Application Type	Original BLA
STN	125706/0
CBER Received Date	Dec 31, 2019
PDUFA Goal Date	Sept 30, 2020
Division / Office	DCEPT/OTAT
Committee Chair	Matthew Klinker
Clinical Reviewer(s)	Kristin Baird
Project Manager	Adriane Fisher
Priority Review	Yes
Reviewer Name(s)	Stan Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Lead, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Mesoblast Inc.
Established Name	Remestemcel-L
(Proposed) Trade Name	RYONCIL
Pharmacologic Class	Mesenchymal stromal cells
Formulation(s), including Adjuvants, etc.	Mesenchymal stromal cells Allogeneic cell product comprised of culture-expanded adult mesenchymal stromal cells (ce-MSC) isolated from bone marrow of healthy adult donors
Dosage Form(s) and Route(s) of Administration	IV infusion
Dosing Regimen	2 ×106 ce-MSC/kg body weight
Proposed Indication(s) and Intended Population(s)	Treatment of Steroid-refractory acute Graft versus Host Disease in pediatric patients

Table of Contents

GLOSSARY

AE	adverse event
aGVHD	acute graft-versus-host disease
AHUS	atypical hemolytic uremic syndrome
AlloHSCT	allogeneic hematopoietic stem cell transplantation
AML	acute myeloid leukemia
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CSR	clinical study report
DSMB	Data Safety Monitoring Board
FAS	Full Analysis Set
FTD	Fast Track Designation
GI	gastrointestinal
GMP	Good Manufacturing Practice
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HR	heart rate
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IBMTR	International Bone Marrow Transplant Registry
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
mFAS	Modified Full Analysis Set
MR	mixed response
MSC	mesenchymal stromal cell
OR	overall response
PP	Per Protocol
PR	partial response
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	standard of care
STEAE	serious treatment-emergent adverse event
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNF-α	tumor necrosis factor-alpha
Treg	regulatory T cell
VGPR	very good partial response

1. Executive Summary

This BLA seeks licensure of remestemcel-L for the treatment of steroid-refractory acute graft versus host disease (aGVHD) in pediatric patients, whose aGVHD has failed to respond to treatment with systemic corticosteroids.

The primary source of evidence to support this application is a Phase III, single-arm, multicenter (20 sites) study (MSB-GVHD001/002) that enrolled 55 pediatric subjects with steroid refractory (SR) aGVHD. The primary efficacy endpoint was overall response rate (ORR) at day 28, which is defined as the proportion of subjects with either a complete response (CR) or partial response (PR), assessed by the study site investigator.

As a stand alone trial, Study MSB-GVHD001/002 met its primary efficacy endpoint with an ORR of 69.1%, rejecting the pre-specified null hypothesis of 45%. However, these results should be considered in the context that, in total, 654 subjects have been enrolled in several clinical trials for the treatment of SR-aGVHD as well as newly diagnosed aGVHD. This includes two randomized, placebo-controlled studies, Study 265 and Study 280, both of which failed to meet their primary endpoints of improvement of durable complete response, defined as sustained CR > 28 days of duration, when compared to placebo. The applicant conducted a subgroup analysis of Study 280 based on 28 padiatric patients and detected a promising treatment effect, which motivated the launch of Study MSB- GVHD001/002. However, such a post-hoc subgroup analysis does not provide meaningful supportive evidence for Study MSB-GVHD001/002 as it was descriptive and hypothesis-generating only. The single-arm design of Study MSB- GVHD001/002 complicates its ability to provide confirmatory evidence; a randomized, placebo-controlled pediatric study would have provided more directly interpretable evidence.

An Oncologic Drugs Advisory Committee meeting was held on August 13th, 2020, to discuss: a) whether Study GVHD-001/002, a single-arm trial, provides sufficient evidence of clinical benefit in the treatment of SR-aGvHD in pediatric patients, and b) the relevance of the two previously conducted randomized, double blind, placebo controlled, multicenter studies in adults that failed to meet their primary efficacy endpoints.

The committee voted nine "yes" to one "no" on the question, "Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD?"* The committee member voting no stated that the clinical evidence was not high quality, not compelling, and not sufficiently rigorous to meet regulatory standards. Other committee members noted that although there were issues identified with the clinical trial design, this trial provided supportive 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. 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.

---

* The vote at the meeting was recorded as eight "yes" to two "no," but the applicant's subsequent press release indicated that one of the "no" votes was made in error. This is consistent with the committee discussion following the vote.

In my evaluation, this BLA submission has not provided adequate evidence to support the applicant's proposed pediatric indication for Remestemcel-L. Additional adequate and well-controlled clinical studies, preferably in the form of randomized, controlled trials if possible, would be needed to provide substantial evidence of effectiveness to support approval.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

GVHD is a progressive and lethal complication of hematopoietic
stem cell transplantation (HSCT) and donor leukocyte infusion. While aGVHD is common among patients with allogeneic transplantation, overall, it is a rare disease. Based on information submitted by the applicant, worldwide, approximately 7,125 cases of aGVHD (including 1,125 to 1,200 pediatric cases) are reported per year. aGVHD potentially involves multiple organ systems, with varying degrees of clinical severity.

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

Currently, there are no approved therapies in the United States for treatment of aGVHD, including steroid-refractory aGVHD.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Two prior randomized, double-blind, placebo-controlled studies failed to meet the intended objectives: Study 265, where 192 newly diagnosed Grades B-D aGVHD. (non-steroid refractory) *adult* patients were treated. The remestemcel-L treatment regimen as well as the primary study endpoint used (durable complete response) was different from that would be used for the current treatment indication.Study 265 failed to meet its intended objective: demonstration of superiority of remestemcel-L to placebo on durable ($\geq$ 28 days) complete response. The top line results were 45% of remestemcel-L recipients achieved durable complete response compared to 46% of placebo patients, a notably negative result. The applicant did not list study 265 as pertinent for the current product indication.

The second study, study 280, included 244 Grades B-D SR-aGVHD subjects, including 28 pediatric patients. The primary endpoint, durable ($\geq$ 28 days) complete response, showed no significant difference between groups, 35% for remestemcel-L vs 30% for placebo, p=0.45. In a post-hoc analysis, the sponsor considered overall response (OR) as a primary endpoint for Study 280 and compared OR between groups. The overall response rate (ORR) was 58% for remestemcel-L vs 51% for placebo, p=0.31.

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

9/25/1998	Initial IND Submitted (Sponsor Osiris Therapeutics)

12/2005	Orphan Drug Designation granted for aGVHD
1/25/2007	Type A Meeting to discuss a SPA submission – non-concurred
11/16/2007	FTD Granted for treatment of patients with grade II to IV GI GVHD after alloHSCT (Allogeneic hematopoietic stem cell transplantation) to resolve acute GI GVHD by day 42 after treatment
10/09/2008	Pre-BLA Package
04/23/2009	BLA data submission plan
03/05/2010	BLA Withdrawal
1/31/2014	Change in Sponsor from Osiris to Mesoblast, Inc.
2/17/2014	Request for (b) (4) for treatment of pediatric severe steroid refractory aGVHD, post allogeneic hematopoietic stem cell transplant for hematologic malignancies. Request for (b) (4) denied.
9/5/2014	New Phase 3 Protocol MSB-GVHD001, A Single-arm, Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human MSCs, for the Treatment of Pediatric Patients who have Failed to Respond to Steroid Treatment for Acute GVHD
9/12/2014	New Phase 3 Protocol MSB-GVHD002, Safety Follow-up Through 180 Days for MSB-GVHD001
2/28/2017	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
4/5/2019	Pre-BLA Meeting

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

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

NA

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

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Study MSB-GVHD001, which is the focus of this review.

The applicant also summarized data from an EAP (expanded access program) study (Protocol 275). As shown in Table 1, an ORR of 65% was reported for this study with pediatric patients. As an EAP study rather than a clinical experiment designed to support decision making, no hypotheses were specified, no sample size calculation conducted, and no statistical analyses performed. The phase of the study was said to be "Treatment Protocol", not a Phase 1-3 study. Such a study is not amenable to rigorous statistical analysis and it is not further reviewed in this memo.

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

This statistical review memo is based on clinical study reports and data sets submitted in module 5 of the BLA submission.

5.3 Table of Studies/Clinical Trials

Table 1 lists of studies pertinent to the pediatric indication.

GVHD Treatment Study	Phase	Indication	Design	Subjects	Number enrolled/treated	Efficacy Results
MSB-GVHD001 2015--2018	3	SR-aGVHD	Single-arm, open lable, multicenter	Pediatric	55/54	ORR 69% CR 29% PR 40%
Protocol 275 2007--2015	EAP	SR-aGVHD	EAP	Pediatric	242/241	ORR 65% CR 14% PR 53%
Protocol 280 2006--2009	3	SR-aGVHD	Randomized, double blind, placebo controlled, multicenter	Adult and Pediatric	Adult + Ped (260/244) Ped (28/27)	ORR MSC 35% ORR Placebo 30%

(Source: Module 5 Clinical Study Reports, Tabular listing of all clinical studies)
EAP: (expanded access program) study

The applicant states that Study 265 is a failed placebo controlled study of adults only. Since no pediatric patients were enrolled in this study, its efficacy results are not listed in Table 1.

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.

There were two clinical discussion questions and one clinical voting question presented to the committee:

FDA 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.

FDA 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.

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**

Summary of Clinical Discussion:
The committee member voting no stated that the clinical evidence was not high quality, not compelling, and not sufficiently rigorous to meet regulatory standards. Other committee members noted that although there were issues identified with the clinical trial design, this trial

provided supportive 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.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study MSB-GVHD001)

6.1.1 Objectives

The primary objectives were:

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, and
2) to gather additional information on the safety of Remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT

The seconary objectives included were to determine the correlation between response to Remestemcel-L at Day 28 and survival at Day 100.

6.1.2 Design Overview

MSB-GVHD001 was a Phase 3, open-label, single-arm, multicenter study to evaluate the efficacy and safety of Remestemcel-L in pediatric subjects with aGVHD who had failed to respond to systemic steroid treatment. The study planned to treat at least 48 male and female pediatric subjects (ages 2 months to 17 years, inclusive) with aGVHD following allogeneic HSCT that had failed to respond to treatment with systemic corticosteroid therapy. Enrolled subjects had Grades C and D aGVHD involving the skin, liver, and/or GI tract, or had Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.

6.1.3 Population

The population was subjects aged 2 months to 17 years inclusive and diagnosed with Grades B-D aGVHD who failed to respond to first-line corticosteroid treatment. Detailed inclusion and exclusion criteria are in Section 9.3 of the clinical study report.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated with intravenous (IV) Remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight at screening, twice per week for each of 4 consecutive weeks (Initial Therapy). Eligible subjects were permitted to receive an additional 4, once-weekly infusions of

Remestemcel-L (Continued Therapy) at the Initial Therapy dose of 2×10^6 MSCs/kg actual body weight at screening. Eligible subjects were permitted to receive GVHD Flare Therapy, which consisted of an additional 4 twice-weekly infusions of Remestemcel-L at the Initial Therapy dose of 2×10^6 MSCs/kg actual body weight at screening.

6.1.6 Sites and Centers

This study was to be conducted at 20 study centers in the US.

6.1.7 Surveillance/Monitoring

A DSMB was chartered to monitor and evaluate the safety of all subjects in this study. All safety data accrued up to the cut-off point defined in the DSMB Charter was collected and presented in a tabular format to the DSMB. The DSMB was permitted to make recommendations regarding stopping the trial early due to safety issues or continueing the trial as planned.

In addition to the regular monitoring of safety, one interim analysis was planned for futility. The interim analysis occurred after approximately 30 treated subjects were assessed for the 28-day ORR. The interim analysis was conducted by an external CRO, and the DSMB reviewed the results. The final recommendation regarding stopping or continuing the study based on the futility analysis was conveyed to the Applicant.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: ORR (complete response [CR] + partial response [PR]) at Day 28 post initiation of Remestemcel-L therapy

The study protocol also included several secondary efficacy endpoints:
• Overall survival (OS) at Day 100 post initiation of Remestemcel-L therapy
• OS at Day 100 post initiation of Remestemcel-Ltherapy, stratified by responder status at Day 28 (responder versus non-responder)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypothesis:

H_0: *ORR* $\leqslant$ 0.45   vs.   H*a*: *ORR* >0.45

Comment: The null hypothesis was set at 45% ORR based on data showing comparable Day 28 OR rates for historical populations of aGVHD patients treated with standard of care. An effect size of 20% was proposed by the applicant as clinically meaningful based on discussion with clinical experts, and therefore 65% ORR was assumed as the alternative hypothesis for sample size calculations.

Comment: The basis for the 45% null hypothesis is discussed in detail in Dr. Baird's clinical review memo. The FDA clinical review team agreed with an effect size of 20% over a null hypothesis of 0.45 to be clinically meaningful. The FDA clinical review team further states that

in addition to the background provided by the applicant, the team also looked at other resources for information and concluded that they added support for the selected null hypothesis by the sponsor.

Analysis populations
  a. Full Analysis Set (FAS): all enrolled subjects. This is also the ITT population dataset.
  b. Modified Full Analysis Set (mFAS) population: all enrolled and vial-treated subjects. The bag-treated subjects were excluded from the mFAS population.
  c. The Treated (Safety) population : all subjects treated with Remestemcel-L.
  d. Per-Protocol (PP) population: All subjects who had no major protocol violations during the study.

Statistical methods

Primary analysis
The null hypothesis on ORR at Day 28 less than 0.45 was specified to be tested based on the FAS (ITT) dataset using exact binomial test. Sensitivity, or supportive, analyses were based on mFAS population and PP population.

Secondary analysis
The secondary efficacy analyses were performed using binomial test based on the FAS (ITT) dataset. The analyses were repeated for the mFAS and PP populations for the following key secondary endpoint:
  • Overall survival (OS) at Day 100 post initiation of Remestemcel-L therapy (yes/no)
  • OS at Day 100 post initiation of Remestemcel-L therapy (yes/no), stratified by response status at Day 28 (responder versus non-responder)

Sample size
The planned sample size based on the primary study hypotheses is 55 to ensure at least 80% power for a 2-sided alpha level of 0.05 using the exact Binomial test, where the ORRs assumed under the null and alternative hypotheses are 45% and 65%, respectively.

Interim analyses
One interim analyses for futility was to be performed at 50% enrollment.

Subgroup analysis
The required subgroup analyses based on age, sex, and race (21 CFR 314.50(d)(5)(v) and (vi)(a)) were not presented in the study report. I performed the subgroup analyses and presented the findings to the clinical reviewer.

Missing data
If the OR status was missing then it is imputed as non-response for the primary endpoint analysis.

6.1.10 Study Population and Disposition

Fifty-five (55) subjects were enrolled, 54 subjects received Remestemcel-L (one subject's condition worsened before the Remestemcel-L arrived and could not be infused), and 42 subjects (76.4%) completed the study.

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

The following table (Table 2) summarizes subject demographics for the ITT, Treated, mFAS, and PP populations. Subjects in ITT were primarily male (63.6%) and white (56.4%). The mean (SD) age was 7.3 (5.45) years.

Table 2. Demographics, etc.

Parameter	ITT Population (Applicant's FAS) N = 55	Treated (Safety) Population N = 54	Modified Full Analysis Set Population N = 47	Per Protocol Population N = 51
Sex, n (%)				
Male	35 (63.6)	35 (64.8)	27 (57.4)	32 (62.7)
Female	20 (36.4)	19 (35.2)	20 (42.6)	19 (37.3)
Race, n (%)				
White	31 (56.4)	30 (55.6)	27 (57.4)	28 (54.9)
Black or African American	8 (14.5)	8 (14.8)	7 (14.9)	8 (15.7)
Asian	3 (5.5)	3 (5.6)	3 (6.4)	3 (5.9)
American Indian or Alaska Native	3 (5.5)	3 (5.6)	3 (6.4)	3 (5.9)
Native Hawaiian or Pacific Islander	0	0	0	0
Other	10 (18.2)	10 (18.5)	7 (14.9)	9 (17.6)
Ethnicity, n (%)				
Hispanic or Latino	18 (32.7)	18 (33.3)	13 (27.7)	16 (31.4)
Not Hispanic or Latino	36 (65.5)	35 (64.8)	33 (70.2)	35 (68.6)
Missing	1 (1.8)	1 (1.9)	1 (2.1)	0
Age (years)				
n	55	54	47	51
Mean (SD)	7.3 (5.45)	7.4 (5.43)	7.0 (5.27)	7.5 (5.45)
Median	7.0	7.0	7.0	7.0
Min, Max	0, 17	0, 17	0, 17	0, 17
Age (months)				

n	55	54	47	51
Mean (SD)	93.5 (65.26)	95.0 (64.96)	89.1 (63.57)	96.0 (65.16)
Median	91.0	93.0	84.0	95.0
Min, Max	7, 215	7, 215	7, 215	7, 215
Height (cm)				
n	54	53	46	50
Mean (SD)	120.1 (35.53)	121.1	117.1 (34.02)	121.3 (35.24)
Median	125.5	127.0	118.5	128.5
Min, Max	57, 196	57, 196	57, 175	57, 196
Weight (kg)				
n	55	54	47	51
Mean (SD)	28.82 (18.924)	29.15	27.77	29.09
Median	25.50	25.80	25.50	26.10
Min, Max	4.6, 90.1	4.6, 90.1	4.6, 90.1	4.6, 90.1

SD=standard deviation.
Note: Percentages were based on the total number of subjects in each analysis population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3. Baseline disease characteristics of subjects who received at least one dose of Remestemcel-L are summarized in the following table.

Parameter	ITT Population (Applicant's FAS) N = 55	Treated, or Safety population N= 54	Modified FAS Population N = 47	Per Protocol 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				
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	16 (29.1)	16 (29.6)	14 (29.8)	15 (29.4)
Upper GI involvement at baseline, n (%)				

Score 0 = No protracted nausea and	48 (87.3)	47 (87.0)	40 (85.1)	44 (86.3)
Score 1 = Persistent nausea, vomiting, or	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 GI,				
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

6.1.10.1.3 Subject Disposition

Table 4. Subject disposition is listed in the following table (all enrolled subjects).

Disposition/Reason	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 Applicant	0
Death	9 (16.4)
Other	Total Remestemcel-L n (%)
Due to shipping delay, not able to give dose before worsening	2 (3.6)
PI decided to not continue with MSC infusions	
	1 (1.8%)

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

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 5 below presents ORR at 28 days after one dose of Remestemcel-L for ITT population with 55 subjects. The treated population (n=54) and the per-protocol population gave almost identical results.

Table 5. Overall Response (OR) at 28 Days Post Initiation of Remestemcel-L Therapy (ITT Population)

Parameter	Total Remestemcel-L N = 55
Overall response (OR) at Day 28, n (%)	
Responder	38 (69.1)
Complete response (CR)	16 (29.1)
Partial response (PR)	22 (40.0)
Missing	0
p-value[a]	0.0003

[a] p-value calculated from the binomial distribution for "Responder" versus "Non-responder," under the assumption of a 0.45 success rate for the null hypothesis.

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

Among the 54 treated subjects, the FDA clinical reviewer re-adjudicated the overall response data for 9 subjects (affecting both the denominator and numerator for the response rates) and requested that I perform sensitivity analyses on the re-adjudicated dataset by excluding different numbers of patients. There are 34 OR responders out of 45 by excluding the nine readjudicated subjects and the estimated ORR is 75.6%; 37 responders out of 48 by excluding six subjects with ORR of 77.1%; 35 OR responders out of 50 by excluding four subjects with ORR of 70%. None of these analyses changed the statistical significance of the difference from the null hypothesis of ORR rate of 0.45. The results were not materially changed from those in the table.

6.1.11.2 Analyses of Secondary Endpoints

Overall survival at Day 100 post initiation of Remestemcel-L therapy:

Overall survival was 74.5% (41/55) through 100 days (±7 days) of follow-up. Of the 38 responders at Day 28, 33 (86.8%) were alive at Day 100 (Table 6), compared with 8 of 17 non-responders (47.1%) at Day 28, with a p-value of 0.0032.

Note: The p-value should only be interpreted as a test of association between day 28 ORR and overall survival rate at day 100. The results show that day 28 ORR was positively associated with day 100 survival rate.

Table 6. Overall Survival (OS) Rate at Day 100 Post Initiation of Remestemcel-L Therapy, Stratified by Overall Response (OR) at Day 28 (ITT Population)

Parameter	Day 28 OR Responder N = 38	Day 28 Non-OR Responder N =17	Total Remestemcel-L N = 55
Day 100 overall survival, n (%)			
Survivor	33 (86.8)	8 (47.1)	41 (74.5)
Non-survivor	5 (13.2)	9 (52.9)	14 (25.5)
p-value[a]	0.0032		

Column header for the three data columns is grouped under: **Total Remestemcel-L(N = 55) Overall Response (OR) at Day 28**

[a] p-value is from a CMH test stratified by baseline aGVHD grade not shown here.

6.1.11.3 Subpopulation Analyses

The BLA did not include the usual and customary subgroup analysis based on the baseline characteristics. Per the request of the clinical review team, I conducted subgroup/subpopulation analyses and investigated, especially, the potential differential effect of OR effected by these baseline factors that defne relevant subgroups of subjects, specified by the clinical reviewer. The results are tabulated here:

	ORR			
	Responder		Non-responder	
Age (N)	N	%	N	%
0 – 12 years	20	68.97%	9	31.03%
12 to 17 years	10	71.43%	4	28.57%
17 years and greater	8	66.67%	4	33.33%
Sex				
F	12	60.00%	8	40.00%
M	26	74.29%	9	25.71%
Pooled Race Group 1				
Non-White	17	70.83%	7	29.17%
White	21	67.74%	10	32.26%
Ethnicity				
HISPANIC OR LATINO	13	72.22%	5	27.78%
NOT HISPANIC OR LATINO	24	66.67%	12	33.33%
Baseline Organ Involvement Category				
Lower GI Only	14	66.67%	7	33.33%
Multi-Organ (Any Combination)	12	60.00%	8	40.00%
Skin Only	12	85.71%	2	14.29%
MacMillan Risk Score				
High risk (HR)	27	67.50%	13	32.50%
Standard risk (SR)	11	73.33%	4	26.67%
Baseline Grade aGVHD				
Grade B	3	50.00%	3	50.00%
Grade C	16	69.57%	7	30.43%

Grade D	19	73.08%	7	26.92%
HLA Compatibility Match				
Matched	20	74.07%	7	25.93%
Mismatched	18	64.29%	10	35.71%
HLA Compatibility Related				
Related	9	69.23%	4	30.77%
Unrelated	29	69.05%	13	30.95%
Type of Transplant				
Bone Marrow	24	80.00%	6	20.00%
Cord Blood	8	72.73%	3	27.27%
Peripheral Blood Stem Cell (PBSC)	6	42.86%	8	57.14%
Underlying Malignancy at Transplant				
ACUTE Lymphoblastic Leukemia (ALL)	9	75.00%	3	25.00%
ACUTE Myeloid Leukemia-Primary (AML)	10	55.56%	8	44.44%
Chronic Myeloid Leukemia (CML)	4	100.00%	0	0.00%
Hodgkin's Lymphoma	1	100.00%	0	0.00%
Myelodysplastic Syndrome (MDS)	1	50.00%	1	50.00%
Other	13	72.22%	5	27.78%
Baseline Skin Involvement Score				
0= No rash	17	68.00%	8	32.00%
1= Maculopapular rash, <25% of body surface	2	66.67%	1	33.33%
2= Maculopapular rash, 25-50% of body surface	1	50.00%	1	50.00%
3= Generalized erythroderma	10	71.43%	4	28.57%
4= Generalized erythroderma with bullous formation and desquamation	8	72.73%	3	27.27%

I then performed analyses examining the statistical association of OR with the factors listed above. There was no significant association detected in ORR with any of these factors. For instance, age was classified into three levels, "0-7 years", "8-12 years" and "13-17 years" and there was no evidence of differential distribution of ORR across the age levels. This is likely due to the fact that the study was not designed with such subgroup analyses in consideration, leading to a lack of adequate sample size in each subgroup and lack of stratification of patients at baseline.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.10.1.3 above on subject disposition contains subject completion and early termination informstion. Subjects who dropped out of the study were included in the analyses. Missing data for the primary endpoint (ORR at Day 28), including missing assessments and missing staging data for any organ, were imputed as non-responders.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for Study MSB-GVHD001. For data summary, the safety analysis set in this section includes a total of 44 subjects who received at least one dose of Remestemcel-L.

6.1.12.3 Deaths

There were 13 deaths (24.1﹪) at the 100-day follow-up in study MSB-GVHD001. According to the applicant, none were directly attributed to the study treatment with Remestemcel-L.

6.1.12.4 Non-fatal Serious Adverse Events

The study reported 23 non-fatal SAEs.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This Biologics Licensure Application (BLA) seeks licensure of Remestemcel-L for the treatment of Steroid-refractory acute Graft versus Host Disease in pediatric patients. The applicant conducted a phase 3, open-label, single-arm, multicenter study (MSB-GVHD001/002) to support its application. The primary efficacy endpoint is overall response rate (ORR) at Day 28 post initiation of Remestemcel-L therpay, which is defined as the proportion of subjects with either a complete response (CR) or partial response (PR) at Day 28, as assessed by the investigators themselves.

The primary efficacy analysis for Remestemcel-L was based on the ITT population, which included all 55 enrolled subjects. The null hypotheseis of ORR ≤ 45% was rejected with a p-value = 0.0003. The estimated ORR at Day 28 was 69.1%. (Table 5 above.) The primary efficacy analysis based on the ITT set was supplemented and supported by analyses based on the mFAS and the per-protocol sets. The FDA clinical reviewer re-adjudicated the overall response data for some study subjects and the efficacy analysis repeated on the re-adjudicated data led to qualitatively similar results.

In addition to study MSB-GVHD001/002, the applicant also summarized data from a EAP (expanded access program) study (Protocol 275). As shown in Table 1, an ORR of 65% was reported for this study with pediatric patients. As an EAP study rather than a clinical experiment designed to support decision making, no hypotheses were specified, no sample size calculation conducted, and no statistical analyses performed. The phase of the study was said to be "Treatment Protocol", not a Phase 1-3 study. The EAP did not contribute useful evidence for this statistical review.

The applicant also analyzed the pediatric patients subgroup of Study 280, a randomized, placebo-controlled study of 260 patients with SR-aGVHD, grades B-D, including 28 pediatric patients. The study failed its primary objective/hypothesis, but the Day 28 ORR post-hoc pediatric subgroup exploratory analysis trended favorably for Remestemcel-L treated subjects in Grade C and D. There were 14 pediatric patients each in the Remestemcel-L and placebo groups with resultant OR rates of 64% and 36%, respectively. Based on the results of this subgroup analysis the applicant launched the single arm study MSB-GVHD001/002, attempting to confirm the treatment effect. However, Study MSB-GVHD001/002 was design as a single-arm study without a concurrent control group. Its results are therefore much more ambiguous and difficult to use for decision-making than a placebo-controlled randomized trial. Considering that pediatric patients

were included successfully in a previous randomized trial conducted by the applicant, it does not appear there would have been an inherent practical or ethical barrier to conducting a randomized trial in pediatric patients.

The safety analysis set included 54 subjects that were treated with Remestemcel-L. Thirteen (13) subjects (24%) died at the 100-day follow-up; none of these deaths were directly attributed to the study treatment with Remestemcel-L according to the applicant. There were 23 non-fatal SAEs.

10.2 Conclusions and Recommendations

Study MSB- GVHD001/002, an open-label, single-arm study, met its prespecified objective of gathering data and rejection of the pre-specified null hypothesis of 28-day ORR ≤ 45%. The open-label single arm design relies on comparison with a non-concurrent performance goal (45% ORR), but there is no way of knowing what the results would have been for a control group if one had been included in this trial. In addition, the lack of independent adjudication adds further potential for biased results.

The expanded access protocol, Study 275, is not suitable for supporting regulatory decision-making due to its design.

I conclude that this BLA submission has not provided sufficient statistical evidence to support the applicant's proposed pediatric indication for Remestemcel-L. My conclusion is based substantially on the negative results of the two previously conducted randomized, double-blind, placebo-controlled, multicenter studies, both of which failed to meet their primary efficacy endpoints. Additional adequate and well-controlled clinical studies, preferably in the form of randomized controlled trials if a suitable control group can be identified, would be needed to provide substantial evidence of effectiveness to support approval.