

BLA Clinical Review Memorandum

Application Type	BLA
STN	125706/0
CBER Received Date	January 31, 2020
PDUFA Goal Date	September 30, 2020
Division / Office	DCEPT/OTAT
Priority Review	Yes Kristin Baird
Reviewer Name(s)	Kristin Baird, MD -S Donna Przepiorka, MD PhD <small>Digitally signed by Kristin Baird -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kristin Baird -S, 0.9.2342.19.200300.100.1.1=0011061363 Date: 2020.08.31 10:59:25 -0400'</small>
Review Completion Date / Stamped Date	August 28, 2020 / August 31 2020
Applicant	Mesoblast, Inc.
Established Name	Remestemcel-L Ex Vivo Cultured Adult Human Mesenchymal Stem Cells MSCs
Proposed Trade Name	REMESTEMCEL-L
Pharmacologic Class	Undetermined
Formulation(s), including Adjuvants, etc.	REMESTEMCEL-L is provided as a frozen cell suspension in cryogenic vials. The active ingredient in REMESTEMCEL-L is comprised of culture-expanded mesenchymal stromal cells (ceMSC) isolated from the bone marrow of healthy adult human donors. Each cryovial contains nominally 25 x 10 ⁶ ce-MSCs in 3.8 mL (6.68 x 10 ⁶ cells/mL) formulated in Plasma Lyte-A (70% v/v), Human Serum Albumin (HSA) Solution (25% 20% v/v) and Dimethyl sulfoxide (DMSO) (10% v/v). The product contains trace amounts of porcine or bovine proteins. The product is thawed and resuspended in Plasma-Lyte A prior to intravenous administration.
Dosage Form(s) and Route(s) of Administration	REMESTEMCEL-L is available as a cell suspension for intravenous infusion in a concentration of 6.68 X

	10e6 ce-MSCs per mL in 3.8 mL contained in a 6 mL cryovial.
Dosing Regimen	<p>The recommended dose of REMESTEMCEL-L is 2×10^6 ce- MSC/kg body weight.</p> <p>For the initial treatment, patients should be treated with REMESTEMCEL-L twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart. The product may be administered once a week for an additional 4 weeks if the symptoms have not completely resolved.</p> <p>If the symptoms recur after a complete response (CR), treatment may be repeated.</p>
Indication(s) and Intended Population(s)	Treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients.
Orphan Designated Yes/No	Yes

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GLOSSARY

Glossary

AE	Adverse event
AESI	Adverse event of special interest
aGVHD	Acute graft-versus-host disease
ALL	Acute lymphoblastic leukemia
allo-HST	Allogeneic hematopoietic stem cell transplant
ASBMT	American Society of Blood and Marrow Transplantation
ATG	Anti-thymocyte globulin
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
cGVHD	Chronic graft-versus-host disease
CMC	Chemistry, manufacturing, and controls
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CyA	Cyclosporin
DIS	Division of Inspections and Surveillance
DOR	Duration of response
EAP	Expanded access protocol
eCTD	Electronic Common Technical Document
EFS	Event-free survival
(b) (4)	
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
FD&C Act	Food Drug and Cosmetics Act
FK506	Tacrolimus
GVHD	Graft-versus-host disease
GRMP	Good review management principles
HR	Hazard ratio
HRQOL	Health related quality of life
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
ICH	International Conference on Harmonisation
IL	Interleukin
ISE	Integrated summary of efficacy
ITT	Intent-to-treat
JAK	Janus-activated kinase
kg	Kilogram
KGF	Keratinocyte growth factor
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MSC	Mesenchymal stem cells
MTX	Methotrexate
NDA	New drug application
NME	New molecular entity

OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
PD	Pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	Package insert
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PT	Preferred Term
QOL	Quality of life
RCT	Randomized Controlled Trial
REMS	Risk evaluation and mitigation strategy
RMS/BLA	Regulatory management system for the biologics license application
RTF	Refuse to file
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
SPU	Single patient use
SR	Steroid refractory
T1DM	Type 1 diabetes mellitus
TEAE	Treatment-emergent adverse event
TNF	Tissue necrosis factor
TR	Treatment refractory
TP	Treated population
VGPR	Very good partial response

1. EXECUTIVE SUMMARY

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.

There are no drugs approved for treatment of SR-aGVHD in patients less than 12 years old.

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. Remestemcel-L is not approved in the US for any indication.

The Applicant submitted the results of Study MSB-GVHD001 as the primary evidence to support the marketing application. Study 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 study was designed to determine if the Day-28 overall response rate (ORR) exceeded 45%. Day-28 ORR with durability has been used as a measure of benefit for treatments of aGVHD.

Between 2015 and 2017, 55 pediatric patients were enrolled on Study MSB-GVHD001 in the United States. These 55 patients comprise the FAS that was used for the primary analysis of Day-28 ORR, the primary 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. The primary endpoint analysis 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.

Although the null rate was prespecified in the statistical analysis plan (SAP), there were 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.

Additionally, the Applicant provided the results of two randomized, double-blind, placebo-controlled trials of remestemcel-L for treatment of aGVHD. Study 280 was a comparison of standard salvage regimens with or without remestemcel-L for treatment of SR-aGVHD; and Study 265 was a comparison of standard steroids with or without remestemcel-L for treatment of newly-diagnosed aGVHD. Both Studies failed to meet their primary objective to demonstrate an improvement in the rate of CR > 28 days duration, and no treatment effect was detected even when these Studies were reanalyzed using Day-28 ORR. For completeness, the Applicant also submitted results for Study 275, a single-arm expanded access protocol for treatment of pediatric patients with SR-aGVHD.

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. There were substantial differences between the clinical trials regarding the patient population and treatment plan, so there was no pooling of safety data.

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

A substantial issue regarding this Biologics License Application (BLA) 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, Study 265 and Study 280, which failed to meet their primary efficacy objectives. In comparison to Study MSB-GVHD001, Studies 265, 275 and 280 have substantial differences in the patient populations, trial design, study conduct, and primary endpoint evaluations. 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.

An Oncologic Drugs Advisory Committee (ODAC) meeting to discuss manufacturing issues, in the morning session of the ODAC and in the afternoon, clinical session to discuss: a) the adequacy of the design of Study 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 was held on August 13, 2020.

The discussion focused the following issues:

- CMC: Discussion of control of product quality for remestemcel-L with respect to identity, safety, purity and potency. This included FDA's concerns regarding:
 - Critical Quality Attributes (CQAs) may not by themselves ensure adequate control of clinical effectiveness of individual lots of product
 - Product comparability submission under IND with same CQAs was not acceptable
 - Adequacy of the potency assay established by the Applicant for remestemcel-L.
- Clinical:
 - Discussion of trial design strengths and weaknesses of the design of Study MSB-GVHD001
 - Discussion of whether the results of Studies 265 and 280 are relevant to the effectiveness of remestemcel-L for the treatment of pediatric SR-aGVHD.
 - Discussion of whether an additional clinical trial to support the effectiveness of the remestemcel-L in pediatric SR-aGVHD is required.

Ultimately, the committee voted 9 to 1 that the available data supports the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD. See Section 5.4.1 for a summary of the August 13, 2020 ODAC Meeting.

Based on the efficacy results of Study MSB-GVHD001, which were statistically significant and durable, the unmet medical need, and the favorable safety profile, the clinical reviewer recommends: Approval.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Study MSB-GVHD001 enrolled 55 and treated 54 patients. The enrolled patients were primarily male (63.6%) and white (56.4%). The mean age was 7.3 years. Thirty-three percent were Latino. Most patients were transplanted with a myeloablative conditioning regimen and the majority were transplanted for acute and chronic leukemias (61.8%). At baseline, most subjects were classified to have either Grade C (41.8%) or Grade D (47.3%) aGVHD. The median time from HCST to onset of aGVHD was 35.0 days (range 9 to 170 days). The median time from onset of aGVHD to initiation of remestemcel-L treatment was 12.0 days (range 4 to 142 days). The median time from onset of steroid-refractory aGVHD to initiation of remestemcel-L treatment was 3.5 days (range 1 to 10 days).

None of the analyses revealed any impact of demographic or disease characteristics on outcome measures.

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section of Review
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO) - PedsQL™ questionnaire	6.1.11.5
<input checked="" type="checkbox"/>	Observer reported outcome (ObsRO) - Pediatric Global Health-Related Quality Of Life HRQOL Parent Proxy Report	6.1.11.5
<input type="checkbox"/>	Clinician reported outcome ClinRO)	
<input checked="" type="checkbox"/>	Performance outcome (PerfO) - Karnofsky/Lansky	6.1.11.5
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a well-established treatment for hematologic diseases that cannot be cured with conventional treatments. More than 1 million hematopoietic stem cell transplantations have been performed, 40% of which were allogeneic. The most common life-threatening complication is graft-versus-host disease (GVHD), which occurs when immunocompetent T cells in the donated graft recognize the recipient's the host's) cell as foreign. The resulting immune response activates donor T cells to initiate cytolytic activity and attack the recipient's antigen-bearing cells. Given the number of allo-HCTs performed, approximately 5000 patients/year develop aGVHD in the United States US); of those, approximately 300-400 are pediatric patients [D'Souza 2017]. The risk of developing GVHD is dependent on many factors, including the stem cell source, age of the patient, conditioning, and GVHD prophylaxis used.

Signs of typical acute GVHD (aGVHD) include a maculopapular rash; hyperbilirubinemia with jaundice due to damage to the small bile ducts, leading to cholestasis; nausea, vomiting, and anorexia; and watery or bloody diarrhea and crampy abdominal. The diagnosis of aGVHD relies on the assessment of target organs by means of clinical and laboratory analyses with or without biopsy. The severity is graded clinically by tabulating the extent of the involvement of the three main target organs: the skin (the site of the most frequent and often the earliest clinical manifestation), the gastrointestinal tract the second most common site), and the liver. Grade 1 aGVHD is considered to be mild, grade 2 moderate, grade 3 severe, and grade 4 very severe. Despite prophylaxis with immunosuppressants, acute GVHD may still occur; among all patients undergoing allo-HCT, 30 to 50% have aGVHD (grades 1–4) and 14% have severe acute GVHD grades 3–4) [Zeiser 2017].

The combinations of calcineurin inhibitor (CNI) and methotrexate (MTX or CNI and mycophenolate are used most commonly to prevent GVHD in allo-HCT recipients. In general, once aGVHD occurs, the drugs used for prophylaxis are continued and additional immunosuppressive agents are added. aGVHD is treated first with glucocorticoids, such as methylprednisolone (MP), based on randomized, controlled trials [van Lint 1998]. About 50% of patients will respond to methylprednisolone. Patients with grade 3, 4 acute GVHD tend to have poorer outcomes. If patients progress or are not improved after steroid therapy, they will get salvage (second-line) immunosuppressive therapy. Patients with acute GVHD that is resistant to treatment with glucocorticoids have a dismal long-term prognosis, with an overall survival rate of only 5 to 30%. Prognostic factors for long-term outcome include serum biomarkers, such as ST2 and REG3-alpha, and grade [Major-Monfried et al. 2018]. Steroid-refractory grade IV aGVHD is typically fatal [Jacobsohn 2007; Deeg 2007; Jaglowski 2014; Martin 2012].

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Ruxolitinib (Jakafi, Incyte), a JAK1/JAK2 inhibitor is the only approved product for the treatment of SR-aGVHD. There are no drugs approved for treatment of SR-aGVHD in patients less than 12 years old.

Ruxolitinib was approved for treatment of SR-aGVHD in adult and pediatric patients 12 years and older in May 2019. Approval was based on Study INCB 18424-271 (REACH-1; NCT02953678), an open-label, single-arm, multicenter trial that included 49 patients with grades 2-4 SR-aGVHD occurring after allo-HSCT [Przepiorka et al. 2019]. Table 1 shows the results for the REACH-1

efficacy population; the overall response rate was 57% (95% CI: 42%, 71%). In REACH-2, the subsequent randomized trial for SR-aGVHD (not reviewed by FDA), the reported ORR was 62% with ruxolitinib and 39% with best available therapy [Zeiser et al 2020].

Table 1: Ruxolitinib for Treatment of SR-aGVHD

	Ruxolitinib Approval	REACH-2	
	Primary Efficacy Population N=49	Ruxolitinib n=154	Control n=155
Overall Response ^a	28 (57%	96 (62%	61 (39%
95% CI)	42%, 71%)	54%, 70%)	32%, 48%)
Complete Response	15 (31%	53 (34%	30 (19%
Very Good Partial Response	2 (4%)	-	-
Partial Response	11 (22%	-	-
Median duration of response	16 days	-	-
95% CI	9 days, 83 days		
Median time to death or new therapy	173 days	-	-
95% CI	66 days, NE		

Abbreviations: NE, not estimable

^a Overall responses includes CR + VGPR + PR

Source: Ruxolitinib US Prescribing Information (February 2020); Zeiser et al. (2020)

Multiple other immunosuppressive drugs have been studied in retrospective analyses or Phase 1 or 2 trials off-label for treatment of SR-aGVHD. No agent has been identified as being superior to others. A 2012 comprehensive review performed by the American Society of Blood and Marrow Transplantation (ASBMT) analyzed CR/PR rates for second-line therapies used in aGVHD treatment trials [Martin 2012]. The authors identified the asymptotic CR/PR rate for the aggregated 29 studies as 58%, but the response definition and timing of assessment were not standardized. There were only 2 studies in this series that reported Day-28 response with response specifically excluding further systemic treatment. In these 2 studies, which included 101 patients treated with antithymocyte globulin, the CR rate was 20% and the CR/PR rates were 18% and 54% [Martin 2012].

2.3 Safety and Efficacy of Pharmacologically-Related Products

Product Background

Product Name: Remestemcel-L

Chemical Name Structure: Remestemcel-L is composed of ex-vivo culture-expanded adult and human mesenchymal stromal cells (ceMSCs) derived from bone marrow aspirates.

Safety Risks

There are no approved ceMSCs. Based on the proposed mechanism of action of remestemcel-L (immunosuppression), the potential safety risks include infection and relapse. Based on the product class (third-party somatic cells capable of proliferation), the potential safety risks include transmission of infection, ectopic tissue formation and anti-HLA antibody formation. Based on the

drug product formulation (including DMSO as well as bovine, porcine and human protein), the potential safety risks include hypersensitivity reactions and infusions reactions, including nausea, vomiting, diarrhea, renal failure, hypertension, arrhythmias, bronchospasm and cardiac arrest. [Santos, Figueria-Coelho et al. 2003]

2.4 Previous Human Experience with the Product Including Foreign Experience)

The remestemcel-L product that is the focus of this biologics license application has not been marketed anywhere in the world.

In Canada, remestemcel-L received conditional approval (cNDS) from Health Canada in 2012 for SR-aGVHD in pediatric patients under the tradename/proprietary name, PROCHYMAL. The product has not been marketed.

In Japan, TEMCELL® HS Injection (JCR Pharmaceuticals Co., Ltd.), which is a human allogeneic bone marrow derived MSC product, was approved 26Nov2016 for the treatment of aGVHD in both adults and children after HSCT. This was based on 75 patients enrolled on the pediatric expanded access protocol (EAP) trial, 12 single-patient use (SPU) Studies and the 27 pediatric patients from Study 280 (14 treated/13 placebo).

TEMCELL® HS Injection was developed by JCR Pharmaceuticals Co., Ltd. after in-licensing the technology for manufacturing hematopoietic MSCs from Osiris Inc. The technology has since been acquired by Mesoblast and is the basis of the development of remestemcel-L for treatment of SR-aGVHD in pediatric patients. The JCR application in Japan relied on the Osiris-generated pre-clinical and clinical data. TEMCELL® HS Injection is in the same product class as Mesoblast's remestemcel-L. It cannot be considered identical, due to differences in manufacturing steps, (b) (4), and concentration of the final formulation.

[Source: Mesoblast BLA submission Module 1.13.10]

2.5 Summary of Pre- and Postsubmission Regulatory Activity Related to the Submission

Regulatory Background Timeline

09/25/1998	Initial IND Submitted (Sponsor Osiris Therapeutics)
07/1/2004	Type C Meeting to obtain FDA agreement on plans for toxicology studies to support product development of OTI-010 and filing the BLA.
12/2005	Orphan Drug Designation granted for aGVHD
01/25/2007	Type A Meeting to discuss a CMC SPA submission – non-concurred.
11/16/2007	FTD Granted for the treatment of patients with grade II to IV GI GVHD after allo-HCT to resolve acute GI GVHD by day 42 after the treatment.
10/09/2008	Pre-BLA Package
01/20/2009	BLA 125334 Part 1 received.
04/23/2009	BLA data submission plan
12/22/2009	Type A Teleconference Meeting
03/05/2010	BLA 125334 Withdrawal
02/11/2011	Type A- Pre-BLA/Face to Face
01/04/2013	Clinical Study Report of expanded access protocol #275
01/31/2014	Change in Sponsor from Osiris to Mesoblast, Inc.
02/17/2014	Request for (b) (4) for treatment of pediatric severe steroid refractory aGVHD, post allogeneic hematopoietic stem cell transplant for hematologic malignancies.
05/15/2014	Request for (b) (4) denied

05/20/2014	The sponsor requested an informal meeting to discuss why (b) (4) was denied. FDA advised the sponsor that a single-arm trial that isolated the effect of Prochymal in a population with no available therapy might be sufficient to support AA, but a randomized trial would be needed for regular approval.
07/9/2014	Type C meeting
09/5/2014	New Phase 3 Study MSB-GVHD001, A Single-arm, Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stem Cells, for the Treatment of Pediatric Patients who have Failed to Respond to Steroid Treatment for Acute GVHD.
09/12/2014	New Phase 3 Study MSB-GVHD002, Safety Follow-up Through 180 Days of Treatment with Remestemcel-L in Study MSB-GVHD001 in Pediatric Patients who Have Failed to Respond to Steroid Treatment for Acute GVHD.
10/9/2015	CMC product comparability study
06/9/2016	Type C meeting to discuss the CMC and facilities topics pertaining to remestemcel-L, nonclinical and clinical programs, and regulatory pathways in support of a BLA filing for (remestemcel-L) in the treatment of pediatric aGVHD.
02/28/2017	FTD Granted for the treatment of steroid refractory acute graft-versus-host disease intended to improve overall response rate of acute graft-versus-host disease in pediatric patients.
11/29/2018	Type C / Pre-IND Teleconference Meeting
04/05/2019	Pre-BLA Meeting
06/04/2019	First portion of BLA 125796 submitted
01/31/2020	BLA 125706 received
03/20/2020	BLA Applicant orientation meeting
06/01/2020	BLA Midcycle Communication
07/23/2020	BLA Late Cycle Meeting
08/13/2020	ODAC Meeting

Key Regulatory Advice

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.
- Study 275 is not an adequate and well-controlled trial and does not provide confirmatory evidence of efficacy to support a license application.
- In two meetings between Mesoblast and FDA in July of 2014 (CBER Meeting ID: 9418) and June of 2016 (CBER Meeting ID: 10206), after FDA's review of preliminary results from Study 275, Mesoblast was informed that the analysis of Study 275 may provide some support for remestemcel-L's clinical benefit in treating patients who had failed to respond to steroid therapy, but that the analysis was confounded by multiple concomitant GVHD treatments. FDA therefore recommended Mesoblast conduct an adequately-designed and well-controlled trial for treatment of SR-aGVHD in pediatric patients.

- Study 280 is a negative trial, so subgroup analyses would not be sufficient to support a marketing application.
- The results of Studies 275 and 280 may inform hypotheses 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 Study MSB-GVHD001 as the sole basis of efficacy. The Information requests to the Applicant from the Clinical Review Team can be found in Table 2.

Table 2: BLA Information Requests (IR) from Clinical and Statistical Reviewers

Clinical Information Request	Date of Request
Clinical IR #1	1/31/2020
Clinical IR #2	2/10/2020
Clinical IR #3	2/13/2020
Clinical IR #4 IR #5	2/25/2020
Clinical IR #5 IR #6	3/4/2020
Clinical IR #6 IR # 8	3/6/2020
Clinical IR #7 IR #10	3/23/2020
Clinical IR #8 IR #11	3/26/2020
Clinical IR #9 IR #12	4/1/2020
Clinical IR #10 IR #13	4/2/2020
Clinical IR #11 IR #14	4/6/2020
Clinical IR #12 IR #22	6/2/2020
General IR IR#29	7/1/2020
Clinical IR #13 IR #30	7/8/2020

The BLA clinical review covered the original BLA submission and the following amendments (Table 3):

Table 3: BLA Amendments – Clinical

Amendment Number	Date of submission	Amendment Description - Clinical Summary
0	05/29/2019	Original Submission
1	09/04/2019	Request for review of proposed proprietary name
2	12/27/2019	Clinical module
4	2/11/2020	Response to Clinical IR #1/teleconference summary
5	2/21/2020	Updated clinical datasets ISS/ISE; Additional response to Clinical IR #1
6	2/27/2020	Response to Clinical IR #4
7	3/2/2020	Updated clinical datasets ISS/ISE; Response to Clinical IR #5
8	3/3/2020	Response to Clinical IR #2; Updated datasets GVHD-001
9	3/6/2020	Response to Clinical IR #3; Updated datasets studies 260, 261, 265, 280
12	3/11/2020	Response to Clinical IR #5; Updated datasets ISS/ISE
13	3/16/2020	Response to Clinical IR #6; Updated datasets studies 260, 261, 265, 280
16	4/2/2020	Response to Clinical IR #8; Updated CRFs study GVHD-001
17	4/7/2020	Response to Clinical IR #7; Updated datasets GVHD-001, ISS/ISE
20	4/23/2020	Response to Clinical IR #9; Updated datasets ISS/ISE
21	5/1/2020	Response to Clinical IR #7; Updated datasets GVHD-001, ISS/ISE
22	5/4/2020	Response to Clinical IR #4
25	5/13/2020	Updated PI
31	6/12/2020	Response to Clinical IR #7 & #10; biomarker report, clin/pharm summary
32	6/15/2020	Response to IR #24; Updated ISE datasets following midcycle meeting
40	7/6/2020	Response to IR #27 immunogenicity)
41	7/10/2020	Response to IR #29 Applicant Briefing Document TOC
43	7/14/2020	Response to Clinical IR #13

No amendments received after July 15, 2020 were reviewed by the Clinical Review Team.

2.6 Other Relevant Background Information

For a single-arm trial for treatment of steroid-refractory aGVHD to be interpretable, it is critical that the accrued patients have unequivocal steroid-refractory disease. Patients who did not receive an adequate trial of steroids or who are improving after only a short course of steroids would not be unequivocally steroid-refractory. For the definition of steroid-refractory acute GVHD, FDA has accepted the following criteria: (a) progressed after 3 days of treatment with MP 2 mg/kg/day equivalent, (b) did not improve after 7 days of treatment with MP 2 mg/kg/day equivalent, (c) progressed to a new organ after treatment with MP 1 mg/kg/day equivalent for skin and upper gastrointestinal (GI) GVHD, or (d) recurred during or after a steroid taper [Przepiorka, et al. 2019].

For treatment of aGVHD, CR+PR at day 28 is a recognized efficacy endpoint [NIH-FDA aGVHD Endpoint Workshop, 2009; Pavletic, 2012], and response criteria have been established [Martin et al. 2009]. FDA also considers duration of response an important element of the assessment of benefit [Przepiorka, et al. 2019].

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

In the initial submission, the data supporting the efficacy endpoint were not provided in a reviewable format. Corrected datasets were submitted, and at the time of filing, the application was adequately organized and integrated to accommodate the conduct of a complete clinical review.

During the course of the review, the following issues with data quality were identified:

- Multiple datasets were submitted as compressed files. The Applicant was requested to submit data files individually rather than in compressed format. The application contains both the individual and compressed formats.
- The Applicant was asked to provide flags to identify the drugs used for salvage treatment of acute GVHD after start of study therapy. The ISS data file adcm.xpt contains variables for such flags (PRREGFL, GVTRTFL, ANTNEOFL, IMMUNOFL), but the definitions for these variables is not consistent with the request. An excel spreadsheet was provided by email on 02/28/202 with the information requested. As of the date of finalization of this review, the ISS adcm.xpt has not been corrected.
- A revised version of the ISE adefx.xpt was received on 7/15/2020. In this file, one or more elements of the GVHD staging data after Day 28 was missing for approximately 7% of the assessments. For the purposes of calculation of DOR, duration was calculated using only nonmissing data.
- The ISS file adex.xpt variable EXTRT was blank for approximately 94% of the rows. For the purposes of this review, the treatment administered was imputed to be the drug listed in the variable TRT01A when EXTRT was blank. It should be noted that EXTRT was complete for all entries for Study MSB-GVHD001.
- As of 7/15/2020, all revisions to the data were made in the ISS/ISE datasets only. The individual study datasets were not updated. The ISS/ISE datasets were used for this review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant provided adequate documentation that the research study conducted was in accordance with Good Clinical Practices.

The Office of Compliance and Biologics Quality Bioresearch Monitoring Branch (BIMO) conducted inspections for Study MSB-GVHD001 at Duke University Medical Center (Durham, NC), Memorial Sloan Kettering Cancer Center (New York, NY), Lurie Children's Hospital (Chicago, IL) and Oregon Health and Science University, Doernbecher Children's Hospital (Portland, OR). These sites had the highest accrual, highest number of study violations per patient, and/or greatest impact on the primary endpoint.

At the time of this review, inspection review of all four sites have been completed and revealed *No Action Indicated*. The Applicant (Mesoblast) was not audited. Based on the inspection results, the study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indication.

3.3 Financial Disclosures

Covered clinical study (name and/or number): GVHD-001		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 34 principal investigators/232 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry: Financial Disclosure by Clinical Investigators. No financial conflicts of interest were identified.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Remestemcel-L drug substance consists of viable mesenchymal stromal cells for allogeneic use. With intravenous administration, systemic dissemination is expected. Remestemcel-L drug product is formulated at 6.68×10^6 cells/mL in Plasma Lyte A with human serum albumin (HSA) and dimethylsulfoxide (DMSO).

Hypersensitivity and acute infusion reactions to remestemcel-L are potential risks, and these reactions may be due to the product, dimethyl sulfoxide (DMSO), trace amounts of porcine and

bovine proteins, or human albumin. For these reasons, patients are premedicated and monitored for signs and symptoms of hypersensitivity reactions when remestemcel-L is administered. Additionally, due to the ability of human mesenchymal stromal cells to differentiate into mesenchymal lineage cells, such as bone, cartilage and fat cells, under specific conditions in the laboratory, there is a theoretical risk of ectopic tissue or tumor formation following treatment with remestemcel-L.

Since ceMSC is allogeneic product, there is a potential for development of anti-drug (donor) antibodies (ADA) or anti-HLA antibodies.

Since 2003, 608 DP lots were dispositioned for release and used in the clinical studies. The clinical trial lots were produced using 3 different manufacturing processes (DP1, DP2 and DP3) Table 4). DP3 is the proposed commercial process. Comparability of product produced by these 3 processes was not established. [Source: CMC communication from Mathew Klinker, email received: Tuesday, March 17, 2020 3:24 PM]

Table 4: Summary of DP Lots Used In Clinical Trials During Manufacturing Development

DP Manufacturing Development Stage ^a	Site	Year	DP Lots Released	DCB used in DP Manufacture
DP1	Osiris Baltimore or LWI	2003- 2007	(b)	(4)
DP2	LWI	2008 and 2009		
DP3 (commercial process)	LBSS	2015 to present		

[Source: Mesoblast Module 3.2.P.2.3.3 Manufacturing Process Development, Table 11]

Table 5 shows the manufacturing processes used for the lots by GVHD clinical trial. Product from DP2 was used for 8 patients in Study MSB-GVHD001; additional statistical analyses will need to be performed to assess the clinical comparability of the DP2 lots used in this trial. The lack of comparability of DP1 to DP3 precludes use of nearly all other GVHD trials in the assessment of efficacy. The safety data from all lots can be relied upon only as class-specific data.

Table 5: Summary of DP Lots Used in aGVHD Clinical Trials

Drug Product Utilized	GVHD Study ID #						
	GVHD 001	GVHD 260	GVHD 265	GVHD 270	GVHD 275	GVHD 276	GVHD 280
DP1		X	X	X	X		X
DP2	X (n=8)		X		X	X	X
DP3	X n= 46)						

[Source: FDA generated table from Report MR-104, Attachment 7.1. Report MR-104, Attachment 7.2]

4.2 Assay Validation

Immunogenicity assay validation data were not submitted.

4.3 Nonclinical Pharmacology/Toxicology

Remestemcel-L is a human-specific drug product; there is no relevant animal species to test pharmacokinetics. No animal studies have been performed to evaluate the effects of remestemcel-L on carcinogenesis, mutagenesis or impairment of fertility.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for remestemcel-L is unknown but may be related to the immunomodulatory activities of ceMSCs. Data from in vitro studies demonstrate that ceMSCs inhibit T cell activation as measured by proliferation and secretion of pro-inflammatory cytokines.

4.4.2 Human Pharmacodynamics (PD)

The Applicant provided the following PD information: human pharmacodynamic data were obtained from analysis of blood samples in pediatric subjects with steroid-refractory aGVHD (n=40; age range 0.6-17 years) following treatment with remestemcel-L at a dose of 2x10⁶ cells/kg. At baseline, elevated levels of tumor necrosis factor receptor type I (TNFR1) and suppressor of tumorigenicity 2 (ST2) were observed consistent with the inflammatory state of aGVHD. Treatment with remestemcel-L reduced the levels of TNFR1 and ST2 by 76% and 72%, respectively at Day 180 as compared to baseline values. Further, the circulating levels of CD3+CD4+CD25+HLA-DR+ T cells, which represent activated T cells, were reduced by 54% at Day 180 following treatment with remestemcel-L as compared to the baseline values.

Data to confirm the % change at 180 as compared to baseline values for levels of TNFR1, ST2 and circulating levels of CD3+CD4+CD25+HLA-DR+ T cells were not provided.

4.4.3 Human Pharmacokinetics (PK)

Pharmacokinetic studies of remestemcel-L have not been performed in humans.

4.5 Statistical

The statistical reviewer replicated the primary study endpoint analyses cited by the applicant were supported by the submitted data. The statistical review further performed subgroup analyses and sensitivity analyses as requested by the clinical review team. None of the analyses performed changed the highly significant departure from the null hypothesis of ORR rate of 0.45.

4.6 Pharmacovigilance

No safety concerns have been identified that would require a REMS or PMR. The Applicant's proposed intervention plan for identified risks: acute infusion reaction, infections, pulmonary complications, and neurologic events include routine pharmacovigilance interventions. In addition, routine pharmacovigilance will be employed to monitor potential risks of: ectopic tissue formation, suspect transmission of infectious agents, hypersensitivity to porcine/bovine excipients, adverse effects from DMSO exposure, and new malignancy.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

One single-arm trial, Study MSB-GVHD001, provides the main clinical data for the BLA application. The primary efficacy analysis for the BLA was based on data from Study MSB-GVHD001 (n=54, treated population).

The clinical review focused on confirmation of the primary endpoint, overall response rate (ORR) at day 28, through examination of the primary datasets, the submitted electronic case report forms

(eCRFs) and correlation with secondary endpoints such as complete response (CR) at day 28, overall survival (OS) at day 100, and exploratory endpoints such as duration of response (DOR), as well as an analysis of safety and the overall benefit and risk evaluation (Section 6.0 of this review).

The supportive efficacy and safety analysis set included data from the several additional aGVHD treatment trials including Studies: MSB-GVHD001/002, 275, 280, 260, 261, and 265. Due to differences in patient population, trial design, study conduct, primary endpoint evaluations and drug products used, the additional aGVHD studies will be discussed in composite in Section 7.0 of this review. In addition, because of the substantial differences between the clinical trials regarding the patient population and treatment plan, the results are presented side-by-side and there was no pooling of data.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- IND 7939 eCTD documents and FDA reviews
- BLA 125706 eCTD documents, datasets, and clinical amendments listed in Table 3 (Section 2.5 of this review), which include the Applicant's responses to clinical IRs.

5.3 Table of Studies/Clinical Trials

Nineteen clinical studies were conducted, 14 prospective treatment trials and 5 follow up safety trials, in addition to several individual subject expanded access protocols under IND #007939 and multiple emergency compassionate use investigator-initiated trials. A total of 1,517 subjects have participated in studies worldwide involving the use of remestemcel-L. Across all studies, a total of 1,114 subjects have been exposed to remestemcel-L, and 403 have received placebo. In the aGVHD studies, 654 (333 pediatric and 321 adult) subjects received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. An overview of all studies is shown in Table 6.

Table 6: List of Studies

Study Identifier (Phase)	Indication	Subjects (N)	Efficacy	Safety
MSB-GVHD001 (Phase 3)	SR aGVHD	Pediatric; 55 enrolled, 54 treated	Y	Y
MSB-GVHD002 (Phase 3)	SR aGVHD	Pediatric; 32 enrolled	Y	Y
Study 275a (EAP)	SR aGVHD	Pediatric; 241 enrolled and treated	Y	Y
280 (Phase 3)	Other GVHD	Total 259 enrolled; Adult: Remestemcel-L: 159 / Placebo: 73 Pediatric: Remestemcel-L:14/Placebo:13	Y	Y
265 (Phase 3)	Other GVHD	Total 194 enrolled Remestemcel-L: 97 / Placebo: 95	Y	Y
260 (Phase 2)	Other GVHD	Adult: 32 enrolled and treated	N	Y
261 (Phase 2)	Other GVHD	Adult: 32 enrolled	N	Y
276 (EAP)	Other GVHD	Adult: 18 enrolled and treated	N	Y
207	SSS aGVHD	Adult, single subject treated	N	Y
208, 209	SSS aGVHD	Adult: 1/ Pediatric: 1	N	Y
GVHD 270/271/270E	SSS aGVHD	11 enrolled (10 adults, 1 pediatric)	N	Y
210	SSS aGVHD	Adult; 2 subjects treated	N	Y
215-218, 220-222, 224-225, 227-233, 235-236	SSS aGVHD	Pediatric; 10 single subjects treated	N	Y
Investigator Initiated Studies	SSS aGVHD	Pediatric: 12 Adult: 4		
401 (Phase 1)	AMI	Adults: 60 enrolled, 53 treated Remestemcel-L: 34/ Placebo: 19	N	Y
402 (Phase 1)	AMI	Same as Study 401	N	Y

403 (Phase 2)	AMI	Adults: 220 enrolled Remestemcel-L: 110 / Placebo: 110	N	Y
601 (Phase 2)	CD	Adults: 10 enrolled Remestemcel-L Low Dose 2M cells/kg: 5 Remestemcel-L High Dose 8M cells/kg:5	N	Y
602 (Phase 2)	CD	Same as Study 601	N	Y
603 (Phase 3)	CD	Adults: 269 enrolled Remestemcel-L: 171 / <u>Placebo</u> : 98	N	Y
610 (extension study for 603)	CD	Adult subjects: Enrolled & randomized: 69	N	Y
611 (extension study for 603)	CD	Adults: 73	N	Y
620 (EAP)	CD	Adults: 13 enrolled	N	Y
801 (Phase 2)	COPD	Adults: 62 enrolled Remestemcel-L: 30 / Placebo: 32	N	Y
901 (Phase 2)	T1DM	63 enrolled, Remestemcel-L: 42 (9 pediatric) / Placebo: 21 (3 pediatric)	N	Y

[FDA analysis]

5.4 Consultations

5.4.1 Advisory Committee Meeting

An ODAC meeting was held on August 13, 2020 to discuss the product quality and efficacy of Biologics License Application (BLA) 125706, remestemcel - L for the treatment of SR-aGVHD in pediatric patients. The morning session addressed CMC issues and questions, and the afternoon session addressed the clinical review issues.

Product Quality Session

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

Discussion Question #2: 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.

Summary of CMC Discussion: The CMC discussion was primarily theoretical, and no specific advice was given to FDA.

Clinical Session

Discussion Question #1: 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.

Discussion Question #2: 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 remain unclear.

2a: 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.

2b: 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.

Summary of Clinical Discussion:

The one dissenting committee member voiced that the clinical evidence was not high quality, not compelling, and not sufficiently rigorous to meet regulatory standards. The remaining committee members discussed that although there were issues identified with the clinical trial design, this trial provided evidence of efficacy in SR-aGVHD in pediatric patients which is a serious unmet medical need, and the safety profile was favorable when compared to current SOC practices. Additionally, some AC members noted that it may be difficult to perform a randomized, placebo-controlled trial in this disease setting, since use of placebo may not be ethical. Most members additionally voiced a recommendation that the Applicant perform additional adequate and well-controlled studies, such as a head-to-head comparison to other treatments for aGVHD, to confirm the efficacy signal, further explore efficacy in adults with aGVHD, evaluate additional biomarker data, and identify prognostic indicators of response to this therapy.

Voting Question #1: Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD?

Vote: Yes = 9 No = 1 Abstain = 0

5.4.2 External Consults/Collaborations

None

5.5 Literature Reviewed

1. 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.
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.

3. Deeg HJ, How I treat refractory acute GVHD. *Blood*. 2007 May 15; 109(10): 4119–4126.
4. D’Souza A, Lee S, Zhu X, et al. Current use and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2017 September; 23(9): 1417–1421.
5. Faraci M, Calevo MG, et al. 2019) Etanercept as treatment of steroid-refractory acute GVHD in pediatric patients. *Biol Blood Marrow Transplant*;25(4):743-748.
6. FDA Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft FDA Guidance for Industry, 2019. <https://www.fda.gov/media/133660/download>
7. FDA Guidance for Industry Clinical Trials Endpoints for Approval of Cancer Drugs and Biologics. <https://www.fda.gov/media/71195/download>
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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MSB-GVHD001

Study MSB-GVHD001, “A Single-arm, Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid Treatment for Acute GVHD.”

6.1.1 Objectives (Primary, Secondary, Exploratory)

Primary Objectives

1. To evaluate the efficacy of remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT.
2. To gather additional information on the safety of remestemcel-L in pediatric subjects with Grades B-D aGVHD that has failed to respond to steroid treatment post allogeneic HSCT.

Secondary Objectives

1. To determine the correlation between response to remestemcel-L at Day 28 and survival at Day 100.
2. To obtain quality of life data on remestemcel-L-treated subjects via the Pediatric Quality of Life Inventory (PedsQL™); and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report (Appendix 3).
3. To measure the functional status of remestemcel-L-treated subjects using the Karnofsky/Lansky scale (Appendix 4).

Exploratory Objective

1. To capture and analyze biomarker expression by remestemcel-L-treated subjects.

6.1.2 Design Overview

This trial was a prospective, multi-center, single-arm study.

6.1.3 Population

Eligible subjects were male and female, between the ages of 2 months and 17 years inclusive, with aGVHD following allogeneic hematopoietic stem cell transplant (HSCT) that has failed to respond to treatment with systemic corticosteroid therapy. Subjects may have had Grades C and D aGVHD involving the skin, liver and/or gastrointestinal (GI) tract or Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease. Acute GVHD was defined as the presence of skin rash and/or persistent nausea, vomiting, and/or diarrhea and/or cholestasis

presenting in a context in which aGVHD is likely to occur and where other etiologies such as drug rash, enteric infection, or hepatotoxic syndromes were unlikely or had been ruled out.

Steroid refractory was defined as any Grade B-D (IBMTR grading) aGVHD that shows progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day of methylprednisolone or equivalent.

6.1.4 Study Treatments or Agents Mandated by the Study

Initial Therapy

Subjects were to be treated with intravenous (IV) remestemcel-L at a dose of 2×10^6 MSC/kg (actual body weight at screening) twice per week for each of 4 consecutive weeks. Infusions were to be administered at least 3 days apart and no more than 5 days apart for any infusion. All 8 infusions must be administered by Day 28 ± 2 days.

Subjects may continue to be treated with a stable dose of systemic steroid therapy until they are eligible for steroid taper and may continue on an established regimen of baseline prophylactic therapy following initiation of remestemcel-L (Day 0). No other medications for the treatment of aGVHD are to be introduced to subjects during the initial 28 days post remestemcel-L administration unless disease progression, as defined below, has occurred. Addition of other secondary line agents prior to Day 28 would constitute failure to respond, in which case, the treated subject would remain on the study for safety follow up.

Any changes in baseline prophylaxis regimen should be recorded in the eCRF and reason for change in regimen should be discussed with the Medical Monitor. Changes in dose or prophylactic agent due to administration route intolerance or toxicities are allowed at the discretion of the investigator with prior approval from the Medical Monitor as these changes could be confused as second-line therapies.

Steroid taper

If improvement in GVHD, as defined by OR, is observed for a period of 3-5 days and after at least two doses of remestemcel-L, the dosing of methylprednisolone or equivalent may be tapered. A steroid taper rate of at least 10% of the dose per week, not exceeding 25% of the dose per week, is recommended as described in Appendix 5 of the clinical trial, with the goal of discontinuing steroid by 10 weeks after initiating taper.

6.1.5 Directions for Use

- Premedicate with diphenhydramine 0.5-1 mg/kg (up to 50 mg) and hydrocortisone 0.5-1 mg/kg (up to 50 mg) 30-60 minutes prior to administration of each dose of RYONCIL
- For patients weighing 35 kg and above, infuse RYONCIL intravenously at a controlled rate of 4-6 mL/minute using an infusion pump.
- For patients weighing less than 35 kg, infuse RYONCIL over 60 minutes.
- In the event that the patient develops tachypnea, cyanosis, hypoxemia, hypotension or other signs of an infusion reaction, discontinue treatment with RYONCIL and provide appropriate care.

6.1.6 Sites and Centers

Study MSB-GVHD001 was open at 27 centers in the U.S., and 20 centers enrolled subjects onto the trial.

6.1.7 Surveillance/Monitoring

Table 7: MSB-GVHD001 Study Calendar for Monitoring

Study Days	Screening/Baseline	Treatment										Study Visits			End of Study Day 100	Unscheduled
	Day -4 to Day -1	Day 0	Day 7	Day 14	Day 21	Day 28 ^e	Day 35	Day 42	Day 49	Day 56	Weekly (From Day 63 to Day 100) ^a	±7 days				
Visit window	N/A	N/A	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±7 days				
Infusions ^{a, b, c, d}	No infusions scheduled	← ← Infusions 2x per week → →					If eligible, infusions 1x per week (continued therapy) or 2 x per week (flare therapy)					No infusions scheduled				
Screening/Baseline/Follow-up Assessments																
Demography/informed consent ^e	X															
Inclusion/exclusion criteria	X															
Vital signs (HR, BP, Temp, RR, Oxygen Saturation)	X	X		X	X	X	X	X	X	X	X	X	X	X		
Height and weight	X													X		
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X	X		
CMV screening ^f	X		X	X	X	X	X	X	X	X	X	X	X	X		
HIV and hepatitis testing ^g	X															
Oncology history: Underlying malignant or leukemic disease/conditioning regimen/HSCT/diagnosis of initial GVHD/diagnosis of steroid refractory GVHD	X															
Medical history and current conditions	X															
Hospitalization information (if applicable) ^h	X					X							X	X		
Hematology laboratory tests ⁱ	X					X							X	X		
Chemistry laboratory tests	X					X							X	X		
Urinalysis	X					X							X	X		
ESR (local labs only)	X					X							X	X		
Optional Biomarkers ^j	X					X							X	X		
Acute GVHD assessment (Skin, Lower GI, Upper GI, Liver) ^{a, b}	X			X	X	X	X	X	X	X	X	X	X	X		
Chronic GVHD Assessment	X			X	X	X	X	X	X	X	X	X	X	X		
Prior and concomitant medication ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Transfusion ^l														X		
[Optional] CT scan or MRI (Chest, Abdomen and Pelvis) ^m	X												X	X		
12-Lead ECG	X												X	X		
Karnofsky or Lansky scale ⁿ	X					X					X		X	X		
Quality of Life Measures ^o	X					X					X		X	X		
Termination/end of study													X	X		
TREATMENT																
Investigational agent infusions ^{c, d, p}		X	X	X	X	X	X	X	X	X	X			X		
Investigational agent pre-medication		X	X	X	X	X	X	X	X	X				X		
Continued/flare treatment ^q						X					X			X		
Therapy assessment/current GVHD response status ^b				X	X	X	X	X	X	X	X		X	X		
SAFETY ASSESSMENTS																
Pregnancy test ^q	X										X		X	X		
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Infusional toxicity ^r		X	X	X	X	X	X	X	X	X	X	X	X	X		

- Weekly GVHD assessments must be performed after infusion of the 2nd dose of remestemcel-L for that week. The weekly assessment visits should be conducted at least 24 hours after the most recent remestemcel-L infusion.
- The Day 28 and Day 56 assessments must be at least 24 hours after the last dose of remestemcel-L is administered.
- Infusion will be administered at least 3 days apart and a maximum of 5 days apart. All 8 infusions (Initial therapy) must be administered within 28 days (± 2 days). All infusion doses will be based on weight determined at screening.
- Eligible subjects will receive an additional 4 once weekly infusions ± 2 days) within 1 week after Day 28 until Day 56. Subjects who have a GVHD flare of Grade B-D after achieving a CR at day 28 or day 56 (following Continued Therapy) and before day 70 may receive additional remestemcel-L treatment per the Initial Therapy plan.
- When possible, subjects should be presented with the IRB/EC approved consents for MSB-GVHD001 and MSB-GVHD002 simultaneously at the time of consent onto this Study.
- CMV screening will be conducted weekly during the study. Investigators should provide standard of care treatment for viral infections as appropriate, including prophylaxis and treatment if there is evidence of viral reactivation and/or infection.
- If HIV and/or hepatitis testing was performed within 3 months of screening, the results from these tests may be used instead. The determination of active hepatitis B or C is at the discretion of the Investigator.
- Record all hospital stays occurring during the course of the trial starting with the hematopoietic stem cell (HSC) transplant hospitalization.

- i. Collection for local labs should be performed for all patients at screening. If the age/weight of the subject permits, collection for central labs should also be performed at screening, in addition, in order to facilitate comparison of later samples sent to the central lab. If age/weight of the patient does not allow for this additional blood volume, then local labs at screening will serve as baseline labs. Viral screening will also be performed at screening with exception of CMV, which will be conducted as noted in the table above.
- j. Biomarkers may include IL-2Ra, soluble IL-2Ra, soluble TNFRI, hepatic growth factor, Elafin, and Islet-derived 3a, assessed by (b) (4), CD3+, CD4+, CD8+, and CD25+ T- cell counts, which will be measured by (b) (4).
- k. Remestemcel-L treatment for flare to be added where applicable. Flare therapy must be initiated before Day 70.
- l. Total number of units transfused of blood product will be recorded in the eCRF during study.
- m. CT/MRI scans are optional and may be omitted at the discretion of the Investigator, provided the rationale for omission is documented in the source documents.
- n. Lansky scale for subjects less than 16 years of age; Karnofsky for subjects 16 years of age and older. See Appendix 4 for the Karnofsky and Lansky scales.
- o. Quality of life will be assessed using the PedsQL and the pediatric global health-related quality of life (HRQOL) Parent Proxy Report
- p. Infusions noted in this table are limited to those just prior to assessments
- q. A serum pregnancy test will be performed at Screening for all females with child bearing potential. Post-screening, a urine dipstick pregnancy test will be performed on all females with childbearing potential at Day 56, Day 100, and for Unscheduled Visits. If there is a positive urine dipstick, a serum sample should be sent to central lab for confirmation. Guidance on childbearing potential and pregnancy testing is located in Appendix 6.
- r. Infusional toxicity on each day of remestemcel-L administration from the start of infusion to two hours after start of IMP administration.

[Source: Mesoblast BLA submission, Module 5.3.5.1, Clinical Study Report MSB-GVHD001, section 16.1]

6.1.8 Endpoints and Criteria for Study Success

Efficacy Endpoints

Primary Endpoint

1. The primary endpoint is the rate of overall response (OR), defined as complete response (CR) or partial response (PR; see Table 4 in Study MSB-GVHD001), in the study population at 28 days post initiation of therapy (Study Day 1, identified as Day 0 in the Study) with remestemcel-L.

Secondary Endpoints

1. OS at Day 100 post initiation of remestemcel-L therapy
2. OS at Day 100 post initiation of remestemcel-L therapy, stratified by responder status at Day 28 (responder versus nonresponder)
3. OS at Day 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade and organ involvement
4. Rate of VGPR at Day 28 post initiation of remestemcel-L therapy
5. Rates of OR and CR + VGPR at Day 56 and Day 100 post initiation of remestemcel-L therapy
6. Rates of OR and CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by organ involvement
7. Rates of OR and CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by individual subject organ involvement and MacMillan risk score at baseline
8. Rates of OR and CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by baseline GVHD grade
9. Rate of aGVHD progression requiring additional GVHD medications/therapy through Day 100 post initiation of remestemcel-L therapy
10. Effect of additional remestemcel-L therapy after Day 28 on rate of OR and CR + VGPR at Days 56 and 100 post initiation of remestemcel-L therapy
11. Assessment of change in organ involvement and organ staging, from baseline to Day 28 post initiation of remestemcel-L therapy.

Exploratory Endpoints

1. Change in use of concomitant medications for acute GVHD

2. Change in quality of life from baseline (as assessed by the PedsQL™ and the HRQOL Parent Proxy Report)
3. Change in functional status from baseline (as assessed with the Karnofsky/ Lansky Performance scores)
4. Duration of overall response from Day 28 through Day 100.
5. Survival from date of transplant
6. Change in biomarker expression (optional).

Safety Endpoints

1. Adverse events
2. Serious Adverse Events
3. Infusional toxicity
4. Formation of ectopic tissue foci.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Applicant's pre-specified Statistical Analysis Plan (Statistical Analysis Plan v5.0 08 February 2018) is outlined below, see the CBER Statistician's review and Section 6.1.11 (Efficacy Analysis) for additional FDA statistical considerations.

Sample size

The primary efficacy endpoint of the trial as Day-28 overall response rate within the FAS population. In this study, a 28-day OR rate for a subject population treated only with steroids was anticipated to be 65% based on the rate seen in Study 275 and for the remestemcel-L-treated pediatric subgroup of Study 280. Hence, $p=0.65$ was chosen as the alternative hypothesis.

For assessment of efficacy, an effect size of 20% was deemed clinically meaningful based on discussion with clinical experts on aGVHD. The null hypothesis using 45% OR was calculated as a rate that was 20 points lower than the anticipated 65% OR rate to remestemcel-L.

The null and alternative hypotheses were $H_0: p = 0.45$ vs. $H_a: p \neq 0.45$.

A sample size of 48 subjects was calculated to allow testing of the hypothesis with 80% power and a 2-sided alpha of 5%. Enrollment of an additional 10% was planned to allow sufficient power for analysis in the per study population.

Review Comment: The Applicant's approach to determination of the null rate calculated backwards from the target rate) is not an acceptable method. The null rate should be based on data as might be generated in a control arm. Additional justification was requested.

To this end, the Applicant provided the following:

- 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). [FDA Analysis]

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 [FDA Guidance for Industry E10]. 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%).
- 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). [Rashidi et al 2019]
- A prospective study evaluating the use of etanercept in 25 children with grade II-IV SR-aGVHD (using the modified Glucksberg criteria [Przepiorka 1995]) which observed an ORR of 68% (17/25) at Day 7. The study stopped accrual prematurely when the null hypothesis of 40% was excluded [Faraci 2019].
- 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 [Sleight 2007].
- 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 IV aGVHD 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% [Khandelwal 2016].

Review Comment: 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 [Gatza 2020]. 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 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.

It is acknowledged, however, that although approval requires a demonstration of clinical benefit, there is no regulatory requirement to show superiority to other drugs. There are no contemporary data on outcome of untreated SR-aGVHD; physicians do not leave this disorder untreated, since it is known to be fatal. Hence, the 45% null rate proposed by the Applicant seems more than adequate as a basis of comparison to no treatment.

Analysis populations proposed in the Statistical Analysis Plan (SAP)

Safety Population The safety population included all subjects who signed the ICF and received at least 1 dose of remestemcel-L (complete or partial).

Full Analysis Set: Subjects who provided informed consent, were screened, and found eligible for study, were included in the FAS population. The FAS population was used for the primary efficacy analysis (OR at Day 28). Secondary efficacy analyses were also performed on the FAS population.

Modified Full Analysis Set: The mFAS population was the same as the FAS population but included only vial-treated subjects. The bag-treated subjects were excluded from the mFAS population.

Per Study Population: The Per Study (PP) population included all subjects who had no major study violations during the study. In addition to using Inclusion Criteria 1 to 4 and Exclusion Criteria 1 to 3 to define the PP population, subjects were excluded from the PP population if they received second-line GVHD treatment within the period of Initial Therapy and/or Continued Therapy but did not discontinue remestemcel-L infusions, or if their infusion schedule/frequency was not followed for Initial Therapy and/or Continued Therapy for reasons other than treatment failure.

Interim Analyses

An interim futility analysis was planned after 30 subjects were treated, and futility at this interim analysis was to be based on the Bayesian predictive probability of a significant treatment effect at the final analysis given the available data.

Statistical Methodologies

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Confidence intervals, if presented, will be two-sided at the 95% confidence level. All statistical tests will be two-sided at the $\alpha < 0.05$ level of significance, unless otherwise noted.

The baseline value for a variable is defined as the last non-missing observation taken prior to or on the first dose date of study treatment. By this definition of baseline, post-baseline means data collected after first infusion (complete or partial) of study treatment. Data collected at unscheduled time points will not be summarized at the unscheduled time points but will be considered as for baseline.

The first dose date will be considered as 'Study Day 1'. Study day, the actual day relative to start of treatment, will be calculated from Study Day 1.

As recent developments in the field also suggest, a risk-scoring methodology will be applied to patients in this study to explore response to treatments based on risk. The MacMillan risk score is derived to classify patients into the two groups of High Risk (HR) and Standard Risk (SR). Standard Risk is defined at the baseline as skin stage 1-3, lower GI stage 0 and liver stage 0; both skin and liver stages 0 and lower GI stage 1-2; skin stage 1-3, lower GI stage 1-2, and liver stage 0; or skin stage 1-3, lower GI stage 0 and liver stage 1-4. All other patients are considered High Risk.

Secondary Analyses

The secondary efficacy analyses will be performed using the FAS. The analyses will be repeated for the mFAS and PP populations for the following key secondary endpoint:

- Overall survival at Day 100 post initiation of remestemcel-L therapy.

Subgroup Analysis

Corresponding outputs will be based on shells used for the full sample. A title displaying the subgroup label will be added between the output title and the analysis set description title.

Two options for displaying the subgroup levels are given:

- if space permits, a leading column can be added to the original shell labeled with the subgroup label
- the subgroup variable is used as page-by variable, the label and the current value of the subgroup are displayed between titles and results on the output, there will be an empty line between titles and subgroup description, as well as between subgroup description and results <subgroup label>: <current value of subgroup>

Displaying subgroup as page-by variable is the preferred option, if not otherwise specified.

N in the outputs is the number of subjects in the subgroup or the subset. If neither subgroup nor subset is used, N is the number of subjects in the analysis set.

Exploratory Analyses

1. *Change in use of concomitant medications for acute GVHD*: Concomitant medications will be coded using the most recent WHO Drug Dictionary (WHO- DD) and summarized by ATC (Level 2) code. The numbers and percentages of patients using concomitant medications will be summarized.
2. *Change in Quality of Life From Baseline (as assessed by PedsQL™ and the HRQOL Parent Proxy Report)*: The PedsQL™ questionnaire and the HRQOL Parent Proxy Report will be used to evaluate quality of life. Each item response will be summarized by the number and percentage of subjects selecting each respective response. The mean of total scores and subscores, based on available evaluations, will be presented with the standard deviations, median, minimum, median, and maximum. No imputation method will be used for the missing score. Change from baseline values will be examined within shift tables (numbers and percentages), and the mean, standard deviations, minimum, median, and maximum for the change from baseline will be presented.
3. *Change in Functional Status From Baseline (as assessed with the Karnofsky/ Lansky Performance scores)*: Functional status will be assessed using the Karnofsky/Lansky performance scales. These scores will be summarized by numbers and percentages within each scale level by appropriate age categories. Change from baseline values will also be examined within shift tables.

4. *Duration of Overall Response from Day 28 through Day 100*

Definition of duration of best) response: For nonresponders at Day 28, the duration of response is undefined and will be set to missing.

For responders at Day 28 the duration of response is defined as follows: There is a GVHD assessment and a response assessment at each weekly scheduled visit. If this response is the same or better than the Day 28 response, then the subject will be deemed to have maintained response ("Response_maintain "=1). If at any weekly scheduled visit 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" assessment will be based on organ staging; it 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. It is the same as the number of weeks that the response at Day 28 was maintained.

Duration of response will be summarized by descriptive statistics - mean, standard deviation, median, minimum and maximum.

Sensitivity Analyses

To examine whether the treatment effect was consistent for all enrolled and received any amount of investigational agent, the primary efficacy analysis will be performed on all treated subjects from the FAS and subjects from the mFAS and PP populations.

For subjects who died, the time to event will be calculated from date of transplant, and date of aGVHD onset, in addition to date of treatment initiation. All other subjects will be censored, and survival time will be calculated from the date of transplant, or date of aGVHD onset, to the date of last contact. The associations with Overall response at Day 28 will be tested using a CMH test stratifying by baseline aGVHD grade. The Kaplan-Meier curves will be plotted by Day 28 responder and non-responder groups, and differences between these survival groups will be tested for a statistically significant difference using the log-rank test stratified by the sites. The odds ratio for survival at Day 100 given responder status at Day 28 will be presented and tested for statistical significance (whether statistically significantly greater than 1). In addition, a similar second analysis will be conducted but this time, considering the starting point of the survival analysis as Day 28 (instead of baseline). This exploratory analysis will be conducted because Day 28 OR is not known at the start of treatment.

Missing Data

For mFAS or FAS analyses, any subject with a missing Day 28 Overall Response assessment will be deemed to be a nonresponder for the primary efficacy analysis. No imputation method will be used for other missing measurements in the study.

[Source: Mesoblast BLA, GVHD-001 1619 statplan, 5.3.5.1]

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Applicant performed analysis of the primary efficacy endpoint and key secondary efficacy endpoints using the mFAS and PP populations were performed as sensitivity.

Summary of the analysis populations:

- The FAS population (55 subjects) included all enrolled subjects and was used for the primary and secondary efficacy analyses.
- The Safety population 54 subjects was used for the safety analyses. One subject in the FAS population was enrolled in the study but did not receive remestemcel-L due to worsening of subject's medical condition prior to receipt of remestemcel-L at the site.
- The mFAS population 47 subjects) included subjects in the FAS population who were treated with remestemcel-L packaged in cryogenic vials instead of cryogenic bags.
- The PP population (51 subjects) included all subjects who had no major study violations during the study.

The primary efficacy analysis (OR at Day 28 post initiation of remestemcel-L therapy) and the key secondary efficacy analysis (OS at Day 100 post initiation of remestemcel-L therapy) performed on the mFAS and PP populations were used to assess sensitivity and therefore were considered supportive.

Table 8: Applicant's Analysis Sets

Population	Total Remestemcel-L n (%)
Subjects enrolled	55
Full Analysis Set (FAS) population	55 (100)
Safety population	54 (98.2)
Modified Full Analysis Set (mFAS) population	47 (85.5)
Per Protocol population	51 (92.7)

Notes: Percentages were based on the total number of subjects enrolled.

The FAS population was defined as subjects who signed the informed consent form, were screened, and were found eligible to enter the study.

The Safety population was defined as subjects who signed the informed consent form and received at least 1 dose of study treatment (complete or partial).

The mFAS population consisted of the vial-treated subjects from the FAS population.

The Per Study population was defined as all subjects who had no major Study violations during the study.

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 11.1]

Table 9: All subjects who were excluded from any Applicant analysis set and the reason(s) for the exclusion.

Country/Subject Identifier	Age/Sex/Race	Excluded From	Reason
(b) (6)	2y10m/M/Wh	mFAS	Bag-treated subject
	16y1m/M/Bl	mFAS	Bag-treated subject
	6y8m/M/Ot	mFAS	Bag-treated subject
	8y4m/M/Ot	mFAS	Bag-treated subject
	14y8m/M/Ot	mFAS	Bag-treated subject
	13y5m/M/Wh	PP	Subject (b) (6) received rituximab on Day -2, prior to starting MSC infusions. The site confirmed in response to a query that rituximab was given for GVHD prophylaxis.
	1y3m/F/Wh	Safety	Subject did not receive at least 1 dose of remestemcel-L (complete or partial).
		PP	Subject (b) (6) was enrolled but did not receive any MSC infusions, as the subject's condition worsened prior to IP arrival on site.
	3y9m/M/Wh	PP	Treatment plan for Continued Therapy was not followed. Subject received MSC infusions twice a week instead of once a week as per protocol. Subject excluded from Day 100 Per Protocol population
	0y10m/M/Wh	mFAS	Bag-treated subject
	15y0m/M/Wh	mFAS	Bag-treated subject
	15y4m/M/Wh	mFAS	Bag-treated subject
	2y4m/M/Ot	PP	Major protocol deviation. Subject was unable to return to the clinical site for study visits after Day 28 due to relapse of AML.

AML = acute myeloid leukemia; Bl = Black; F = Female; GVHD = graft-versus-host disease; IP = investigational product; M = Male; mFAS = Modified Full Analysis Set; MSC = mesenchymal stromal cell; N = no; Ot = Other; PP = Per Study; Wh = White; Y = Yes. Note: Only subjects excluded from at least 1 analysis population were presented in this listing.

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 11.1]

6.1.10.1.1 Demographics

Subjects in the FAS were primarily male (63.6%) and white (56.4%). The mean (SD) age was 7.3 (5.45) years. The study cohort included 8 infants (ages 1 month 0 <2 years), 31 children (ages 2 years to <12 years), and 12 adolescents (ages 12 years to < 17 years).

Table 10: GVHD-001 Demographics treated population

	Total N=54
Age (months)	
Median	93
Min, Max	7, 215
Gender	
Male	35 (65%)
Female	19 (35%)
Race	
White	30 (56%)
American Indian or Alaska Native	3 (5%)
Asian	3 (5%)
Black or African American	8 (15%)
Other	10 (19%)
Ethnicity	
Hispanic or Latino	18 (33%)
Non-Hispanic or Latino	36 (67%)

[Source: FDA table generated from Mesoblast BLA submission, GVHD001 ADSL]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 11: Subject Underlying Disease/Transplant Characteristics

Parameter	Full Analysis Set Population N = 55	Safety Population N = 54	Modified Full Analysis Set Population N = 47	Per Study Population N = 51
Underlying malignancy at transplant, n				
Acute lymphoblastic leukemia (ALL)	12 (21.8)	12 (22.2)	8 (17.0)	12 (23.5)
Acute myeloid leukemia-primary (AML)	18 (32.7)	17 (31.5)	17 (36.2)	14 (27.5)
Chronic myeloid leukemia (CML)	4 (7.3)	4 (7.4)	4 (8.5)	4 (7.8)
Multiple myeloma	0	0	0	0
Myelodysplastic syndrome (MDS)	2 (3.6)	2 (3.7)	2 (4.3)	2 (3.9)
Non-Hodgkin's lymphoma	0	0	0	0
Hodgkin's lymphoma	1 (1.8)	1 (1.9)	1 (2.1)	1 (2.0)
Other sickle cell, thalassemia, other anemias, other congenital	18 (32.7)	18 (33.3)	15 (31.9)	18 (35.3)
Conditioning regimen used, n (%)				
Myeloablative	47 (85.5)	46 (85.2)	40 (85.1)	43 (84.3)
Reduced intensity	6 (10.9)	6 (11.1)	5 (10.6)	6 (11.8)

Non-myeloablative	1 (1.8)	1 (1.9)	1 (2.1)	1 (2.0)
Missing	1 (1.8)	1 (1.9)	1 (2.1)	1 (2.0)
Transplant donor, n (%)				
Related	13 (23.6)	13 (24.1)	11 (23.4)	11 (21.6)
Unrelated	42 (76.4)	41 (75.9)	36 (76.6)	40 (78.4)
HLA compatibility, n (%)				
Matched	27 (49.1)	27 (50.0)	25 (53.2)	26 (51.0)
Mismatched	28 (50.9)	27 (50.0)	22 (46.8)	25 (49.0)
Type of transplant, n (%)				
Bone marrow	30 (54.5)	29 (53.7)	26 (55.3)	27 (52.9)
Peripheral blood stem cell (PBSC)	14 (25.5)	14 (25.9)	12 (25.5)	13 (25.5)
Cord blood	11 (20.0)	11 (20.4)	9 (19.1)	11 (21.6)
Donor lymphocyte infusion (DLI)	0	0	0	0

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 11.2.2]

Table 12: Baseline aGVHD Disease Characteristics

Parameter	Full Analysis Set Population N = 55	Safety Population N = 54	Modified Full Analysis Set Population N = 47	Per Study Population N = 51
Grade of aGVHD at initial diagnosis, n (%)				
Grade A	2 (3.6)	2 (3.7)	1 (2.1)	2 (3.9)
Grade B	16 (29.1)	15 (27.8)	13 (27.7)	13 (25.5)
Grade C	26 (47.3)	26 (48.1)	23 (48.9)	26 (51.0)
Grade D	11 (20.0)	11 (20.4)	10 (21.3)	10 (19.6)
Grade of aGVHD at steroid-refractory diagnosis, n (%)				
Grade A	0	0	0	0
Grade B	5 (9.1)	5 (9.3)	5 (10.6)	5 (9.8)
Grade C	28 (50.9)	28 (51.9)	24 (51.1)	26 (51.0)
Grade D	22 (40.0)	21 (38.9)	18 (38.3)	20 (39.2)
Grade of aGVHD at baseline, n (%)				
Grade A	0	0	0	0
Grade B	6 (10.9)	6 (11.1)	6 (12.8)	6 (11.8)
Grade C	23 (41.8)	23 (42.6)	19 (40.4)	21 (41.2)
Grade D	26 (47.3)	25 (46.3)	22 (46.8)	24 (47.1)

Time from HSCT to onset of aGVHD (days)				
n	55	54	47	51
Mean (SD)	50.2 (39.24)	50.6 (39.49)	50.5 (39.32)	49.2 (39.16)
Median	35.0	36.0	37.0	35.0
Min, Max	9, 170	9, 170	9, 170	9, 170
Time from onset of aGVHD to initiation of study drug (days)				
n	54	54	46	51
Mean (SD)	18.4 (22.35)	18.4 (22.35)	19.0 (24.06)	18.7 (22.96)
Median	12.0	12.0	12.0	12.0
Min, Max	4, 142	4, 142	4, 142	4, 142
Time from onset of steroid-refractory aGVHD to initiation of study drug (days)				
n	54	54	46	51
Mean (SD)	3.9 (2.24)	3.9 (2.24)	4.0 (2.37)	3.9 (2.25)
Median	3.5	3.5	3.5	3.0
Min, Max	1, 10	1, 10	1, 10	1, 10
Skin involvement at baseline, n (%)				
Score 0 = No rash	25 (45.5)	25 (46.3)	22 (46.8)	23 (45.1)
Score 1 = Maculopapular rash,	3 (5.5)	3 (5.6)	3 (6.4)	2 (3.9)
Score 2 = Maculopapular rash,	2 (3.6)	2 (3.7)	2 (4.3)	2 (3.9)
Score 3 = Generalized erythroderma	14 (25.5)	14 (25.9)	11 (23.4)	14 (27.5)
Score 4 = Generalized erythroderma	11 (20.0)	10 (18.5)	9 (19.1)	10 (19.6)
Lower GI involvement at baseline, n (%)				
Score 0 = <10 mL/kg/day	14 (25.5)	14 (25.9)	11 (23.4)	14 (27.5)
Score 1 = 10-19 mL/kg/day	5 (9.1)	5 (9.3)	4 (8.5)	5 (9.8)
Score 2 = 20-30 mL/kg/day	7 (12.7)	6 (11.1)	7 (14.9)	6 (11.8)
Score 3 = >30 mL/kg/day	13 (23.6)	13 (24.1)	11 (23.4)	11 (21.6)
Score 4 = Severe abdominal pain with or without ileus, or stool with frank blood or melena	16 (29.1)	16 (29.6)	14 (29.8)	15 (29.4)
Upper GI involvement at baseline, n (%)				
Score 0 = No protracted nausea and vomiting	48 (87.3)	47 (87.0)	40 (85.1)	44 (86.3)
Score 1 = Persistent nausea, vomiting, or anorexia	7 (12.7)	7 (13.0)	7 (14.9)	7 (13.7)

Liver involvement at baseline, n (%)				
Score 0 = <2.0 mg/dL	44 80.0	44 (81.5)	38 (80.9)	42 (82.4)
Score 1 = 2.1-3.0 mg/dL	8 14.5	7 13.0	6 12.8	7 13.7
Score 2 = 3.1-6.0 mg/dL	3 5.5	3 (5.6)	3 (6.4)	2 (3.9)
Score 3 = 6.1-15.0 mg/dL	0	0	0	0
Score 4 = >15.0 mg/dL	0	0	0	0
Number of organs involved (skin, lower				
One organ	35 (63.6)	35 (64.8)	30 (63.8)	33 (64.7)
Two organs	13 (23.6)	13 (24.1)	11 (23.4)	13 (25.5)
Three organs	7 (12.7)	6 11.1)	6 12.8)	5 9.8)
Organs involved at baseline, n (%)				
Skin only	14 (25.5)	14 (25.9)	11 (23.4)	14 (27.5)
Lower GI only	21 (38.2)	21 (38.9)	19 (40.4)	19 (37.3)
Multi-organ (any combination)	20 36.4)	19 (35.2)	17 36.2)	18 35.3)
MacMillan risk score, n (%)				
Standard risk	15 (27.3)	15 27.8)	13 (27.7)	15 29.4)
High risk	40 (72.7)	39 (72.2)	34 (72.3)	36 (70.6)

aGVHD = acute graft-versus-host disease; GI = gastrointestinal; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; SD = standard deviation.

Notes: Percentages were based on the total number of subjects in each analysis population. MacMillan risk score was derived as described in MacMillan 2015.64

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 11.2.3]

6.1.10.2 Subject Disposition

Fifty-five subjects were enrolled, 54 subjects received remestemcel-L (1 subject's condition worsened before the remestemcel-L arrived and could not be infused), and 42 subjects 76.4% completed the study.

All 54 treated were eligible for Day 28 evaluation.

For 9 subjects, death was the primary reason for early termination from the study. Another 2 subjects died after being terminated from the study Investigator decision for 1 subject and an AE for 1 subject . In addition, 2 subjects who completed the study died within the Day 100 window ± 7 days). Finally, 1 subject who terminated the study early due to withdrawal of consent was lost to follow-up, with the subject's vital status at Day 100 remaining unknown. This subject is assumed to have died in all survival analyses.

Forty-two subjects therefore completed day 100 evaluation.

Table 13: Subject Disposition (All Enrolled Subjects)

Disposition/Reason	Total Remestemcel-L n %
Subjects enrolled	55 100
Subjects treated with investigational medicinal product	
Yes	54 (98.2)
No	1 (1.8)
Subjects completed the MSB-GVHD001	
Yes	42 (76.4)
No	13 (23.6)
Primary reason for early termination in MSB-GVHD001	
Inclusion criteria	0
Exclusion criteria	0
MSC infusion	0
Disease progression/relapse	0
Adverse event	1 (1.8)
Withdrawal of consent	1 (1.8)
Lost to follow-up	0
Study terminated by Sponsor	0
Death	9 (16.4)

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 10.1]

MSC mesenchymal stromal cell; PI Principal Investigator.

Notes: Percentages were based on the total number of subjects enrolled.

In addition to the 9 subjects who had “Death” as a primary reason of early termination (ET) in MSB-GVHD001, another 5 subjects, for a total of 14 subjects, were considered as deceased (or non-survivors for the MSB-GVHD001 study. Of these 5 subjects: 1 subject (b) (6) was lost to follow-up after withdrawing consent and discontinuing on Day 5, and was assumed dead in survival analyses; 2 subjects early terminated ET for a reason other than “Death” and died at a later date in the Day 1-100 window Subject (b) (6) ET on Day 30 due to “Other” reason and died on Day 63, and Subject (b) (6) ET on Day 35 due to “Adverse event” and died on Day 66; and 2 subjects completed the MSB-GVHD001 study but died soon after (Subjects (b) (6) and (b) (6) died on Day 102 and Day 100, respectively).

Reviewer Comment: FDA confirmed subject eligibility, primary endpoint evaluations and reason for dropout. Study dropout does not appear to have affected the data analysis.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The response rate reported by the Applicant was replicated by FDA analysis.

FDA-defined Analysis Populations

Full Analysis Set (FAS) n = 55

All subjects who enrolled on study, were included in the FAS population.

Treated Population (TP) n = 54

Subjects who provided informed consent, were screened, were confirmed to have SR-aGVHD and treated with at least one dose were included in the TP. All treated subjects had a Day 28 evaluation

Safety Population n = 54

The Safety population included all subjects who signed the ICF and received at least 1 dose of remestemcel-L (complete or partial).

Sensitivity Analysis Population n = 45

Sensitivity analysis population excludes nine subjects who may have confounders to determination of ORR at Day 28. This population is used in sensitivity analyses.

Six subjects that received concomitant medications that could potentially impact the Day 28 primary endpoint analysis:

1. (b) (6) (ecluzimab for HUS)
2. (b) (6) (rituximab for EBV)
3. (b) (6) (rituximab prophylaxis)
4. (b) (6) (rituximab for EBV)
5. (b) (6) (basiliximab for GVHD prophylaxis)
6. (b) (6) (basiliximab for GVHD prophylaxis)

An additional 4 subjects were excluded from the ITT when it was determined they had improving in GVHD symptoms after they met the determination of steroid refractoriness, but prior to enrollment:

1. (b) (6)
2. (b) (6)
3. (b) (6)
4. (b) (6)

One subject, (b) (6) was on both lists. The analysis of the primary efficacy endpoint was performed using the sensitivity analyses group.

Primary Efficacy Endpoint: Overall Response (OR) at Day 28

Between 2015 and 2017, 55 pediatric patients were enrolled on Study 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 14 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 14: MSB-GVHD001 - Primary Endpoint Analysis (Day-28 ORR)

Analysis Set	N	Day-28 CR n, %	Day-28 PR n, %	Day-28 ORR	
				n, %	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 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%.

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoint outcomes are listed in Table 15 below. The FDA review team was able to confirm the secondary endpoint analyses performed on the FAS population as provided by the Applicant.

Table 15: Summary of Secondary Endpoint Outcomes

Secondary Endpoint	% n/total)
OS at Day 100	74.5% 41/55
OS at Day 100, stratified by responder status at Day 28	
responder	86.6% (33/38)
nonresponder	47.1% 8/17
OS at Day 100, stratified by baseline aGVHD grade and organ involvement	
Grade B	50% (3/6)
Grade C	82.6% (19/23)
Grade D	73.1% 19/26
OS, stratified by organs involved at baseline	
Skin only	78.6 (11/14)
Lower GI only	76.2 (16/21)
Multi-organ	70.0 14/20
Rate of CR + VGPR at Day 28	
CR + VGPR responder	38.2% (21/55)
CR	29.1% (16/55)
VGPR	9.1% 5/55
Rate of CR + VGPR at Day 56	
CR + VGPR responder	41.8% (23/55)
CR	30.9% (17/55)
VGPR	10.9% 6/55
Rate of CR + VGPR at Day 100	
CR + VGPR responder	50.9% (28/55)
CR	43.6% (24/55)
VGPR	7.3% 4/55
Rate of OR, CR + VGPR, stratified by organs involved at baseline at day 28	
Skin only	85.7%, 57.1%, 21.4%
Lower GI only	66.7%, 28.6%, 9.5%
Multi-organ	60%, 10%, 0%

Rate of OR, CR + VGPR, stratified by organs involved at baseline at day 100	
Skin only	85.7%, 42.9%, 28.6%
Lower GI only	71.4%, 61.9%, 0%
Multi-organ	55%, 25%, 0%
OR, CR, VGPR, stratified by MacMillian Risk Factor at Day 28	
standard risk	73%, 40%, 20%
high risk	67.5%, 25%, 5%
OR, CR, VGPR, stratified by MacMillian Risk Factor at Day 56	
standard risk	66.7%, 40%, 20%
high risk	55%, 27.5%, 7.5%
OR, CR, VGPR, stratified by MacMillian Risk Factor at Day 100	
standard risk	80%, 46.7%, 20%
high risk	65%, 42.5%, 2.5%
OR, CR, VGPR, stratified by aGVHD baseline score at Day 28	
Grade B	50%, 16.7%, 16.7%
Grade C	69.6%, 39.1%, 13%
Grade D	73.1%, 23.1% 3.8%
OR, CR, VGPR, stratified by aGVHD baseline score at Day 56	
Grade B	50%, 33.3%, 0%
Grade C	60.9%, 34.8%, 17.4%
Grade D	57.7%, 26.9%, 7.7%
OR, CR, VGPR, stratified by aGVHD baseline score at Day 100	
Grade B	50%, 50%, 0%
Grade C	73.9%, 39.1%, 13%
Grade D	69.2%, 46.2%, 3.8%
Second-Line aGVHD Medication/Therapy by Therapy Period	
Initial Therapy (Day 1 to Day 28)	
Receiving second-line medication/therapy	7.3% (4/55)
Not receiving second-line medication/therapy	90.9% (50/55)
Missing/no data	1.8% (1/55)
After Initial Therapy (Day 29 to end of MSB-GVHD001)	
Receiving second-line medication/therapy	7.3% (4/55)
Not receiving second-line medication/therapy	89.1% (49/55)
Missing/no data	3.6% 2/55
[Source: FDA abridged table, derived from Clinical Study Report, Report No. MSB-GVHD001, Sections 11.4.1.2.1 - 11.4.1.2.9]	
Abbreviations: CR, complete response; OR, overall response; OS, overall survival; PR, partial response; VGPR, very good partial response	

Table 16: Effect of Continued Remestemcel-L Therapy After Day 28 on OR, CR + VGPR at Day 56 and Day 100 Post Initiation of Remestemcel-L Therapy (FAS Population)

Parameter	Received Continued Therapy Post Day 28			No Post Day 28 Continued Therapy		
	Day 28 PR	Day 28 MR	Total (PR + MR) NN = 23	Day 28 CR	Day 28 NR NN =	Total (CR + NR) NN =
Rate of OR at Day 56, n (%)						
OR responder	16 (76.2)	1 50.0	17 (73.9)	14 (87.5)	0	14 (58.3)
CR	5 23.8	0	5 21.7	12 (75.0)	0	12 (50.0)

PR	11 (52.4)	1 (50.0)	12 (52.2)	2 (12.5)	0	2 (8.3)
VGPR	4 (19.0)	0	4 (17.4)	2 (12.5)	0	2 (8.3)
Non-OR	4 (19.0)	0	4 (17.4)	2 (12.5)	4 (50.0)	6 (25.0)
MR	0	0	0	2 (12.5)	1 (12.5)	3 (12.5)
NR	3 (14.3)	0	3 (13.0)	0	2 (25.0)	2 (8.3)
Progression	1 (4.8)	0	1 (4.3)	0	1 (12.5)	1 (4.2)
Missing	1 (4.8)	1 (50.0)	2 (8.7)	0	4 (50.0)	4 (16.7)
Rate of CR + VGPR at Day 56, n (%)						
CR + VGPR responder	9 (42.9)	0	9 (39.1)	14 (87.5)	0	14 (58.3)
Non-CR + VGPR responder	11 (52.4)	1 (50.0)	12 (52.2)	2 (12.5)	4 (50.0)	6 (25.0)
Missing	1 (4.8)	1 (50.0)	2 (8.7)	0	4 (50.0)	4 (16.7)
Rate of OR at Day 100, n %						
OR responder	19 (90.5)	0	19 (82.6)	14 (87.5)	3 (37.5)	17 (70.8)
CR	10 (47.6)	0	10 (43.5)	12 (75.0)	2 (25.0)	14 (58.3)
PR	9 (42.9)	0	9 (39.1)	2 (12.5)	1 (12.5)	3 (12.5)
VGPR	3 (14.3)	0	3 (13.0)	1 (6.3)	0	1 (4.2)
Non-OR	1 (4.8)	0	1 (4.3)	1 (6.3)	3 (37.5)	4 (16.7)
MR	1 (4.8)	0	1 (4.3)	1 (6.3)	1 (12.5)	2 (8.3)
NR	0	0	0	0	0	0
Progression	0	0	0	0	2 (25.0)	2 (8.3)
Missing	1 (4.8)	2 (100)	3 (13.0)	1 (6.3)	2 (25.0)	3 (12.5)
Rate of CR + VGPR at Day 100, n %						
CR + VGPR responder	13 (61.9)	0	13 (56.5)	13 (81.3)	2 (25.0)	15 (62.5)
Non-CR + VGPR responder	7 (33.3)	0	7 (30.4)	2 (12.5)	4 (50.0)	6 (25.0)
Missing	1 (4.8)	2 (100)	3 (13.0)	1 (6.3)	2 (25.0)	3 (12.5)

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 11.4.1.2.9]

CR = complete response, EOT = end of trial; FAS = Full Analysis Set; MR = mixed response, N = population total; NN = subgroup total; NR = no response; OR = overall response; PR = partial response, VGPR = very good partial response.

Notes: Overall response corresponded to subjects with a CR or PR. Response was derived from underlying data and not taken directly from Investigator's assessment.

Percentages were based on the total number of subjects in the FAS population, in each group.

The "Day 100/EOT" visit for Subjects (b) (6) was performed more than 7 days after Day 100. The data from this "Day 100/EOT" visit were still being used as the "Day 100" for these subjects.

6.1.11.3 Subpopulation Analyses

FDA confirmed the Applicant's subpopulation analysis of Day-28 ORR (Table 17). 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.

Table 17: MSB-GVHD001 Subpopulation Analyses

	ORR (CR + PR)		Complete Response (CR)		Partial Response (PR)		Total N
	N	%	N	%	N	%	
Age N							
0 – < 12 years	20	69%	11	38%	9	31%	29
12 to < 17 years	10	71%	2	14%	8	57%	14
17 years and greater	8	67%	3	25%	5	42%	12
Sex							
F	12	60%	5	25%	7	35%	20
M	26	74%	11	31%	15	43%	35
Pooled Race Group 1							
Non-White	17	71%	8	33%	9	37%	24
White	21	68%	8	26%	13	42%	31
Ethnicity							
HISPANIC OR LATINO	13	72%	7	39%	6	33%	18
NOT HISPANIC OR LATINO	24	67%	8	22%	16	44%	36
Baseline Organ Involvement Category							
Lower GI Only	14	67%	6	29%	8	38%	21
Multi-Organ (Any Combination)	12	60%	2	10%	10	50%	20
Skin Only	12	86%	8	57%	4	29%	14
MacMillan Risk Score							
High risk (HR)	27	67%	10	25%	17	42%	40
Standard risk (SR)	11	73%	6	40%	5	33%	15
Baseline Grade aGVHD							
Grade B	3	50%	1	17%	2	33%	6
Grade C	16	70%	9	39%	7	30%	23
Grade D	19	73%	6	23%	13	50%	26
HLA Compatibility Match							
Matched	20	74%	9	33%	11	41%	27
Mismatched	18	64%	7	25%	11	39%	28
HLA Compatibility Related							
Related	9	69%	5	38%	4	31%	13
Unrelated	29	69%	11	26%	18	43%	42
Type of Transplant							
Bone Marrow	24	80%	9	30%	15	50%	30
Cord Blood	8	73%	5	45%	3	27%	11
Peripheral Blood Stem Cell (PBSC)	6	43%	2	14%	4	29%	14
Underlying Malignancy at Transplant							
ACUTE Lymphoblastic Leukemia (ALL)	9	75%	6	50%	3	25%	12
ACUTE Myeloid Leukemia-Primary (AML)	10	56%	3	17%	7	39%	18
Chronic Myeloid Leukemia (CML)	4	100%	1	25%	3	75%	4
Hodgkin's Lymphoma	1	100%	0	0%	1	100%	1
Myelodysplastic Syndrome (MDS)	1	50%	0	0%	1	50%	1
Other	13	72%	6	33%	7	39%	18
Baseline Skin Involvement Score							
0= No rash	17	68%	7	28%	10	40%	25
1= Maculopapular rash, <25% of BSA	2	67%	1	33%	1	33%	3
2= Maculopapular rash, 25-50% of BSA	1	50%	0	0%	1	50%	2
3= Generalized erythroderma	10	71%	5	36%	5	36%	14
4= Generalized erythroderma with bullous formation and desquamation	8	73%	3	27%	5	45%	11

[Source: FDA Analysis; Abbreviation BSA, body surface area]

6.1.11.4 Dropouts and/or Discontinuations

Missing data for the primary endpoint (OR at Day 28), including missing assessments and missing staging data for any organ, were imputed as “Nonresponder.” No other imputation was planned, as specified in the SAP.

Fifty-five subjects were enrolled, 54 subjects received remestemcel-L (1 subject’s condition worsened before the remestemcel-L arrived and could not be infused) and were evaluable for the primary endpoint measure. Forty-two subjects (76.4%) completed the study.

Reviewer Comment: Dropouts do not appear to have affected study integrity.

6.1.11.5 Exploratory and Post Hoc Analyses

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. Therefore, the data for DOR may not be complete for all treated patients. 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. Table 18 shows the approach to computing DOR used by the Applicant and the definition that has been accepted by FDA.

Table 18: Computation of DOR

Applicant-defined DOR ^a	<p>The number of weeks that the response at Day 28 was maintained.</p> <ul style="list-style-type: none"> • 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	<p>The interval from the Day-28 response to progression, new systemic therapy for acute GVHD or death from any cause.</p>

	<ul style="list-style-type: none"> 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 as 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 Study 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, but the Applicant did not.

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 19 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 19: 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

Product/lot Information Analysis

Of the 54 patients treated in MSB-GVHD001, eight subjects received drug product from the second manufacturing process (DP2) formulated in bags rather than from the proposed commercial

manufacturing process DP3) formulated in vials. Of the eight patients, there were 2 nonresponders and 6 responders:

Table 20: Subjects treated with DP2

Subject Identifier for the Study	AVALCAT2
(b) (6)	Responder
(b) (6)	Nonresponder
(b) (6)	Responder
(b) (6)	Nonresponder
(b) (6)	Responder

[Source: FDA generated table from ADOR/ADSL datasets]

There was no significant finding of association between manufacturing process and the overall response, the Fisher exact test statistic value is 1 (Table 21).

Table 21: Outcomes comparing Subjects treated with DP2 versus DP3

Manufacturing Process	Responder (CR+PR)		Total
	n	%	n
DP2 (Bags)	6	75%	8
DP3 (Vials)	32	70%	46

[Source: FDA statistical reviewer generated table from ADOR/ADSL datasets]

Biomarker and Cytokine Data Analysis

The Applicant supplied biomarker data under amendment 17 April 7, 2020, in response to Clinical IR #7 (IR #10) sent on 3/23/2020. Additional biomarker data was requested on June 2, 2020 (FDA IR #22) and a formal biomarker data analysis from the Applicant was received June 12, 2020 (125706.31). The biomarker portion of the study was optional, and of the 55 subjects enrolled into MSB-GVHD001, only 40 of these subjects participated in the biomarker sub-study.

Review Comment: Therefore, evaluation of these biomarkers is exploratory, and the analysis was descriptive in nature. In addition, there is no reliable quantitation of certain biomarker data, due to capping of upper limits, therefore no substantial conclusion can be drawn from available data.

Patient Reported Outcomes (PRO) and Functional Status Analyses

PRO and function status measures were exploratory endpoints. Quality of life (QOL) assessment tools included the PedsQL for subjects and HRQOL Parent Proxy Report. Functional status from baseline was assessed by the Karnofsky/Lansky Performance Scores.

(b) (4)

3 pages determined to be not releasable: (b)(4);(b)(6)

(b) (4)

6.1.12 Safety Analyses

6.1.12.1 Methods

See Section 8.0 *Integrated Overview of Safety* of this review memo for the review of relevant safety data from MSB-GVHD001/002.

6.1.13 Study Summary and Conclusions

Study MSB-GVHD001 met its primary objective; the Day-28 ORR was 69.1% (95% CI: 55.2, 80.9) in the FAS, %, excluding the null hypothesis of 45%. 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 observed safety profile revealed no safety signal of concern, with limited treatment-associated SAEs.

6.2 Additional Trials in Patients with Acute GVHD

The Applicant conducted four additional prospective clinical trials of remestemcel-L, two intermediate size expanded access studies, and numerous single-patient expanded access treatments for treatment of aGVHD (Table 26). See Section 7 for discussion of the relevant efficacy information and Section 8 for discussion of the relevant safety information.

Table 26: Trials in Patients with Acute GVHD

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 \geq 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 \geq 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

Study	Study Design	Population	Treatment
	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

Source: FDA Analysis

6.3 Additional Trials in Patients with Disorders Other Than GVHD

The Applicant conducted six additional prospective clinical trials of remestemcel-L and one intermediate size expanded access study for treatment of disorders other than aGVHD (Table 27). Efficacy information from these trials are not considered in this review. See Section 8 for discussion of the relevant safety information.

Table 27: Trials in Patients with Disorders Other Than GVHD

401/402	401: Phase 1 randomized, double-blind, placebo-controlled, dose-escalation	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
	Safety study		
	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	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 × 10 ⁶ cells days 7 and 14 Arm C: 400 × 10 ⁶ cells Days 0 and 3; 200 × 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 × 10 ⁶ cells days 7 and 14 Arm C: 400 × 10 ⁶ cells Days 0 and 3; 200 × 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 × 10 ⁶ cells on Days 0, 30, 60, 90
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 × 10 ⁶ cells/kg on Days 0, 30, 60

Source: FDA Analysis

Prospective clinical studies of remestemcel-L for treatment of aGVHD were conducted under IND 007939. In the aGVHD studies, 654 (333 pediatric and 321 adult) subjects received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. Table 28 lists the Applicant's prospective studies for treatment of aGVHD.

Table 28: 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
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

Table 28: Prospective Studies of Remestemcel-L for Treatment of aGVHD

Study	Study Design	Population	Number Planned	Number Enrolled	Treatment	Primary Endpoint
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

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

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1 Treatment of SR-aGVHD

7.1.1 Methods of Integration

The Applicant proposed the indication "for the treatment of steroid refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients."

The clinical development program consisted of Study MSB-GVHD001, a prospective single-arm trial in the intended population. Since this is the only trial in the intended population and the only trial that used drug product comparable to the to-be-marketed formulation, Study MSB-GVH001 is the primary basis of efficacy. The design of Study MSB-GVH001 is described in Section 6.1.

Review Comments: The clinical development program includes only one applicable trial. For a single trial to be used as the basis for marketing approval, FDA expects that the trial is well-designed, well-conducted and provides statistically-persuasive efficacy findings that are robust and so compelling as to make a second trial unethical or practically impossible to perform. The adequacy of the design of the trial is discussed in detail in Section 6.1.8. No trial conduct issues were identified by on-site inspections (Section 3.2). The focus of this assessment is the review of the findings and any potential mitigating data.

Additional evidence was provided from pediatric patients in the expanded access protocol Study 275) and the pediatric subgroup in the randomized trial Study 280. Because Studies 280 and 265 are randomized trials, they are also included here for consideration in the interpretations of Study MSB-GVHD001. Due to differences in the patient populations and the differences in the drug product used in these trials, the studies are included for completeness of review of the Applicant's submission, results are displayed side-by-side and not pooled for any analyses in the integrated assessment.

Table 29 shows a comparison of the key design elements of the three trials that enrolled pediatric subjects.

	Study 001	Study 280	Study 275
Phase	Phase 3	Phase 3	Expanded access
Ages	Pediatric	Adult and pediatric	Pediatric
Population	SR-aGVHD grade B-D aGVHD (no skin only grade B)	SR-aGVHD grade B-D aGVHD skin only grade B allowed)	SR-aGVHD grade B-D aGVHD skin only grade B allowed)
Design	Single arm, multi-center	Randomized, double- blind, placebo- controlled, multicenter	Single arm
Primary Endpoint	Day-28 ORR	CR \geq 28 days duration	Day-28 ORR
Control Arm	-	SOC + Placebo	-
Treatment Arm	Remestemcel-L 2 × 10 ⁶ cells/kg x 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8 (continuation)	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

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

Study MSB-GVHD001 is contrasted to Study 280 which was a randomized, placebo-controlled trial that evaluated the efficacy of remestemcel and investigator's choice of additional salvage or second line therapy verses salvage therapy plus placebo in 241 mostly adult patients with grades B-D SR-aGVHD. The third study, Study 275, was the expanded access protocol which specifically enrolled pediatric patients with SR-aGVHD also allowed investigator's choice of additional salvage or second line therapy.

There are significant differences between Studies 001, 275 and 280. The most prominent difference is that Studies 275 and 280 permitted additional salvage aGVHD therapies at study entry at the discretion of the treating physician. This is contrasted to Study 001, where no additional salvage immunosuppressive agents were allowed. Additionally, both Studies 280 and 275 allowed the milder, grade B skin-only aGVHD. And finally, the primary endpoint of Study 280 was a CR of 28 days duration or greater.

7.1.2 Demographics and Baseline Characteristics

A detailed description of the demographics and disease characteristics of the patients in Study MSB-GVHD001 is provided in Section 6.1.10. Table 30 shows a side-by-side comparison of the characteristics of the pediatric patients in Studies MSB-GVHD001, 280 and 275.

	Study 001	Study 280 Pediatric subgroup		Study 275
	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L

Number of patients enrolled/ treated	55	173/163	87/81	242/241
Number of pediatric patients enrolled/treated	55/54	14/14	14/13	241/241
Median age years (range)	7.75 (0.6, 17.9)	7.1 (1.3, 14.8)	10.5 (1.4, 17.6)	9.6 (0.3, 18.2)
% Male	65%	50.0%	69.2%	61.4%
% non-White	44%	28.6%	38.5%	40.2%
% Hispanic	33%	50%	15.4%	18.7 %
Baseline GVHD Grade				
B (B skin alone)	10.9 % (n/a)	21.4 (7.1%)	23.1% (0%)	19.9% (9.5%)
C/D	89.1%	78.6%	76.9%	80.1%

Source: FDA analysis; Abbreviations: GVHD, graft-versus-host disease; Rem-L, remestemcel-L; SOC, standard of care therapy

Eligibility for the Study MSB-GVH001 required that patients have aGVHD that shows progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day of methylprednisolone or equivalent.

Reviewer Comments:

- **The eligibility criteria are consistent with the intended population of patients with steroid-refractory disease as discussed in Section 2.6. The exclusion of patients with Grade B skin alone disease enriched the study cohort for those with the worst prognosis.**
- **It is difficult to make comparisons between the pediatric patient population in Study 280 due to the very small numbers, but in general the studies were matched for gender and race, however in Study MSB-GVHD001, there is a higher proportion of patients with higher disease severity (Grade C/D), fewer patients with Grade B and no patients with grade B skin-only disease.**

7.1.3 Subject Disposition

A detailed description of the disposition of the patients in Study MSB-GVHD001 is provided in Section 6.1.10. Table 31 summarizes the numbers of pediatric patients treated in Studies MSB-GVHD001, 280 and 275.

Table 31: Pediatric SR-aGVHD Trials - Subject Disposition

	Study 001	Study 280 Pediatric subgroup		Study 275
	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L
Number of patients enrolled/ randomized	55	173/163	87/81	242
Number of pediatric patients enrolled/randomized	55	14/14	14/13	242
Number of pediatric patients treated	54	14	13	241

Source: FDA Analysis; Abbreviations: Rem-L, remestemcel-L; SOC, standard care salvage therapy

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for Study MSB-GVHD001 was Day-28 ORR.

Review Comment: As discussed in Section 2.6, Day-28 ORR is an accepted endpoint for assessment of treatments of aGVHD. However, to establish clinical benefit, durability of the response must also be demonstrated.

As shown in Table 14, the Day-28 ORR for Study MSB-GVHD001 was 69.1% (95% CI: 55.2, 80.9) in the FAS and 70.4% (95% CI: 56.3, 82.0) in the treated set. The results of additional sensitivity analyses were consistent with the primary analysis (Table 14). In the component analysis, the CR rate was 29%, and the PR rate was 40% in the FAS.

Review Comment: Under the assumption of a 45% ORR for the null hypothesis rate, this study met its primary objective, and the results were robust.

Table 32 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.

Table 32: Pediatric SR-aGVHD Trials - Day-28 ORR

	MSB-GVHD001	Study 280 Pediatric subgroup		Study 275
Arm	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L
Number of treated patients	54	14	13	242
Day-28 ORR ^b n, % (95% CI)	38 69.1% 55.2, 80.9	9 64.3% 35.1, 87.2	5 38.5% 13.9, 68.4	157 65.1% 58.8, 71.1

Source: FDA Analysis; Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; Rem-L, remestemcel-L; SOC, standard care salvage therapy.

Review Comment: Keeping in mind the potential pitfalls of subgroups analyses and of comparing results across independent studies, 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. Further, the pediatric subpopulation comparison within Study 280 appears to have a substantial numerical difference between treatment arms for Day-28 ORR, but it should be noted that the treatment effect, as measured by the difference between arms (25.8%), has a large confidence interval (95% CI: -10.6% to 62.3% that crosses 0. As this is an analysis of a small subgroup, the results might be appropriate for only hypothesis generation, but would not generally be considered evidence of a treatment effect.

7.1.5 Analysis of Secondary Endpoint(s)

The secondary endpoints in Study MSB-GVHD001 included alternative measures of response, such as ORR at Day 56 or at Day 100, and measures of survival. The complete set of secondary endpoints is described in Section 6.1.8. The results of the secondary endpoint analyses for Study MSB-GVHD001 are shown in Table 15.

The Applicant provided several secondary endpoint analyses of the pooled pediatric population in their integrated analysis of efficacy. These included survival analyses, subgroup analyses based on aGVHD baseline grades, and aGVHD severity risk scores. As described previously, the pooling of data is problematic due to differences in the trial designs, particularly the use of additional salvage therapies in Studies 280 and 275. Further, none of the analyses are convincing due to

lack of statistical significance, large confidence intervals and issues with missing data. Therefore, FDA assessment of secondary endpoint outcomes relies on the single arm trial of MSB-GVHD001, which showed none to be statistically informative (Section 6.1.11.2). Additionally, the meaningfulness of time-to-event measures such as overall survival (OS) are difficult to assess as none of the trials were designed to adequately explore this endpoint.

In Study 280, OS at 100 days post first infusion, a secondary endpoint showed there were no significant differences observed in survival in the treated group versus placebo group. Overall 52.1% of patients in the remestemcel-L group survived >100 days post first infusion compared to 50.6% of patients in the placebo group.

For Study 275, subjects were only followed to Day 100. Insufficient data from 107 / 242 subjects were available for analysis of OS to Day 180, making this data uninterpretable.

Review Comment: 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, are difficult to interpret in a single-arm trial and will not be discussed further.

7.1.6 Other Endpoints

Biomarker Evaluation

The FDA assessment of biomarker data submitted by the applicant for Study MSB-GVHD001 is discussed in section 6.1.11.5 and is inconclusive due to missing data. No other studies provided biomarker data.

Functional and Quality of Life Assessments

The Karnofsky Performance Status, Lansky Performance Status, and Quality of Life measures were evaluated in Study MSB-GVHD001 (see section 6.1.11.5) and Study 280. In Study 280, (b) (4)

7.1.7 Subpopulations

MSB-GVHD001

See Section 6.1.11.3 for a discussion of the subgroup analyses for the Study MSB-GVHD001. As described, 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).

Review Comment: The small numbers in each subgroup do not allow for firm conclusions where there are differences. The results for the subgroup analyses of Day-28 ORR in general are consistent with the primary analysis.

Study 280

In Study 280, the ORR at Day 28 stratified by GvHD organ (skin, lower GI and liver) was as follows: for patients with liver involvement at baseline, 54.8% of remestemcel-L treated patients and 21.1% of placebo-treated patients were responders at Day 28. For patients with lower GI involvement at Baseline, 56.5% in the remestemcel-L group and 42.4% in the placebo group were responders at Day 28. For patients with skin involvement at baseline, the treated and placebo results were comparable (remestemcel-L: 57.6%, placebo: 55.8%). Also, in Study 280, a subpopulation

analysis of the primary endpoint in the pediatric subgroup suggested an improvement in pediatric subjects (63%) versus adult subjects (35%) and lead to the pursuit of the Phase 3 development of remestemcel-L in SR-aGVHD in pediatric subjects, resulting in Study MSB-GVHD001 and the EAP Study 275.

Study 275

A summary of OR at Day 28 by key baseline characteristics was evaluated. The ORR at Day 28 was consistent across baseline organ involvement; gender, age, donor and stem cell source, aGVHD Grade at baseline, MacMillan Risk Score, and underlying malignancy. Additional analyses evaluating number of prior GVHD therapies, and additional concomitant GVHD therapy revealed no differences in outcomes.

7.1.8 Persistence of Efficacy

See Section 6.1.11.5 of this review for a discussion of computation of DOR for Study MSB-GVHD001. FDA calculated a median DOR of 54 day (range: 7, 159+ days) (Table 18 in Section 6.1.11.5). Additionally, the median time to death or need for new therapy for aGVHD was 111.5 days (range: 9,182+ days).

Review Comment: Of note is that due to incomplete enrollment onto MSB-GVHD002, the measures of durability of response is limited due to the lack of follow-up to Day 180. Nonetheless, the duration of response and the time to new therapy or death are clinically meaningful as observed with even the limited follow-up.

DOR was not evaluated in the integrated efficacy analysis due to multiple confounding factors the use of additional salvage therapy in Studies 265, 280 and 275, which would make the assessment of DOR uninterpretable. Furthermore, Study 280 measured mean CR status and thus was not comparable to Study MSB-GVHD001. DOR was not measured on Study 275.

7.1.9 Product-Product Interactions

No formal analysis of product-product interactions was performed by FDA. Patients with aGVHD are typically on many medications including anti-infective agents and other supportive care measure. All patients enrolled were on concomitant corticosteroids, aGVHD prophylaxis regimens and on Studies 280 and 275, additional aGVHD treatment. The additional aGVHD medications utilized by patients on Study 280 and Study 275 can be found in Table 33. In general, there was no difference in outcomes between the remestemcel-L and placebo treatment groups with respect to baseline concomitant medications.

Table 33: Additional aGVHD therapies allowed on Study 280 and Study 275

Concomitant GVHD Therapy	Study 275 N = 241)	Study 280 Rem + SOC arm N = 163)	Study 280 Rem + placebo arm N = 81)
	N %	N %	N %
Mycophenolate mofetil	51 (21)	52 (32)	26 (32)
Infliximab	35 (14)	38 (23)	15 (18)
Sirolimus	21 (9)	6 (4)	3 (4)
Etanercept	19 (8)	20 (12)	11 (14)
Basiliximab	6 (2)	6 (4)	0
Daclizumab	5 (2)	17 (10)	13 (16)
Rituximab	5 (2)	1 (<1)	1 (1)

ATG (all types)	5 (2)	38 (23)	17 (21)
Pentostatin	n/a	7 (4)	8 (10)
Campath	n/a	1 (<1)	0
ECP	n/a	5 (3)	2 (2)
Tacrolimus	n/a	31 (19)	20 (25)
Ciclosporin	n/a	17 (10)	12 (15)
Denileukin Diftitox	n/a	7 (4)	3 (4)
Other	n/a	15 (9)	7 (9)
None	n/a	23 (14)	5 (6)

Source: FDA Analysis adapted from CSR 275, CSR 280 Table 14.1-1.3.2.3

Abbreviations: aGVHD, acute graft versus host disease; Rem-L, remestemcel-L; SOC, standard care salvage therapy.

Table 34: Day 28 ORR by concomitant GVHD Therapies on Study 275 was reported as follows:

Prior and Concomitant GVHD Therapy N (%)	OR at Day 28
Additional Concomitant GVHD Therapy	
Mycophenolate mofetil	31/51 (60.8%)
Infliximab	17/35 (48.6)
Sirolimus	13/21 (61.9)
Etanercept	11/19 (57.9)
Basiliximab	2/6 (33.3)
Daclizumab	5/5 (100.0)
Rituximab	4/5 (80.0)
ATG	2/5 (40.0)

[Source Clinical Study Report Final Expanded Protocol Study No. 275]

Although outcomes measures by concomitant GVHD Therapies on Study 280 was pre-specified in the SAP, these analyses were not provided by the Applicant. In response to FDA IR #22, received June 16, 2020, where the Applicant was asked to provide the following analysis: “Q3: Conduct analyses of Day-28 response and duration of response in Study 280 and Study 275 by concurrent use of cytokine inhibitors and submit the results. Include results from the placebo arm from Study 280 for comparison”, Mesoblast provided the data of five pre-specified efficacy endpoints: Durable Complete Response (DCR: complete response of at least 28 days duration within the first 100 days of follow-up); Induction of Complete Response (CR); Duration of Complete Response (CR); Overall Survival (OS) at Day 100; and Overall Survival (OS) at Day 180. They reported results for the subgroups of Etanercept or Infliximab exposure, for the two subgroups of anti-TNF exposure combined, and for all other subjects (i.e., those not exposed only to one of the two anti-TNF agents). Across all endpoints, they observed no significant differences, either for the comparison of remestemcel-L vs. controls for those treated with anti-TNF agents, or for the comparison within the remestemcel-L arm between those treated with anti-TNF agents and those who were not.

Table 35: Efficacy outcomes comparison of remestemcel-L vs. controls for those treated with anti-TNF agents

Endpoint/Subgroup	Remestemcel-L	Placebo
DCR	n/N (%)	n/N (%)
Overall	60/163 (37%)	26/81 (32%)
Etanercept	7/23 (30%)	5/11 (46%)
Infliximab	12/27 (44%)	3/11 (27%)
Etanercept or Infliximab	19/50 (38%)	8/22 (36%)
No Etanercept or Infliximab	41/113 (36%)	18/59 (31%)
Induction of Complete Response	n/N (%)	n/N (%)
Overall	94/163 (58%)	44/81 (54%)
Etanercept	12/21 (57%)	6/11 (55%)
Infliximab	17/27 (63%)	6/11 (55%)
Etanercept or Infliximab	29/48 (60%)	12/22 (55%)
No Etanercept or Infliximab	65/115 (57%)	32/59 (54%)
Duration of Complete Response	Median Days (N)	Median Days (N)
Overall	40.5 (163)	37.5 (81)
Etanercept	39.5 (21)	57.5 (11)
Infliximab	36.0 (27)	39.0 (11)
Day 100 Overall Survival	n/N (%)	n/N (%)
Overall	85/163 (52%)	41/81 (51%)
Etanercept	10/21 (48%)	6/11 (55%)
Infliximab	15/27 (56%)	4/11 (36%)
Etanercept or Infliximab	25/48 (52%)	10/22 (45%)
No Etanercept or Infliximab	60/115 (52%)	31/59 (53%)
Day 180 Overall Survival	n/N (%)	n/N (%)
Overall	56/163 (34%)	34/81 (42%)
Etanercept	6/21 (29%)	6/11 (55%)
Infliximab	10/27 (37%)	4/11 (36%)
Etanercept or Infliximab	16/48 (33%)	10/22 (45%)
No Etanercept or Infliximab	40/115 (35%)	24/59 (41%)
Source: Protocol 280 Clinical Study Report, post-text tables: DCR (14.2-1.1.2, 14.2-1.1.7.3); Induction of CR (14.2-1.11.1, 14.2-1.11.6.3); Duration of CR (14.2-1.16.1.1, 14.2-1.16.1.4); Day 100 OS (14.2-1.2.2, 14.2-1.2.6.3); Day 180 OS (14.2-1.3.2, 14.2-1.3.6.3).		
Note: For the primary endpoint of DCR, there were 27 remestemcel-L subjects concomitantly treated only with Etanercept and 23 treated only with Infliximab. For controls, 11 subjects were treated at baseline with each anti-TNF agent. Subject counts remain consistent for all other endpoints for controls; however, 2 remestemcel-L subjects are dropped from the Etanercept subgroup for all other endpoints.		

[Source: MSB Response to FDA IR_2020_06_02 RFI#22_CMC June 16, 2020]

Reviewer Comment: Differences in efficacy outcomes based on subgroup analyses of concomitant aGVHD therapies are difficult to interpret. The data from Study 280 do not suggest any differences between treatment and placebo arms.

7.1.10 Additional Efficacy Issues/Analyses

Dose-Efficacy Analyses

Dosing of remestemcel-L is based on the patient's body weight. The recommended dose of remestemcel-L is 2×10^6 ce-MSK/kg (actual body weight), twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart. The product may be administered once a week for another 4 weeks, based on the initial response and the severity of residual symptoms.

The development of remestemcel-L dosing occurred under IND 7939. Nonclinical and clinical studies conducted in this setting established feasible dose ranges for remestemcel-L, and its safety. After preliminary pre-clinical studies, two early Phase 1 clinical studies were conducted to examine the safety and feasibility of IV administration of remestemcel in subjects undergoing HSCT for hematological malignancies (Studies 201, 202). Adult subjects were treated with a single IV dose of remestemcel-L (1×10^6 , 2.5×10^6 or 5×10^6 cells/kg) obtained from HLA-matched siblings. In Study 202, 8 pediatric subjects were treated with a single infusion of remestemcel-L 2 doses of 5×10^6 cells/kg or a single dose of 10×10^6 cells/kg). In both studies, IV administration was feasible and was not associated with infusional or long-term toxicities. In parallel with the EAP for the treatment of subjects with severe, treatment refractory aGVHD, a phase 2, open-label, dose-comparison study was initiated to evaluate the effects of remestemcel-L on newly-diagnosed aGVHD in adults (N=32, Study 260). Subjects were randomized to receive remestemcel-L at a dose of 2×10^6 cells/kg or 8×10^6 cells/kg. Subjects received two infusions, 3 days apart, as an adjunct to standard corticosteroid therapy. Ninety-four percent of evaluable subjects 29/31 exhibited an initial response to treatment. Of the 23 subjects who achieved an initial complete response, 5 experienced aGVHD flares that required second line therapy during the first 28 days. No infusional toxicities or ectopic tissue formation were observed. There were no significant differences between the two dose groups in clinical response or safety endpoints. The data from this study provided further evidence of the safety of IV administered remestemcel-L in patients with aGVHD and indicated no apparent advantage to a dose greater than 2×10^6 cells per infusion. Further, the data also suggested the requirement for more than 2 doses of remestemcel-L to maintain a complete response.

Reviewer Comment: Based on these early findings, subsequent studies of remestemcel-L therapy in subjects with treatment-refractory aGVHD employed a dose of 2×10^6 cells/kg and a treatment regimen of 8 doses, administered twice a week, at least 3 days apart, for 4 weeks. It appears that repeated dosing is considered necessary to induce and maintain responses.

Mount Sinai Acute GVHD International Consortium (MAGIC) database comparison of Day 28 ORR

In the integrated analysis of efficacy, the Applicant included a post-hoc analysis using the Mount Sinai Mount Sinai Acute GVHD International Consortium (MAGIC) database as an external control group. MAGIC maintains a research database and biorepository that includes detailed clinical data on patients with aGVHD. The Applicant identified 30 pediatric patients transplanted 2005 - 2019 who received salvage therapy for grades B-D SR-aGVHD (excluding grade B skin alone as in MSB-GVHD001). The Day-28 ORR for pediatric patients after first salvage therapy was 43%.

Review Comment: The main limitation of this analysis is that it was performed post hoc and although there were similar features to the enrollment criteria for Study MSB-GVHD001, this group was not controlled for comparison to Study MSB-GVHD001 by additional factors calling into question the “exchangeability” of this population to the study population as an external control. As such, no firm conclusions can be drawn from this analysis.

Assessment of Evidence of Activity in Other Settings

Table 36 summarizes the key design elements for the randomized, placebo-controlled aGVHD remestemcel-L trials, Studies 265 and 280. It should be noted that these trials did not use drug product manufactured using the commercial process.

Table 36: Adult and Pediatric aGVHD Trials - Randomized, Placebo-controlled Trials

	Study 265	Study 280
Phase	Phase 3	Phase 3
Ages	Adult	Adult and pediatric
Population	Newly-diagnosed 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
Primary Endpoint	CR \geq 28 days duration	CR \geq 28 days duration
Control Arm	Steroids + Placebo	SOC + Placebo
Treatment Arm	Steroids + remestemcel-L 2 \times 10 ⁶ cells/kg x 2 infusions/ week x Weeks 1-2, then 1 infusion/week x Weeks 3-4	SOC + remestemcel-L 2 \times 10 ⁶ cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8

Source: FDA Analysis

Abbreviations: aGVHD, acute graft versus host disease, CR, complete response; SOC, standard care salvage therapy.

Study 265 evaluated the efficacy of remestemcel-L in combination with systemic corticosteroid therapy in 192 adult patients with newly-diagnosed grades B-D aGVHD. The study population and treatment regimen in Study 265 differs from that of MSB-GVHD001 in that this was an adult population and patients were newly diagnosed aGVHD rather than steroid refractory. Study 280, as discussed above, evaluated the efficacy of remestemcel plus investigator's choice of additional salvage therapy in 242 patients with grades B-D SR-aGVHD. This is in contrast to MSB-GVHD001, where no additional salvage immunosuppressive agent was allowed. As such, there are substantial differences between the randomized, placebo-controlled remestemcel-L aGVHD trials and MSB-GVHD001 in study populations and the treatment plans.

Review Comment: Based on the substantial differences in the design of Studies 265 and 280 in comparison to MSB-GVHD001, the results of these studies are not applicable to the proposed indication. The design of each does, however, isolate the treatment effect when used in the context of the respective trials.

Table 37 compares the efficacy outcomes of Study MSB-GVHD001 to outcomes reported in the two randomized, placebo-controlled trials. The primary endpoint of Studies 265 and 280 was a CR that lasted >28 days duration. Post-hoc analyses of 265 and 280 were performed to evaluate the ORR at day 28, however, it is difficult to make cross-study comparisons, due to the different patient populations, and the allowance for salvage aGVHD therapies on Study 280. Most importantly, however, is the fact that no treatment effect was observed in either of the two, prior randomized, placebo-controlled trials. The ORR in the remestemcel treatment arms ranged from 54-70% with wide confidence intervals.

Table 37: Efficacy Outcomes in MSG-GVHD001 and the Randomized, Place-Controlled Trials

	Study 001	Study 265		Study 280	
	Rem- L	Steroids + Rem-L	Steroids + Placebo	SOC + Rem-L	SOC + Placebo
Number of patients	54	97	95	173	87
CR lasting \geq 28 days	-	45%	46%	35%	30%
Day-28 ORR^b 95% CI	70.4% 56.3, 82.0)	60% 49.3, 69.6)	61% 50.5, 70.9)	54% 46.0, 61.3)	47% 36.3, 58.1)
Day-28 CR	29.6%	41%	49%	25%	23%
Day-28 PR	40.7%	19%	12%	29%	24%

Source: FDA Analysis

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response, Rem-L, remestemcel-L; SOC, standard care salvage therapy.

Reviewer Comments: Based on the results shown in Table 37, one can conclude that remestemcel – L is not effective when used as an add-on therapy for the treatment of newly-diagnosed or SR-aGVHD. The lack of superiority of combination regimens over single potent immunosuppressive drugs for treatment of SR-aGVHD is well-established in the literature, and the observed outcomes of these trials is not unexpected. The results do not detract of the finding of single-agent activity in MSB-GVHD001.

Additionally, clinical trials have been conducted in various other disease entities, including: type 1 diabetes mellitus, Crohn’s Disease, myocardial infarction, and severe chronic obstructive pulmonary disease (see Table 27 in Section 6.3). Several of these studies have been large randomized trials with greater than 200 subjects randomized, and a treatment effect has not been identified in any of the previous studies for any other disease indication.

Review Comment: The lack of efficacy in unrelated conditions has little relevance to this review.

7.1.11 Efficacy Conclusions

Study 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, and the results were consistent across subpopulations and secondary efficacy endpoints.

The limitations of the single-arm study design of MSB GVHD001 include a lack of randomization which can lead potentially to differences in the trial population compared to the external control population which may lead to differences in outcomes that are unrelated to the investigational treatment and a lack of blinding may introduce bias in concomitant treatment or endpoint assessments.

Additional data were provided from Study 265, 275 and 280. In comparison to Study MSB-GVHD001, Studies 265, 275 and 280 have substantial differences in the patient populations, trial design, study conduct, and primary endpoint evaluations. Additionally, these studies used drug product manufactured using a different process. As such, the results of analyses of these trials are not applicable to the proposed indication and do not detract from the .

The results of Study MSB-GVHD001 are concluded to be evidence of effectiveness of remestemcel-L for treatment of SR-aGvHD in pediatric patients.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

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 review:

- The 54 patients treated with remestemcel-L on Study MSB-GVHD001 were used primarily to assess the safety profile in the intended population. These were the only patients treated with drug product made using the proposed commercial manufacturing process (DP3). 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 Study 265 (n=186) and Study 280 (n=244), the two randomized trials for patients with aGvHD, were used for comparative analyses to enable identification of adverse reactions. These patients were treated with drug product made using manufacturing processes not established as producing comparable product (see Section 4.1), but results of the safety analyses may be acceptable as class-related. On Study 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 Study 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).
- 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).

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 review of the safety profile of remestemcel-L focuses primarily on the safety events in the 54 patients treated with remestemcel-L on Study MSB-GVHD001 to assess the safety profile in the intended population.

Data in the ISS dataset was used for the review of safety. MedDRA Adverse Events Diagnostic MAED) (b) (4) was used to assess for safety signals. Unless stated otherwise, all p-values are unadjusted for multiplicity and should be interpreted with caution.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

An overview of all studies used in the safety review is shown in Table 38.

Table 38: 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
Trials for Other Diseases			

Study	Study Design	Population	Treatment
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; 100×10^6 cells days 7 and 14 Arm C: 400×10^6 cells Days 0 and 3; 200×10^6 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; 100×10^6 cells days 7 and 14 Arm C: 400×10^6 cells Days 0 and 3; 200×10^6 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: 100×10^6 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: 2×10^6 cells/kg on Days 0, 30, 60

Source: FDA adapted table from Mesoblast BLA submission

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 39: Demographics aGVHD Safety Analysis Cohorts

	Cohort A (N=309)	Cohort B (N=149)	Cohort C (N=127)	Cohort A+B (N=458)	All Remestemcel- L (N=585)	Control (N=173)
Age (Years)						
Mean	8.94	47.30	48.56	21.42	27.31	44.11
SD	5.467	12.531	11.786	19.867	21.545	15.501
Median	8.40	49.60	50.30	14.15	17.00	47.30
Min - Max	0.3-18.2	19.1-69.6	20.5-67.7	0.3-69.6	0.3-69.6	1.3-68.3
n	309	149	127	458	585	173
Gender, n (%)						
Male	190 (61.5)	84 (56.4)	82 (64.6)	274 (59.8)	356 (60.9)	101 (58.4)
Female	119 (38.5)	65 (43.6)	45 (35.4)	184 (40.2)	229 (39.1)	72 (41.6)
Race, n (%)						
American Indian / Alaska Native	6 (1.9)	1 (0.7)	0 (0.0)	7 (1.5)	7 (1.2)	0 (0.0)
Asian	16 (5.2)	1 (0.7)	1 (0.8)	17 (3.7)	18 (3.1)	1 (0.6)
Black / African American	58 (18.8)	9 (6.0)	5 (3.9)	67 (14.6)	72 (12.3)	13 (7.5)
Native Hawaiian / Pacific Islander	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)	1 (0.2)	2 (1.2)
White	184 (59.5)	129 (86.6)	112 (88.2)	313 (68.3)	425 (72.6)	147 (85.0)
Other	45 (14.6)	8 (5.4)	9 (7.1)	53 (11.6)	62 (10.6)	10 (5.8)
Ethnicity, n (%)						
Hispanic or Latino	70 (22.7)	10 (6.7)	11 (8.7)	80 (17.5)	91 (15.6)	10 (5.8)
Not Hispanic or Latino	230 (74.4)	120 (80.5)	99 (78.0)	350 (76.4)	449 (76.8)	131 (75.7)

[Source: Mesoblast Module 5.3.5.3 Integrated Summary of Safety/ ISS Table 14.1.3.1]

Table 40: Subject Demographics- non-aGVHD Cohorts

n (%)	AMI		COPD		T1DM		CD	
	Remeste mcel-L N = 144	Control N = 129	Remeste mcel-L N = 30	Control N = 32	Remeste mcel-L N = 42	Control N = 21	Remeste mcel-L N = 244	Control N = 48
Age (Years)								
Mean	58.08	57.59	68.49	64.53	22.46	23.08	41.11	40.26
SD	11.165	10.863	7.487	8.801	5.630	5.505	12.799	12.033
Median	58.65	57.90	68.75	65.25	22.70	23.70	39.50	39.30

Min - Max	28.3-84.2	31.5-81.4	54.5-80.7	47.7-79.8	12.6-34.8	12.6-33.6	18.9-68.3	20.4-70.2
n	144	129	30	32	42	21	244	48
Gender, n (%)								
Male	121 (84.0)	104 (80.6)	18 (60.0)	18 (56.3)	30 (71.4)	10 (47.6)	114 (46.7)	24 (50.0)
Female	23 (16.0)	25 (19.4)	12 (40.0)	14 (43.8)	12 (28.6)	11 (52.4)	130 (53.3)	24 (50.0)
Race, n (%)								
American Indian / Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	1 (2.1)
Asian	3 (2.1)	1 (0.8)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.8)	3 (1.2)	0 (0.0)
Black / African American	5 (3.5)	3 (2.3)	1 (3.3)	3 (9.4)	6 (14.3)	0 (0.0)	12 (4.9)	3 (6.3)
Native Hawaiian / Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	131 (91.0)	123 (95.3)	29 (96.7)	28 (87.5)	34 (81.0)	19 (90.5)	219 (89.8)	43 (89.6)
Other	5 (3.5)	2 (1.6)	0 (0.0)	0 (0.0)	2 (4.8)	1 (4.8)	3 (1.2)	1 (2.1)
Ethnicity, n (%)								
Hispanic or Latino	10 (6.9)	13 (10.1)	0 (0.0)	0 (0.0)	2 (4.8)	1 (4.8)	4 (1.6)	1 (2.1)
Not Hispanic or Latino	134 (93.1)	116 (89.9)	30 (100.0)	32 (100.0)	40 (95.2)	20 (95.2)	240 (98.4)	47 (97.9)

[Source: Mesoblast Module 5.3.5.3, Integrated Summary of Safety, ISS Table 14.1.3.6 through Table 14.1.3.9]

Study MSB-GHVD001/002

Safety Population

The Safety population (n = 54) included all subjects who signed the ICF and received at least 1 dose of remestemcel-L (complete or partial).

Extent of Exposure

Table 41 summarizes remestemcel-L infusion information and extent of exposure for all subjects who received at least 1 infusion of remestemcel-L (54 subjects) and for the subgroups of subjects who were treated with remestemcel-L that were provided either cryogenic vials (DP3) (46 subjects) or cryogenic bags (DP2) (8 subjects) during manufacturing.

The majority of subjects (46/54 or 85.2%) received 5 to 12 infusions. Ten subjects missed a total of 13 infusions. Reasons for missing infusions included AEs/SAEs (5), lack of efficacy (2), and other (6; 4 of them were due to the start of second-line therapy). Two subjects each had 1 infusion interrupted. One subject had the interrupted infusion restarted. A total of 535 infusions were administered to the 54 subjects. The mean (SD) number of infusions per subject was 9.9 (3.28).

Table 41: Study Drug Infusion Information and Extent of Exposure

Study Drug Infusion Therapy Parameter	Remestemcel-L Bag N = 8	Remestemcel-L Vial N = 46	Total Remestemcel-L N = 54
All infusion therapies			
Total number of infusions given, n	76	459	535
Average number of infusions			
N	8	46	54

Mean (SD)	9.5 2.07)	10.0 3.45)	9.9 3.28)
median	8.0	11.5	10.0
Min, Max	8, 12	1, 16	1, 16
Total number of infusions, n (%)			
1 - ≤4	0	3 (6.5	3 (5.6
5 - ≤8	5 62.5	16 (34.8	21 (38.9
9 - ≤12	3 (37.5	22 (47.8	25 (46.3
≥13	0	5 (10.9	5 9.3
Subjects with any missed infusion(s), n (%)			
Total number of missed infusions, n	0	13	13
Reason for missed infusion(s), n (%) ^a			
AE/SAE	0	5 (38.5)	5 (38.5)
Lack of efficacy	0	2 (15.4)	2 (15.4)
Missed visit	0	0	0
Other	0	6 (46.2)	6 (46.2)
Any infusion(s) interrupted, n (%)			
Total number of interrupted infusions, n	0	2 (4.3)	2 (3.7)
Infusions restarted, n (%) ^b			
Yes	0	1 (50.0)	1 (50.0)
No	0	1 (50.0)	1 (50.0)
Reason interrupted, n (%) ^b			
Infusion toxicity	0	1 (50.0)	1 (50.0)
Other adverse event	0	0	0
SaO2 decreased	0	0	0
Prochymal infusion bag was expired	0	0	0
Treating physician discretion	0	0	0
Patient withdrew consent	0	0	0
Other	0	1 (50.0)	1 (50.0)
Average duration of each infusion (min)			
n	8	46	54
Mean SD	59.016 74.5563	62.478 58.3325	61.965 60.2060
Median	41.042	61.000	61.000
Min, Max	8.25, 233.38	11.00, 419.73	8.25, 419.73
Average total volume administered at each infusion (mL)			
n	8	46	54
Mean (SD)	28.0 (14.22)	48.6 (5.86)	45.6 (10.52)
Median	32.0	47.9	47.2

Min, Max	9, 48	41, 67	9, 67
Total volume administered, all infusions (mL)			
n	8	46	54
Mean (SD)	271.5 (169.04)	485.0 (176.91)	453.4 (190.29)
Median	260.0	498.5	482.4
Min, Max	72, 576	54, 809	54, 809

[Source: Clinical Study Report, Report No. MSB-GVHD001, Section 12.1]

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 the review:

Review Comment: The number of patients treated and the distribution by demographics is considered adequate to develop a safety profile generalizable to patients with aGVHD in the US. The lack of dose-finding for the drug product made using manufacturing process DP3 precludes an analyses of dose-safety, so class-effects will be relied upon where possible.

8.2.3 Categorization of Adverse Events

Treatment-emergent AEs were defined as AEs that started or worsened after the first dose of remestemcel-L. Adverse events were coded by the applicant according to MedDRA version 20.0 and graded according to CTCAE version 3. Events identified as GVHD or as the primary hematologic disorder were excluded from the analyses. In order to improve the accuracy of estimating the risk of adverse reactions, grouped terms were used by FDA for some analyses, as described in the Table below.

Table 42: Grouped terms used by FDA for analyses

GPTERM	GPBASIS
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Acute kidney injury	Acute renal failure (SMQ)
Bacterial infection	HLGT Bacterial infectious disorders
Cough	HLT Coughing and associated symptoms
Diarrhoea	HLT Diarrhoea (excl infective)
Dizziness	Vestibular disorders (SMQ)
Dyspnoea	HLT Breathing abnormalities
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)
Hypersensitivity	Anaphylactic reaction/Hypersensitivity (SMQ)
Hypertension	Hypertension (SMQ)
Infection	HLGT Infections - pathogen unspecified
Infusion related reaction	PTs Infusion or site reactions
Jaundice	HLT Cholestasis and jaundice
Oedema	HLT Oedema NEC
Rash	HLT Rashes, eruptions and exanthems NEC
Thrombosis	Embolitic and thrombotic events (SMQ)
Viral infection	HLGT Viral infectious disorders

FDA focused on acute infusion reactions, serious infections, and ectopic tissue formation as AEs of special interest (AESI) as defined in Section 8.4.6. Adverse events of special interest were

flagged by the Applicant as *Adverse Event of Interest* in the ADAE Dataset and included the following:

- Acute infusion reactions
- Serious infections
- Serious pulmonary complications
- Pneumatosis intestinalis
- Serious neurological events
- Ectopic tissue formation.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

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

In general, there were otherwise substantial differences between the clinical trials with regard to the patient population and treatment plan, so data were pooled only for analyses of rare events as indicated in Section 8.2.2.

8.4 Safety Results

8.4.1 Deaths

There were 422 deaths reported in the integrated safety database; 229 occurred within 30 days of the last dose of remestemcel-L. Table 43 shows the percentage of deaths within 30 days of the last dose of remestemcel-L by Study and arm.

Table 43: 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%
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%

Table 43: 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	%
		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

Review Comment: In the randomized trials, there was no apparent difference between the remestemcel-L and placebo arms in the incidence of deaths. Given the complicate course of patients with acute GVHD, there are multiple potential causes of death. The non-GVHD studies provide for a clean assessment of the risk of fatal adverse reactions. The lack of any fatal adverse reaction among the 460 patients treated with remestemcel-L in the non-GVHD studies suggests that the risk is low. However, there is still a need to assess the population-specific risk.

In Study MSB-GVHD001, there were 14 deaths reported among 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 44 shows the FDA-adjudicated root causes of death. There were no cases with remestemcel-L adverse reactions as the root cause of death.

Table 44: Study 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

[Source: FDA reviewer generated table from ADAE/ADSL datasets, GVHD001/002 CSR and Patient narratives]

Review Comment: The analysis of causes of death in Study GVHD001/002 confirm the low risk of fatal adverse reactions from remestemcel-L.

8.4.2 Serious Adverse Events

In Study MSB-GVHD001, an SAE was reported for 42 (77.8%) patients. The most common System Organ Class (SOC) for SAEs was Infections and infestations (37%). SAEs reported in more than 3% of patients are shown by SOC in Table 45. The most common (>3%) serious

adverse events were bacterial infection (20%), infection (15%), viral infection (11%), pyrexia (9%), respiratory failure (9%), pneumatosis intestinalis 7%), haemorrhage (6%), acute respiratory distress syndrome (4%), acute respiratory failure 4%), dehydration (4%), dyspnoea 4% , haemolytic uraemic syndrome (4%), multiple organ dysfunction syndrome (4%), posterior reversible encephalopathy syndrome (4%), and thrombosis (4%).

Table 45: Study GVHD-001-Serious Adverse Events by SOC

System Organ Class*	N	Proportion %
Infections and infestations	20	37
Respiratory, thoracic and mediastinal disorders	12	22
General disorders and administration site conditions	8	15
Gastrointestinal disorders	7	13
Immune system disorders	6	11
Blood and lymphatic system disorders	5	9
Vascular disorders	5	9
Metabolism and nutrition disorders	4	7
Cardiac disorders	3	6
Neoplasms benign, malignant and unspecified	3	6
Nervous system disorders	3	6

[Source: FDA generated table from ADAE/ADSL datasets]; * MedDRA level term = System Organ Class (SOC)

Table 46: Serious Adverse Events Occurring in > 5% for Pediatric Subjects in Studies MSB-GVHD001, Study 280, Study 275

High Level Term	Number of subjects	Proportion %
Infections - pathogen unspecified	41	13
Respiratory disorders	41	13
Bacterial infections	32	10
Immune disorders	22	7
Viral infections	22	7
General system disorders	21	7
Gastrointestinal haemorrhages	18	6
Fungal infections	17	5

Source: FDA Analysis

Review Comment: Serious adverse events in the pediatric population mirror those observed in the overall safety population.

8.4.3 Study Dropouts/Discontinuations

Study MSB-GVHD001

Seven (13%) patients had an adverse event resulting in withdrawal. Adverse events that resulted in withdrawal included acute respiratory distress syndrome in 2 (4%) patients and cardiac failure, hypermetabolism, hypersensitivity, hypotension, multiple organ dysfunction syndrome, somnolence, and viral infection in one patient each (each patient may have had more than one event).

8.4.4 Common Adverse Events

Study MSB-GVHD001

The Safety population (n = 54) included all subjects who received at least 1 dose of remestemcel-L. FDA safety analysis confirms the Applicant's safety analyses. The Applicant reports that all 54 subjects in the safety population experienced at least 1 TEAE during the study. Table 47 shows the incidence of TEAE by SOC, and Table 48 shows the incidence of individual TEAEs (using grouped terms).

Table 47: Treatment Emergent Adverse Events Occurring in > 5% of Subjects by SOC

SOC	Number of subjects	Proportion %
Infections and infestations	47	87
Gastrointestinal disorders	33	61
General disorders and administration site conditions	29	54
Metabolism and nutrition disorders	28	52
Investigations	27	50
Respiratory, thoracic and mediastinal disorders	26	48
Immune system disorders	22	41
Skin and subcutaneous tissue disorders	19	35
Musculoskeletal and connective tissue disorders	18	33
Vascular disorders	18	33
Blood and lymphatic system disorders	17	32
Renal and urinary disorders	17	32
Psychiatric disorders	16	30
Nervous system disorders	13	24
Cardiac disorders	12	22
Injury, poisoning and procedural complications	12	22
Endocrine disorders	11	20
Hepatobiliary disorders	7	13
Neoplasms benign, malignant and unspecified	7	13
Eye disorders	4	7
Ear and labyrinth disorders	3	6

Source: FDA Analysis; *SOC terminology

Table 48: All-Grade TEAE Occurring in > 10% of Subjects

<i>PT</i>	Y (N = 54)	
	<i>Number of subjects</i>	<i>Proportion (%)</i>
Viral infection	30	56
Bacterial infection	23	43
Infection	21	39
Pyrexia	19	35
Haemorrhage	18	33
Abdominal pain	11	20
Acute kidney injury	11	20
Hypertension	11	20

Oedema	11	20
Vomiting	10	19
Diarrhoea	9	17
Hypokalaemia	9	17
Rash	9	17
Arthralgia	8	15
Cough	8	15
Fungal infection	8	15
Hyperglycaemia	8	15
Hypersensitivity	8	15
Hypotension	8	15
Hypomagnesaemia	7	13
Thrombosis	7	13
Hypogammaglobulinaemia	6	11

Source: FDA analysis
*Includes grouped terms

Reviewer Comments: The most common AEs observed in the study were infections, gastrointestinal disorders, and respiratory complications (Table 47). This is consistent with literature reports of varying treatments used for GVHD [Malard F, et al. 2020][García-Cadenas et al. 2017][Hsu B, et al. 2001][Onishi C, et al. 2010][von Bubnoff N, et al. 2018][Arai S, et al. 2002]. 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. Thus, leading to high rates of infection-related mortality and decreased OS in this population [Martin PJ, et al. 2020].

Treatment emergent infections occurring on Study MSB-GVHD0001 are reported in Table 49.

Table 49: Most common infections in Study MSB-GVHD001

Adverse Events: Infections	Number of subjects	Proportion %
Viral infectious disorders	30	56
Bacterial infectious disorders	24	44
Infections - pathogen unspecified	22	41
Fungal infectious disorders	8	15

Source: FDA Analysis, ADAE, TRTEM FL = Y

Reviewer Comments: Rates of infection on Study MSB-GVHD001 are consistent with expected rates reported in the literature for this patient population.

The most common Grade ≥ 3 TEAE are shown in the Table below:

Table 50: Grade >=3 TEAE Occurring in > 5% of Subjects		
	Y (N = 54)	
PT	Number of subjects	Proportion (%)
Bacterial infection	10	19
Infection	8	15
Viral infection	8	15
Haemorrhage	7	13
Hypokalaemia	6	11
Respiratory failure	5	9
Abdominal pain	4	7
Hypertension	4	7
Hyperglycaemia	3	6
Hypersensitivity	3	6
Neutropenia	3	6
Vomiting	3	6

Source: FDA analysis
*Includes grouped terms

Viral infection (4%) was the only TEAE reported by investigators for 2 or more patients as at least possibly related to remestemcel-L

Studies 280 and 265

As it is difficult to discern drug-related adverse events in a single-arm trial like MSB-GVHD001, FDA also assessed the randomized trials Study 280 and Study 265 to determine if there was a consistent difference in the incidence of any TEAE between the remestemcel-L and placebo arms.

For Study 280, the randomized trial for patients with SR-aGVHD, Table 51 shows the adverse events occurring with an incidence at least 5% greater in the remestemcel-L arm. For Table 51, all TEAEs through study follow-up are shown. 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%).

Table 51: Study 280: Adverse Events with > 5% Difference Between Arms

Adverse Event*	Remestemcel-L N = 163		Placebo N = 81		% Risk Difference
	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
Hypokalaemia	35	21	11	14	8
Dyspnoea	43	26	15	19	8
Abdominal distension	16	10	2	2	7
Hyperkalaemia	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
Hyperglycaemia	32	20	11	14	6

Source: FDA analysis
*Includes grouped terms

For Study 265, the randomized trial for patients with newly-diagnosed aGVHD, Table 52 shows the adverse events occurring with an incidence at least 5% greater in the remestemcel-L arm. For Table 52, all treatment-emergent adverse reactions through study follow-up are shown. 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 52: Study 265: Adverse Events with > 5% Difference Between Arms

Adverse Event*	Remestemcel-L N = 95		Placebo N = 91		% Risk Difference
	Number	%	Number	%	
Oedema	39	41	29	32	9
Pyrexia	20	21	12	13	8
Haemorrhage	34	36	26	29	7
Infection	40	42	32	35	7
Dyspnoea	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

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

8.4.5 Clinical Test Results

Study MSB-GVHD001

Fifty-one laboratory value abnormalities were observed on Study MSB-GVHD001 (Table 53), only 2 laboratory events were deemed as SAEs and both were deemed to be possibly related to remestemcel-L, 1 event of platelet count decreased and 1 event neutrophil count decreased. All other laboratory events were mild and deemed unrelated per the investigator. None lead to study termination or discontinuation of remestemcel-L, although dosing was noted to be interrupted for 1 AST elevation, 1 ALT elevation and 1 cholesterol elevation.

Table 53: MSB-GVHD001 - Laboratory Adverse Events

Reported Term for Adverse Event	Number
Alanine aminotransferase ALT increased	14
Aspartate aminotransferase AST increased	1
Bilirubin elevated	2
Cholesterol, high	1
Creatinine increased	8
Decreased anion gap	1
Decreased haptoglobin	1
Decreased platelets	1
Decreased serum chloride	4

Elevated alkaline phosphatase	1
Elevated blood urea nitrogen	1
Elevated ESR	2
Elevated GGT levels	1
Elevated serum triglycerides	1
Elevated thyroid stimulating hormone	1
Intermittent low serum IGG	1
Low bicarbonate level	1
Low vitamin d serum level	2
Neutrophil count decreased	1
Phosphorous above normal range	2
Platelet count decreased	1
White blood cell count decreased	2
Worsening neutrophil count decrease	1

Source: FDA Analysis

Reviewer Comment: Abnormal laboratory adverse events do not appear to be a concern for the use of remestemcel-L.

8.4.6 Adverse Events of Special Interest

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 (Table 54). Two of the three subjects received additional remestemcel infusions, one without further events reported, but the other appeared to have DMSO neurotoxicity with two subsequent infusions. The latter events resolved without intervention, but remestemcel-L administration was then discontinued.

Table 54: FDA analysis - Study GVHD-001 Remestemcel-L - Infusion Reactions

Preferred Term (PT)	Remestemcel-L (N = 54)	
	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.

Review Comment: There risk of infusion reactions appears to be mitigated by premedications, monitoring and infusion interruption as specified in the protocol. For safe use postmarketing, the same parameters should be included in labeling.

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 [Malard 2020][García-Cadenas 2017][Hsu 2001][Onishi 2010][von Bubnoff 2018][Arai 2002]. 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 55 shows the incidences of Grades 3-5 and fatal infections in Studies 265, 280 and MSB-GVHD001. In Study 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 55: AESI: Severe and Fatal Infections*

	Study 265		Study 280		Study 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 Study MSB-GVHD001, one case in Study 275, and three cases of PTLD in Study 280 (one on the placebo arm and two on remestemcel-L). The risk of PTLD was not higher with remestemcel-L in these Studies.

Review Comment: There is no evidence to suggest that use of remestemcel-L is associated with an increased risk of infections.

Ectopic Tissue Formation

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).

Ectopic tissue formation was ascertained by serial CT scans of the chest, abdomen and pelvis. As shown in Table 56 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 Study MSB-GVHD001.

Table 56: Ectopic Tissue Formation - Imaging Schedule by Study

Study	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

The Applicant provided the analysis of the CT scans in a revised ISS adae.xpt (Response to Information Request 7/15/2020). Although it is noted that derived data from imaging results should be submitted in adfa.xpt, given that the information was submitted so late in the review, this version of adae.xpt was accepted for FDA's analysis of CT scans for ectopic tissue. The file included 1,640 results. There was no date of imaging for 4 results; these 4 cases were not included in the analysis (all were reported negative for ectopic tissue). In 22 cases, there were duplicate results for the same patient and date, some of which gave conflicting information; for the purposes of this review, when a "Yes" and a "No" were reported in the duplicates, the "Yes" was chosen for the analysis.

Postbaseline scan results were identified for 530 patients, including 397 treated with remestemcel-L and 133 treated with placebo. Table 57 shows the percentage of patients treated with study drug who had follow-up CT scans at each timepoint. Note the median and range of the window for each timepoint in the second row of the table; CTs at unscheduled visits were included in the analysis. Few patients on Study MSB-GVHD001 participated. Few patients on the GVHD Studies completed scheduled CTs past Months 3. For Studies AMI401/402 (myocardial infarction) and T1DIAB901 (type 1 diabetes), compliance with the scheduled long-term follow-up CT scans was 76% to 100% at various timepoints.

Table 57: Ectopic Tissue Formation - Compliance with Imaging Schedule

STUDYID	Median Day (range)	Baseline		Month 1		Month 3		Month 6		Year 1		Year 2	
		N	%	N	%	N	%	N	%	N	%	N	%
	TRT01A												
MSB_GVHD001	Remestemcel-L	15	28%	3	6%	9	17%	2	4%	0	0%	0	0%
GVHD280	Remestemcel-L	149	91%	13	8%	1	1%	47	29%	0	0%	0	0%
	Placebo	71	88%	13	16%	0	0%	27	33%	0	0%	0	0%

Table 57: Ectopic Tissue Formation - Compliance with Imaging Schedule

STUDYID	Median Day (range)	Baseline		Month 1		Month 3		Month 6		Year 1		Year 2	
		N	%	N	%	N	%	N	%	N	%	N	%
		-3 (-311 to 1)		13 (2 to 59)		97 (60 to 127)		183 (135 to 271)		365 (291 to 560)		729 (636 to 813)	
GVHD265	TRT01A	87	92%	13	14%	61	64%	2	2%	12	13%	0	0%
	Placebo	85	93%	8	9%	56	62%	2	2%	9	10%	0	0%
GVHD260/261	Remestemcel-L	21	66%	24	75%	0	0%	2	6%	17	53%	11	34%
	Placebo	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GVHD270	Remestemcel-L	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
GVHD275	Remestemcel-L	221	91%	33	14%	126	52%	2	1%	0	0%	0	0%
GVHD276	Remestemcel-L	14	78%	1	6%	5	28%	0	0%	0	0%	0	0%
AMI401/402	Remestemcel-L	34	100%	0	0%	0	0%	33	97%	32	94%	30	88%
	Placebo	19	100%	0	0%	0	0%	19	100%	19	100%	18	95%
CROHN601/602	Remestemcel-L	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
T1DIAB901	Remestemcel-L	0	0%	0	0%	0	0%	1	2%	0	0%	32	76%
	Placebo	0	0%	0	0%	0	0%	0	0%	0	0%	20	95%

Source: FDA Analysis

Nineteen cases were flagged by the Applicant as showing ectopic tissue on CT scan. Table 58 shows the Applicant's description of each case. The Applicant concluded that none of the cases was due to remestemcel-L. No biopsy reports were available for review by FDA.

Table 58: Ectopic Tissue Formation - Description for Positive CT Scans

Subject	Treatment	Study Day	Applicant's Description
(b) (6)	Remestemcel-L	367	No details provided
	Remestemcel-L	180	No details provided
	Remestemcel-L	183	No details provided
	Placebo	366	No details provided
	Placebo	184	No details provided
	Remestemcel-L	363	Recurrent lymphoma
	Remestemcel-L	781	Progression of Hodgkins disease
	Remestemcel-L	742	Calcified right hilar lymph node. large calcified granuloma in right lower
	Remestemcel-L	707	Refractory/relapsed non-Hodgkin's lymphoma
	Remestemcel-L	370	Non-Hodgkin's lymphoma
	Remestemcel-L	30	New soft tissue nodule-injection or bx site. Decrease in size of soft tissue density behind the left scapula. New soft tissue injection or bx site.
	Remestemcel-L	55	Not clinically significant
	Remestemcel-L	89	New ectopic tissue, not clinically significant
	Remestemcel-L	14	Atypical pneumonitis; 2 nodules-1 right upper lobe, 1 left lower lobe

Table 58: Ectopic Tissue Formation - Description for Positive CT Scans

Subject	Treatment	Study Day	Applicant's Description
(b) (6)	Remestemcel-L	111	No new disease appreciated. Pleural thickening consistent with fat. Increase intra-abdominal fat.
	Remestemcel-L	95	Two nodules are appeared in the left lung since the previous scan. These nodules are considered as sign of fungal infection and treated with antifungus treatment.
	Remestemcel-L	181	Abnormal; clinically significant
	Placebo	183	Two lesions are again identified within the liver. the largest lesion borders
	Remestemcel-L	102	Multiple bladder calculi, small pericardial effusion mild mosaic attenuation lungs minimal atelectasis, diffuse bowel wall thickening mild periportal, pericholicystic and mesenteric edema.

Source: Excerpted from adae.xpt submitted 7/15/2020

Review Comment: Although no cases of ectopic tissue formation were attributed to remestemcel-L, several cases had missing or incomplete descriptions and no follow-up, and there were no histology or molecular reports 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. Therefore, there remains some uncertainty about the risk of ectopic tissue formation. This can be addressed by enhanced pharmacovigilance.

8.5 Additional Safety Evaluations

8.5.1 Dose-Dependency for Adverse Events

The Applicant did not provide a formal dose-toxicity analysis. They noted that in the clinical trials of Crohn's disease, patients received a maximum of over 2,000 x 10⁶ cells without substantial toxicity, and that adults treated for aGVHD were treated with a 2-fold median higher dose than in the pediatric patients without an apparent increase in TEAE (Module 5.3.5.3 Integrated Summary of Safety Section 14).

Study MSB-GVHD001 was the only trial using the proposed commercial formulation, and the patient in this study used a uniform dosing regimen with duration of dosing dependent in part on response. Therefore, a dose-toxicity analysis would not be possible in this population.

8.5.2 Product-Demographic Interactions

The Applicant noted the following based on the ISS population:

- The majority of aGVHD subjects were male (60.9%). No clinically meaningful differences in the incidence or type of AEs or SAEs were noted between male and female subjects.
- An analysis of AEs and SAEs was conducted comparing subjects by race (white vs non-white). The majority of aGVHD subjects were white (72.6%). Overall, the incidence of AEs was similar between white and non-white subjects.
- An analysis of AEs and SAEs was conducted comparing subjects by ethnicity, Hispanic or Latino, non-Hispanic Latino, or not reported. The majority of aGVHD subjects were not Hispanic or Latino (76.8%). Overall, the incidence of AEs was similar between Hispanic and non-Hispanics.

- Subjects who received a PBSC transplant had the highest incidence of SAEs (n=252, 76.6% vs control n=104, 75.9%) compared to bone marrow transplant n=118, 65.9% vs control n=20, 80.0%) or cord blood (n=82, 66.1% vs control n=15, 100.0%. Overall, subjects who received a cord blood transplant had lower incidence of AEs.

[Source: Mesoblast BLA 125706 2.7.4 Summary of Clinical Safety]

Table 59 shows FDA's analysis of TEAE by gender in increasing order of the difference in incidence. Only TEAE with a risk difference > 15 % are shown. The significance of these differences is difficult to interpret in the setting of the almost 2:1 ratio of male to female subjects.

Table 59: Study MSB-GVHD001 TEAEs by Gender

TEAE - Preferred Term	Female (N = 19)		Male (N = 35)		Risk Difference %
	N	%	N	%	
BK virus infection	0	0	7	20	- 20
Acute AML	3	16	0	0	16
Diarrhoea	6	32	3	9	23

Source: FDA Analyses; AML, acute myeloid leukemia; N, number; TEAE, treatment emergent adverse event

Table 60 shows the TEAE by race in increasing order of the difference in incidence. Only TEAE with a risk difference > 15 % are shown.

Table 60: Study MSB-GVHD001 TEAEs by Race

TEAE - Preferred Term	Non-White N = 24		White N = 30		Risk Difference (%)
	N	%	N	%	
Hypertension	1	4	9	30	-26
Cough	1	4	6	20	-16
Agitation	4	17	0	0	17
Hypophosphataemia	4	17	0	0	17

Source: FDA Analyses; N, number; TEAE, treatment emergent adverse event

Table 61 shows the TEAE by ethnicity in increasing order of the difference in incidence. Only TEAE with a risk difference > 15 % are shown.

Table 61: Study MSB-GVHD001 TEAEs by Ethnicity

TEAE - Preferred Term	Hispanic/Latino N = 18		Not Hispanic/Latino N = 35		Risk Difference (%)
	N	%	N	%	
Hypertension	1	6	9	26	-20.16
Electrocardiogram QT prolonged	3	17	0	0	17
Flatulence	3	17	0	0	17
Hyperbilirubinaemia	3	17	0	0	17
Skin hyperpigmentation	3	17	0	0	17

Source: FDA Analysis; n, number; TEAE, treatment emergent adverse event

Table 62 shows the TEAE by age group in decreasing order of the difference in incidence. Only TEAE with a risk difference > 15 % are shown.

Table 62: Study MSB-GVHD001 TEAEs by Age Group

TEAE - Preferred Term	13-17 years N 12)		8-12 years N 14)		0-7 years (N = 28)		13-17 yrs vs. 0-7 yrs	8-12 yrs vs. 0-7 yrs
	N	%	N	%	N	%	Risk Difference %	Risk Difference %
Hypomagnesaemia	0	0	0	0	7	25	-25	-25
Hypokalaemia	0	0	3	21	6	21	-21	0
Hypertension	0	0	4	29	6	21	-21	7
Hypotension	0	0	3	21	5	17	-18	4
Diarrhoea	0	0	4	29	5	17	-18	11
Escherichia urinary tract infection	2	17	0	0	0	0	17	0
Muscle atrophy	2	17	0	0	0	0	17	0
Muscle spasms	2	17	0	0	0	0	17	0
Joint swelling	2	17	1	7	0	0	17	7
Oral candidiasis	2	17	1	7	0	0	17	7
Rash papular	2	17	1	7	0	0	17	7
Oedema peripheral	3	25	3	21	2	7	18	14
Cystitis haemorrhagic	3	25	1	7	1	4	21	4
Transaminases increased	3	25	1	7	1	4	21	4
Cytomegalovirus infection	3	25	0	0	0	0	25	0
Hypoxia	3	25	1	7	0	0	25	7
Arthralgia	4	33	2	14	2	7	26	7
Vomiting	2	17	1	7	7	25	-8	-18
Pyrexia	3	25	7	50	9	32	-7	18
Chronic graft versus host disease	2	17	3	29	1	4	13	18

Source: FDA Analysis; n, number; TEAE, treatment emergent adverse event

Reviewer Comments: In Study MSB-GVHD001, the differences in the observed rates of TEAEs between the demographic characteristics of sex, race groups, ethnicity groups, and age groups are not statistically significant and difficult to interpret due to small numbers in these patient groups.

8.5.3 Product-Disease Interactions

FDA conducted an analysis of TEAE by baseline aGVHD grade. Table 63 shows the TEAE incidence by grade for TEAEs occurring in at least 15% of patients with Grade D aGVHD.

Table 63: TEAE incidence by grade for TEAEs occurring in at least 15% of patients with Grade D aGVHD

PT	Grade B (N = 6)		Grade C (N = 23)		Grade D (N = 25)	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Bacterial infection	0	0	7	30	16	64
Viral infection	2	33	14	61	14	56
Haemorrhage	1	17	6	26	11	44
Pyrexia	1	17	9	39	9	36
Abdominal pain	0	0	3	13	8	32
Infection	4	67	9	39	8	32
Oedema	1	17	2	9	8	32
Rash	1	17	1	4	7	28
Arthralgia	1	17	1	4	6	24
Acute kidney injury	2	33	4	17	5	20
Hypersensitivity	0	0	3	13	5	20
Hypertension	0	0	6	26	5	20
Thrombosis	0	0	2	9	5	20
Vomiting	1	17	4	17	5	20
Cushingoid	0	0	1	4	4	16
Fungal infection	0	0	4	17	4	16
Respiratory failure	0	0	1	4	4	16
Sinus tachycardia	0	0	1	4	4	16

Source: FDA Analysis

Review Comment: Bacterial infection is the only TEAE with a substantial trend for incidence correlating with baseline aGVHD grade. It is not possible to conclude the risk is increased due to remestemcel-L, since patients with greater mucosal damage such as those with higher grade GVHD will have a higher risk of infection.

8.5.4 Product-Product Interactions

Specific product-product interaction studies with remestemcel-L have not been performed. Patients with aGVHD are typically on many medications, including additional immunosuppressive agents, antimicrobials, and medications for other various co-morbidities. It is theoretically possible that some types of concomitant medications may impact the bioavailability, distribution, or function of remestemcel-L in aGVHD. See Section 7.1.9 for a discussion of concomitant aGVHD therapy use with remestemcel-L.

No suspected product/drug interactions with remestemcel-L have been identified in the clinical data to date.

8.5.5 Human Carcinogenicity

See Section 8.4.8 *Adverse Events of Special Interest* of this review for a discussion of the potential for ectopic tissue formation.

8.5.6 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.7 Immunogenicity (Safety)

Since ceMSC is an allogenic product, there is a potential for development of anti-drug (donor) antibodies (ADA) or anti-HLA antibodies. Humoral immune response was not characterized in pediatric patients with aGVHD in the Study MSB-GVHD001. Previously, the Applicant characterized the humoral immune response (ADA and anti-HLA antibodies) in two clinical studies in patients with Crohn's disease and type 1 diabetes. For Crohn's disease, 1 out of 25 patients (4 %) was tested positive for anti-HLA antibodies, but no patient was tested positive for ADA up to Day 56 following remestemcel-L treatment. For type 1 diabetes, 13 out of 42 (31%) for remestemcel-L treated and 5 out of 21 (24 %) subjects in the placebo group had at least one positive test for anti-HLA antibodies at any time point. Six out of 42 (14%) for remestemcel-L treated subjects and 0 out of 21 (0 %) subjects in the placebo group tested positive for ADA during the 1-year follow-up period, respectively.

[Source: MSB Response to FDA IR_2020_06_29 RFI#27_Clinical July 6, 2020]

Review Comment: The clinical significance of ADA or anti-HLA antibodies following treatment with remestemcel-L is not fully understood. A substantial proportion of patients undergoing HSCT have anti-HLA antibodies (Koclega et al 2012), and when directed against the donor, they are associated with graft rejection (Morin-Zorman et al. 2016); anti-HLA antibodies are also a risk factor for refractoriness to platelet transfusions in this population (Solves et al 2018). Additional information is needed to determine whether pre-existing anti-HLA antibodies impact the efficacy of remestemcel-L, and whether patients in this population develop ADA that might result in refractoriness to platelet transfusions.

8.5.8 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

In general, the analyses of safety data in studies of remestemcel-L identified no safety signal of concern. Missing information about the ectopic tissue cases precludes firm conclusions, and this risk can be evaluated further postmarketing with enhanced pharmacovigilance. Additional studies are warranted to assess the impact of ADA/anti-HLA antibodies on safety in the aGVHD population.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The Sponsor states that there are no available data with remestemcel-L use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with remestemcel-L to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if remestemcel-L has the potential to be transferred to the fetus. Use of remestemcel-L in women who are pregnant is not recommended.

There were noted to be two pregnancies reported in the ISS in non-aGVHD studies, subjects (b) (6), however, both subjects were on placebo arms their respected trials.

9.1.2 Use During Lactation

There is no information regarding the presence of remestemcel-L in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for remestemcel-L and any potential adverse effects on the breastfed infant from remestemcel-L or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of remestemcel-L for treatment of steroid-refractory acute graft-vs-host disease have been established in pediatric patients 1 month to < 17 years old. Use of remestemcel-L in these age groups is supported by evidence from an adequate and well-controlled trial with additional safety data from other trials. The trials included 35 infants (1 month to < 2 years old), 157 children (2 years to < 12 years old), and 101 adolescents (12 years to < 17 years old). There were no clinically meaningful differences in efficacy or safety across the age groups. The population targeted for use is the pediatric population.

9.1.4 Immunocompromised Patients

The population targeted for use is an immunocompromised population.

9.1.5 Geriatric Use

The effectiveness of remestemcel-L for treatment of steroid-refractory acute graft-vs-host disease have not been established in geriatric patients.

One hundred forty-four subjects 65 years of age and older have been enrolled onto remestemcel-L treatment trials, 93 of those have been treated with remestemcel-L, and 25 of those on aGVHD trials.

Table 64: Number of subjects greater than 65 years of age treated with remestemcel-L

Study Identifier	Number
AMI401/402	13
AMI403	27
COPD801	20
CROHN603	13
GVHD260/261	2
GVHD265	4
GVHD270	1
GVHD280	13

Source: FDA Analysis

Overall, the safety profile in the geriatric subgroup only differed from the complete safety population in that coronary artery disorders and cardiac arrhythmias occurred at a higher frequency in this population than younger subjects, however there was not a significant difference between remestemcel-L treated subjects and placebo controls.

Table 65: Adverse events in subjects greater than 65 years of age treated with remestemcel-L

Adverse Event	Remestemcel – L n=93		Placebo n=51		% Risk Difference
	Number	%	Number	%	
Bacterial infections	8	8.6	2	3.92	4.68
Coronary artery disorders	6	6.45	3	5.88	0.57
Infections - pathogen unspecified	6	6.45	2	3.92	2.53
Cardiac arrhythmias	5	5.38	5	9.8	-4.43
Viral infections	5	5.38	3	5.88	-0.51
Lower respiratory tract disorders	5	5.38	2	3.92	1.45
Immune disorders	5	5.38	1	1.96	3.42
General system disorders	4	4.3	1	1.96	2.34
Neurological disorders	4	4.3	1	1.96	2.34
Gastrointestinal haemorrhages	4	4.3	0	0	4.3
Heart failures	4	4.3	0	0	4.3
Bronchial disorders	3	3.23	1	1.96	1.27
Respiratory disorders	3	3.23	1	1.96	1.27
Fungal infections	3	3.23	0	0	3.23
White blood cell disorders	3	3.23	0	0	3.23

Source: FDA Analysis

Although efficacy has not been established for the geriatric patient population, safety does not appear to be a concern.

10. CONCLUSIONS

Study MSB-GVHD001 provided evidence of efficacy for remestemcel-L in the pediatric SR-aGVHD patient population, in that it showed a 69.1% 95% CI: 55.2, 80.9) Day-28 ORR with durability. There is no safety signal of concern.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Steroid-Refractory aGVHD (SR-aGVHD)

The most common life-threatening complication of allogeneic HCT is GVHD. Given the number of allo-HCTs performed, approximately 5000 patients/year develop aGVHD in the United States (US); of those, approximately 300-400 are pediatric patients [D'Souza 2017]. The risk of developing GVHD is dependent on many factors, including the stem cell source, age of the patient, conditioning, and GVHD prophylaxis used. aGVHD relies on the assessment of target organs by means of clinical and laboratory analyses with or without biopsy. The severity is graded clinically by tabulating the extent of the involvement of the three main target organs: the skin (the site of the most frequent and often the earliest clinical manifestation), the gastrointestinal tract (the second most common site), and the liver. Grade 1 aGVHD is considered to be mild, grade 2 moderate, grade 3 severe, and grade 4 very severe. Despite prophylaxis with immunosuppressants, acute GVHD may still occur; among all patients undergoing allo-HCT, 30 to 50% have aGVHD (grades 1–4) and 14% have severe acute GVHD (grades 3–4) [Zeiser 2017]. The natural history of the disease is ill-defined, due to the life-threatening nature of the disease, it is not left untreated. In the early days of allo-HCT, high-grade SR-aGVHD was almost universally fatal.

The combinations of calcineurin inhibitor (CNI) and methotrexate (MTX) or CNI and mycophenolate are used most commonly to prevent GVHD in allo-HCT recipients. In general, once aGVHD occurs, the drugs used for prophylaxis are continued and additional immunosuppressive agents are added. aGVHD is treated first with glucocorticoids, such as methylprednisolone (MP), based on randomized, controlled trials [reference]. About 50% of patients will respond to methylprednisolone. Patients with grade 3 to 4 acute GVHD tend to have poorer outcomes. If patients progress or are not improved after steroid therapy, they will get salvage (second-line) immunosuppressive therapy. Patients with acute GVHD that is resistant to treatment with glucocorticoids have a dismal long-term prognosis, with an overall survival rate of only 5 to 30%.

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 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). 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. All are stated to have only Category 2A evidence. There was not sufficient data to recommend use of one agent over others. 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. There are no drugs with demonstrated superiority in combination trials for treatment of aGVHD.

In summary, SR-aGVHD is a debilitating condition that is usually fatal if not treated. This is an unmet medical need in that there is only one approved therapy for patients 12 years and older with SR-aGVHD and none available for the younger pediatric population.

Evidence and Uncertainties

Study MSB-GVHD001 was a single-arm trial of remestemcel-L for treatment of pediatric patients with Grades B-D (excluding Grade B skin-alone) SR-aGVHD. The study met its primary objective; the Day-28 ORR was 69.1% (95% CI: 55.2, 80.9) in the FAS, excluding an ORR < 45%. 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 the single-arm study design of MSB-GVHD001 include 1) the challenges to minimizing bias as with the subjective nature of aGVHD grading, 2) inability to ascertain the similarities in prognostic factors, both known and unknown, between MSB-GVHD001 study and the historical control data provided, and 3) the adequacy of the historical data to support a null hypothesis. As the Applicant provided raw data to support staging for the analysis of the primary endpoint and the data were verified by inspection, it is concluded that the data are adequate to assess the activity of remestemcel-L in this study. With regard to the null hypothesis, it is noted that there is no regulatory requirement to demonstrate superiority over other drugs, approved or used off-label. As noted by some of the Advisory Committee members, it may be difficult to perform a randomized, placebo-controlled trial, since the use of placebo is not ethical in this disease setting. There is uncertainty about the ORR used for the study hypotheses, since there

are no contemporary data on outcomes of patients with SR-aGVHD who go untreated, but due to the usual fatal outcome of this disease, there is no reason to expect that it would be greater than the 45% proposed by the Applicant. As such, the observed ORR is considered clinically meaningful.

The Applicant also submitted the results of Study 275, an expanded access protocol for remestemcel-L in combination with other immunosuppressive drugs for treatment of pediatric patients with SR-aGVHD. In this study, the Day-28 ORR was 65%. It is noted that a single-arm combination study does not isolate the treatment effect of the investigational product, so the results from this study are not informative.

The Applicant also provided the results of two randomized, double-blind, placebo-controlled trials of remestemcel-L in combination with other immunosuppressive drugs 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 > 28 days duration, and no treatment effect was detected even when these protocols were reanalyzed using Day-28 ORR. As neither trial tested remestemcel-L as monotherapy, it is not clear that these results are relevant to the proposed indication of monotherapy for treatment of SR-aGVHD. Additionally, neither study used drug product made using the proposed commercial manufacturing process.

Lastly, the safety profile of remestemcel-L was considerable acceptable for the intended population. There were no fatal adverse reactions, and the withdrawal rate was only 13%. Although infections were the most common adverse event, the incidences of infections and of severe infections were not higher than expected for this population. Infusion reactions were rare. There remains some uncertainty about the risk of ectopic tissue formation, but this can be addressed by enhanced pharmacovigilance. The only remaining uncertainty is whether pre-existing anti-HLA antibodies impact the efficacy of remestemcel-L, and whether patients in this population develop ADA that might result in refractoriness to platelet transfusions; these can be addressed in a postmarketing study.

Conclusions and Reasons

SR-aGVHD is a serious and life-threatening disease, and there are currently no available, approved treatments for this condition in pediatric patients less than 12 years old, thus, SR-aGVHD represents an unmet medical need. Study MSB-GVHD001 met its primary objective; the results were statistically significant, the measured response was durable, and the results were consistent across subpopulations and secondary efficacy endpoints. Thus, Study MSB-GVHD001 supports the efficacy of Remestemcel-L treatment in pediatric a-GVHD patient population, the risks of treatment are minimal, therefore resulting in a favorable overall risk-benefit profile.

Table 66: Risk and Benefit Assessments

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> The most common life-threatening complication of allogeneic hematopoietic stem cell transplant alloHSCT is GVHD. Given the number of alloHSCTs performed, approximately 5000 patients/year develop aGVHD in the United States (US); of those, approximately 300-400 are pediatric patients. Despite prophylaxis with immunosuppressants, acute GVHD (aGVHD) may still occur; among all patients undergoing alloHSCT, 30 to 50% have aGVHD (grades 1–4) and 14% have severe acute GVHD (grades 3–4). The natural history of the disease is ill-defined, due to the life-threatening nature of the disease, it is not left untreated. High-grade SR-aGVHD is usually fatal if left untreated. 	<ul style="list-style-type: none"> Steroid refractory aGVHD is a difficult to treat, life-threatening, serious condition, that if not fatal, can lead to debilitating short-term and chronic morbidity.
Unmet Medical Need	<ul style="list-style-type: none"> At the present time, ruxolitinib is the only product FDA approved for the treatment of SR-aGVHD in patients 12 years or greater. 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. All are stated to have only Category 2A evidence. There is not sufficient data to recommend use of one agent over others. 	<ul style="list-style-type: none"> In children younger than 12 years of age, there is an unmet medical need for the treatment of steroid refractory aGVHD
Clinical Benefit	<ul style="list-style-type: none"> Study MSB-GVHD001 was a single-arm trial of remestemcel-L for treatment of pediatric patients with Grades B-D (excluding Grade B skin-alone) SR-aGVHD. The study enrolled 55 children 7 months to 17 years old, and 54 were treated with remestemcel-L monotherapy. The Day-28 ORR was 69.1% (95% CI: 55.2, 80.9), and the responses were durable. 	<ul style="list-style-type: none"> The magnitude of ORR and durability of response to treatment demonstrate that remestemcel-L is active in this disease.
Risk	<ul style="list-style-type: none"> There were no fatal adverse reactions, and the withdrawal rate was only 13%. The incidence of infections was not higher than expected for this population. Infusion reactions were rare. There remains some uncertainty about the impact of pre-existing and treatment-emergent anti-HLA antibodies for this treatment. 	<ul style="list-style-type: none"> The safety profile is acceptable for the intended population. Additional study of ADA is warranted.
Risk Management	<ul style="list-style-type: none"> The premedications and safety monitoring plan in Study MSB-GVHD001 were effective in mitigating serious potential toxicities. 	<ul style="list-style-type: none"> If remestemcel-L were approved for children, routine measures, such as the labeling would be sufficient to mitigate risks.

11.2 Risk-Benefit Summary and Assessment

Given the observed clinically-meaningful response rate and the durability of the responses, and with the labeling modifications in place, the clinical benefit of remestemcel-L appears to outweigh the risks for treatment of steroid-refractory acute GVHD in pediatric patients.

11.3 Discussion of Regulatory Options

Remestemcel-L for the treatment of pediatric SR-aGVHD, based on the Day-28 ORR and durability, is under consideration for regular approval.

Consideration was given to accelerated approval with the requirement for an additional trial using OS as the clinical benefit endpoint. However, given that SR-aGVHD is a highly morbid disease, and that ORR was shown to correlate with reduced nonrelapse mortality, Day-28 ORR is considered a clinical benefit in itself. Additionally, due to the competing causes of death in the HSCT population, it would be difficult to interpret an OS outcome in the absence of an ORR improvement. Due to the short follow-up needed to assess ORR and durability, there is no regulatory pathway for accelerated approval for treatments of SR-aGVHD.

A question was also raised about whether a randomized trial should be required. As noted by some of the Advisory Committee members, it may be difficult to perform a randomized, placebo-controlled trial for treatment of aGVHD, since the use of placebo is not ethical in this disease setting. Additionally, in view of the high Day-28 ORR and favorable safety profile with remestemcel-L in MSB-GVHD001, equipoise may be lost and there may be challenges in accruing to a trial comparing remestemcel-L to more toxic therapies or those with reported lower response rates.

11.4 Recommendations on Regulatory Actions

According to my review of the clinical data, I recommend Approval, based on the following:

1. SR-aGVHD is a serious and life-threatening disease.
2. There are no available, approved treatment for this condition in pediatric-aged patients, and thus, SR-aGVHD represents an unmet medical need.
3. There is no requirement to demonstrate superiority over other treatments.
4. Study 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.
5. Although the null-hypothesis was initially poorly constructed by the Applicant, further explorations supports the determination of the null of 45%. In particular, the FDA analysis of the 33 subjects on Study 265 with newly diagnosed aGVHD who received steroids and placebo, who were found to be SR at day 7 and had 42% at the day 35 evaluation and the approval of Jakafi® by FDA, which was supported by a similar, single arm trial which excluded a null of 40%
6. There is no safety signal of concern which is in stark contrast to standard of care therapies, which are extremely immunosuppressive and lead to increased infection-related mortality in this already vulnerable population.

7. The concomitant use of additional salvage treatment for aGVHD in Study 280 makes the failure of the study difficult to interpret and the implications for the remestemcel-L product unclear.
8. The ability to perform a subsequent randomized, placebo-controlled trial in pediatric SR-aGVHD is unlikely.

11.5 Labeling Review and Recommendations

Labeling revisions suspended July 30, 2020. Prior to this, the following major suggested revisions (abbreviated) were identified:

1. Applicant asked to clarify how to differentiate between hypersensitivity reactions and acute infusion reactions
2. Applicant instructed to include all adverse reactions rather than events identified as "related" by the investigator and to include incidences for treatment-emergent all-grade and grades 3-4 adverse reactions.
3. Applicant instructed to include immunogenicity information.
4. Applicant instructed to include pregnancy outcomes information from non-aGVHD clinical trials.
5. Applicant informed only the primary efficacy endpoint is included in the PI.

11.6 Recommendations on Postmarketing Actions

The following postmarketing requirement is recommended:

Evaluate the impact of pre-existing and treatment-emergent anti-HLA antibodies and anti-drug antibodies on the safety and efficacy of remestemcel-L in the treatment of acute graft-vs-host disease. Submit the results of a prospective clinical trial that includes serial assessments of anti-HLA antibodies and anti-drug antibodies and an analysis to test for correlations between such antibodies and safety and efficacy outcomes.