

## **MEMORANDUM**

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**FDA / CBER / OTAT**

**BLA 125706 / 0**

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**Applicant** Mesoblast Inc.

**Product / Trade Name** Remestemcel-L-rknd  
RYONCIL

**Proposed Indication** Treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients

### **Background**

Mesoblast, Inc., submitted this Biologics License Application (BLA) for marketing approval of remestemcel-L for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients. The purpose of this memo is to provide my perspective on the clinical evidence of effectiveness and the Chemistry, Manufacturing, and Controls (CMC) issues, and my decision regarding the regulatory action (i.e., marketing approval vs. a complete response (CR)) for this BLA.

I appreciate the many thoughtful reviews and memos that contribute to the regulatory consideration of this BLA. This memo focuses on only the clinical, statistical, and CMC reviews. Therefore, this memo reflects my consideration of the reviews and memos provided by Drs. Baird and Przepiorka (clinical, Oncology Center of Excellence (OCE), 8/31/2020), George (clinical, OCE, 9/10/2020), Theoret (clinical, OCE, 9/12/2020), Lin (biostatistics, 8/25/2020), and Klinker, Bauer, Degheidy, Kitchel, Lessey-Morillon, and Nguyen (CMC, 9/22/2020), the proceedings of the Oncologic Drugs Advisory Committee (ODAC) Meeting on August 13, 2020, including the statements submitted to the docket for that meeting, the Office of Hematology and Oncology Products (OHOP) multidisciplinary review (5/24/2019) supporting the FDA marketing approval of ruxolitinib (Jakafi; Incyte Corporation; 2019), and discussions with the primary reviewers, their supervisors, and senior regulators in the OCE and the Center for Biologics Evaluation and Research (CBER).

SR-aGvHD is a life-threatening disease, with no FDA-approved treatment for patients under age 12. The clinical and statistical reviews and memos agree that the proposed primary evidence of effectiveness comes from a single, single-arm study (Study MSB-GVHD001) using an external control (comparator), that the product has a relatively benign safety profile, and that the product's mechanism of action is unclear. This conclusion regarding the product's mechanism of action is supported by the CMC review.

### **Perspectives on the Clinical, Statistical, and CMC Reviews and Memos**

Please see the review documents and memos for details of this BLA. My perspectives

on these reviews and memos include the following:

Clinical review (Baird / Przepiorka): This review concludes that the evidence of effectiveness from Study MSB-GVHD001 provides substantial evidence of effectiveness that is sufficiently compelling such that, in this life-threatening disorder, an additional clinical trial would not be ethical or feasible, such that this single study is sufficient to support marketing approval. The review points to the statistical significance of the primary efficacy analysis, the durable “response”, consistent results across subgroups, and the consistent results across secondary endpoints. I believe that these efficacy results may all be due to bias in subject selection, baseline grading of disease, and outcome assessment, in the treatment group, relative to the comparator.

The review supports traditional approval, and states that the primary endpoint is clinically meaningful, such that accelerated approval is not appropriate for this application.

Clinical Hematology Branch Chief memo (George): This memo concludes that the evidence of effectiveness is not sufficient to support BLA approval. The memo expresses a variety of concerns, including (but not limited to) the potential for bias in the assessment of a largely subjective grading of disease severity and outcome assessment, the unclear mechanism of action, the negative results from two randomized studies (Studies 265 and 280) of the product in the treatment of GvHD, and the selection of the comparator. I agree with all of these concerns.

Oncology Center of Excellence memo (Theoret): This memo generally agrees with the Baird / Przepiorka review. The memo concludes that the application provides substantial evidence of effectiveness and meets the statutory standards for accelerated approval under 21 CFR 601, subpart E. The memo also cites 21 CFR 312, Subpart E which emphasizes the importance of regulatory flexibility in serious and life-threatening diseases with no FDA-approved treatment options. The memo acknowledges that due to weaknesses in the trial design, the magnitude of remestemcel’s benefit is uncertain, but concludes that considering the relatively benign safety profile, the product is expected to have an overall favorable benefit-risk profile.

I believe that the uncertainty in the quantitation of the treatment effect is a reflection that Study MSB-GVHD001 is not a well-controlled trial (see further discussion below). In my view, the statutory requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) apply to all applications, including an application for the treatment of a life-threatening disease with an unmet need. I am not aware of anything in Subpart E, or in any other FDA regulation, guidance, or policy that supports that a study that is not well-controlled can provide the substantial evidence of effectiveness required by the FD&C Act.

Statistical review (Lin): This review concludes that, due to weaknesses in the design of Study MSB-GVHD001, the BLA does not provide sufficient evidence of effectiveness to support approval of the BLA. I generally agree with this review and its conclusion.

CMC review (Klinker / Bauer / Degheidy / Kitchel / Lessey-Morillon / Nguyen): There

are multiple CR issues associated with the absence of a reliable potency assay, as discussed by the ODAC. Additional clinical or product characterization data will be necessary to resolve the potency assay issues. I agree with the conclusions of this review.

### **Regulatory Requirements for Marketing Approval of a BLA**

To meet the requirements of the FD&C Act, marketing approval of a BLA requires substantial evidence of effectiveness “consisting of adequate and well-controlled investigations” (FD&C Act, Sec 505 (d)(6)(e)).

21 CFR 314.126 describes the characteristics of an adequate and well-controlled study: These characteristics include, but are not limited to, the following:

314.126 (b)(2): “The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.” ... (v) “Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include ...”

The difficulty in quantitating the drug effect of remestemcel is acknowledged in the reviews/memo from Drs. George and Theoret.

314.126 (b)(4): “The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as ... severity of disease ....”

The subjective grading of GvHD allows for biased enrollment, particularly for upgrading the severity at the time of enrollment. Possible motivations for such upgrading include the objective of enrolling subjects and completing the trial, the objective of obtaining access to remestemcel for desperate patients with a life-threatening disease (particularly since Mesoblast discontinued the Expanded Access study when Study MSB-GVHD001 was initiated), and the objective of obtaining a positive study efficacy result. Such upgrading need not be conscious / deliberate / intentional, and can represent biased enrollment, not fraudulent enrollment.

314.126 (b)(5): “Adequate measures are taken to minimize bias on the part of the ... observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.”

It is not clear that any measures, such as blinding, were taken to minimize bias of the observers of the data in Study MSB-GVHD001.

314.126 (b)(6): “The methods of assessment of subjects’ response are ... reliable.”

Outcome assessment in Study MSB-GVHD001 is subjective and highly

subject to bias in a single-arm, unblinded study, and therefore is not reliable.

21 CFR 314.126 (e): “Uncontrolled or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy.”

If there are adequate and well-controlled investigations, then FDA considers whether there is substantial evidence of effectiveness. In deciding whether there is substantial evidence of effectiveness, FDA generally considers all relevant information (i.e., the “totality of the evidence”), and considers the prevalence of the disease and the unmet need. If the FDA determines that there is substantial evidence of effectiveness, then the FDA considers whether that evidence supports traditional approval or accelerated approval, and whether the product’s benefits justify the risks in the proposed indicated population. This assessment of the balance of benefits and risks includes consideration of the unmet need. If there are no adequate and well-controlled investigations that provide evidence of effectiveness, then the BLA does not meet the statutory requirement for marketing approval.

Features of a single-arm study that allow for a rigorous assessment of treatment effect include, but are not limited to: Eligibility criteria that are objective and resistant to bias, to help ensure that the study subjects truly have the disease, and severity of disease, that are comparable to the comparator; a primary efficacy outcome that does not occur, or occurs very rarely, in the absence of intervention, and outcome measures that are objective and resistant to bias. For example, single-arm studies in oncology can 1) enroll subjects whose diagnosis and stage of disease can be confirmed by pathology specimens and reports, cell counts, and imaging studies and reports, 2) rely on efficacy outcomes such as response rates, which can be confirmed by pathology specimens and reports, cell counts, and imaging studies and reports, and 3) use efficacy outcomes that do not occur in the absence of intervention, such as complete responses, that can be rigorously confirmed, in patients with relapsed/refractory disease. Study MSB-GVHD001 lacks such features that help to control for bias. Therefore, the study results are highly subject to bias, and do not provide rigorous evidence of effectiveness.

The statutory requirement for substantial evidence, including adequate and well-controlled investigations, applies just as much to accelerated approval as to traditional approval. Thus, Study MSB-GVHD001 does not support either accelerated approval or traditional approval.

## **Summary**

The proposed evidence of effectiveness comes from a single, single-arm trial, with design elements that make the trial highly susceptible to bias, with uncertainty regarding magnitude of treatment effect, and post-hoc selection of the comparator. In addition, the product’s mechanism of action is unclear, and the development of this product includes multiple, failed, randomized trials, including trials in closely related indications, that suggest that this product is not active in the treatment of GvHD, or any other inflammatory disorder in which the product has been studied.

### **Advisory committee**

The objectives of FDA advisory committee (AC) meetings include obtaining advice and/or providing transparency regarding regulatory decisions. FDA appreciates the perspectives of the scientists, clinicians, and statisticians who serve on these committees and participate in these deliberations. Particularly, such meetings can be helpful in considering questions such as whether an outcome measure is clinically meaningful, whether an effect on a particular endpoint is reasonably likely to predict an effect on another endpoint, whether a treatment's benefits justify its risks, the design of confirmatory studies that might be necessary to support marketing approval, and the strengths and weaknesses of alternative statistical approaches to data analysis. In that context, I appreciate the ODAC 9-1 vote that the single-arm study provides evidence supporting the efficacy of remestemcel for the treatment of pediatric patients with SR-aGvHD.

However, AC members generally are not qualified by either training or experience to know, understand, or apply regulatory standards. Therefore, FDA did not ask this ODAC to consider what constitutes substantial evidence of effectiveness, or whether the single-arm study is adequate and well-controlled, for regulatory purposes. Only one member of the AC expressed substantial concern regarding the ability of the BLA to meet regulatory standards for marketing approval. However, the meeting's only substantial discussion of regulatory standards for evidence of effectiveness was provided in Scott M. Lassman's written submission to the docket, which includes a "Citizen's Petition" that argues against marketing approval of remestemcel. Such docket submissions may come from individuals with a conflict of interest with regard to the marketing application, and therefore may be a biased presentation of the issues. However, I generally agree with the concerns raised in that "Citizen's Petition" with regard to the failure of this BLA to meet regulatory standards.

During the AC discussion of CMC issues, AC members expressed concern regarding the potency assay. However, the AC did not provide any consensus conclusions or recommendations on how to resolve those potency assay issues.

### **Regulatory precedent**

Ruxolitinib received marketing approval in 2019 based partially on evidence from a single-arm study in GvHD. However, the regulatory considerations for the ruxolitinib BLA were very different than for the remestemcel BLA. For example, the OHOP clinical review of the ruxolitinib application considered that the product had demonstrated effectiveness in other diseases, myelofibrosis and polycythemia vera. The evidence of effectiveness in these other diseases included randomized trials using primary endpoints that were objective and resistant to bias (i.e., well-controlled studies). In addition, the OHOP approval of ruxolitinib considered that the mechanism of action of ruxolitinib was well established. This contrasts markedly with the remestemcel BLA, where previous randomized trials suggest that the product is not effective, the primary endpoint is subjective, and the mechanism of action is unclear. Thus, the evidence supporting the marketing approval of ruxolitinib was substantially different than the evidence proposed to support effectiveness in the remestemcel BLA, which relies on one single-arm study.

These differences in the regulatory considerations limit the value of the ruxolitinib BLA as a precedent for the remestemcel BLA.

## **Conclusion**

In multiple randomized investigations, including two failed studies in GvHD, this product has provided no evidence of efficacy for any indication. The design of Study MSB-GVHD001 appears to be an effort by Mesoblast to avoid conducting a randomized, well-controlled trial. Although the conduct of such trials can be challenging, several products (including remestemcel) have been studied in randomized trials in GvHD, including SR-aGvHD. Therefore, a randomized trial in GvHD is feasible.

The proposed evidence of effectiveness from Study MSB-GVHD001 is most likely a manifestation of multiple forms of bias facilitated by the single-arm trial design. In the absence of a well-controlled investigation, the evidence is not sufficient to determine that remestemcel is, or is not, effective for the treatment of SR-aGvHD. The difficulty in establishing the product's mechanism of action is most likely a reflection of its lack of activity. The relatively benign safety profile could be a reflection of the inactivity of this product. In summary, I doubt that this product has any clinically meaningful activity in SR-aGvHD or any other form of GvHD.

As regulators, the FDA mission includes facilitating the development of new products, particularly to address unmet medical needs. However, even when there is a life-threatening disease with no approved treatment, we must not ignore regulatory standards of evidence. Our obligation to patients is that the products that receive FDA approval must meet the requirements of the FD&C Act.

This BLA does not include an adequate and well-controlled investigation that provides evidence of effectiveness. Thus, this BLA does not meet the statutory requirement for marketing approval of remestemcel for the proposed indication.

In addition, the CMC issues regarding remestemcel's potency require that the applicant submit additional clinical or product characterization data to support marketing approval.

## **Regulatory Action**

Complete response letter that includes specific comments regarding 1) the need for evidence of effectiveness from at least one adequate and well-controlled investigation in adult and/or pediatric GvHD, to meet the statutory requirement for substantial evidence of effectiveness, 2) the need for a potency assay that meets CMC requirements, 3) in the absence of evidence of effectiveness, a discussion of labeling would be premature, and 4) the need for inspection of the manufacturing site in Singapore, per CBER Office of Compliance and Biologics Quality (OCBQ).