The issue of reliable prediction of biological activity is particularly challenging for MSCs. Substantial functional heterogeneity has been observed between MSC batches derived from different donors and expanded using different tissue culture conditions or duration, even though all of these batches meet the ISCT criteria for MSCs. This suggests that quality attributes, especially those related to potency, need to be robustly informative to detect functional differences between MSC preparations and be applied rigorously so that batches meeting acceptance criteria for potency will be consistently clinically effective.

Although the quality attributes used by the Applicant are consistent with the cell surface markers widely used to identify MSCs [2], these attributes may not fully capture crucial biological heterogeneity in MSC DP lots. For example, during expansion in culture, MSCs can undergo measurable changes in functional attributes, including decreases in proliferation [4], decreases in colony-forming activity[4], decreases in adipogenic [4, 5] and osteogenic [6] activity, and decreases in immunosuppressive activity [7]. Despite these changes, however, MSCs with these decreased activities can continue to meet the ISCT criteria identifying MSCs. Additionally, these biological activities can vary between MSCs derived from different donors [4-7]. The process used to manufacture MSCs in these studies is similar to manufacturing used by the Applicant and other sponsors of MSC-based clinical trials.

While it is not established how the specific *in vitro* assays discussed above relate to the *in vivo* activity of remestemcel-L, it is possible that the quality attributes used by the Applicant and other sponsors of MSC-based clinical trials are not capable of detecting biological heterogeneity arising from variability related to allogeneic donor-specific differences and duration in culture. In turn, this undetected heterogeneity may also be related to the lack of correlation between the potency assay and clinical outcomes. A review of data from MSC-based clinical trials under FDA purview suggests this possibility [8]. The Applicant has proposed specifications for both potency and activity assays that are based solely on a minimum threshold value, which may further limit the ability of these assays to account for functional heterogeneity of remestemcel-L lots.

The first stage of the manufacturing process for remestemcel-L is the expansion of MSCs derived from a single allogeneic donor into an intermediate donor cell bank (DCB). Each DCB is then further expanded to create multiple lots of remestemcel-L DP (see Section 1.2 *Manufacturing Process* in the Applicant's briefing document). MSCs in culture cannot expand indefinitely and are reported to show a decrease in attributes related to MSC quality after extended expansion, therefore, new DCBs must be produced on a regular basis. Each DCB is tested using similar CQAs as those used for control of the DP and better characterization of DCB may also be beneficial in improving the quality and/or consistency of the DP. When new DCBs or other changes are introduced into the manufacturing process, however, the lack of CQAs related to clinical effectiveness limits the ability of the Applicant's analytical methods to

demonstrate that DP made after these changes maintains the same potency and quality as DP made before these changes.

As stated above, FDA's position is that the analytical methods used for product characterization of remestemcel-L do not have a demonstrated relationship with clinical outcomes. We ask the committee to consider the product attributes identified by the Applicant as CQAs and discuss whether they are adequate to ensure that the manufacturing process will produce lots of consistent quality. Additionally, given the limitations of the current CQAs, and the state of knowledge in the field of MSC, we ask that the committee discuss other product characteristics not previously identified as CQAs for remestemcel-L that might provide more meaningful measures of product quality and potency.

5. DRAFT POINTS FOR DISCUSSION BY THE ADVISORY COMMITTEE

(1) Product quality attributes measured for remestemcel-L are intended to ensure that key qualities of the DP are maintained consistently from lot to lot. Please discuss the adequacy of the potency assay established by the Applicant for remestemcel-L.

(2) In addition to discussion of potency, please discuss other possible product quality attributes or characteristics that could be controlled to better assure the continued quality of remestemcel-L with regard to safety or effectiveness of the product.

6. REFERENCES

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