FDA Briefing Document

Oncologic Drugs Advisory Committee (ODAC) Meeting

Session on Clinical Evidence (PM 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 effectiveness and safety 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 is intended instead to focus on issues identified by the FDA for discussion by the advisory committee. 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

AE	Adverse event
AESI	Adverse event of special interest
aGVHD	Acute graft-versus-host-disease
ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
BLA	Biologics License Application
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CML	Chronic myelogenous leukemia
COPD	Chronic obstructive pulmonary disease
DOR	Duration of response
EAP	Expanded Access Protocol
EFS	Event-free survival
FAS	Full analysis set
FD&C Act	Food Drug and Cosmetics Act
FDA	Food and Drug Administration
HR	High risk
HSCT	Hematopoietic stem cell transplantation
ITT	Intent-to-treat
kg	Kilogram
MAGIC	Mt. Sinai Acute GVHD International Consortium
Max	Maximum
MDS	Myelodysplastic syndrome
Mg	Milligrams
MI	Myocardial infarction
mITT	Modified intent-to-treat
Min	Minimum
MSC	Mesenchymal stem cell
N	Number
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival

PBMTC	Pediatric Blood and Marrow Transplant Consortium
PBSC	Peripheral blood stem cell
PR	Partial response
PTLD	Post-transplant lymphoproliferative Disease
RCT	Randomized Controlled Trial
Rem-L	Remestemcel-L
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
SR	Steroid refractory
T1DM	Type 1 diabetes mellitus
TEAE	Treatment-emergent adverse event
TP	Treated population
TR	Treatment resistant

1. INTRODUCTION

1.1 Proposed Indication

The Applicant is seeking approval of remestemcel-L for the indication: Treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients.

1.2 Purpose of the Meeting

The purpose of this Advisory Committee meeting is to discuss a) the adequacy of the design of Protocol MSB-GVHD001 and b) whether the totality of evidence supports a conclusion that remestemcel-L is effective for treatment of SR-aGVHD in pediatric patients.

The Applicant submitted the results of Protocol MSB-GVHD001[1] to support their marketing application. Protocol MSB-GVHD001 was a prospective, multicenter, single-arm trial of remestemcel-L for treatment of pediatric patients with SR-aGVHD grades B-D (excluding grade B skin alone). The primary endpoint of the trial was the proportion of patients in the full analysis set (FAS) with overall response (defined as complete response (CR) + partial response (PR)) at 28 days after initiation of therapy. The protocol was designed to determine if the Day-28 overall response rate (ORR) exceeded 45%. The study hypothesis and the null ORR were prespecified in the statistical analysis plan (SAP); however, the justification provided for the null rate in the Statistical Analysis Plan (SAP) was that it was 20 percentage points lower than that achieved with remestemcel-L in post hoc analyses of the pediatric subgroups in other protocols of remestemcel-L for treatment of aGVHD.

To further establish the appropriateness of 45% as the null Day-28 ORR, the Applicant also provided post hoc analyses of ORR in patients with SR-aGVHD treated with standard care therapies in the pediatric subgroup in the control arm of Protocol 280, pediatric patients with SR-aGVHD in the Mount Sinai Acute GVHD International Consortium (MAGIC) database, and patients with newly-diagnosed aGVHD who failed treatment with steroids but continued on steroids alone in Protocol 265. Additional evidence was obtained from the published literature. FDA seeks input from the committee regarding the persuasiveness of these data as historical controls to establish the null hypothesis for the purposes of quantitating a treatment effect in a single-arm trial of a new therapy for SR-aGVHD in pediatric patients. Furthermore, FDA seeks

[1] Protocol MSB-GVHD001 is the main treatment trial; follow-up on this protocol is through Study Day 100. Protocol MSB-GVHD002 provides for additional follow-up of patients from Protocol MSB-GVHD001 through 180 days from the start of Protocol MSB-GVHD001. In this document, FDA's analyses use data pooled from Protocol MSB-GVHD001 and MSB-GVHD002; the results of these analyses are reported under Protocol MSB-GVHD001.

input regarding the suitability of the single-arm design of Study MSB-GVHD001 in the context of minimizing bias given the following: the subjective nature of aGVHD grading, comparability between the known and unknown prognostic factors between this study and the historical controls and the influence of confounding factors such as preparative regimen or supportive care measures on efficacy outcomes.[2]

In Protocol MSB-GVHD001, the Day-28 ORR in the FAS was 69.1% (95% CI: 55.2, 80.9); the protocol met the primary objective to exclude a 45% ORR. The Applicant provided as supporting information the Day-28 ORR (65.1%; 95% CI: 58.8, 71.1) in 241 pediatric patients with SR-aGVHD treated with standard salvage therapy plus remestemcel-L in Protocol 275 (an expanded access protocol) and the Day-28 ORR (64.3%; 95% CI: 35.1,87.2) in 14 patients treated with standard salvage therapy plus remestemcel-L in a subgroup analysis of the investigational arm of Protocol 280 (a randomized trial). It is noted that in Protocols 275 and 280, patients were treated with combination therapy rather than remestemcel-L alone.

Lastly, the Applicant provided the results of two randomized, double-blind, placebo-controlled trials of remestemcel-L for treatment of aGVHD. Protocol 280 was a comparison of standard salvage regimens with or without remestemcel-L for treatment of SR-aGVHD; and Protocol 265 was a comparison of standard steroids with or without remestemcel-L for treatment of newly-diagnosed aGVHD. Both protocols failed to meet their primary objective to demonstrate an improvement in the rate of CR $\geq$ 28 days duration, and no treatment effect was detected even when these protocols were reanalyzed using Day-28 ORR.

Therefore, FDA seeks input from the committee on whether the results of Protocol MSB-GVHD001, the one statistically-positive single-arm trial, in a landscape of the multiple negative clinical trials for the treatment of aGVHD, including randomized controlled trials, is adequate to allow one to conclude that remestemcel-L is effective in the treatment of SR-aGVHD in pediatric patients.

[2] Center for International Blood and Marrow Transplant Research. Acute Graft-versus-Host Disease (GVHD) Workshop. Available at https://www.cibmtr.org/Meetings/Materials/GVHDworkshop/Pages/index.aspx. Accessed July 1, 2020.

2. REGULATORY BACKGROUND

2.1 Treatments of SR-aGVHD

The proposed regulatory pathways for approval of drugs for treatment or prevention of aGVHD and the supporting evidence for establishment of those pathways was discussed at the open public workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation held May 19, 2009. The conclusion of this workshop was that response at Day 28 were a valid marker for trials that were designed to assess the efficacy outcomes for treatment of aGVHD trials.[2,3]

At the present time, ruxolitinib is the only product FDA approved for the treatment of SR-aGVHD. The approval of ruxolitinib in May 2019 was based on Study INCB18424-271 (REACH-1; NCT02953678), an open-label, single-arm, multicenter trial that included 49 patients with grades 2-4 SR-aGVHD treated with ruxolitinib monotherapy. The primary endpoint of the study was Day-28 ORR. The statistical analysis plan indicated that a positive result is concluded if the lower limit of the 95% CI of the ORR was above the prespecified threshold of 40%.[5] The Day-28 ORR was 57.1% (95% CI: 42.2–71.2), the median duration of response was 0.5 months (95% CI: 0.3–2.7), and the median time from Day-28 response to either death or need for new therapy for acute GVHD was 5.7 months (95% CI: 2.2 to not estimable).

FDA frequently requires a randomized trial to support traditional approval. FDA has considered single-arm trials to support a marketing approval in instances where there are no available therapies that would be considered standard of care, where the effect of response is presumed to be attributable to the investigational product.[4] FDA concluded for ruxolitinib that since the disease is life-threatening, there were no approved therapies, there was no optimal therapy of aGVHD identified, the efficacy endpoint was objective, the activity of the drug was established in other diseases that shared similar pathophysiology as with aGVHD, and there was a substantial safety database, a single-arm trial as the sole basis of efficacy would be acceptable. Further, the Day-28 ORR of 57.1% with a lower 95% CI bound excluding 40% with durability was considered clinically meaningful for patients with SR-aGVHD.[5] Lastly, due to the fact that the lowest available strength of ruxolitinib precluded safe treatment in infants and children, the indication was limited to patients 12 years and older.[5]

[3] Pavletic SZ. (2012) Response as an endpoint in treatment trials for acute GVHD. Bone Marrow Transplant 47:161.
[4] FDA Guidance for Industry Clinical Trials Endpoints for Approval of Cancer Drugs and Biologics.
[5] Przepiorka D, Luo L, et al. (2019) FDA Approval summary: Ruxolitinib for treatment of steroid-refractory acute graft-versus-host disease. Oncologist 24:1-7

There are no drugs approved for treatment of SR-aGVHD in patients less than 12 years old. There are 14 drugs listed in the National Comprehensive Cancer Network (NCCN) guidelines as "suggested" systemic agents for treatment of SR-aGVHD.[6] All are stated to have only Category 2A evidence. There was not sufficient data to recommend use of one agent over others.[7,8] Ruxolitinib is the only drug reported to demonstrate an improvement over other therapies for Day-28 ORR in a randomized trial (REACH-2) in the modern era.[9]

2.2 Remestemcel-L: Drug Development History

The Applicant provided safety and efficacy information from 14 prospective clinical trials of remestemcel-L for treatment of aGVHD, acute myocardial infarction, chronic obstructive pulmonary disease, diabetes mellitus or Crohn's disease conducted over more than 20 years (Appendix 1). Remestemcel-L is not approved in the US for any indication.

Clinical studies of remestemcel-L for treatment of aGVHD were conducted under IND 007939, received in 1998. Table 1 lists the Applicant's prospective studies for treatment of aGVHD.

Table 1: Prospective Studies of Remestemcel-L for Treatment of aGVHD

Study	Study Design	Population	Number Planned	Number Enrolled	Treatment	Primary Endpoint
MSB-GVHD001[a]	Single-arm study	Children with SR-aGVHD grade B-D	48	55	Remestemcel-L	Day-28 ORR
280	Randomized double-blind placebo-controlled	Patients with SR-aGVHD grade B-D	240	260	Arm A: SOC + placebo Arm B: SOC + remestemcel-L	CR lasting >= 28 days
275	Expanded Access	Children with SR-aGVHD grade B-D	-	242	SOC + remestemcel-L	NA
276	Expanded Access	Adults with SR-aGVHD grade C-D	-	19	SOC + Remestemcel-L	NA

[6] Hematopoietic cell transplantation (HCT): Pre-transplant recipient evaluation and management of graft-versus-host disease (Version 2.2020). Accessed at https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf on July 1, 2020.
[7] Martin PJ, Rizzo JD, et al. (2012) First- and second-line systemic treatment of acute graft-versus-host disease: Recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 18: 1150-1163.
[8] Martin PJ. (2020) How I treat steroid-refractory acute graft-versus-host disease. Blood 135:1630-1638.
[9] Zeiser R, von Bubnoff N, et al. (2020) Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 382:1800-1810.

Table 1: Prospective Studies of Remestemcel-L for Treatment of aGVHD

Study	Study Design	Population	Number Planned	Number Enrolled	Treatment	Primary Endpoint
265	Randomized, double-blind, placebo-controlled	Adults with new aGVHD grade B-D	184	193	Arm A: Steroids + placebo Arm B: Steroids + remestemcel-L	CR lasting >= 28 days
260	Randomized dose-finding study	Adults with new aGVHD grade 2 - 4	50	33	Steroids + remestemcel-L	CR or PR by Day 28
270/270E	Single-arm study	Patients with TR-aGVHD grade 3 - 4	30	16	SOC + remestemcel-L	CR or PR by Day 28

Source: FDA analysis
[a] See Footnote 1 regarding pooling of follow-up data from Protocol MSB-GVHD002.
Abbreviations: aGVHD, acute graft-versus-host disease; CR, complete response; ORR, overall response rate; NA, not applicable; PR, partial response; SOC, standard care salvage treatment; SR, steroid-refractory

Accruals for Protocol 265, a Phase 3 trial for treatment of newly-diagnosed aGVHD, and Protocol 280, a Phase 3 trial for treatment of SR-aGVHD, were completed in January 2008 and May 2009, respectively. The first module of a marketing application was submitted to BLA 125334 on 1/20/2009. Due to the fact that Protocol 265 and Protocol 280 did not have a positive outcome, FDA recommended that additional prospective trials be conducted. The BLA was withdrawn on 3/5/2010.

Since 2009, FDA provided the Applicant with advice on the clinical development program for treatment of aGVHD in six meetings. Key points emphasized by FDA included:

- A single-arm trial that is designed to provide a quantitative evaluation of outcomes in the face of heterogeneity in the patient population may fulfill the regulatory requirements as noted in 21 CFR 314.126. Case-control studies or modeling from historical controls are two potential methods to achieve this when the eligible population is exceedingly small. Such a study would need to be designed and reviewed prior to its conduct.

- Protocol 275 is not an adequate and well-controlled trial and does not provide confirmatory evidence of efficacy to support a license application.

- Protocol 280 is a negative trial, so subgroup analyses would not be sufficient to support a marketing application.

- The results of Protocol 275 and 280 may inform a hypothesis for design of a prospective trial. The sponsor should consider conducting a randomized clinical trial to provide confirmatory evidence of the efficacy of the study agent in the treatment of GVHD.

- FDA recommended a new randomized trial of remestemcel-L versus standard of care for treatment of steroid-refractory acute GvHD, indicating that such a study would likely be feasible in the adult population. A randomized, controlled study in the adult population could potentially also confirm clinical benefit in the pediatric population, depending on the results.

- MSB-GVHD001, a single-arm trial in pediatric patients permits use of other agents, such as those used in prophylaxis, that may affect efficacy outcomes. This confounds the interpretation of the treatment effect of remestemcel-L. In the absence of an appropriate concurrent or historical control, the treatment effect of remestemcel-L will be difficult to discern.

- The null hypothesis for MSB-GVHD001 is not based on data from a historical control population. In the absence of data from appropriate historical controls, FDA is unable to agree that the proposed null hypothesis is acceptable.

- Given the absence of appropriate concurrent or historical controls, MSB-GVHD001 does not appear to be an adequate and well-controlled study. Thus, the trial as designed may not be sufficient to provide primary evidence of effectiveness to support a marketing application.

- Any claim of efficacy based on MSB-GVHD001 needs to take into account all studies of remestemcel-L for treatment of aGVHD, including the failed trials.

On 1/31/2020, the Applicant submitted BLA 125706 for remestemcel-L for treatment of SR-aGVHD in pediatric patients with the results of Protocol MSB-GVHD001 as the sole basis of efficacy.

3. PROTOCOL MSB-GVHD001: STUDY DESIGN ISSUES

3.1 Background

To obtain marketing approval, the Food Drug and Cosmetics Act (FD&C Act) requires that sponsors provide substantial evidence of safety and efficacy of their products based on the conduct of adequate and well-controlled studies.

An externally-controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal control group consisting of patients from the same population assigned to a different treatment. The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting. The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of this latter comparator is particularly problematic (such trials are usually considered uncontrolled) because general impressions are so often inaccurate.[10]

The International Conference on Harmonisation (ICH) E10 guidance describes the expectations when choosing an external control for a clinical trial. It is always difficult, and in many cases impossible, to establish comparability of the treatment and control groups and thus to fulfill the major purpose of a control group. The groups can be dissimilar with respect to a wide range of factors other than use of the study treatment that could affect outcome, including demographic characteristics, diagnostic criteria, stage or severity of disease, concomitant treatments, and observational conditions (such as methods of assessing outcome). Such dissimilarities can include important but unrecognized prognostic factors that have not been measured. As such, externally-controlled trials can be subject to bias and may overestimate efficacy of test therapies. Tests of statistical significance carried out in such studies may be less reliable than in randomized trials.

The key objective of FDA's review of Protocol MSB-GVHD001 was to determine if the trial provides substantial evidence of effectiveness for the proposed indication. The discussion herein focuses on specific aspects of the trial design.

3.2 FDA's Findings

Protocol MSB-GVHD001 was a prospective, multicenter, single-arm trial of remestemcel-L for treatment of pediatric patients with SR-aGVHD with 100 days of follow-up. Protocol MSB-GVHD002 provided for safety follow-up through 180 days from start of treatment with remestemcel-L. A detailed description of the protocols is provided in Section 5.3 of the Applicant's Briefing Document. FDA confirmed that the eligibility criteria adequately describe patients with SR-aGVHD and that the patients accrued (see Tables 30-32 in the Applicant's Briefing Document) were consistent with this description.

[10] FDA Guidance for Industry E10 Choice of Control Group and Related Issues in Clinical Trials https://www.fda.gov/media/71349/download

The primary endpoint of the trial was the proportion of patients in the full analysis set (FAS) with ORR (defined as CR + PR) at 28 days after initiation of therapy. The response criteria are described in Table 23 of the Applicant's Briefing Document. The definition of duration of response (DOR), however, is not included in the consensus response criteria, and the method used by the Applicant did not follow the advice provided by FDA; this is discussed further in Section 3.2.2 below.

With regard to the study design parameters, according to the statistical analysis plan (SAP Section 7), the stated null and alternative hypotheses for MSB-GVHD001 were Ho: $p = 0.45$ vs. Ha: $p \neq 0.45$. The SAP further stated that "p=0.65 was chosen as the alternative hypothesis," which FDA inferred to mean that for sample size calculation the study would have the stated Type I and Type II error to exclude a 45% response rate if the true rate was 65%. Although FDA agreed that an effect size of 20% might be clinically meaningful, additional justification for the null rate of 45% was requested. To this end, ***the Applicant provided the following:***

- (MSB-GVHD001 SAP Section 7) Based on the results of Protocols 275 and 280 using SOC + remestemcel-L for treatment of patients with SR-aGVHD, the expected ORR in this population using remestemcel-L alone would be 65%. Per the Applicant, since a 20% effect size is clinically meaningful, the null is set at 45% (calculated from 65% minus 20%).

- (Summary of Clinical Efficacy Section 2.7.3.1.6.6.1) In the SOC + placebo arm of Protocol 280, the ORR was 74% for patients with "standard risk" SR-aGVHD and 37% for those with "high-risk" SR-aGVHD. Assuming accrual of "standard risk" to "high risk" patients at 3:1 in MSB-GVHD001, the risk-adjusted null rate would be 46% for a study of 60 patients.

- (Response to Information Request received 4/23/2020) In the steroids + placebo arm of Protocol 265, there were 33 patients identified as not responding to steroids by Day 7 who continued on study. Of these 33 patients, 14 (42%; 95% CI: 26% – 61%) achieved CR or PR at the Day 35 assessment (28 days later).

A key consideration in the selection of an external or historical control as the basis of a trial design is the assurance that the controls are similar to the study patients with regard to baseline characteristics important to the efficacy outcomes being assessed and concurrent treatments.[8] As Protocol 265 and 280 accrued largely adults, the information outlined above was not considered adequate justification for the null rate in the pediatric population. ***FDA, however, also took into account the following about pediatric patients in particular***:

- (Protocol 280 Pediatric Subpopulation Clinical Study Report Table 11.5) In the SOC + placebo arm of Protocol 280, the Day-28 ORR was 36% (95% CI: 12.8, 64.9) for the 14 pediatric patients accrued. The patients were not stratified by age at enrollment.

- (Summary of Clinical Efficacy Table 44) In the Mount Sinai Acute GVHD International Consortium (MAGIC) database, there were 30 pediatric patients transplanted 2005 - 2019 who received a salvage therapy for grades B-D SR-aGVHD (excluding grade B skin alone as in MSB-GVHD001). For these 30 pediatric patients, the Day-28 ORR after first salvage therapy was 43% (95% CI: 25%-63%). The Day-28 ORR for the pediatric patients was slightly higher than that for the 95 adult patients with grades B-D SR-aGVHD (35%; 95% CI 25%-45%).

- (Rashidi et al 2019)[11] In a retrospective analysis of Day-28 ORR for second-line therapy for SR-aGVHD, the Day-28 ORR was 34% (95% CI: 23% - 48%) for the 61 pediatric patients. In this study, the pediatric subgroup had the lowest Day-28 ORR (34% for patients < 18 years; 36% for patients 18-40 years, and 43% for patients > 40 years).

- A prospective study evaluating the use of etanercept in 25 children with grade II-IV SR-aGVHD (using the modified Glucksberg criteria[12]) which observed an ORR of 68% (17/25) at Day 7. The study stopped accrual prematurely when the null hypothesis of 40% was excluded.[13]

- A retrospective analysis from the Pediatric Blood and Marrow Transplant Consortium (PBMTC) evaluated the efficacy and safety of infliximab 10 mg/kg i.v. once a week for a median of eight doses (range 1-162) in 24 children with steroid-resistant GVHD. The overall response rate, defined as the maximal response with 56 days of starting treatment was 82% (12 CR+6 PR), was reported in 22 evaluable children.[14]

- In a single-center, prospective study of alemtuzumab as a second-line agent for SR aGVHD in pediatric and young adults. Alemtuzumab was administered for grades II to

[11] Rashidi A, DeFor TE, et al (2019) Outcomes and predictors of response in steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 25:2297-2302.
[12] Przepiorka, D. Weisdorf D, Martin P, et al. (1995) 1994 consensus conference on AGVHD grading Bone Marrow Transplant, 15:825-828
[13] Faraci M, Calevo MG, et al. (2019) Etanercept as treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. Biol Blood Marrow Transplant;25(4):743-748.
[14] Sleight, B., Chan, K., et al. (2007) Infliximab for GVHD therapy in children. Bone Marrow Transplant 40, 473–480.

IV aGVHD[9] if patients did not improve within 5 days or worsened within 48 hours after corticosteroids. The ORR was 67% at 4 weeks, with complete response (CR) in 40%, partial response (PR) in 27%, and no response in 33%.[15]

Extrapolating historic data for Day 28 ORR in pediatric patients with SR-aGVHD is challenging. Often, pediatric patients are incorporated into adult studies, but with limited representation[6,16]. Of the limited publications evaluating aGVHD treatment in this patient population, most provide inadequate data due to various design flaws such as: limited numbers of patients, case-series reports, varied primary endpoint measures, single-institution enrollment, various grading scales employed, diverging definitions of steroid refractoriness, retrospective analyses, etc. The ORRs observed in the small studies[11,12,13] ranged from 67-82%, although there were limitations in these small studies in that they employed different primary endpoints, different definitions of steroid refractoriness, and different aGVHD assessment timepoints and grading scales.

3.3 Summary

Day-28 ORR with durability has been used as a measure of benefit for treatments of aGVHD. Protocol MSB-GVHD001 was a single-arm trial designed to determine if the Day-28 ORR exceeded 45% for pediatric patients with SR-aGVHD grades B-D treated with remestemcel-L. Although the null rate and hypothesis were prespecified in the SAP, there was some limitations with regard to how 45% was chosen for the null rate, and it is uncertain as to whether the data cited for use as historical controls are sufficient to establish the null hypothesis for the purposes of quantitating a treatment effect in a single-arm trial of a new therapy for SR-aGVHD in pediatric patients.

4. PROTOCOL MSB-GVHD001: EFFICACY RESULTS ISSUES

4.1 Background

For a single trial to be used as the basis for marketing approval, it must be well-designed, well-conducted and provide statistically-persuasive efficacy findings that are robust and so compelling as to make a second trial unethical or practically impossible to perform.

[15] Khandelwal P, Emoto C, et al. A prospective study of alemtuzumab as a second-line agent for steroid-refractory acute graft-versus-host disease in pediatric and young adult allogeneic hematopoietic stem cell transplantation. (2016) Biol Blood Marrow Transplant 22:2220-2225.

[16] Gatza E., Reddy P., et al., (2020) Prevention and treatment of acute graft-versus-host disease in children, adolescents, and young adults. Biol Blood Marrow Transplant 00: 1-12

A substantial issue regarding this Biologics License Application is how to consider the positive outcome of the current single-arm clinical trial, MSB-GVHD001 in the setting of the historical data to serve as an external control in the choice of a null hypothesis, the limitations with minimizing bias, impact of confounding factors and a clinical development program for remestemcel which includes two randomized Phase 3 clinical trials for the treatment of aGVHD, Protocol 265 and Protocol 280, which failed to meet their primary efficacy objectives. For completeness, the Applicant also submitted results for Protocol 275, a single-arm expanded access protocol for treatment of pediatric patients with SR-aGVHD.

For this discussion, FDA focused on the outcome of Day-28 ORR as a measure of efficacy. Because of differences in the study populations and treatments (discussed in Section 4.3 below), the results for each protocol are presented side-by-side rather than pooled.

4.2 FDA's Review of Protocol MSB-GVHD001 Efficacy Outcomes

4.2.1 Day-28 Overall Response (ORR)

Between 2015 and 2017, 55 pediatric patients were enrolled on Protocol MSB-GVHD001 in the United States. These 55 patients comprise the full analysis set (FAS) that was used for the primary analysis of Day-28 ORR, the primary endpoint. Table 2 presents the analyses of the primary efficacy endpoint. FDA confirmed the Applicant's finding of 16 patients with CR and 22 patients with PR at the Day-28 assessment for a total of 38 responders. The ORR was 69.1% with a 95% CI of 55.2 - 80.9. Under the assumption of a 45% ORR for the null hypothesis, this study met its primary objective.

Table 2: MSB-GVHD001 - Primary Endpoint Analysis (Day-28 ORR)

Analysis Set	N	Day-28 CR n, %	Day-28 PR n, %	Day-28 ORR n, %	Day-28 ORR 95% CI
Full Analysis Set	55	16 29.1%	22 40.0%	38 69.1%	(55.2, 80.9)
Treated Set	54	16 29.6%	22 40.7%	38 70.4%	(56.3, 82.0)
Sensitivity Set 1	45	15 33.3%	19 42.2%	34 75.6%	(60.5, 87.1)
Sensitivity Set 2	55	15 27.3%	19 34.5%	34 61.8%	(47.8, 74.6)

Source: FDA analysis
Abbreviations: CI, confidence interval; CR, complete response; ORR overall response rate; PR, partial response

FDA conducted three additional analyses of Day-28 ORR. The first was performed in only the 54 patients who were treated (one patient withdrew within one day of consent due to worsening condition). In the Treated Set, Day-28 ORR was 70.4%. Additionally, FDA performed two sensitivity analyses excluding nine subjects who had confounders for determination of ORR at

Day 28 (Sensitivity Set). These analyses excluded the one patient who withdrew, six subjects who received concomitant medications[17] that could potentially impact the Day 28 primary endpoint analysis and four subjects who did have active aGVHD but with aGVHD symptoms that improved by one grade in the interval between the determination of steroid refractoriness and baseline aGVHD evaluation. One subject was excluded for both reasons; therefore, the total number excluded in the sensitivity analysis was 10 subjects. In the Sensitivity Set 1, these subjects were removed from the analysis and the Day-28 ORR was 75.6%. In the second sensitivity analysis, Sensitivity Set 2, the subjects excluded in Sensitivity Set 1 were analyzed as treatment failures, resulting in an ORR of 61.2%.

FDA also acknowledges the additional analyses of the primary endpoint performed by the Applicant as described in Tables 33-36 of the Applicant's Briefing Document.

The Applicant also provided comparative analyses to support the Day-28 ORR results from MSB-GVHD001.

- In the first comparative analysis (Integrated Summary of Efficacy Section 3.3), the Applicant compared Day-28 ORR for the Treated Set in MDS-GVHD001 vs 77 patients from the SOC + placebo arm of Protocol 280 (excluding patients with grade B skin only disease). Since the demographic characteristics and baseline disease parameters differed substantially between the two populations (discussed in Section 4.3), the validity of this analysis is unclear.

- In the second comparative analysis (Summary of Clinical Efficacy Section 2.7.3.3.1; Table 40 in the Applicant's Briefing Document), the Applicant compared Day-28 ORR for the Treated Set in MBS-GVHD001 vs a cohort from the MAGIC database that included 30 pediatric patients treated for SR-aGVHD grades B-D (excluding patients with grade B skin-only disease). Although FDA is open to use of Real-World Evidence[18] for support of marketing applications, FDA has concerns regarding the MAGIC database comparison as reported by the Applicant for the following reasons:
  - The MAGIC cohort comparison was not part of the original statistical analysis plan (SAP) for Protocol MBS-GVHD001 and there was no a priori specified hypothesis.
  - The SAP for this post hoc analysis was not submitted for FDA review.

[17] Concomitant medications prior to day 28 include: eculizumab (n = 1) for hemolytic uremic syndrome; rituximab (n = 3) 2 for EBV viremia/infection, and 1 for GVHD prophylaxis; and basiliximab (n = 2) for GVHD prophylaxis.
18 Real-World Evidence. Available at https://www fda.gov/science-research/science-and-research-special-topics/real-world-evidence. Accessed 01 July 2020.

- Post-hoc "between group" comparisons are difficult to interpret, because statistical comparison between a single-arm study and historical data confounds the treatment effect estimation and hypothesis testing with "between-study" effects. Additionally, there was no matching performed or other methods to reduce differences between the groups.
- The raw data were not submitted for review.

Lastly, FDA confirmed the Applicant's subpopulation analysis of Day-28 ORR (Appendix 2). The only result of note was the Day-28 ORR by type of stem cell source; subjects receiving peripheral blood stem cell (PBSC) grafts had a lower ORR (43%) than those receiving bone marrow or cord blood grafts (80% and 73%, respectively). However, the small numbers in each subgroup do not allow for firm conclusions from these differences.

4.2.2 Duration of Response

For the assessment of the clinical meaningfulness of a response outcome in a single-arm trial, the duration of response (DOR) is an important consideration; hence, some degree of precision in measurement of DOR is desirable. FDA identified two issues with the analysis of DOR as provided by the Applicant.

First, GVHD assessment was provided weekly through Study Day 100 on MSB-GVHD001, and then only on Study Days 120, 140, 160 and 180 and for only the subset of patients who agreed to participate in MSB-GVHD002. Hence the data may not be complete. Information through Study Day 100 is likely reliable, but this would limit the expected timeframe over which durability of the response could be evaluated.

Second, the computed DOR will depend on the definition used, especially when there is substantial missing data. FDA has published the definitions of DOR in use for regulatory applications.[5] Table 3 shows the approach to computing DOR used by the Applicant and the definition that has been accepted by FDA.

Table 3: Computation of DOR

Applicant-defined DOR[a]	The number of weeks that the response at Day 28 was maintained. • If the response at the weekly assessment is the same or better than the Day 28 response, then the subject will be deemed to have maintained response ("Response_maintain"=1). If the response deteriorates for two successive assessments, then the Day 28 response then "Response_maintain"=0. • A "same or better response than at Day 28" is either maintenance of the organ staging across all organs or improvement in some organ staging and maintenance in all others with respect to the organ staging at Day 28. • The length of the run of the value of "1" in the variable "Response_maintain" beginning from Day 35 till Day 100 will be defined as the duration of response.
FDA-defined DOR[b]	The interval from the Day-28 response to progression, new systemic therapy for acute GVHD or death from any cause. • Progression is defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment (i.e., progression from nadir). • New therapy is defined as a new systemic treatment for aGVHD or an increase in the dose of corticosteroids to methylprednisolone 2 mg/kg (+/- 10%) equivalent.
FDA-defined alternative measure of durability[b]	The interval calculated from Day-28 response to either death or need for new therapy for acute GVHD.

[a] MSB-GVHD001 Statistical Analysis Plan version 5.0
[b] Przepiorka D, Luo L, et al. (2019) FDA Approval summary: Ruxolitinib for treatment of steroid-refractory acute graft-versus-host disease. Oncologist 24:1-7.

FDA's and the Applicant's definitions differ with regard to whether progression is called on the basis of one assessment or on the basis of two consecutive assessments, and whether progression is called in comparison to the Day-28 response or in comparison to the nadir response at Day 28 or later.

There were also differences in how flare therapy was handled in calculating DOR. In Protocol MSB-GVHD001, patients with a CR were eligible for additional doses of remestemcel-L for treatment of flares. Of the 38 responders in the ITT population, 6 subjects received additional doses of remestemcel-L as flare therapy. For the purpose of calculating DOR, FDA considered such flare therapy as additional new therapy for aGVHD.

Lastly, it is acknowledged that FDA's definition of DOR does not take into account that GVHD may flare and resolve without additional systemic treatment. Therefore, an additional measure of

time to either death or need for new therapy for aGVHD (without consideration of flares as progression) is evaluated as an alternative representation of the durability of the response.

Table 4 shows the observed median and range of the DOR and the additional measure of durability as calculated by FDA. The median follow-up of the 38 responders was 150.5+ days (4.9 months) (range 15-182+ days). The median observed DOR as defined by FDA was 54 days (1.7 months), and the median observed additional measure of durability was 111.5 days (3.7 months.

Table 4: MSB-GVHD001 - Duration of Day-28 ORR

Definition Used	Duration of ORR days (n=38)		Duration of CR days (n=16)		Duration of PR days (n=22)	
	Median	Range	Median	Range	Median	Range
Applicant-defined DOR[a]	70.5	1, 171	N/A	N/A	N/A	N/A
FDA-defined DOR[b]	54	7, 159+	50.5	10, 158+	57.5	7, 159+
FDA-defined alternative measure of durability[b]	111.5	9, 182+	112+	16, 172+	111.5	9, 182+

Source: [a] MSB-GVHD001 Clinical Study Report [b] FDA analysis. See Table 3 for details of the definitions.
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; N/A, not available, ORR overall response rate; PR, partial response

4.2.3 Secondary Endpoint Outcomes

FDA confirmed the Applicant's analyses of the secondary response endpoints, including rates of CR + VGPR at Days 28, 56, and 100 stratified by organ involvement, baseline aGVHD grade and MacMillan risk score for the FAS population. Although the response measures at later timepoints showed internal consistency with the analysis of the primary endpoint, none of these analyses were statistically informative. The time-to-event measures, such as OS (see Applicant's Briefing Document Section 5.3.3), are difficult to interpret in a single-arm trial and will not be discussed further.

4.3 FDA's View of Protocols 265, 275 and 280

Table 5 summarizes the key design elements for the additional remestemcel-L trials, Protocols 265, 275 and 280.

Table 5: Key Design Elements of Additional Remestemcel-L Protocols for aGVHD

	Protocol 265	Protocol 280	Protocol 275
Phase	Phase 3	Phase 3	EAP
Ages	Adult	Adult and pediatric	Pediatric
Population	Newly-diagnosed grade B-D aGVHD (skin only grade B allowed)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)
Design	Randomized, double-blind, placebo- controlled, multicenter	Randomized, double-blind, placebo- controlled, multicenter	Expanded access
Primary Endpoint	CR $\geq$ 28 days duration	CR $\geq$ 28 days duration	Day-28 ORR
Control Arm	Steroids + Placebo	SOC + Placebo	-
Treatment Arm	Steroids + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-2, then 1 infusion/week x Weeks 3-4	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8

Source: FDA analysis
Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; SOC, standard care salvage therapy.

Protocol 265 evaluated the efficacy of remestemcel-L in combination with systemic corticosteroid therapy in 192 patients with newly-diagnosed grades B-D aGVHD. The study population and treatment regimen in Protocol 265 differs from that of MSB-GVHD001. Protocol 280 evaluated the efficacy of remestemcel plus investigator's choice of additional salvage therapy in 244 patients with grades B-D SR-aGVHD. The third protocol, Protocol 275, was specifically for pediatric patients with SR-aGVHD grade B-D. In Protocol 275, addition of other aGVHD therapies was permitted at study entry at the discretion of the treating physician. This is in contrast to MSB-GVHD001, where no additional salvage immunosuppressive agent was allowed. As such, there are substantial differences between the additional remestemcel-L trials and MSB-GVHD001 in study population and the treatment plan.

Table 6 shows the efficacy results for Protocols 265, 280 and 275. FDA confirmed that, based on the prespecified primary endpoint of CR lasting $\geq$ 28 days, Protocols 265 and 280 failed to meet the primary objective. Similarly, on re-evaluation using the current recommended endpoint of Day-28 ORR, there was no significant difference between study arms for either protocol. Neither protocol provides evidence that remestemcel-L has a treatment effect. The differences in Day 28 ORR outcomes in Studies 280 and 275, 54% vs 64% and grade B subjects 47% vs 67% in the both trials are unclear. Nevertheless, these differences raise concerns regarding the variability in results across studies.

Table 6: Efficacy Outcomes in Additional Remestemcel-L Trials for aGVHD

	Protocol 265		Protocol 280		Protocol 275
	Steroids + Rem-L	**Steroids + Placebo**	**SOC + Rem-L**	**SOC + Placebo**	**SOC + Rem- L**
Number of patients in FAS	97	95	173	87	242
CR lasting ≥ 28 days[a]	45%	46%	35%	30%	-
Day-28 ORR[b]	60%	61%	54%	47%	64%
Day-28 CR	41%	49%	25%	23%	12%
Day-28 PR	19%	12%	29%	24%	52%
Subgroup analyses[b]					
Grade B number of patients	47	42	38	22	48
Grade B Day-28 ORR	62%	64%	47%	59%	67%
Day-28 CR	57%	62%	39%	41%	21%
Day-28 PR	4%	2%	8%	18%	46%
Grade C/D number of patients	50	53	135	65	194
Grade C/D Day-28 ORR	58%	58%	56%	43%	63%
Day-28 CR	26%	40%	21%	18%	10%
Day-28 PR	32%	19%	36%	25%	53%

Source: FDA analysis from ADEFF/ISE population
Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; Rem-L, remestemcel-L; SOC, standard care salvage therapy.
[a] Prespecified primary endpoint in Protocols 265 and 280
[b] Post hoc re-analysis for Protocol 265 and 280

Table 7 below shows a side-by-side displays of FDA's analysis of results of studies of remestemcel-L for treatment of SR-aGVHD in pediatric patients. Keeping in mind the potential pitfalls of subgroups analyses and of comparing results across independent protocols, it is of interest that the Day-28 ORR is consistently 64% - 69% in remestemcel-L-treated pediatric patients with or without additional standard care salvage therapy (Table 7).

Table 7: Day-28 ORR in Studies of Pediatric Patients with SR-aGVHD

	MSB-GVHD001	Protocol 280 (Pediatric subgroup)		Protocol 275
Arm	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L
Number of treated patients	54	14	13	241
Day-28 ORR[b] (95% CI)	69.1% (55.2, 80.9)	64.3% (35.1,87.2)	38.5% (13.9, 68.4)	65.1% (58.8, 71.1)

Source: [a] Per protocol analysis for Protocols 265 and 280 as reported in the respective Clinical Study Reports; [b] Per protocol analysis for Protocol 275 and post hoc analysis for Protocols 265 and 280;
Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; Rem-L, remestemcel-L; SOC, standard care salvage therapy.

Further, the pediatric subpopulation comparison within Protocol 280 appears to have a substantial numerical difference between treatment arms for Day-28 ORR, but as this is analysis of a small subgroup (note broad confidence intervals), the results might be appropriate for only hypothesis generation, but would not generally be considered evidence of a treatment effect.

4.4 Summary

Protocol MSB-GVHD001 met its primary objective; the Day-28 ORR was 69.1% (95% CI: 55.2, 80.9) in the FAS. The primary endpoint results in MSB-GVHD001 were statistically significant, the measured response was durable (median 54 days), and the results were consistent across subpopulations and secondary efficacy endpoints.

The limitations of single-arm study design of MSB GVHD001 include a) the challenges to minimizing bias as with the subjective nature of aGVHD grading b) inability to ascertain the similarities in prognostic factors, both known and unknown, between MSB-GVHD001 study and the historical control data c) the influence of confounding factors such as preparative regimen or supportive care measures on efficacy outcomes d) the adequacy of the historical data to support a null hypothesis e) the clinical development program with two randomized studies with negative results and f) the differences in outcomes observed in the Day 28 ORR (Table 6) in the FAS populations of Studies 280 and 275 in Day 28 ORR in the FAS subjects receiving SOC + remestemcel and in the subgroup of grade B subjects.

Additional data were provided from Protocol 265, 275 and 280. In comparison to Protocol MSB-GVHD001, Protocols 265, 275 and 280 have substantial differences in the patient populations, trial design, study conduct, and primary endpoint evaluations:

- Difference in primary endpoints CR sustained > 28 days versus ORR at Day 28
- Differences in populations

  - ages (pediatric versus adult subjects)
  - disease state (newly diagnosed aGVHD versus SR-aGVHD)
  - disease stage (allowing grade B skin-only disease)
- Difference in treatment regimens
- The impact of concomitant medications (positively or negatively) on efficacy outcomes in Studies 280 and 275, particularly in light of the unknown mechanism of action of remestemcel-L.
- Limitations in reporting of DOR and variability in duration of follow-up (Day 180 versus Day 90)

Due to these design differences, it is unclear that these study results are relevant to the proposed indication for use of remestemcel-L as a single-agent treatment of SR-aGVHD in pediatric patients, but it raises the uncertainties associated with interpreting the observed efficacy outcomes between studies.

Additionally, although designed to isolate the treatment effect of remestemcel-L, Protocols 265 and 280, were negative based on the analysis of the prespecified primary endpoint and 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 immune modulated diseases such as type 1 diabetes mellitus and Crohn's Disease.

Therefore, it is unclear how to interpret the results of one statistically-positive single-arm trial in a landscape of multiple negative clinical trials, including several randomized, controlled trials that failed to show a treatment effect.

5. SAFETY OF REMESTEMCEL-L

5.1 Background

FDA reviewed the safety data for 1,517 patients in clinical trials and expanded access protocols. These included 1,114 patients treated with remestemcel-L and 403 treated with placebo. FDA utilized 3 main cohorts for this discussion:

- The 1,114 patients treated with remestemcel-L were assessed for fatal adverse reactions and for the occurrence of ectopic tissue formation. The median number of doses of remestemcel-L administered was 6 (range 1-32), and treatment was administered over a median of 26 days (range 1-378 days).

- The 54 patients treated with remestemcel-L on Protocol MSB-GVHD001 were used primarily to assess the safety profile in the intended population. The median number of doses administered was 10 (range 1-16), and treatment was administered over a median of 43 days (range 1-104 days).

- The patients treated on Protocol 265 (n=186) and Protocol 280 (n=244), the two randomized trials for patients with aGVHD, were used for comparative analyses to enable identification of adverse reactions. On Protocol 265, the median number of doses administered was 6 (range 1-6), and treatment was administered over a median of 23 days (range 1-34 days). On Protocol 280, the median number of doses administered was 8 (range 1-28), and treatment was administered over a median of 26 days (range 1-97 days).

In general, there were substantial differences between the clinical trials with regard to the patient population and treatment plan, so there was no pooling of data, and the results are presented side-by-side. FDA's discussion of the safety profile of remestemcel-L focuses on fatal adverse reactions, common adverse reactions and adverse events of special interest (AESI).

5.2 FDA's Findings

5.2.1 Fatal Adverse Reactions

There were 422 deaths reported in the integrated safety database; 229 occurred within 30 days of the last dose of remestemcel-L Table 8 shows the percentage of deaths within 30 days of the last dose of remestemcel-L by protocol and arm.

Table 8: Integrated Safety Database - Deaths Within 30 Days of Last Remestemcel-L Dose

Study	Population	Treatment	N Treated	Death with 30 days of last dose	
				N	%
MSB_GVHD001	GVHD	Remestemcel-L	54	7	13%
280	GVHD	Remestemcel-L	163	58	36%
		Placebo	81	31	38%
265	GVHD	Remestemcel-L	95	12	13%
		Placebo	91	15	16%
260/261	GVHD	Remestemcel-L	32	4	13%
		Placebo	1	1	100%
275	GVHD	Remestemcel-L	242	64	26%
276	GVHD	Remestemcel-L	18	10	56%
270	GVHD	Remestemcel-L	11	7	64%

Table 8: Integrated Safety Database - Deaths Within 30 Days of Last Remestemcel-L Dose

Study	Population	Treatment	N Treated	Death with 30 days of last dose	
				N	%
Single-patient use	GVHD	Remestemcel-L	39	19	49%
401/402	Myocardial infarction	Remestemcel-L	34	0	0%
		Placebo	19	0	0%
403	Myocardial infarction	Remestemcel-L	110	0	0%
		Placebo	110	1	1%
601/602	Crohn's Disease	Remestemcel-L	10	0	0%
603	Crohn's Disease	Remestemcel-L	221	0	0%
		Placebo	48	0	0%
620	Crohn's Disease	Remestemcel-L	13	0	0%
801	Chronic obstructive pulmonary disease	Remestemcel-L	30	0	0%
		Placebo	32	0	0%
901	Type 1 diabetes mellitus	Remestemcel-L	42	0	0%
		Placebo	21	0	0%

Source: FDA analysis

In Protocol MSB-GVHD001, there were 14 deaths reported of the 54 treated subjects; 7 deaths (50% of deaths) occurred within 30 days of the last dose of remestemcel-L. In the GVHD trials, FDA adjudicated the root cause of death as relapse for any patient who died after relapse on study, as GVHD for any patient who died with active GVHD, and infection for any patient who died of infection without active GVHD. Table 9 shows the FDA-adjudicated root causes of death. There were no cases with remestemcel-L adverse reactions as the root cause of death.

Table 9: MSB-GVHD001- FDA-Adjudicated Root Cause of Death

Root Cause of Death	Deaths	Deaths within 30 Days of Last Dose of Remestemcel-L
GVHD	9	5
Relapse	2	1
Infection	2	0
Other ^	1	1

^accident

Similarly, in Studies 280 and 265, there were no cases with remestemcel-L adverse reactions as the root cause of death. Incidences of death were equal between the placebo arm and the

remestemcel-L arm in both studies. In the trials of remestemcel-L in patients with diseases other than GVHD, there were no deaths within 30 days of the last dose of remestemcel-L reported.

5.2.2 Common Adverse Reactions

Protocol MSB-GVHD001

The safety population (n = 54) included all subjects who received at least 1 dose of remestemcel-L. FDA safety analysis confirmed the Applicant's safety analyses (see Applicant's Briefing Document Section 6.2.2) and revealed no safety signal of concern. The most common AEs observed in the study were infections, gastrointestinal disorders, and respiratory complications. This is consistent with literature reports of varying treatments used for GVHD.[19,20,21,22,23,24] In particular, patients with SR-aGVHD have high rates of infection with 1-year incidence of bacterial, viral, and fungal infections was 74%, 65%, and 14%, respectively.[8] High rates of infection-related mortality lead to decreased OS in this population.[9,10] Bacterial infections are the most common infection leading to death in this population.

Protocols 280 and 265

For Protocol 280, the randomized trial for patients with SR-aGVHD, Table 10 shows the adverse events occurring with an incidence at least 5% greater in the remestemcel-L arm. For Table 10, all treatment-emergent adverse reactions through study follow-up were used in the analysis. If the time period of analysis is limited to 30 days after the last dose of remestemcel-L, fungal infection is the only adverse event to occur with at least a 5% greater incidence in the remestemcel-L arm (11% vs 4%).

[19] Malard, F., Huang, X., et al. (2020) Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia 34, 1229–1240.
[20] García-Cadenas, I., Rivera, I., et al. (2017) Patterns of infection and infection-related mortality in patients with steroid-refractory acute graft versus host disease. Bone Marrow Transplant 52, 107–113
[21] Hsu B, May R, et al. (2001) Use of antithymocyte globulin for treatment of steroid-refractory acute graft-versus-host disease: an international practice survey. Bone Marrow Transplant 28(10):945-950.
[22] Onishi C, Ohashi K, et al. (2010) A high risk of life-threatening infectious complications in mycophenolate mofetil treatment for acute or chronic graft-versus-host disease. Int J Hematol.;91(3):464-470.
[23] von Bubnoff, N., Ihorst, G., et al. (2018) Ruxolitinib in GvHD (RIG) study: a multicenter, randomized phase 2 trial to determine the response rate of Ruxolitinib and best available treatment (BAT) versus BAT in steroid-refractory acute graft-versus-host disease (aGvHD). BMC Cancer 18, 1132
[24] Arai S, Margolis J, et al. (2002) Poor outcome in steroid-refractory graft-versus-host disease with antithymocyte globulin treatment. Biol Blood Marrow Transplant; 8(3):155-160.

Table 10: Protocol 280: Adverse Events with > 5% Difference Between Arms

	Remestemcel-L (N = 163)		Placebo (N = 81)		% Risk Difference
Adverse Event*	**Number**	**(%)**	**Number**	**(%)**	
Bacterial infection	91	56	31	38	18
Fungal infection	47	29	14	17	12
Hypertension	31	19	7	9	10
Confusional state	27	17	6	7	9
Anorexia nervosa	13	8	0	0	8
Anxiety	23	14	5	6	8
Hypokalemia	35	21	11	14	8
Dyspnea	43	26	15	19	8
Abdominal distension	16	10	2	2	7
Hyperkalemia	20	12	4	5	7
Rash	24	15	6	7	7
Tremor	21	13	5	6	7
Insomnia	23	14	6	7	7
Mucosal inflammation	12	7	1	1	6
Hyperglycemia	32	20	11	14	6

Source: FDA analysis *Includes grouped terms

For Protocol 265, the randomized trial for patients with newly-diagnosed aGVHD, Table 11 shows the adverse events occurring with an incidence at least 5% greater in the remestemcel-L arm. For Table 11, all treatment-emergent adverse reactions through study follow-up were used in the analysis. If the time period of analysis is limited to 30 days after the last dose of remestemcel-L, adverse events that occurred with an incidence at least 5% greater with remestemcel-L than with placebo included edema, hemorrhage, thrombosis, back pain, pyrexia, rash, jaundice and fungal infection.

Table 11: Protocol 265: Adverse Events with > 5% Difference Between Arms

	Remestemcel-L (N = 95)		Placebo (N = 91)		% Risk Difference
Adverse Event*	**Number**	**(%)**	**Number**	**(%)**	
Edema	39	41	29	32	9
Pyrexia	20	21	12	13	8
Hemorrhage	34	36	26	29	7
Infection	40	42	32	35	7
Dyspnea	21	22	14	15	7
Thrombosis	15	16	9	10	6
Hypotension	18	19	12	13	6
Pollakiuria	8	8	3	3	5
Chills	9	9	4	4	5

Source: FDA analysis *Includes grouped terms

In general, with the exception of infections, the comparative analysis of adverse events in these two randomized trials did not reveal remarkable differences in safety between remestemcel-L and placebo.

5.2.3 Adverse Events of Special Interest (AESI)

AEs of special interest to FDA in subjects treated with remestemcel-L included acute infusion reactions, serious infections, and ectopic tissue formation.

Acute Infusion Reactions: Acute infusion reactions were defined as adverse reactions temporally associated with remestemcel-L administration during a 2-hour observation period following infusion. Infusion reactions occurred in 3 subjects and were self-limited and reversible with supportive measures (See Table 12). Two of the three subjects were able to receive additional remestemcel infusions one without further events reported, the other appeared to have DMSO neurotoxicity with two subsequent infusions. These events resolved without intervention; however, remestemcel-L administration was then discontinued.

Table 12: MSB-GVHD001 - Remestemcel-L Infusion Reactions

	Remestemcel-L (N = 54)	
Preferred Term (PT)	**Number of subjects**	**Proportion (%)**
Dyspnea	1	1.85
Hypotension	1	1.85
Somnolence	1	1.85

[Source: FDA analysis]

No infusion reactions were identified in Studies 265 and 280.

Serious Infections: Subjects in the aGVHD disease population are at high risk of serious infections due to their primary medical conditions as well as the transplantation procedures and immunosuppressants.[8-13] Infections were reported as the most frequent SAE from prior remestemcel-L studies, and similar incidences were observed between MSC and placebo arms in prior randomized remestemcel-L studies. A total of 17 subjects (31.5%) experienced 26 serious infection events. Eleven subjects (20.3%) experienced serious bacterial infections, 6 subjects (11.1%) experienced serious virus infections, 2 subjects (3.7%) experienced serious fungal infections, and 5 subjects (9.3%) experienced serious non-pathogen-specified infections (e.g., pneumonia, sepsis). These rates are compatible with reported rates in this population.

Table 12 shows the incidences of grades 3-5 and fatal infections in Protocols 265, 280 and MSB-GVHD001. In Protocol MSB-GVHD001, there were no fatal infections within 30 days of the last dose of remestemcel-L; 19% of the patients had a grade 3 or 4 infection, largely bacterial or etiology not specified. In the randomized trials, there was a slightly higher incidence of grades 3-5 and fatal infections in the remestemcel-L study arms.

Table 13: AESI: Severe and Fatal Infections*

	Protocol 265		Protocol 280		Protocol MSB-GVHD001
	Steroids + Rem-L (n=95)	**Steroids + Placebo (n=91)**	**SOC + Rem-L (n=163)**	**SOC + Placebo (n=81)**	**Rem-L (n=54)**
Grade 5 Infections	6 (6%)	6 (7%)	19 (12%)	6 (7%)	0
Grade 3-5 Infections	27 (28%)	22 (24%)	53 (33%)	22 (27%)	10 (19%)
Bacterial	15 (16%)	11 (12%)	21 (13%)	9 (11%)	5 (9%)
Fungal	6 (6%)	3 (3%)	13 (8%)	0	0
Viral	10 (11%)	7 (8%)	13 (8%)	6 (7%)	2 (4%)
Mycobacterial	0	0	1 (< 1%)	0	0
Not specified	13 (13%)	10 (11%)	22 (13%)	12 (15%)	4 (7%)

Source: FDA analysis
Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; Rem-L, remestemcel-L; SOC, standard care salvage therapy.
*Within 30 days of last dose of remestemcel-L

There was one case of post-transplant lymphoproliferative disorder (PTLD) in Protocol MSB-GVHD001, one case in Protocol 275, and three cases of PTLD in Protocol 280 (one on the placebo arm and two on remestemcel-L). There was no evidence that the risk of PTLD was higher with remestemcel-L in these protocols.

Ectopic Tissue: Ectopic tissue formation, particularly bone formation, was previously reported with the use of MSCs[25,26,27] and therefore was an event of interest. For the safety analysis, the Applicant defined ectopic tissue as "tissue in areas of the body it would not normally be found," and ectopic tissue formation attributable to remestemcel-L was considered an adverse reaction (ISS Section 8.9.2.4).

[25] Kusuma GD, Menicanin D, et al. (2015) Ectopic Bone Formation by Mesenchymal Stem Cells Derived from Human Term Placenta and the Decidua. PLOS ONE 10(10): e0141246.
[26] Fennema EM, Tchang LAH, et al. (2018) Ectopic bone formation by aggregated mesenchymal stem cells from bone marrow and adipose tissue: A comparative study. J Tissue Eng Regen Med;12(1):e150-e158.
[27] Lukomska, B., Stanaszek, L., et al. (2019) Challenges and Controversies in Human Mesenchymal Stem Cell Therapy. Stem Cells International; Vol 2019, Article ID 9628536,

Ectopic tissue formation was ascertained by serial CT scans of the chest, abdomen and pelvis. As shown in Table 14, serial CT scans were scheduled in 10 of the 14 clinical studies at various timepoints from 28 days to 2 years from start of study. CT scans were optional in Protocol MSB-GVHD001/002.

Table 14: Ectopic Tissue Formation - Imaging Schedule by Protocol

Protocol	Population	Planned Duration of Safety Follow-up	Planned Postbaseline Imaging Schedule
MSB- GVHD001/ MSB- GVHD002	Children with SR-aGVHD	180 days	Day 100* and Day 180*
280	Patients with SR-aGVHD	180 days	Day 180
275	Children with SR-aGVHD	100 days	Day 100
276	Adults with SR-aGVHD	100 days	Day 100
265	Adults with new aGVHD	90 days	Day 90 and Year 1
260/261	Adults with new aGVHD	2 years	Day 28, Year 1 and Year 2
270/270E/271	Patients with TR-aGVHD	1 year	Day 28 and Year 1
401/402	Adults with acute MI	2 years	Month 6, Year 1 and Year 2
403	Adults with acute MI	2 years	-
601/602	Adults with TR Crohn's Disease	2 years	Year 1 and Year 2
603/610/611	Adults with TR Crohn's Disease	2 years	-
620	Adults with TR Crohn's Disease	1 years	-
801	Adults with COPD	2 years	-
901	Patients 12-35 years old with T1DM	2 years	Year 2

Source: FDA analysis

Postbaseline scan results were identified for 530 patients, including 397 treated with remestemcel-L and 133 treated with placebo. Few patients on the GVHD protocols completed scheduled CTs past Month 3. For Protocols 401/402 (myocardial infraction) and 901 (type 1 diabetes), compliance with the scheduled long-term follow-up CT scans was 76% to 100% at various timepoints. Nineteen cases were flagged by the Applicant as showing ectopic tissue on CT scan. In the randomized trials, there was no substantial difference between the treatment arms in the proportion of patients with scans showing ectopic tissue. Table 56 in the Applicant's Briefing Document shows cases from Protocols MSB-GVHD001, 265 and 275. Although the Applicant concluded that none of the cases was due to remestemcel-L, there were no histology or molecular reports available for review to confirm that the lesions were not due to remestemcel-L. Additionally, there were fewer than 100 patients at each long-term follow-up timepoint.

5.3 Summary

In general, no safety signal of concern was identified in the studies of remestemcel-L.

6. POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

The Applicant is seeking approval of remestemcel-L for the indication of treatment of steroid-refractory acute graft-versus-host disease in pediatric patients based on results from a single trial, Protocol MSB-GVHD001. Although the study reached the primary endpoint goal of a 28-day ORR at 69.1%, it is unclear whether this one single-arm trial provides evidence of clinical benefit in the treatment of SR-aGvHD in pediatric patients. Furthermore, it is unclear if the durability of response requires continued infusions of remestemcel-L. Finally, the relevance of the two previously conducted randomized, double-blind, placebo-controlled, multicenter studies that failed to meet their primary efficacy endpoints is uncertain.

Topic for Discussion #1: Protocol MSB-GVHD001 was a single-arm trial designed to determine if the Day-28 ORR exceeded 45% for pediatric patients with SR-aGVHD grades B-D treated with remestemcel-L. Although the null rate and hypothesis were prespecified in the SAP, there were some limitations with regard to how 45% was chosen for the null rate, and it is uncertain as to whether the data cited for use as historical controls are sufficient to establish the null hypothesis for the purposes of quantitating a treatment effect in a single-arm trial of a new therapy for SR-aGVHD in pediatric patients.

Given these limitations, what are the strengths and weaknesses of the study design?

Topic for Discussion #2: The primary endpoint results in MSB-GVHD001 were statistically significant, the measured response was durable (median 54 days), and the study results were consistent across subpopulations and secondary efficacy endpoints. However, the results of Protocols 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.

Therefore, how are the results of one positive single-arm trial interpreted in a landscape of multiple negative clinical trials, including several randomized, controlled trials that failed to show a treatment effect of remestemcel-L?

Does the fact that Study 265 and Study 280 were conducted over ten years ago impact how they should be considered in this context?

Is an additional clinical trial in the SR-aGVHD population required for confirmation of the effectiveness of the product? What trial design trial would be required to provide evidence of effectiveness in this indication?

Appendix 1: Clinical Trials of Remestemcel-L

Study	Study Design	Population	Treatment
Trials for aGVHD			
MSB-GVHD001/ MSB-GVHD002	MSB-GVHD001: Single-arm study Primary endpoint: Day-28 ORR	Children with SR-aGVHD grade B-D Planned: 48 Enrolled: 55 Treated: 54	Remestemcel-L 2 × 10^6 cells/kg IV 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8
	MSB-GVHD002: Safety follow-up through day 180	Planned: 40 Enrolled: 32	No treatment.
280	Randomized double-blind placebo-controlled Primary endpoint: CR lasting >= 28 days	Patients with SR-aGVHD grade B-D Planned: 240 Randomized: 260 Treated: 244	Arm A: SOC + Placebo Arm B: SOC + remestemcel-L 2 × 10^6 cells/kg IV 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8
275	Expanded Access Protocol	Children with SR-aGVHD grade B-D Enrolled: 242 Treated: 241	SOC + remestemcel-L 2 × 10^6 cells/kg IV 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8
276	Expanded Access Protocol	Adults with SR-aGVHD grade C-D Planned:120/year Enrolled: 18 Treated: 18	Remestemcel-L 2 × 10^6 cells/kg IV 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8
265	Randomized, double-blind, placebo-controlled Primary endpoint: CR lasting >= 28 days	Adults with new aGVHD grade B-D Planned: 184 Randomized: 193 Treated: 192	Arm A: Steroids + Placebo Arm B: Steroids + remestemcel-L IV 2 × 10^6 cells/kg x 2 infusions/week x Weeks 1-2, then 1 infusion/week x Weeks 3-4
260/261	260: Randomized open-label dose-finding study Primary endpoint: CR or PR by Day 28	Adults with new aGVHD grade 2 - 4 Planned: 50 Enrolled: 33 Treated: 32	Arm A: Steroids + remestemcel-L 2 × 10^6 cells/kg IV Days 1 and 4 Arm B: Steroids + remestemcel-L 8 × 10^6 cells/kg IV Days 1 and 4
	261: Safety follow-up through 2 years	Planned: 50 Enrolled: 28	No treatment.
270/270E/271	270/270E: Single-arm study Primary endpoint: CR or PR by Day 28	Patients with TR-aGVHD grade 3 - 4 Planned: 30 Enrolled: 16 Treated: 15	Remestemcel-L 8 × 10^6 cells/kg IV up to a total of 8 infusions at least 72 hours apart within the 28-day study period
	271: Safety follow-up through 12 months	Planned: 50 Enrolled: 7	No treatment.
207-210, 215-218, 220-222, 224-225, 227, 233, 235-236	Single Patient Use	SR/TR-aGVHD Enrolled: 23 Treated: 23	Remestemcel-L 2 to 8 × 10^6 cells/kg IV in various schedules

Study	Study Design	Population	Treatment
Trials for Other Diseases			
401/402	401: Phase 1 randomized, double-blind, placebo-controlled, dose-escalation Safety study	Adults with acute MI Planned: 48 Randomized: 60 Treated: 53	Remestemcel-L IV Cohort 1: 0.5 × 10^6 cells/kg once Cohort 2: 1.6 × 10^6 cells/kg once Cohorts 3 and 4: 5 × 10^6 cells/kg once
	402: Safety follow-up through 2 years	Eligible: 53 Enrolled: 52	No treatment.
403	Phase 2 randomized, double-blind, placebo-controlled Primary endpoint: Change in LV ESV	Adults with acute MI Planned: 220 Randomized: 220 Treated: 220	Arm A: Placebo Arm B: Remestemcel-L IV 200 × 10^6 cells once
601/602	601: Phase 2 single-arm Primary endpoint: CDAI reduction > 100	Adults with TR Crohn's Disease Planned: 12 Enrolled: 10 Treated: 10	Remestemcel-L IV 2 × 10^6 cells/kg x 2 infusions 7 days apart or 8 × 10^6 cells/kg x 2 infusions 7 days apart
	602: Safety follow-up	Planned: 10 Enrolled: 9	No treatment.
603/ 610/611	603: Randomized, double-blind, placebo-controlled	Adults with TR Crohn's Disease Planned: 450 Randomized: 269 Treated: 269	Remestemcel-L IV Arm A: Placebo Arm B; 200 × 10^6 cells Days 0 and 3; 100 x 10^6 cells days 7 and 14 Arm C: 400 × 10^6 cells Days 0 and 3; 200 x 10^6 cells days 7 and 14
	610: Placebo- controlled retreatment	Treated: 68	Remestemcel-L IV Arm A: Placebo Arm B; 200 × 10^6 cells Days 0 and 3; 100 x 10^6 cells days 7 and 14 Arm C: 400 × 10^6 cells Days 0 and 3; 200 x 10^6 cells days 7 and 14
	611: Open label retreatment	Treated: 72	Remestemcel-L IV 200 × 10^6 cells Day 42, 84 and 126
620	Expanded Access Protocol Safety Study	Adults with TR Crohn's Disease Treated: 13	Remestemcel-L IV 200 × 10^6 cells on Days 0, 3, 7 and 14 then tapering in frequency at the investigator's discretion
801	Phase 2, randomized, double-blind, placebo-controlled Safety study	Adults with moderate or severe chronic obstructive pulmonary disease (COPD) Planned: n/a Randomized: 62 Treated: 62	Remestemcel-L IV Arm A: Placebo Arm B: 100 x 10^6 cells on Days 0, 30, 60, 90

Study	Study Design	Population	Treatment
901	Randomized, double-blind, placebo- controlled	Patients 12-35 years old with Type 1 diabetes mellitus (T1DM) Planned: 63 Randomized: 63 Treated: 63	Remestemcel-L IV Arm A: Placebo Arm B: 2 × 106 cells/kg on Days 0, 30, 60

Source: FDA analysis

Appendix 2: Study MSB-GVHD001 Subpopulation Analyses

	ORR (n=55)		CR (n=55)		PR (n=55)	
Age (N)	**N**	**%**	**N**	**%**	**N**	**%**
0 – < 12 years	20	68.97%	11	37.93%	9	31.03%
12 to < 17 years	10	71.43%	2	14.29%	8	57.14%
17 years and greater	8	66.67%	3	25.00%	5	41.67%
Sex						
F	12	60.00%	5	25.00%	7	35.00%
M	26	74.29%	11	31.43%	15	42.86%
Pooled Race Group 1						
Non-White	17	70.83%	8	33.33%	9	37.50%
White	21	67.74%	8	25.81%	13	41.94%
Ethnicity						
HISPANIC OR LATINO	13	72.22%	7	38.89%	6	33.33%
NOT HISPANIC OR LATINO	24	66.67%	8	22.22%	16	44.44%
Baseline Organ Involvement Category						
Lower GI Only	14	66.67%	6	28.57%	8	38.10%
Multi-Organ (Any Combination)	12	60.00%	2	10.00%	10	50.00%
Skin Only	12	85.71%	8	57.14%	4	28.57%
MacMillan Risk Score						
High risk (HR)	27	67.50%	10	25.00%	17	42.50%
Standard risk (SR)	11	73.33%	6	40.00%	5	33.33%
Baseline Grade aGVHD						
Grade B	3	50.00%	1	16.67%	2	33.33%
Grade C	16	69.57%	9	39.13%	7	30.43%
Grade D	19	73.08%	6	23.08%	13	50.00%
HLA Compatibility Match						
Matched	20	74.07%	9	33.33%	11	40.74%
Mismatched	18	64.29%	7	25.00%	11	39.29%
HLA Compatibility Related						
Related	9	69.23%	5	38.46%	4	30.77%
Unrelated	29	69.05%	11	26.19%	18	42.86%
Type of Transplant						
Bone Marrow	24	80.00%	9	30.00%	15	50.00%
Cord Blood	8	72.73%	5	45.45%	3	27.27%
Peripheral Blood Stem Cell (PBSC)	6	42.86%	2	14.29%	4	28.57%
Underlying Malignancy at Transplant						
Acute Lymphoblastic Leukemia (ALL)	9	75.00%	6	50.00%	3	25.00%
Acute Myeloid Leukemia-Primary (AML)	10	55.56%	3	16.67%	7	38.89%
Chronic Myeloid Leukemia (CML)	4	100.00%	1	25.00%	3	75.00%
Hodgkin's Lymphoma	1	100.00%	0	0.00%	1	100.00%
Myelodysplastic Syndrome (MDS)	1	50.00%	0	0.00%	1	50.00%
Other	13	72.22%	6	33.33%	7	38.89%
Baseline Skin Involvement Score						
0= No rash	17	68.00%	7	28.00%	10	40.00%
1= Maculopapular rash, <25% of body surface	2	66.67%	1	33.33%	1	33.33%
2= Maculopapular rash, 25-50% of body surface	1	50.00%	0	0.00%	1	50.00%

	ORR (n=55)		CR (n=55)		PR (n=55)	
Age (N)	**N**	**%**	**N**	**%**	**N**	**%**
3= Generalized erythroderma	10	71.43%	5	35.71%	5	35.71%
4= Generalized erythroderma with bullae/desquamation	8	72.73%	3	27.27%	5	45.45%

Source: FDA analysis