FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
August 13, 2020 (**PM Session**)

QUESTIONS

BLA 125706

Remestemcel-L

Applicant: Mesoblast, Inc.

PROPOSED INDICATION: Treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients.

Clinical Discussion

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.

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.

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