Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
August 13, 2020

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed biologics license application (BLA) 125706, for remestemcel-L (ex-vivo culture-expanded adult human mesenchymal stromal cells suspension for intravenous infusion), submitted by Mesoblast, Inc. The proposed indication (use) for this product is for the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. The morning session discussed issues related to the characterization and critical quality attributes of remestemcel-L as they relate to clinical effectiveness. The afternoon session discussed results from clinical trials included in BLA 125706.

These summary minutes for the August 13, 2020 meeting of Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration were approved on October 5, 2020.

I certify that I attended the August 13, 2020 meeting of the ODAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Yu, PharmD	Philip C. Hoffman, MD
Acting Designated Federal Officer, ODAC	Chairperson, ODAC

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
August 13, 2020

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 13, 2020. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Mesoblast, Inc. The meeting was called to order by Philip C. Hoffman, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Yu, PharmD (Acting Designated Federal Officer). There were approximately 1100 people online. There were a total of eight Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed biologics license application (BLA) 125706, for remestemcel-L (ex-vivo culture-expanded adult human mesenchymal stromal cells suspension for intravenous infusion), submitted by Mesoblast, Inc. The proposed indication (use) for this product is for the treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. The morning session discussed issues related to the characterization and critical quality attributes of remestemcel-L as they relate to clinical effectiveness. The afternoon session discussed results from clinical trials included in BLA 125706.

Attendance:
ODAC Members Present (Voting): Jorge A. Garcia, MD, FACP; Susan Halabi, PhD; Christian S. Hinrichs, MD; Philip C. Hoffman, MD (Chairperson); Anthony D. Sung, MD

ODAC Members Not Present (Voting): Jaffer A. Ajani, MD; Massimo Cristofanilli, MD, FACP; David E. Mitchell (Consumer Representative); Alberto S. Pappo, MD

ODAC Member Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Temporary Members (Voting): Nancy J. Bunin, MD (Afternoon Session Only); Sandra Finestone, PsyD (Acting Consumer Representative; Afternoon Session Only); Naynesh R. Kamani, MD (Afternoon Session Only); Sean J. Morrison, PhD (Morning Session Only); Diana L. Pearl (Patient Representative); Pamela G. Robey, PhD (Morning Session Only); Ilyas Singec, MD, PhD (Morning Session Only); Mark C. Walters, MD (Afternoon Session Only)

FDA Participants (Non-Voting): Richard Pazdur, MD (Afternoon Session Only); Wilson Bryan, MD; Marc R. Theoret, MD (Afternoon Session Only); Raj K. Puri, MD, PhD; Steven Oh, PhD (Morning Session Only); Steven R. Bauer, PhD; Bindu George, MD (Afternoon Session Only); Donna Przepiorka, MD, PhD (Afternoon Session Only); Kristin Baird, MD (Afternoon Session Only); Matthew Klinker, PhD; Stan Lin, PhD (Afternoon Session Only); Zhenzhen Xu, PhD (Afternoon Session Only)

Designated Federal Officer (Non-Voting): Joyce Yu, PharmD (Acting)

Open Public Hearing Speakers:
Morning Session: Arnold Caplan, PhD; Kameron Kooshesh; Jacques Galipeau, MD, FRCP(C)
Afternoon Session: Allyson Bradley; Mercedes Bazán; Ivan Harrison III; Meredith Cowden; Christina Wiedl, DO (Virginia Commonwealth University Medical Center)

The agenda was as follows:

Morning Session

Call to Order and Introduction of Committee	**Philip C. Hoffman, MD** Chairperson, ODAC
Conflict of Interest Statement	**Joyce Yu, PharmD** Acting Designated Federal Officer, ODAC
FDA Opening Remarks	**Wilson Bryan, MD** Director Office of Tissues and Advanced Therapies (OTAT) Center for Biologics Evaluation and Research (CBER), FDA
GUEST SPEAKER PRESENTATION	
Cell Manufacture for Therapeutic Application	**Sally Temple, PhD** Scientific Director Neural Stem Cell Institute Rensselaer, New York
APPLICANT PRESENTATIONS	**Mesoblast, Inc.**
Introduction to Remestemcel-L	**Geraldine Storton, BSc, MMS, MBA** Head of Regulatory Affairs & Quality Management Mesoblast, Inc.
Manufacturing Process	
Pathophysiology of Acute Graft-versus-Host Disease (aGVHD)	**Silviu Itescu, MD** Chief Executive Officer Mesoblast, Inc.
Mechanism of Action (MoA) of Remestemcel-L in aGVHD	
Potency Assay and Relationship to Clinical Outcomes	

FDA PRESENTATION	
Product Characterization	**Steven Bauer, PhD** Branch Chief Cellular and Tissue Therapy Branch (CTTB) Division of Cellular & Gene Therapies (DCGT) OTAT, CBER, FDA
Clarifying Questions to Presenters	
BREAK	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
LUNCH	

Afternoon Session

Call to Order and Introduction of Committee	**Philip C. Hoffman, MD** Chairperson, ODAC
Conflict of Interest Statement	**Joyce Yu, PharmD** Acting Designated Federal Officer, ODAC
FDA Opening Remarks	**Bindu George, MD** Branch Chief Clinical Hematology Branch (CHB) Division of Clinical Evaluation & Pharmacology/Toxicology (DCEPT) OTAT, CBER, FDA
APPLICANT PRESENTATIONS	**Mesoblast, Inc.**
Introduction to Remestemcel-L	**Geraldine Storton, BSc, MMS, MBA**
Unmet Need in Steroid-Refractory Acute Graft-versus-Host Disease (SR-aGVHD)	**Joanne Kurtzberg, MD** Director, Marcus Center for Cellular Cures Director, Pediatric Blood and Marrow Transplant Program Director, Carolinas Cord Blood Bank Duke University School of Medicine
Remestemcel-L Clinical Efficacy and Safety	**Fred Grossman, DO** Chief Medical Officer Mesoblast, Inc.
Clinical Perspective	**Joanne Kurtzberg, MD**
FDA PRESENTATION	

Clinical Evidence	**Kristin Baird, MD** Clinical Reviewer CHB, DCEPT, OTAT, CBER, FDA
Clarifying Questions to Presenters	
BREAK	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

Product Characterization Discussion – Morning Session

1. **DISCUSSION:** Product quality attributes measured for remestemcel-L are intended to ensure that key qualities of the drug product are maintained consistently from lot to lot.

   Please discuss the adequacy of the potency assay established by the Applicant for remestemcel-L.

   Committee Discussion: *One committee member noted that it was difficult to assess the adequacy of the potency assay due to the complex mechanism of action of remestemcel-L. Another member speculated if whether the existing data, while "imperfect," may be the best available. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** In addition to discussion of potency, please propose and discuss other possible product quality attributes or characteristics that could be controlled to better assure consistent quality of remestemcel-L with regard to safety or effectiveness of the product.

   Committee Discussion: *Overall, members commented that it was difficult to propose other product quality attributes due to the unclear and complex mechanism of remestemcel-L. One committee member suggested the addition of a transcriptomic profile to the product's certificate of analysis for each lot of cells to track product effectiveness and to address the issue of lot-to-lot variability. There was a broader discussion on the use of TNFR-1 expression as a potential quality attribute. Please see the transcript for details of the Committee's discussion.*

Clinical Discussion – Afternoon Session

1. **DISCUSSION:** Limitations of the single-arm study design of MSB-GVHD001 include, but are not necessarily limited to, the following: a) limited ability to ensure that baseline prognostic factors, both known and unknown, were similar in MSB-GVHD001 and the Applicant's control; b) limited ability to ensure that unknown and known potential confounding factors (e.g., additional salvage therapies for treatment of aGVHD) that could influence efficacy outcomes were similar in MSB-GVHD001 and the historical control group; c) potential bias with selection of patients, subjective nature of the assessments to score aGVHD d) the adequacy of the historical data to support a null hypothesis.

   Please discuss the strengths and weaknesses of the design of Study MSB-GVHD001.

   Committee Discussion: *Committee members generally agreed that the strengths of Study MSB-GVHD001 included potentially interesting biomarker data and a high overall response rate. In general, the weaknesses of the trial were noted to be the single-arm design and reliance on historical data. Members debated the feasibility of conducting a randomized controlled trial in pediatric patients with SR-aGVHD and commented a placebo-controlled trial would not be ethical. Additional comments acknowledged that while MSB-GVHD001 was not a randomized study, a high overall response rate in this population was compelling, as was the absence of immunosuppressive adverse events typically seen in the available treatments of aGVHD. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** As noted previously, primary endpoint results in Study MSB-GVHD001 were statistically significant; the measured response was durable (median 54 days). However, the results of Studies 265 and 280, the two randomized trials, did not provide evidence of a treatment effect for remestemcel-L in aGVHD, even when reanalyzed using the efficacy endpoint of Day-28 ORR. In fact, a treatment effect has not been identified in any of the previous clinical trials conducted in various disease entities, including: Type 1 diabetes mellitus, Crohn's Disease, myocardial infarction, or severe chronic obstructive pulmonary disease and the mechanism of action of remestemcel-L in mitigating aGVHD remains unclear.

   a) Please discuss whether the results of Studies 265 and 280 are relevant to the effectiveness of remestemcel-L for the treatment of pediatric SR-aGVHD. In your discussion, please consider not only the similarities and differences in the study populations, but also any other factors (e.g., number of years between studies; pathophysiology of adult aGVHD / SR-aGVHD vs. pediatric aGVHD / SR-GVHD) that you deem relevant.

   b) FDA may require an additional clinical trial to support the effectiveness of the remestemcel-L in pediatric SR-aGVHD. If so, what are your recommendations regarding the design of such a trial? For example, please discuss the population (e.g., aGVHD or SR-aGVHD; adult and/or pediatric), treatment assignment (randomized vs. single-arm), primary and secondary endpoints (e.g., Day-28 ORR, Day 100 survival, Day 180 survival, etc.), and any other aspects of the trial design.

Committee Discussion: *Some committee members noted that Studies 265 and 280 were relevant to the effectiveness of remestemcel-L, but considered factors such as changes in product manufacturing over time and differences in patient population to be significant. In general, members supported that Mesoblast conducts an additional clinical trial. Recommendations regarding such a trial included further testing of the product in adults and/or children with an adequate and well-controlled trial to confirm the efficacy signal. Additional recommendations for a future trial were longer follow-up, biomarker data, identify prognostic features and collection of patient-reported outcomes. Members also considered the length of steroid-free treatment and degree of steroid tapering to be important factors to highlight in future studies. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD?

Vote Result: **Yes: 8** **No: 2** **Abstain: 0**

Committee Discussion: *Majority of the committee members agreed that the available data supports the efficacy of remestemcel-L in SR-aGVHD. Committee members who voted "Yes", also recognized the challenges in feasibility of an additional randomized trial. One member considered the high response rate to be significant in such a disease with poor prognosis. It was further noted that currently available options used in SR-aGVHD have poorer outcomes. The committee member who voted "No", commented that a single-arm trial may not be sufficient to demonstrate efficacy and that further trials are needed. Please note that one member who voted "No", changed their vote due to the compelling medical information provided and nature of the unmet need in this condition. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:18 p.m.