BLA Clinical and Clinical Pharmacology Review and Evaluation

Application Number(s)	125706/0
Application Type	Class 2 Resubmission
CBER Received Date	July 8, 2024
PDUFA Goal Date	January 7, 2025
Division / Office	DCEH/OCE/CBER
Review Completion Date	December 18, 2024
Applicant	Mesoblast, Inc.
Established Name	Remestemcel-L-rknd, *Ex Vivo* Cultured Adult Human Mesenchymal Stem Cells (MSCs)
(Proposed) Trade Name	Remestemcel-L-rknd
Proprietary name	RYONCIL
Pharmacologic Class	Allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy
Orphan Designated (Yes/No)	Yes
Formulation(s)	Remestemcel-L-rknd is provided as a frozen cell suspension in cryogenic vials. The active ingredient in Remestemcel-L-rknd is comprised of culture-expanded mesenchymal stromal cells (MSC isolated from the bone marrow of healthy adult human donors. Each cryovial contains nominally 25×10^6 ce-MSCs in 3.8 mL (6.68×10^6 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-rknd is available as a cell suspension for intravenous infusion in a concentration of 6.68×10^6 culture-expanded MSCs per mL in 3.8 mL contained in a 6 mL cryovial.
Dosing Regimen	The recommended dosage of remestemcel-L-rknd is 2×10^6 mesenchymal stromal cell (MSC)/kg body weight per intravenous infusion given twice a week for 4 consecutive weeks for a total of 8 infusions. Administer infusions at least 3 days apart. Assess response 28 ± 2 days after the first dose • If complete response: no further treatment with remestemcel-L-rknd • If partial or mixed response: repeat administration of remestemcel-L-rknd once a week for additional 4 weeks (4 infusions total) • No response: consider alternative treatments • Recurrence of GvHD after complete response: repeat administration of remestemcel-L-rknd twice a week for an additional 4 consecutive weeks (8 infusions total)
Applicant Proposed Indication(s)	Treatment of steroid-refractory acute graft-versus-host disease in pediatric patients as young as 2 months.
Recommendation on Regulatory Action	Traditional approval
Recommended Indication	Treatment of steroid-refractory acute graft-versus-host disease in pediatric patients 2 months of age and older

Clinical Reviewer: Upendra Mahat, MD
Clinical Pharmacology Reviewer: Million Tegenge, PhD
STN: BLA 125706/0

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Abbreviations: MHB, Malignant Hematology Branch; MORE CC, Medical Oncology Review and Evaluation Cross-center Clinical; OCE, Office of Clinical Evaluation

Additional Reviewers of Application

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Pharmacovigilance	Jonathan Reich
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APLB	Michael Brony/Oluchi Elekwachi

Abbreviations: APLB, Advertising and Promotional Labeling Branch; BIMO, Bioresearch Monitoring; CMC, Chemistry, Manufacturing, and Controls

GLOSSARY

aGVHD	acute graft-versus-host disease
ADA	antidrug antibodies
AE	adverse event
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CD	Crohn's disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	Chemistry, Manufacturing, and Controls
CNI	calcineurin inhibitor
CR	complete response
DOR	duration of response
DP	drug product
EAP	expanded access protocol
ETF	ectopic tissue formation
FAS	full analysis set
FDA	Food and Drug Administration
GI	gastrointestinal
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HLA-DR	human leukocyte antigen DR
HSCT	hematopoietic stem cell transplantation
IL-2Rα	interleukin-2 receptor alpha
IR	information request
IV	intravenous
LSM	least squares mean
MAGIC	Mount Sinai Acute GVHD International Consortium
MBS	Mount Sinai Acute GVHD International Consortium biomarker score
MP	methylprednisolone
MSC	mesenchymal stromal cell
NR	no response
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PK	pharmacokinetics
PP	per protocol
PR	partial response
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
ST2	suppressor of tumorigenesis 2
SR-aGVHD	steroid-refractory acute graft-versus-host disease
TNFR1	tumor necrosis factor receptor-1
TP	treated population

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1. EXECUTIVE SUMMARY

Remestemcel-L (Ryoncil, hereafter referred to as remestemcel-L) is composed of culture expanded mesenchymal stromal cells (MSCs) derived from bone marrow of healthy human donors.

Mesoblast Inc. (the Applicant) submitted a Biologics License Application (BLA) 125706 on January 31, 2020. A Complete Response (CR) Letter was issued on September 30, 2020. The Applicant responded to the September 30, 2020, CR Letter on January 31, 2023. A second CR Letter was issued on August 1, 2023. On July 8, 2024, the Applicant submitted a response to the CR Letter dated August 1, 2023, seeking approval for remestemcel-L for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients as young as 2 months old.

The proposed recommended dose/regimen is:

- Remestemcel-L $2×10^6$ culture-expanded MSCs/kg body weight. 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. If the symptoms recur after a complete response, treatment may be repeated.

Acute GVHD (aGVHD) is a life-threatening complication following allogeneic hematopoietic stem cell transplantation (HSCT). Upfront treatment of aGVHD involves continuation of drugs used for GVHD prophylaxis (often a combination of a calcineurin inhibitor [CNI] and methotrexate or mycophenolate) and addition of corticosteroids. Approximately 60% of patients respond to corticosteroids. Patients who progress on or do not improve with steroid therapy (SR-aGVHD) are often treated with salvage (second line) immunosuppressive therapy such as ruxolitinib, alemtuzumab, anti-thymocyte globulin, etanercept, extracorporeal photopheresis, infliximab etc. or enrolled in clinical trials. Historically, outcomes in patients with SR-aGVHD are poor, with an overall survival (OS) rate of only 5% to 30% (Zeiser et al. 2020) . Ruxolitinib is approved for treatment of SR-aGVHD in patients 12 year or older, based on a single-arm, multicenter study in 49 patients that demonstrated an overall response rate at Day 28 of 57.1% (95% CI: 42.2, 71.2); (Ruxolitinib). There are no therapies approved for treatment of SR-aGVHD in patients younger than 12 years.

The primary evidence supporting the safety and efficacy assessment in this BLA derives from Study MSB-GVHD001. Study MSB-GVHD001 is a single-arm, multicenter trial of remestemcel-L in pediatric patients 2 months to 17 years of age. Key eligibility criteria included presence of SR-aGVHD Grades B to D (excluding Grade B skin alone), as per International Blood and Marrow Transplantation Registry Severity Index Criteria (IBMTR) after receiving allogeneic HSCT. Patients received remestemcel-L at a dose of $2×10^6$ MSCs/kg twice a week for 4 consecutive weeks, for a total of eight infusions Patients with partial or mixed response at Day 28 received additional infusions of remestemcel-L $2×10^6$ MSCs/kg once a week for an additional 4 consecutive weeks. The primary outcome measure in Study MSB-GVHD001 was overall response rate (ORR) at Day 28, defined as the proportion of patients achieving complete response and partial response as assessed using the IBMTR grading system at Day 28. To be considered successful, the trial was designed to demonstrate an overall response rate of 65% at Day 28 with the lower bound of the 95% confidence interval intended to be no lower than 45%. Study MSB-GVHD001 enrolled a total of 55 patients from 20 sites in the United States, 54 of whom comprised the efficacy analysis population. The study population had a median age of 7

years (range: 7 months to 17 years) and the sex, racial, and ethnic composition was as follows: female (36%); White (56%), "Other race" (19%), Black or African American (15%), Asian (6%), American Indian or Alaska Native (6%); Hispanic (33%), non-Hispanic (65%).

Study MSB-GVHD001 met its prespecified criteria for success, demonstrating that treatment with remestemcel-L resulted in an ORR at Day 28 of 70.4% (95% CI: 56.4, 82.0), including a CR rate of 29.6% (95% CI: 18.0, 43.6) and a PR rate of 40.7% (95% CI: 27.6, 55.0). Among the 38 responders, the estimated median duration of response (DOR) was 54 days (range: 7, 159+ days).

The primary safety analysis population comprises the 54 patients treated with remestemcel-L in Study MSB-GVHD001. The most common adverse reactions (≥ 20%) were: viral infectious disorders, bacterial infectious disorders, infection – pathogen unspecified, pyrexia, hemorrhage, edema, abdominal pain and hypertension. Serious adverse reactions occurred in 35 patients (65%) including pyrexia (n=5;9%), respiratory failure (n=5;9%), pneumatosis intestinalis (n=4;7%) and staphylococcal bacteremia (n=3;6%).

There is an extensive regulatory history for this product notable for several BLA submissions and CR actions. Detailed reasons for the regulatory decisions on the preceding BLAs are documented in the respective review documents. Briefly, from the clinical perspective, the primary evidence of efficacy and safety in the initial BLA derived from Study MSB-GVHD001. The primary clinical reviewers (Drs. Kristin Baird and Donna Przepiorka; August 31, 2020) recommended approval, stating the following as reasons for approval: "… 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." The Branch Chief at the time (Dr. Bindu George; September 10, 2020) recommended a CR, stating the following as reasons:

> Absence of data to support a null hypothesis, considerable concerns related to bias due to the single-arm nature with differences between the study group and the external control group in baseline prognostic factors, concomitant medications, absence of a clear MOA and the observation of ORR predominantly in a trial that enrolled a substantially higher population of lower GI involvement where assessments may be subjective, the absence of data to support Day 28 ORR as an the optimal endpoint are factors that contribute to this recommendation.

On September 30, 2020, FDA issued a CR letter, which included a deficiency that Study MSB-GVHD001 did not constitute an adequate and well-controlled study. Upon resubmission of the BLA on January 31, 2023, the FDA again issued a CR Letter, with the clinical review team stating that the Applicant did not provide substantial evidence of effectiveness from an adequate and well controlled investigation given the outstanding chemistry, manufacturing, controls (CMC) deficiencies. The clinical review memorandum (Drs. Upendra Mahat, Mona Elmacken, Donna Przepiorka, Robert Sokolic, Marc Theoret, and Celia Witten; August 1, 2023), also cited limitations of data deriving from an observational study as being insufficient to provide substantial evidence of effectiveness.

Having satisfactorily addressed the CMC deficiencies, and upon consideration of the data submitted in the BLA and FDA's previous assessments of these data (including prior assessments about the adequacy of the design of Study MSB-GVHD001), the clinical review team concludes that Study MSB-GVHD001 represents an adequate and well-controlled trial. There is extensive FDA precedent for basing approvals on single-arm trials that evaluate

response rate including the approval of ruxolitinib, the only other drug approved for SR-aGVHD for patients who are 12 years of age and older, which was based on a single-arm trial evaluating overall response rate at Day 28. The study protocol for Study MSB-GVHD001 specified study objectives, enrollment criteria, outcome measures, and an analysis plan to evaluate outcomes, which help inform FDA's determination that the characteristics of an adequate and well-controlled study are present in Study MSB-GVHD001. The study population enrolled in Study MSB-GVHD001 had no available therapies and was refractory to steroids. In this clinical setting, withdrawal of steroids would not be appropriate in the absence of alternative effective therapeutic options. In this clinical setting, use of salvage therapies or referral to clinical trials is the standard of care (SOC). However, given the high ORR and favorable safety profile observed with remestemcel-L in Study MSB-GVHD001, a trial that would randomize pediatric patients to a control arm comprising unapproved salvage therapy would be unnecessary; additionally, such a trial would likely be infeasible to conduct due to a high risk of patient dropout from the control arm. As such, a single-arm trial is acceptable and sufficient to demonstrate the effectiveness of remestemcel-L.

Although cross-trial comparisons should be interpreted with caution, the effects of remestemcel-L observed in Study MSB-GVHD001 were compared to a historical ORR benchmark of 45% at Day 28. While some of the reviews in the administrative record question the selection of 45% as the cutoff for the lower bound of the 95% CI, we note the effectiveness of ruxolitinib characterized by an ORR of 57.1% (95% CI:42.2, 71.2), albeit in older patients. Additionally, notwithstanding the targeted effect (65%) and lower bound of 95% CI (45%) in Study MSB-GVHD001, a magnitude of ORR of 70.4% (95% CI: 56.4, 82.0) is a clinically meaningful benefit in patients with SR-aGVHD. We note that an Oncologic Drugs Advisory Committee (ODAC) meeting to discuss this BLA was held on August 13, 2020. The Committee voted 9 to 1 that the available data supports the efficacy of remestemcel-L in pediatric patients with SR-aGVHD.

In this request for approval, FDA assessed additional data in the BLA to substantiate the results of Study MSB-GVHD001, as the sole adequate and well-controlled clinical investigation submitted to support the Applicant's claims of effectiveness for the proposed indication; as described in FDA guidance documents, data drawn from one or more sources (e.g., clinical data, mechanistic data, animal data, etc.,) may serve as the confirmatory evidence for this purpose. While there is regulatory precedence in oncology for a single, multicenter, adequate and well controlled investigation to be sufficient to demonstrate the effectiveness of a product, mechanistic/pharmacodynamic data as described below further substantiates the evidence of effectiveness provided by Study MSB-GVHD001:

1. Mechanistic/Pharmacodynamic data: Following HSCT, acute GVHD occurs when donor T cells react to differences in the human leukocyte antigens (HLAs) on the recipient's tissue (Ernst Holler et al. 2024). Activation and proliferation of alloreactive T cells plays a central role in the pathogenesis of aGVHD (Malard et al. 2023). The BLA contains *in vivo* pharmacodynamic (PD) studies from patients treated in Study MSB-GVHD001 and Study MSB-GVHD002, which demonstrate the immunomodulatory effects of remestemcel-L. These studies demonstrate the immunomodulatory effects of remestemcel-L relevant to the pathophysiology of aGVHD. Specifically, treatment with remestemcel-L resulted in a 64% reduction in circulating CD3+CD4+CD25+human leukocyte antigen DR (HLA-DR)+ T cells, compared to baseline, which represents activated T cells. Additionally, two biomarkers—tumor necrosis factor receptor-1 (TNFR1) and suppressor of tumorigenesis 2 (ST2)—have been shown to be released by activated T lymphocytes. Following treatment with remestemcel-L, a decrease in these

biomarkers observed at Day 180 (TNFR1 by 79% and ST2 by 75% compared to baseline)—demonstrates the PD activity that leads to a reduced inflammatory state.

Conclusion

The BLA contains substantial evidence of effectiveness from one adequate and well controlled investigation evaluating the overall response rate (ORR) at Day 28 of remestemcel-L in pediatric patients 2 months or age or older, with SR-aGVHD. Acceptance of ORR at Day 28 as an endpoint denoting clinical benefit was discussed during an open public workshop on "Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation," held May 19, 2009 (Food and Drug Administration and National Institutes of Health 2009); FDA recommendations on the use of this endpoint are also described in the FDA draft guidance, "Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment" (September 2023). The mechanistic/, pharmacodynamic data included in the BLA, serve as confirmatory evidence in the context of a single adequate and well controlled investigation. The clinical data submitted support traditional approval of remestemcel-L for the treatment of SR-aGVHD in pediatric patients 2 months of age and older, at the requested recommended dosage.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Study MSB-GVHD001 enrolled 55 from 20 sites in the United States and treated 54 patients. The demographics of the enrolled population is as follows: median age 7 years (range: 7 months-17 years); females (36.4%); Asian (5%), Black (15%), White (56%); Hispanic/Latino (33%). Most patients (85%) were transplanted with a myeloablative conditioning regimen, and the majority were transplanted for acute and chronic leukemias (61.8%). At baseline, most patients 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: 9-170 days). The median time from onset of aGVHD to initiation of remestemcel-L treatment was 12.0 days (range: 4-142 days). The median time from onset of SR-aGVHD to initiation of remestemcel-L treatment was 3.5 days (range: 1-10 days).

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

1.2 Patient Experience Data

The patient-reported outcome data were submitted with initial BLA submission (Module 6.1.11.5). However, because the study is a single-arm study with no comparator, the patient-reported outcome data is descriptive and is not considered for regulatory decision making.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Allogenic HSCT is a potentially curative therapy for many life-threatening malignant and non-malignant disorders. More than 20,0000 HSCTs are performed in the Unites States each year, 40% of which were allogeneic (Majhail et al. 2015). The most common life-threatening complication is 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 (Malard

et al. 2023). Given the number of allogeneic HSCTs performed, approximately 5,000 patients/year develop aGVHD in the United States; of those, approximately 300 to 400 are pediatric patients (D'Souza et al. 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.

Acute GVHD primarily involves three target organs: skin, gastrointestinal tract (GI), and liver. The diagnosis relies on the assessment of these 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 these target organs. Various grading systems are used in assessment of aGVHD.

The combinations of CNI and methotrexate or CNI and mycophenolate are used most commonly to prevent GVHD in allogeneic HSCT recipients. In general, once aGVHD occurs, the drugs used for prophylaxis are continued, and additional immunosuppressive agents are added. aGVHD is treated first with corticosteroids, such as methylprednisolone, based on randomized, controlled trials (van Lint et al. 1998). About one third of pediatric patients with aGVHD do not respond to upfront corticosteroid therapy (MacMillan et al. 2015; MacMillan et al. 2020). Patients with Grade 3 to 4 aGVHD tend to have poorer outcomes. If patients progress or are not improved after steroid therapy, they will receive salvage (second-line) immunosuppressive therapy. Patients with aGVHD that is resistant to treatment with corticosteroids have a dismal long-term prognosis, with an OS rate of only 5% to 30%. Prognostic factors for long-term outcome include serum biomarkers, such as ST2 and Reg3-alpha, and clinical response to therapy (Major-Monfried et al. 2018). Steroid-refractory Grade 4 aGVHD is typically fatal (Deeg 2007; Jacobsohn and Vogelsang 2007; Martin et al. 2012; Jaglowski and Devine 2014).

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 to 4 SR-aGVHD occurring after allogeneic HSCT (Przepiorka et al. 2020). The ORR (CR+VGPR+PR) was 57% (95% CI: 42%, 71%). In REACH-2, the subsequent randomized trial for SR-aGVHD, the reported ORR was 62% with ruxolitinib and 39% with best available therapy (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 analyzed CR/PR rates for second-line therapies used in aGVHD treatment trials (Martin et al. 2012). The authors identified the CR/PR rate for the aggregated 29 studies as 58%, but the response definition and timing of assessment were not standardized.

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2.3 Safety and Efficacy of Pharmacologically Related Products

Product Background

Product Name: Remestemcel-L

Chemical Name: Remestemcel-L is composed of ex-vivo culture-expanded adult human culture-expanded MSCs derived from bone marrow aspirates.

Safety Risks

There are no approved culture-expanded MSCs. Based on the proposed mechanism of action of remestemcel-L (immunosuppression), the potential safety risks include infection and relapse of underlying disease/malignancy. 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 (DP) formulation (including dimethyl sulfoxide, as well as bovine, porcine and human protein), potential safety risks also include hypersensitivity reactions and infusions reactions (Santos et al. 2003).

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

As per information provided by the Applicant (Module 1.13.10), remestemcel-L has not been marketed anywhere in the world.

Health Canada granted conditional approval to remestemcel-L received in 2012 for the treatment of SR-aGVHD in pediatric patients under the tradename/proprietary name Prochymal, however, 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 on November 26, 2016, for the treatment of aGVHD in both adults and children after HSCT. This was based on 75 patients enrolled on in an EAP trial for pediatric patients, 12 single-patient use 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 preclinical and clinical data. Although 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.

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

Table 1: Regulatory Background Timeline

Date	Description
September 25, 1998	Initial IND Submitted (Sponsor Osiris Therapeutics)
July 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
December 14, 2005	Orphan Drug Designation granted for aGVHD
July 25, 2007	Type A Meeting to discuss a CMC SPA submission – non concurred

Date	Description
November 16, 2007	FTD Granted for the treatment of patients with Grade 2 to 4 GI GVHD after allogeneic HSCT to resolve acute GI GVHD by Day 42 after the treatment
October 9, 2008	Pre-BLA Package
January 20, 2009	BLA 125334 Part 1 received
April 23, 2009	BLA data submission plan
December 22, 2009	Type A Teleconference Meeting
March 5, 2010	BLA 125334 Withdrawal
February 11, 2011	Type A Pre-BLA/Face to Face Meeting
January 4, 2013	Clinical Study Report of expanded access protocol #275
January 31, 2014	Change in Sponsor from Osiris to Mesoblast, Inc
February 17, 2014	Request for (b) (4) for treatment of pediatric severe steroid-refractory aGVHD, post allogeneic hematopoietic stem cell transplant for hematologic malignancies
May 15, 2014	Request for (b) (4) denied
May 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
July 9, 2014	Type C Meeting
September 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
September 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
October 9, 2015	CMC product comparability study
June 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
February 28, 2017	FTD Granted for the treatment of SR-aGVHD intended to improve overall response rate of aGVHD in pediatric patients
November 29, 2018	Type C/Pre-IND Teleconference Meeting
April 5, 2019	Pre-BLA Meeting
May 29, 2019	BLA submitted; Rolling review and priority review requested
June 4, 2019	First portion of BLA 125706 submitted
January 31, 2020	BLA 125706 submitted
March 20, 2020	BLA Applicant orientation Meeting
March 30, 2020	BLA Filling notification; Priority Review Granted
June 1, 2020	BLA Midcycle Communication
July 23, 2020	BLA Late Cycle Meeting
August 13, 2020	ODAC Meeting
September 30, 2020	CR Letter to BLA issued
March 31, 2021	Applicant filed formal dispute resolution request
May 28, 2021	FDA responded to Applicant's formal dispute resolution request
December 27, 2021	CMC Type C Meeting (CRMTS #13687)
January 31, 2023	Applicant resubmitted BLA and a complete response to 09/30/2020 CR Letter
August 1, 2023	CR Letter to BLA issued
September 11, 2023	Type A Meeting (CRMTS #15239)
March 22, 2024	Type C Meeting (CRMTS #15488)
July 8, 2024	Applicant resubmitted BLA and a complete response to 08/2023 CR Letter

Source: BLA 125706 clinical review memo dated August 30, 2020; and Applicant's RL response submitted on July 8, 2024
Abbreviations: AA, accelerated approval; (b) (4) ; CMC, Chemistry, Manufacturing, and Controls; CR, complete response; FTD, fast track designation; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT, hematopoietic

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stem cell transplantation; ODAC, Oncologic Drugs Advisory Committee; SPA, Special Protocol Assessment; SR-aGVHD, steroid-refractory acute graft-versus-host disease

Key Regulatory Advice

Key regulatory issues discussed with Applicant in meetings prior to the August 1, 2023, CR Letter are described in the BLA 125706 clinical review memos dated August 31, 2020, and August 1, 2023. Key clinical issues discussed in meetings after August 1, 2023, are summarized below.

Type A Meeting, September 11, 2023 (CRMTS#15239)

The Applicant proposed to conduct an externally controlled trial comparing remestemcel-L to best available therapy in adults and children over age 12 years with SR-aGVHD that is refractory to both steroids and a second line agent, such as ruxolitinib. The control was to derive from the MAGIC consortium database.

The FDA reiterated that before conducting a future trial with a registrational intent, the Applicant should address the CMC deficiencies, and standardize the product as to its identity, strength, quality, purity, and dosage form to give significance to the results of the investigation as described in 21 CFR 314.126(d). Further, the FDA did not agree that a randomized clinical trial (RCT) with an active control is not feasible in this setting, and expressed significant concerns with the Applicant's proposal. The FDA specifically noted the limitations of an externally controlled trial design and recommended that the Applicant conduct a RCT with best available therapy serving as the treatment administered to a concurrent comparator group. The Applicant countered by providing rationale stating why an RCT with concurrent control would not be feasible in this setting. Specifically, the Applicant noted that given the rare nature of SR-aGVHD, particularly as a disease that is also refractory to a second-line agent such as ruxolitinib, it would not be possible to conduct an RCT. The Applicant also stated that an ongoing RCT for the same indication with a different product, a fecal microbiota transplantation (FMT), through BMT CTN would further make it very challenging to recruit patients into an RCT of remestemcel-L. However, the FDA did not agree that an RCT would not be feasible in this setting. The Applicant asked if a single-arm trial design would be acceptable in patients with SR-aGVHD who are refractory to a second line agent, particularly ruxolitinib. The FDA stated that a single-arm trial design may be appropriate in certain circumstances, such as more refractory or later-line population settings, but reemphasized the recommendation to conduct an RCT for the initial registration of remestemcel-L for the proposed indication, especially given the issues with the potency assay.

Type C Meeting, March 22, 2024 (CRMTS #15488)

The Applicant proposed the following:

- Conduct a single-arm trial of remestemcel-L as a third-line agent in adults and adolescents who have failed steroids and a second-line agent (typically ruxolitinib) and for who there are no other approved therapies.
- If the next trial in adults and adolescents with aGVHD meets its primary endpoint, would FDA consider the EIND study, which was performed with the same standardized product to provide support for approval of remestemcel-L as third-line treatment of aGVHD?

The FDA noted that "based upon additional consideration, the available clinical data from Study MSB-GVHD001 appears sufficient to support submission of the proposed BLA for remestemcel-L for treatment of pediatric patients with steroid refractory acute SR-aGVHD." The FDA further provided additional guidance regarding potency assay and assessment of comparability between remestemcel-L produced at Lonza Singapore Biosciences using original versus new donor cell banks.

The history of Clinical Information Requests is shown in Table 2.

Table 2: Clinical Information Requests and Summary

Amendment Number	Date of Submission	Amendment Description – Clinical Summary
0	May 29, 2019	Original Submission
1	September 4, 2019	Request for review of proposed proprietary name
2	December 27, 2019	Clinical module
4	February 11, 2020	Response to Clinical IR #1/teleconference summary
5	February 21, 2020	Updated clinical datasets ISS/ISE; Additional response to Clinical IR #1
6	February 27, 2020	Response to Clinical IR #4
7	March 2, 2020	Updated clinical datasets ISS/ISE; Response to Clinical IR #5
8	March 3, 2020	Response to Clinical IR #2; Updated datasets GVHD-001
9	March 6, 2020	Response to Clinical IR #3; Updated datasets studies 260, 261, 265, 280
12	March 11, 2020	Response to Clinical IR #5; Updated datasets ISS/ISE
13	March 16, 2020	Response to Clinical IR #6; Updated datasets studies 260, 261, 265, 280
16	April 2, 2020	Response to Clinical IR #8; Updated CRFs Study GVHD-001
17	April 7, 2020	Response to Clinical IR #7; Updated datasets GVHD-001, ISS/ISE
20	April 23, 2020	Response to Clinical IR #9; Updated datasets ISS/ISE
21	May 1, 2020	Response to Clinical IR #7; Updated datasets GVHD-001, ISS/ISE
22	May 4, 2020	Response to Clinical IR #4
25	May 13, 2020	Updated USPI
31	September 12, 2020	Response to Clinical IR #7 & #10; biomarker report, clin/pharm summary
32	June 15, 202	Response to IR #24; Updated ISE datasets following midcycle meeting
40	July 6, 2020	Response to IR #27 (immunogenicity)
41	July 10, 2020	Response to IR #29 (Applicant Briefing Document TOC)
43	July 14, 2020	Response to Clinical IR #13 (Information request #30)
65	January 30, 2023	Response to 9/30/2020 CR Letter, and BLA Resubmission
66	February 9, 2023	Response to Clinical IR #14 (Information request #37)
67	February 10, 2023	Response to Clinical IR #15 (Information request #38)
69	March 21, 2023	Updated USPI
71	April 6, 2023	Response to Clinical/stat IR #16 (Information request #41)
76	May 4, 2023	Response to Clinical/stat IR #17 (Information request #45)
77	May 11, 2023	Response to Clinical/stat IR #18 (Information request #46)
82	May 25, 2023	Response to Clinical/stat IR #19 (Information request #49)
87	June 30, 2023	Response to Clinical IR #20 (Information request #53)
90	July 6, 2023	Corrected Response to Clinical IR #20 (Information request #53)
91	August 15, 2023	Type A Meeting Request
91	September 25, 2023	Type A Meeting Summary submitted by Applicant

Amendment Number	Date of Submission	Amendment Description – Clinical Summary
94	July 8, 2024	Response to 8/1/2023 CR Letter, and BLA Resubmission
95	July 22, 2024	Updated USPI (pdf versions)
96	July 23, 2024	Updated USPI (MS Word versions)
97	August 29, 2024	Response to Clinical IR #21 (F/U to Information request #53)

Source: BLA125706 clinical review memo dated August 30, 2020; and Applicant's RL response submitted on July 8, 2024
Abbreviations: CRF, case report form; F/U, follow up; FTD, fast track designation; GVHD, graft-versus-host disease; IR, information request; ISE, integrated summary of efficacy; ISS, integrated safety summary; TOC, table of contents; USPI, United States Prescribing Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

No issues were identified in this resubmission dated July 8, 2024. See the BLA 125706 clinical review memo dated August 31, 2020, for issues identified during the initial BLA submission.

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 conducted inspections for Study MSB-GVHD001 at Duke University Medical Center (Durham, North Carolina), Memorial Sloan Kettering Cancer Center (New York, New York), Lurie Children's Hospital (Chicago, Illinois) and Oregon Health and Science University, Doernbecher Children's Hospital (Portland, Oregon). These sites had the highest accrual, highest number of study violations per patient, and/or greatest impact on the primary endpoint. The Bioresearch Monitoring inspections of all four sites have been completed and classified as "No Action Indicated" (See the BLA 125706 clinical review memo dated August 31, 2020).

3.3 Financial Disclosures

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry, "Financial Disclosure by Clinical Investigators" (February 2013). No financial conflicts of interest were identified. See the BLA 125706 clinical review memo dated August 31, 2020.

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

4.1 Chemistry, Manufacturing, and Controls

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

Per the CMC review memo, in this BLA resubmission (BLA 125706, SN0093), the Applicant proposed the use of a strengthened potency matrix with two complimentary assays, the (b) (4) assay and the optimized 21371 interleukin-2 receptor alpha (IL-2Rα) Inhibition Bioassay. The (b) (4) assay provides (b) (4)

In addition, the IL-2Rα Inhibition assay measures an attribute

that is related to the mechanism of GVHD. However, the implementation of a major manufacturing change, such as the addition of a new donor cell bank, will require the characterization of additional critical quality attributes, including the development of a reliable potency assay that can support both product quality assurance and shelf-life determination. [(b) (4)]

4.2 Assay Validation

Immunogenicity assay validation data were not submitted.

4.3 Nonclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

Human clinical data from biomarker characterization in Studies MSB-GVHD001 and MSB-GVHD002 provided evidence of the immunomodulatory pharmacodynamic (PD) bioactivity of remestemcel-L in pediatric patients with SR-aGVHD. A summary of the major PD characteristics of culture-expanded MSC from Stud MSB-GVHD001 and Study MSB-GVHD002 is provided below. For details on biomarker results, refer to Section 9.1.6.

4.4.1 Mechanism of Action

The mechanism of action for remestemcel-L is unclear but may be related to the immunomodulatory activities of culture-expanded MSCs. Data from in vitro studies demonstrate that culture-expanded MSCs 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 PD data were obtained from analysis of blood samples in pediatric patients with SR-aGVHD (n=40; age range: 0.6-17 years) following treatment with remestemcel-L at a dose of 2×10^6 cells/kg. At baseline, elevated levels of TNFR1 and ST2 were observed, consistent with the inflammatory state of aGVHD. Treatment with remestemcel-L reduced the levels of TNFR1 and ST2 by 79% and 75%, 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 64% at Day 180 following treatment with remestemcel-L as compared to the baseline values.

Overall, the reduction in levels of secreted factors (TNFR1 and ST2) and activated T cells provide evidence of the immunomodulatory PD effects of remestemcel-L in pediatric patients with SR-aGVHD.

4.4.3 Human Pharmacokinetics

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

4.4.4. Immunogenicity

Since remestemcel-L is an allogeneic product, there is a potential for development of antidrug antibodies (ADA) or anti-HLA antibodies. Humoral immune response was not characterized in pediatric patients with aGVHD in 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%) tested positive for anti-HLA antibodies, but no patient tested positive for ADA up to Day 56 following remestemcel-L treatment. For type 1 diabetes, 13 out of 42 (31%) in remestemcel-L treated, and 5 out of 21 (24%) patients in the placebo group, had at least 1 positive test for anti-HLA antibodies at any time point. Six out of 42 (14%) remestemcel-L treated patients and 0 out of 21 (0%) patients in the placebo group tested positive for ADA during the 1-year follow-up period. The clinical significance of ADA or anti-HLA antibodies following treatment with remestemcel-L is not fully understood.

4.4.5. Dosage Rational

No formal clinical dose-finding or dose regimen optimization studies have been performed during the development of remestemcel-L for treatment of aGVHD in pediatric patients. In early studies, human MSCs were evaluated to treat steroid-refractory, severe aGVHD with a median dose of 1×10^6 cells/kg for one to three infusions. Furthermore, the initial EAP included 10 pediatric patients ages 2 to 15 years who were infused with allogeneic culture-expanded MSC at a dose of 2×10^6 cells/kg twice a week for 4 weeks. In Stud MSB-GVHD001 and Study MSB-GVHD002, treatment with remestemcel-L at a dose of 2×10^6 cells/kg, administered by IV infusion twice a week for 4 weeks was generally safe and well-tolerated through Day 180.

4.5 Statistical

The statistical review team reviewed and confirmed the primary study endpoint analyses. The statistical reviewers further performed subgroup analyses and sensitivity analyses as requested by the clinical review team. These analyses results showed consistent Day-28 ORR exceeding the null rate prespecified in the trial. See the BLA 125706 Statistical review memo dated August 25, 2020.

4.6 Pharmacovigilance

No safety concerns have been identified that would require a risk evaluation and mitigation strategy or postmarketing requirement. The Applicant's proposed intervention plan for identified risks—acute infusion reaction, infections, pulmonary complications, and neurologic events—includes routine pharmacovigilance interventions. In addition, enhanced pharmacovigilance will be recommended to monitor potential risks of ectopic tissue formation and the risk of anti-donor/ anti-HLA antibodies.

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 primary clinical data to support the BLA. Accordingly, the primary efficacy analysis for the BLA is based on data from Study MSB-GVHD001 (n=54, Treated population). The efficacy and safety results were analyzed by FDA using patient level dataset, clinical study reports and ORR electronic Case Report Forms. No

new clinical information was submitted with BLA resubmission on July 8, 2024. This review
provides the data to support labeling and updated safety analyses.

5.2 BLA/IND Documents Evaluated as Part of the Clinical Review

- IND 7939 electronic Common Technical Documents and FDA reviews
- BLA 125706 electronic Common Technical Documents, datasets, and clinical amendments
  listed in Table 2 (Section 2.5 of this review), which include the Applicant's responses to
  clinical information requests (IRs)
- Type 5 Master File (b) (4), submitted by CIBMTR on April 17, 2023

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 patient EAPs under IND #007939 and multiple emergency,
compassionate use, investigator-initiated trials. An overview of all studies is shown in Table 3.

Table 3: List of Studies

Study Identifier (Phase)	Indication	Patients (N)	Efficacy	Safety
MSB-GVHD001 (Phase 3)	SR-aGVHD	Pediatric: 55 enrolled, 54 treated	Yes	Yes
MSB-GVHD002 (Phase 3)	SR-aGVHD	Pediatric: 32 enrolled	Yes	Yes
Study 275a (EAP)	SR-aGVHD	Pediatric: 241 enrolled and treated	Yes	Yes
280 (Phase 3)	Other GVHD	Total: 259 enrolled Adult: Remestemcel-L, 159/Placebo: 73 Pediatric: Remestemcel-L:14/Placebo:13	Yes	Yes
265 (Phase 3)	Other GVHD	Total: 194 enrolled Remestemcel-L: 97/Placebo: 95	Yes	Yes
260 (Phase 2)	Other GVHD	Adult: 32 enrolled and treated	No	Yes
261 (Phase 2)	Other GVHD	Adult: 32 enrolled	No	Yes
276 (EAP)	Other GVHD	Adult: 18 enrolled and treated	No	Yes
207	aGVHD	Adult: single patient treated	No	Yes
208, 209	aGVHD	Adult: 1/ Pediatric: 1	No	Yes
GVHD 270/271/270E	aGVHD	11 enrolled (10 adults, 1 pediatric)	No	Yes
210	aGVHD	Adult: 2 patients treated	No	Yes
215-218, 220-222, 224-225, 227-233, 235-236	aGVHD	Pediatric: 10 single patients treated	No	Yes
Investigator initiated studies	aGVHD	Pediatric: 12 Adult: 4	-	-
401 (Phase 1)	AMI	Adult: 60 enrolled, 53 treated Remestemcel-L: 34/Placebo: 19	No	Yes
402 (Phase 1)	AMI	Same as Study 401	No	Yes
403 (Phase 2)	AMI	Adult: 220 enrolled Remestemcel-L: 110/Placebo: 110	No	Yes
601 (Phase 2)	CD	Adults: 10 enrolled Remestemcel-L Low Dose 2M cells/kg:	No	Yes

Study Identifier (Phase)	Indication	Patients (N)	Efficacy	Safety
		5 Remestemcel-L High Dose 8M cells/kg: 5		
602 (Phase 2)	CD	Same as Study 601	No	Yes
603 (Phase 3)	CD	Adult: 269 enrolled Remestemcel-L: 171/<u>Placebo</u>: 98	No	Yes
610 (extension study for 603)	CD	Adult: 69 enrolled and randomized	No	Yes
611 (extension study for 603)	CD	Adult: 73	No	Yes
620 (EAP)	CD	Adult: 13 enrolled	No	Yes
801 (Phase 2)	COPD	Adult: 62 enrolled Remestemcel-L: 30/Placebo: 32	No	Yes
901 (Phase 2)	TIDM	63 enrolled, Remestemcel-L: 42 (9 pediatric)/Placebo: 21 (3 pediatric)	No	Yes

Source: BLA125706 clinical review memo dated August 31, 2020
Abbreviations: AMI, acute myocardial infarction; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; EAP, expanded access protocol; GVHD, graft-versus-host disease; N, population size; SR-aGVHD, steroid-refractory acute graft-versus-host disease; TIDM, type 1 diabetes mellitus

5.4 Consultations

5.4.1 Advisory Committee Meeting

An Oncologic Drugs Advisory Committee meeting was held on August 13, 2020, to discuss the product quality and efficacy of BLA 125706, remestemcel-L for the treatment of SR-aGVHD in pediatric patients. The morning session addressed CMC issues and questions; the afternoon session addressed clinical review issues.

To the voting question "Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD?" nine out of 10 voted "Yes."

See the BLA 125706 clinical review memo dated August 31, 2020, for further information.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MSB-GVHD001

6.1.1 Trial Design

Study MSB-GVHD001 is the trial providing primary evidence in support of this BLA. The follow-up on this trial was through Study Day 100. Study MSB-GVHD002 is an extension of Study MSB-GVHD001 and it provides safety follow-up of patients from Study MSBGVHD001 through 180 days from the start of Study MSB-GVHD001. Of 54 patients treated in Study MSB-GVHD001, 32 patients were enrolled in Study MSB-GVHD002.

In this document, FDA's analyses used data pooled from Study MSB-GVHD001 and Study MSB-GVHD002; the results of these analyses are reported under Study MSB-GVHD001.

Study MSB-GVHD001 is 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."

See Table 4 for a brief protocol synopsis.

Table 4: Protocol Synopsis, Study MSB-GVHD001

Design	Single-Arm Trial
Sample size	55
Sites	Open at 27 centers in the United States/ 20 centers enrolled patients
Key eligibility	Patients between the ages of 2 months and 17 years inclusive, with aGVHD following allogeneic HCT that had failed to respond to treatment with systemic corticosteroid therapy
Primary objectives	1. To evaluate the efficacy of remestemcel-L in pediatric patients with Grades B to 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 patients with Grades B to D aGVHD that have 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 (QL) data on remestemcel-L-treated patients via the Pediatric Quality of Life Inventory (PedsQL™), and the pediatric global health-related quality of life Parent Proxy Report. 3. To measure the functional status of remestemcel-L-treated patients using the Karnofsky/Lansky scale.
Primary endpoint	The study population rate of overall response at day 28 post initiation of therapy (Day 0) with remestemcel-L.
Secondary endpoints	1. Overall survival at day 100 post initiation of therapy 2. VGPR rate at day 28 post initiation of therapy relative to baseline 3. ORR and VGPR rate at day 100 post initiation of treatment relative to baseline 4. ORR and VGPR rate at days 28 and 100 stratified by organ involvement relative to baseline 5. ORR and VGPR rate at days 28 and 100 stratified by individual patient organ involvement relative to baseline 6. ORR and VGPR rate at days 28 and 100 by baseline GVHD grade relative to baseline 7. Overall survival at day 100 post initiation of therapy stratified by baseline grade and organ involvement 8. Rate of aGVHD activity worsening requiring additional GVHD medications/ therapy through day 100. 9. Effect of additional remestemcel-L therapy at day 28 on ORR and VGPR at days 56 and 100.
Initial treatment	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
Continued treatment	• CR: no further treatment • Partial response/mixed response- repeat remestemcel-L once a week for 4 weeks • No response: consider alternative treatment • Recurrence of GVHD after CR- repeat treatment as initial treatment

Source: Study MSB-GVHD001 Study Protocol
Abbreviations: aGVHD, acute graft versus host disease, HCT hematopoietic cell transplantation, CR, complete response, IV intravenous; ORR, overall response rate, PR, partial response, VGPR, very good partial response

6.1.2 Statistical Considerations & Statistical Analysis Plan

The Applicant's prespecified Statistical Analysis Plan (SAP v5.0 from February 8, 2018) is outlined below; see the CBER Statistician's reviews (Dated August 25, 2020, August 1, 2023

and December 5, 2024) and Section 6.1.11 (Efficacy Analysis) for additional FDA statistical considerations.

Section 7: Sample sizes and power of the SAP v5.0 (BLA 125706, Module 5.3.5.1) states:

> *The primary objective of this trial is to confirm efficacy of remestemcel-L in improving Day 28 overall response rate within the FAS population.*
>
> *For assessment of efficacy, an effect size of 20%, which has been deemed clinically meaningful based on discussion with clinical experts on aGVHD, was used to calculate the null hypothesis. The null hypothesis is further supported by published data showing comparable Day 28 OR rates for historical populations of aGVHD patients treated with second line agents, however no SOC exists and there are no approved therapies for aGVHD in the United States.*
>
> *The 28-days OR rate for all Protocol 275 subjects, which includes those treated with steroid only as well as those treated with steroid plus other second-line agents, was 63.8%. However, for the steroid-only subset of Protocol 275, Day 28 OR was 78.1% (25 of 32 subjects). The Day 28 OR for remestemcel-L-treated pediatric subjects from Protocol 280, which enrolled subjects refractory only to steroids, was 64.3% (9 of 14 subjects). When the steroid-only subjects from Protocol 275 were combined with the remestemcel-L-treated pediatric subjects from 280, the composite Day 28 OR was 73.9% for steroid-only subjects (34 of 46 subjects; Table 9 in Protocol MSB-GVHD001).*
>
> *In this study, a 28-day OR rate for a subject population treated only with steroids was conservatively anticipated to be 65%, a rate seen for Protocol 275 and for the remestemcel-L treated pediatric subgroup of Protocol 280. Hence, p=0.65 was chosen as the alternative hypothesis.*

The SAP prespecified a sample size of 48 patients 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.

During the review of the initial BLA submission in 2020, the clinical review team noted the following (source: BLA 125706 BLA clinical review memo dated August 31, 2020):

"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 in 2020, to which the Applicant provided the following information:

- *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 Study MSB-GVHD001, the risk-adjusted null rate would be 46% for a study of 60 patients.*

- *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].

The review's assessment of above information was as follows:

"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:

- *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.*

- *In the MAGIC database, there were 30 pediatric patients transplanted from 2005 to 2019 who received salvage therapy for Grades B to 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 to 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 evaluated the use of etanercept in 25 children with Grades 2 to 4 SR-aGVHD using the modified Glucksberg criteria (Przepiorka et al. 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 et al. 2019).*

- *A retrospective analysis from the Pediatric Blood and Marrow Transplant Consortium evaluated the efficacy and safety of infliximab 10 mg/kg IV once a week for a median of 8 doses (range 1-162) in 24 children with steroid-resistant GVHD. The ORR, defined as the maximal response within 56 days of starting treatment was 82% (12 CR + 6 PR), was reported in 22 evaluable children (Sleight et al. 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 2 to 4 aGVHD if patients did not improve within 5 days or worsened within 48 hours after corticosteroids. The ORR was 67% at 4 weeks, with a CR in 40%, a PR in 27%, and no response (NR) in 33% (Khandelwal et al. 2016)."

Based on above data, the clinical review team concluded the following (source: BLA 125706 BLA clinical review memo dated August 31, 2020):

"**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 et al. 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% to 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 the 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."

Review comment: Given that patients diagnosed with SR-aGVHD are not left untreated due to high risk of death, contemporary data on the outcome of untreated SR-aGVHD do not exist. Limited historical data report variable ORR with salvage therapies. As noted in a review paper by Gottardi et al, ORR in pediatric patients with SR-aGVHD treated with various salvage therapies ranged from 33% to 100% (Gottardi et al. 2023). It should be noted that these reports include single patient case reports, small case series, retrospective studies and small prospective studies of unapproved therapies which were used in conjunction with steroids and various other therapies used to treat aGVHD; these studies include substantial heterogeneities including but not limited to small sample sizes, varied primary endpoint measures, varied definition and timepoint for response assessment, single-institution enrollment, various GVHD grading systems, different definitions of steroid refractoriness, concomitant use of steroids and other therapies with effect on the disease etc. As such, it is not possible to make any conclusion based on these published studies. Additionally, it should be noted that approval of ruxolitinib for SR-aGVHD in patients 12 years and older tested a null ORR rate of 40% in a single-arm trial.

Based on these considerations, the review team concurs with the conclusion that a historical 45% null ORR benchmark used in Study MSB-GVHD001 is adequate for this disease.

Missing Data

For modified FAS or FAS analyses, any patient with a missing Day-28 ORR assessment was deemed to be a non-responder for the primary efficacy analysis. No imputation method was used for other missing measurements in the study (SAP v5.0 from February 8, 2018).

6.1.3 Study Population and Disposition

Patient Disposition

Fifty-five patients were enrolled, 54 patients received remestemcel-L (1 patient's condition worsened before the remestemcel-L arrived and could not be infused), and 42 patients (76.4%) completed the study. All 54 patients treated were eligible for Day 28 evaluation.
See Table 8 for the summary of patient disposition.

Table 5. Patient Disposition, All Enrolled Patients

Disposition/Reason	Total, n (%)
Patients enrolled	55 (100)
Patients treated with remestemcel-L	-
Yes	54 (98.2)
No	1 (1.8)
Patients 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; and BLA125706 clinical review memo dated August 31, 2020
Notes: Percentages were based on the total number of patients enrolled.
Abbreviations: HSCT, hematopoietic stem cell transplantation; MSC, mesenchymal stromal cell; n, sample size

Demographics

The demographics of FAS and the Treated population are shown in in Table 6.

Table 6: Demographics, Treated Population, Study MSB-GVHD001

Parameter	FAS (N=55)	Treated (N=54)
Age (months)	-	-
Median	91	93
Min, max	7, 215	7, 215
Gender, n (%)	-	-
Male	35 (64)	35 (64)
Female	20 (36)	19 (36)
Race, n (%)	-	-
White	31 (56)	30 (56)
American Indian or Alaska Native	3 (5)	3 (5)
Asian	3 (5)	3 (5)
Black or African American	8 (8)	8 (15)
Other	10 (18)	10 (19)
Ethnicity, n (%)	-	-
Hispanic or Latino	18 (33)	18 (33)
Non-Hispanic or Latino	36 (65)	36 (67)

Source: FDA table generated from Mesoblast BLA submission, GVHD001 ADSL
Abbreviations: ADSL, Analysis Data Model Subject-Level Analysis Dataset; max, maximum; min, minimum; N, population size

Medical/Behavioral Characterization of the Enrolled Population

Table 7: Disease Characteristics, Study MSB-GVHD001

Characteristic	FAS (N=55)	Treated Population N=54
Underlying condition for HSCT, n (%)	-	-
Hematological malignancies	37 (67)	36 (67)
Non-malignant diseases	18 (33)	18 (33)
Conditioning regimens used, n (%)	-	-
Myeloablative	47 (85)	46 (85)
Non-myeloablative	1 (2)	1 (2)
Reduced intensity	6 (11)	6 (11)
Unknown	1 (2)	1 (2)
Transplant donor, n (%)	-	-
Related	13 (24)	13 (24)
Unrelated	42 (76)	41 (76)
HLA compatibility match	-	-
HLA matched	27 (49)	27 (50)
HLA mismatched	28 (51)	27 (50)
Type of transplant, n (%)	-	-
Bone marrow	30 (55)	29 (54)
Cord blood	11 (20)	11 (20)
Peripheral blood stem cells	14 (25)	14 (26)
Grade of aGVHD at diagnosis, n (%)	-	-
A	2 (4)	2 (4)
B	16 (29)	15 (28)
C	26 (47)	26 (48)
D	11 (20)	11 (20)
Grade of SR-aGVHD at baseline, n (%)	-	-
A	0 (0)	0 (0)
B	6 (11)	6 (11)
C	23 (42)	23 (43)
D	26 (47)	25 (46)
Organ involvement at baseline	-	-
Skin only	14 (25)	14 (26)
Lower gastrointestinal only	21 (38)	21 (39)
Multi-organ involvement	20 (36)	19 (35)
Mac Millan Risk Score at baseline		
High risk	40 (73)	39 (72)
Standard risk	15 (27)	15 (28)

Source: FDA analysis of ADSL data
Abbreviations: ADSL, Analysis Data Model Subject-Level Analysis Dataset; aGVHD, acute graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; N, population size; n, sample size

6.1.4 Efficacy Analyses

The Applicant performed analysis of the primary efficacy endpoint and key secondary efficacy endpoints in the FAS population. Additional sensitivity analyses were performed using the modified FAS and Per Protocol (PP) populations.
Summary of the analysis populations:
- The FAS population (55 patients) included all enrolled patients and was used for the primary and secondary efficacy analyses.

- The Safety population (54 patients) was used for the safety analyses. One patient in the FAS population was enrolled in the study but did not receive remestemcel-L due to worsening of their medical condition prior to receipt of remestemcel-L at the site.

- The modified FAS population (47 patients) included patients in the FAS population who were treated with remestemcel-L packaged in cryogenic vials instead of cryogenic bags.

- The PP population (51 patients) included all patients who had no major study violations during the study.

The primary efficacy analysis (overall response 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 modified FAS and PP populations were used to assess sensitivity and therefore were considered supportive.

Table 8: Applicant's Analysis Sets

Population	Total n (%)
Patients enrolled	55
Full analysis set population	55 (100)
Safety population	54 (98.2)
Modified full analysis set population	47 (85.5)
Per protocol population	51 (92.7)

Source: Clinical Study Report, Report No. MSB-GVHD001, section 11.1
Notes: Percentages were based on the total number of patients enrolled.
The FAS population was defined as patients who signed the informed consent form, were screened, and were found eligible to enter the study.
The Safety population was defined as patients who signed the informed consent form and received at least 1 dose of study treatment (complete or partial).
The modified FAS population consisted of the vial-treated patients from the FAS population.
The Per Study population was defined as all patients who had no major Study violations during the study.
Abbreviations: FAS, full analysis set; n, sample size

The original data from the primary efficacy study MSB-GVHD001 were reviewed and adjudicated by the FDA clinical review team during the review of the original submission. See the BLA 125706 clinical review memo dated August 31, 2020. The summary of efficacy results is shown in Table 9.

Table 9: Efficacy Results, Study MSB-GVHD001

Analysis Set	N	Day-28 CR n, %	Day-28 PR n, %	Day-28 ORR n, %	Day-28 ORR 95% CI
Full analysis set	55	16 (29.1)	22 (40.0)	38 (69.1)	(55.2, 80.9)
Treated set	54	16 (29.6)	22 (40.7)	38 (70.4)	(56.4, 82.0)

Source: FDA analysis; BLA 125706 clinical review memo August 31, 2020
Abbreviations: CR, complete response; N, population size; n, sample size; ORR, overall response rate; PR, partial response

Overall response rate at Day 28 by baseline disease severity is as follows: Grade B (3/6, 50.0%), Grade C (16/23, 69.5%), and Grade D (19/25, 76.0%).

DOR is shown in Table 10. The median follow-up of the 38 responders was 150.5+ days (4.9 months) (range: 15-182+ days)

Table 10: Duration of Day-28 Overall Response Rate, Study MSB-GVHD001

Definition Used	Duration of ORR Days (n=38) Median	Duration of ORR Days (n=38) Range	Duration of CR Days (n=16) Median	Duration of CR Days (n=16) Range	Duration of PR Days (n=22) Median	Duration of PR Days (n=22) 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[c]	111.5	9, 182+	112+	16, 172+	111.5	9, 182+

Source: FDA Analysis
a. The number of weeks that the response at Day 28 was maintained.
If the response at the weekly assessment is the same or better than the Day 28 response, then the patient 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.
b. The interval from the Day-28 response to progression, new systemic therapy for aGVHD or death from any cause.
Progression is defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment (i.e., progression from nadir).
New therapy is defined as a new systemic treatment for aGVHD or an increase in the dose of corticosteroids to methylprednisolone 2 mg/kg (+/- 10%) equivalent.
c. The interval calculated from Day-28 response to either death or need for new therapy for aGVHD.
Abbreviations: DOR, duration of response; n, sample size; ORR, overall response rate

Biomarker and Cytokine Data Analysis

The Applicant submitted biomarker data under Amendment 17 on April 7, 2020, in response to a Clinical IR #7 (IR #10) sent on March 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 patients enrolled into Study MSB-GVHD001, only 40 of these patients participated in the biomarker substudy. See 9.1.6. Additional Clinical Pharmacology Review and Analysis.

6.1.5 Safety Analyses

FDA reviewed the safety data for 1,780 patients in clinical trials and EAPs. There were substantial differences between the clinical trials regarding the patient population and treatment plan and the versions of the product used, so no pooling of safety data was performed. See the BLA 125706 clinical review memo dated August 31, 2020.

The primary source of safety data was a total of 54 patients treated with remestemcel-L in Study MSB-GVHD001.

Exposure

The median number of remestemcel-L infusions administered were 10 (range: 1 to 16). The treatment was administered over a median of 43 days (range: 1 to 104 days). Ten patients missed a total of 13 infusions. Reasons for missing infusions included AEs/serious adverse

events (SAEs; 5), lack of efficacy (2), start of second-line therapy (4), and other (2). Two patients each had 1 infusion interrupted. One patient had the interrupted infusion restarted.

Death

Fourteen patients (14/54; 26%) died over the course of Study MSB-GVHD001.

Primary causes of death are as shown in Table 11.

Table 11: Deaths, Study MSB-GVHD001 (N=54)

Primary Cause of Death	N	%
Acute graft-versus-host disease	4	7%
Acute myeloid leukemia	3	6%
Bilateral bronchopneumonia	1	2%
Cardiac arrest	1	2%
Fanconi's anemia	1	2%
Invasive fungal infection	1	2%
Multiple organ failure	1	2%
Mycobacterium avium infection	1	2%
Pulmonary hemorrhage	1	2%

Source: FDA Analysis of ADSL dataset

Reviewer Comment: During the review of initial BLA submission, the FDA adjudicated the causes of death. The causes of deaths are adjudicated as relapse for any patient who died following relapse/worsening of primary disease, as GVHD for any patient who died of active GVHD, infection for any patient who died of infection and organ failure for any patient who died following vital organ failure. Deaths occurred due to following: GVHD (4/54; 7%), Relapse (4/54; 7%), Infection (3/54;6%), organ failure (3/54, 6%). These causes of death appear consistent with the cause of death in patients following allogenic HSCT. It should be noted that in randomized trials (Study 280 and 265), no apparent difference in incidence of deaths between remestemcel-L and placebo arms was observed. Similarly, no fatal adverse events were observed in among 460 patients treated with remestemcel-L in non-GVHD clinical trials. Based on these data, the risk of fatal adverse events with remestemcel-L appears low.

Common Adverse Events

The Adverse Event Analysis Data Set data from this study were re-analyzed using group terms (Table 12) when applicable.

Table 12: Grouped Terms Used by FDA for Analyses

Grouped Terms (FDA GT)	AEDECOD
Affective disorder	Blunt affect
	Depressed affect
	Dysphoria
Anemia	Anaemia
	Anaemia postoperative
	Pallor
Arrythmia	Sinus arrythmia
	Sinus bradycardia
	Sinus tachycardia
	Short PR
	Cardiac arrest
	Non-specific T wave abnormality

Grouped Terms (FDA GT)	AEDECOD
	Prolonged QT
	Prolonged QTc
	QT prolongation on ECG
	Electrocardiogram PR shortened
	Electrocardiogram T wave abnormality
	Electrocardiogram Qt prolonged
Bacterial infectious disorder	Grouped per high-level group term
Edema	Oedema peripheral
	Generalized oedema
	Facial oedema
	Periorbital oedema
Fluid overload	Fluid retention
	Hypervolaemia
Fungal infectious disorders	Grouped per high-level group term
Hemorrhage	Epistaxis
	Large intestinal hemorrhage
	Haematemesis
	Haematochezia
	Gastrointestinal haemorrhage
	Lower gastrointestinal haemorrhage
	Melaena
	Haematuria
Infections - pathogen unspecified	Grouped per high-level group term
Rash	Rash
	Rash papular
	Rash macular
	Rash erythematous
Insomnia	Insomnia
	Sleep disorder
Respiratory distress	Acute respiratory distress syndrome
	Respiratory distress
Respiratory failure	Acute respiratory failure
	Respiratory failure
Tremor	Action tremor
	Tremor
Viral infectious disorders	Grouped per high-level group term

Source: FDA Analysis
Abbreviations: AEDECOD, adverse event identifier obtained from a dictionary; ECG, electrocardiogram; GT, grouped term;
PR, partial response; QT, Q wave T wave; QTc, heart-rate corrected Q wave T wave interval

The results of the safety summary are shown below in Table 13.

Table 13: TEAEs Occurring in >10% of Patients, Study MSB-GVHD001

FDA Group Term[a]	All Grade, n	All Grade[b], %	Grade 3 or Higher, n	Grade 3 or Higher[c], %
Viral infectious disorders	30	56	8	15
Bacterial infectious disorders	24	44	10	19
Infections – pathogen unspecified	22	41	8	15
Pyrexia	19	35	2	4
Hemorrhage	15	28	4	7
Edema	12	22	1	2
Abdominal pain	11	20	4	7
Hypertension	11	20	3	6
Vomiting	10	19	3	6

FDA Group Term[a]	All Grade, n	All Grade[b], %	Grade 3 or Higher, n	Grade 3 or Higher[c], %
Arrhythmia	9	17	2	4
Diarrhea	9	17	1	2
Rash	9	17	0	0
Arthralgia	8	15	0	0
Fungal infectious disorders	8	15	2	4
Hyperglycaemia	8	15	3	6
Hypotension	8	15	2	4
Cough	7	13	0	0
Respiratory failure	6	11	6	11

Source: FDA analysis of ADAE dataset
a. See Table 12
b. National Cancer Institute Adverse Event Common Toxicity Criteria version 4.03.
c. No grade 4 or 5 adverse reactions occurred in the study.
Abbreviations: ADAE, Adverse Event Analysis Data Set; n, sample size, TEAEs, treatment-emergent adverse events

Serious Adverse Events

SAEs occurred in 65% (35/54) patients. The most common SAEs were occurring in ≥5% were: pyrexia (5/54; 9%), respiratory failure (5/54; 9%), pneumatosis intestinalis (4/54; 7%) and staphylococcal bacteraemia (3/54; 6%)

SAEs led to early termination from study in 10 patients (Table 14).

Table 14: Serious Adverse Events Leading to Early Termination From Study MSB-GVHD001

AEDECOD	N	%[a]
Acute myeloid leukaemia recurrent	2	4%
Acute respiratory distress syndrome	2	4%
Multiple organ dysfunction syndrome	2	4%
Respiratory failure	2	4%
Acute graft-versus-host disease	1	2%
Cardiac arrest	1	2%
Cardiac failure	1	2%
Fungal infection	1	2%
Metabolic acidosis	1	2%
Somnolence	1	2%

Source: FDA analysis of ADAE data, study MSB-GVH001
a. Percent calculated using N=54, Treated population.
Abbreviation: AEDECOD, adverse event identifier obtained from a dictionary; N, sample size

Table 15 shows the SAEs occurring in >5% patients.

Table 15: Serious Adverse Events Occurring in >5% Patients

AEDECOD	All Grades, N	All Grades, %	Grade 3 or Higher	Grade 3 or Higher, %
Pyrexia	5	9%	3	6%
Respiratory failure	5	9%	0	0%
Pneumatosis intestinalis	4	7%	0	0%
Acute graft-versus-host disease	3	6%	0	0%

AEDECOD	All Grades, N	All Grades, %	Grade 3 or Higher	Grade 3 or Higher, %
Staphylococcal bacteraemia	3	6%	0	0%

Source: FDA analysis of ADAE dataset
Abbreviations: ADAE, Adverse Event Analysis Data Set; AEDECOD, adverse event identifier obtained from a dictionary; N, population size

Laboratory Abnormalities

Study MSB-GVHD001

See the BLA 125706 clinical review memo for laboratory abnormalities review based on the Adverse Event Analysis Data Set.

In response to FDA's Request For Information #60 on October 16, 2024, the Applicant submitted an Analysis Data Model – Laboratory dataset from Study MSB-GVHD001 and the results of lab shift abnormalities. This analysis was performed based on lab abnormalities that occurred or worsened by at least one grade following treatment with remestemcel-L. The result of this analysis is summarized in Table 16.

Table 16: Laboratory Abnormalities That Worsened From Baseline in ≥10% of Patients, Study MSB-GVHD001 (N=54)

Lab Abnormality	All Grades[a], n (%)	Grade ≥3, n (%)
Creatinine increased	29 (54)	1 (2)
GGT increased	27 (50)	17 (32)
ALT increased	25 (46)	4 (7)
Platelet count decreased	20 (37)	15 (28)
White blood count decreased	20 (37)	4 (7)
Hemoglobin decreased	18 (33)	4 (7)
Glucose increased	17 (32)	3 (6)
AST increased	16 (30)	1 (2)
APTT increased	9 (17)	1 (2)
Bilirubin increased	9 (16)	6 (11)
Alkaline phosphatase increased	7 (13)	0 (0)
Lymphocyte count decreased	7 (13)	2 (4)
Neutrophil count decreased	7 (13)	2 (4)
Potassium decreased	7 (13)	4 (7)
Phosphate decreased	7 (13)	0 (0)
INR increased	6 (11)	0 (0)
Calcium decreased	6 (11)	1 (2)

Source: FDA Analysis of ADLB dataset; and Applicant's response to FDA's Request For Information #60 on October 16, 2024
a. Based on National Cancer Institute Adverse Event Common Toxicity Criteria version 4.03
Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; N, population size; n, sample size

7. INTEGRATED OVERVIEW OF EFFICACY

Primary efficacy in support of this BLA derives from MSB-GVHD001 study. No integrated analysis of efficacy was performed.

7.1 Additional Efficacy Issues/Analyses

During resubmission in 2023, the Applicant submitted new clinical information that included a clinical study report from a retrospective propensity control study from the MAGIC database

(Module 5.3.4.2), and a clinical study report from a long-term survival registry study of patients treated with remestemcel-L conducted by CIBMTR (Module 5.3.4.2).

7.1.1 MAGIC External Control Study

During the review of the initial BLA submission in 2020, the MAGIC external control study was reviewed by the FDA and was considered to be inconclusive in support of the Applicant's claims of effectiveness.

With BLA resubmission on January 31, 2023, the Applicant submitted a new clinical study report from the MAGIC external control study. This retrospective study compared Day-28 ORR and OS up to 6 months between the patients in Study MSB-GVHD001 and a propensity matched control group of 30 patients from the MAGIC database. This analysis reported a Day-28 ORR of 43% in matched external control compared 70% ORR observed in Study MSB-GVHD001.

Review comment: *The study was a retrospective analysis, performed without a prespecified statistical analysis plan a priori and without a prior discussion/agreement with the FDA, the selection of a control group was biased, not fit-for-purpose and not acceptable, and there were several confounders. For example, all patients in Study MSB-GVHD001 were treated between 2015 and 2017, whereas MAGIC control groups were selected from 2005 to 2019; various key data including data on concomitant medications used by patients in this external control group were missing. Based on these considerations, these data are inconclusive and cannot be used as primary evidence for a regulatory decision making (see the BLA 125706 clinical review memo dated August 1, 2023).*

7.1.2 Center for International Blood and Marrow Transplant Research Long-Term Survival Study

On Applicant's behalf, the CIBMTR submitted survival data on 51 pediatric patients with SR-aGVHD, who were previously enrolled in Study MSB-GVHD001 (submitted by CIBMTR as Type 5 master file (b) (4) on April 17, 2023).

The CIBMTR database collects longitudinal survival information of patients in the United States who have undergone allogenic or autologous HSCT. As per the Applicant, upon their request, the CIBMTR performed this study (Study ID: CIBMTR CS22-36, "Clinical Outcomes of Pediatric Patients Treated with Remestemcel-L for Steroid Refractory Acute Graft-Versus-Host Disease on a Phase 3, Single-Arm, Prospective Study") to assess OS up to 4 years after the first dose of remestemcel-L for patients who participated in Study MSB-GVHD001/002. The study was a retrospective observational cohort study of clinical outcomes as reported to the CIBMTR. The inclusion criteria included 1) patients enrolled in Mesoblast's phase 3 clinical trial MSB-GVHD001; 2) patient must have received at least one infusion of remestemcel-L; and 3) had data reported to the CIBMTR, including CIBMTR Research ID, first date of remestemcel-L infusion, and IBMTR Severity Index Grade of aGVHD at the time the patient was enrolled into Mesoblast's clinical trial.

The objectives of this study were 1) to evaluate overall OS after first remestemcel-L treatment at 1, 2, 3 and 4 years; 2) to evaluate relapse/progression after the first remestemcel-L dose at 1, 2, 3, and 4 years; and 3) to determine the cause of death. The submission included information about OS and the causes of death, but did not include information about relapse and progression. The submission also did not include information about the status of response or the use of new systemic therapy for aGVHD.

Clinical Reviewer: Upendra Mahat, MD
Clinical Pharmacology Reviewer: Million Tegenge, PhD
STN: BLA 125706/0

The primary endpoint of the study was the OS where an event was defined as death due to any cause. In the absence of confirmation of death, OS was censured at the date the patient was last known to be alive. OS was assessed at 1, 2, 3, and 4 years following the first remestemcel-L dose by IBMTR Severity Index Grade in patients with adequate follow-up. OS was estimated by the Kaplan Meier method. Survival probability was calculated from the date of the first remestemcel-L dose to the date of event occurred or the date of censoring for those who remained event-free. Median follow-up of survivors was provided.

The secondary endpoint was the cause of death overall and by IBMTR severity index grade.

Disposition of Patients

Table 17 below shows the disposition of patients.

Table 17: Patient Disposition-CIBMTR study

Selection Criteria	Number Excluded	Total Number
Included patients enrolled in phase 3 clinical trial	-	55
Excluded patients who did not receive remestemcel-L	1	54
Excluded patients who declined to participate in CIBMTR's research database	1	53
Excluded patients who were not approached about participating in CIBMTR's research database	2	51

Source: FDA Analysis of ADSL data from CIBMTR long term survival study
Abbreviation: CIBMTR, Center for International Blood and Marrow Transplant Research

Table 18 shows the summary of OS.

Table 18: Overall Survival, Patients Treated, Study MSB-GVHD001 (N=51)

Overall Survival	% OS: KM Estimate of Survival (95% CI) All (n=51)	% OS: KM Estimate of Survival (95% CI) Grade B (n=6)	% OS: KM Estimate of Survival (95% CI) Grade C (n=22)	% OS: KM Estimate of Survival (95% CI) Grade D (N=23)
1-year	62.7 (49.2, 75.4)	50.0 (14.1, 85.9)	72.7 (52.7, 88.8)	56.5 (36.3, 75.7)
2-year	50.8 (37.1, 64.3)	50.0 (14.1, 85.9)	53.6 (32.7, 73.8)	47.8 (28.2, 67.9)
3-year	48.7 (35.1, 62.3)	50.0 (14.1, 85.9)	48.2 (27.5, 69.2)	47.8 (28.2, 67.9)
4-year	48.7 (35.1, 62.3)	50.0 (14.1, 85.9)	48.2 (27.5, 69.2)	47.8 (28.2, 67.9)
Median follow-up, range (months)	62 (15-73)	56 (42-70)	62 (15-73)	62 (46-73)

Source: FDA analysis
Abbreviations: CI confidence interval; KM, Kaplan-Meier; OS, overall survival

Out of the 28 deaths that occurred out of 51 patients, 7 (14%) deaths occurred due to GVHD. Table 19 shows the causes of death.

Table 19: Causes of Death Based on CIBMTR Long-Term Survival Study

Category	All Patients (N=51)	Baseline GVHD Grade B (n=6)	Baseline GVHD Grade C (n=22)	Baseline GVHD Grade D (n=23)
Alive	23 (45%)	3 (50%)	10 (45%)	10 (43%)
Died	28 (55%)	3 (50%)	12 (55%)	13 (57%)
Causes of death	-	-	-	-
Organ failure	8 (16%)	2 (33%)	1 (5%)	5 (22%)
GVHD	7 (14%)	1 (17%)	3 (14%)	3 (13%)

Category	All Patients (N=51)	Baseline GVHD Grade B (n=6)	Baseline GVHD Grade C (n=22)	Baseline GVHD Grade D (n=23)
Primary disease	6 (12%)	0	3 (14%)	3 (13%)
IPn/ARDS	2 (4%)	0	2 (9%)	0 (0%)
Gastrointestinal hemorrhage	1 (2%)	0	0 (0%)	1 (4%)
Graft failure	1 (2%)	0	1 (5%)	0 (0%)
Infection	1 (2%)	0	1 (5%)	0 (0%)
Metabolic acidosis	1 (2%)	0	0 (0%)	1 (4%)
Stroke	1 (2%)	0	1 (5%)	0 (0%)

Source: FDA Analysis: CIBMTR ADSL data
Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research; GVHD graft-versus-host disease; IPn interstitial pneumonitis; ARDS acute respiratory distress syndrome

Reviewer Comment: *The patients with aGVHD who do not respond to upfront steroid therapy have poor outcomes. Limited published literature suggests 2 years survival rate of 35% or less (MacMillan et al. 2002; Westin et al. 2011; Martin et al. 2012; Xhaard et al. 2012; Zeiser et al. 2020). The REACH-2 trial was a randomized controlled trial that compared efficacy and safety of ruxolitinib with investigator's choice of therapy from a list of nine commonly used options in patients 12 years of age or older who had SR-aGVHD. The median OS was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15) (Zeiser et al. 2020).*

It should be noted that there is limited interpretability of time-to-event endpoint results derived from a single-arm trial without a comparator and that the use of literature-based comparator for survival benchmark may introduce the potential for significant bias. Nevertheless, the CIBMTR long-term OS data for patients treated with remestemcel-L in Study MSB-GVHD001 appear numerically higher compared to survival of SR-aGVHD patients reported in available historical literature. This observation indicates directional consistency with efficacy results of pivotal study MSB-GVHD001. Furthermore, there was no detriment in OS observed with the longitudinal follow-up data from CIBMTR, which provides additional support for long term safety.

7.2 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 Day-28 ORR in the Treated population was 70% (95% CI: 56.4, 82.0).

The primary endpoint results in Study MSB-GVHD001 were statistically significant, the measured response was durable, and the results were consistent across subpopulations and secondary efficacy endpoints.

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 DP manufactured using a different process. Given these limitations, the results of analyses of these trials have limited applicability to the current BLA and the proposed indication.

8. INTEGRATED OVERVIEW OF SAFETY

With this BLA resubmission, the Applicant did not provide additional safety data. In the resubmission on January 31, 2023, the Applicant submitted safety data for 1,780 patients
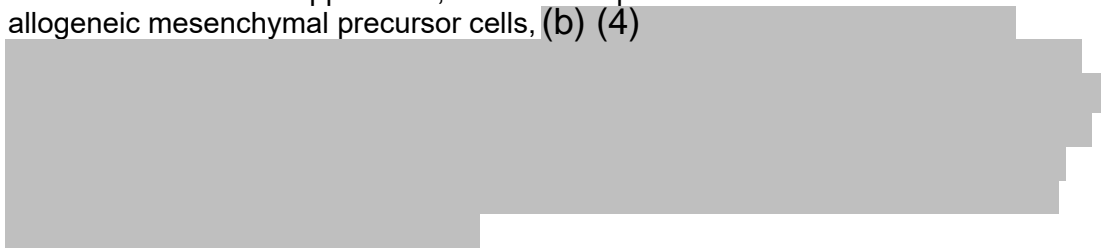
treated with remestemcel-L. Based on these data, no new safety signals were identified. However, uncertainties remain regarding the risk of ectopic tissue formation and anti-donor/anti-HLA antibodies. On August 22, 2024, an information request was sent asking Applicant to provide updated information on following:

1. Ectopic tissue formation (ETF): updated information summarizing how many patients to date across all studies of remestemcel-L.

   Applicant responded that, in the clinical trials of remestemcel-L, 9 patients were identified, with possible ETF in the imaging studies. These scans were evaluated, and it was determined that there were alternative explanations, and none of these patients were considered to have ETF. Biopsies were not performed for any of these cases. The Applicant concluded 'based on the available data, there are no confirmed cases of ETF and there is no evidence that remestemcel-L causes ETF'.

2. Anti-donor/anti-HLA antibodies: Among patients treated under Study MSB-GVHD001, did any patient had pre-existing anti-HLA antibodies? For patients with pre-existing anti-HLA antibodies, what were their clinical responses? Did they develop any refractory cytopenia such as refractory thrombocytopenia?

   The Applicant responded that in the setting of a normal immune system and no concomitant immunosuppression, Mesoblast's prior randomized controlled trials with allogeneic mesenchymal precursor cells, (b) (4)

   No testing for anti-HLA antibodies was performed in Study MSB-GVHD001, and therefore the Applicant was unable to assess whether the pre-existing antibodies might have a bearing on the clinical responses in Study MSB-GVHD001.

Reviewer Comment: Bone marrow derived MSCs have potential for multi-lineage differentiation potential into osteocytes, adipocytes, chondrocytes and skeletal muscle (Moghadam et al. 2014; Okolicsanyi et al. 2015; Wang et al. 2016). Although rare, there are some reports of ectopic tissue formation following MSC administration (Prigozhina et al. 2008; Chu et al. 2020; Wu et al. 2020). Similarly, some patients undergoing alloHSCT may have pre-existing anti-HLA antibodies whereas some may develop these antibodies following HSCT (Detrait et al. 2012; Koclega et al. 2012). These anti-donor/anti-HLA antibodies, if directed against the donor, may be associated with graft failure (Morin-Zorman et al. 2016), and may also increase the risk of refractoriness to platelet transfusions (Solves et al. 2018).

Although the review team acknowledges Applicant's responses to FDA information request dated August 22, 2024, the data provided have important limitations, particularly missing data for many patients. Given these considerations, the review team recommends that the Applicant submit an enhanced pharmacovigilance plan to address these concerns.

8.1 Safety Conclusions

In general, the analyses of safety data in studies of remestemcel-L identified no safety signal of concern. This is uncertainty regarding the risk of ectopic tissue formation and anti-donor/anti-HLA antibodies limits. ese risks can be evaluated further postmarketing with enhanced pharmacovigilance.

9. ADDITIONAL CLINICAL AND CLINICAL PHARMACOLOGY ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The Applicant stated 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 integrated safety summary in non-aGVHD studies: patients (b) (6)   . However, both patients were on placebo arms of the trials. (See the BLA 125706 clinical review memo dated August 31, 2020).

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 Pediatric Research Equity Act Considerations

The safety and effectiveness of remestemcel-L for treatment of SR-aGVHD was established in pediatric patients aged 2 months to 17 years in Study MSB-GVHD001.

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 SR-aGVHD has not been established in geriatric patients.

9.1.6. Additional Clinical Pharmacology Review and Analysis

Patients participating in studies MSB-GVHD001 and MSB-GVHD002 had the option of participating in an exploratory biomarker substudy. Blood samples for biomarker assessments were collected at baseline (prior to treatment with remestemcel-L) and at Days 28, 100, 160, and 180. Frozen samples were sent to a central lab for batched analysis. Plasma levels of IL-

2Rα, TNFR1, IL-8, HGF, elafin, and Reg3α were measured using a (b) (4) immunoassay, while ST2 levels were measured by (b) (4) assay. Immune cell subsets (T cells, B cells and NK cells, regulatory T cells, and activated T cells) were analyzed by (b) (4) Table 20 provides a summary of the assays used for biomarker testing in Studies MSB-GVHD001 and MSB-GVHD002.

The MAGIC algorithm probability, also referred to as the Mount Sinai Acute GVHD International Consortium biomarker score (MBS) is a biomarker algorithm that estimates the probability of 6-month nonrelapse mortality for individual patients during HSCT and in early stages of aGVHD. The MBS has been referred to as a "liquid biopsy" for lower GI injury in aGVHD, which is difficult to treat and is a major cause of death in patients with GVHD as it incorporates two key biomarkers of GI crypt damage, Reg3α and ST2. The MBS was determined using ST2 and Reg3α results in the algorithm below:

$$\log[-\log(1 - MAP)] = -11.263 + 1.844(\log10ST2) + 0.577(\log10Reg3\alpha)$$

Longitudinal biomarker analyses were performed using the restricted maximum likelihood approach to estimate random and fixed effects in a repeated measures, linear mixed effects model. The model allowed accommodation of between-patient and within-patient variation and for post hoc tests to be performed to provide comparisons of biomarker levels between study timepoints (baseline and Days 28, 100, 160, and 180 post first MSC infusion). Study patients were assumed as a random effect and the comparisons between study timepoints to be the fixed effect. The predicted value of each biomarker at each time point was calculated as least squares mean (LSM). Correlations between continuous patient demographics and characteristics, baseline biomarker levels, and responder and survivor probabilities were examined using the Pearson correlation method.

Table 20: Assays for Exploratory Biomarker Testing, Studies MSB-GVHD001 and MSB-GVHD002

Biomarker	Test Method	Assay	Assay Manufacturer	Sample Type	Validation Parameters	Accuracy and Sensitivity Performance
Elafin, HGF, Reg3α, TNFR1, IL-8, IL-2Rα						
ST2						
T cells, B cells, NK cells						
Activated T cell (CD25+, HLA-DR+)						
Treg (CD25+/ CD127lo/-)						

Source: Applicant's Table 2 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
a. Accuracy was determined in validation of the (b) (4) assay for serum (EDTA) samples.
Abbreviations: BCT, blood collection tube; EDTA, ethylenediaminetetraacetic acid; (b) (4) assay; HGF, hepatocyte growth factor; HLA-DR, human leukocyte antigen-DR; IL-2Rα, interleukin-2 receptor-α; IL-8, interleukin-8; LLOQ, lower limit of quantification; NK, natural killer; QC, quality control; Reg3α: regenerating islet-derived protein 3 α; ST2, suppressor of tumorigenicity-2; TNFR1, tumor necrosis factor receptor type I; ULOQ, upper limit of quantification

Results of Pharmacodynamic Biomarker Analysis

Demographics of Patients in Biomarker Analysis

In total, 55 patients were enrolled into Studies MSB-GVHD001 and MSB-GVHD002 (FAS). Fifty-four patients were treated with at least 1 dose of remestemcel-L (safety population), and 40 of these patients further participated in the exploratory biomarker substudy in Studies MSB-GVHD001 and/or MSB-GVHD002 (Table 21). The results displayed in Table 22 demonstrate that the demographics of the patients in the PD biomarker analysis are representative of the overall study patients enrolled in Studies MSB-GVHD001 and MSB-GVHD002.

Table 21: Biomarker Samples Collected, Studies MSB-GVHD001 and MSB-GVHD002

	MSB-GVHD001 (N=36)						MSB-GVHD002 (N=21)			
Subjects (N)	36						21			
Samples (N)	Baseline		Day 28		Day 100		Day 160		Day 180	
	Plasma	Whole Blood	Plasma	Whole Blood	Plasma	Whole Blood	Plasma	Whole Blood	Plasma	Whole Blood
	30	29	34	33	26	24	17	14	20	19

Source: Applicant's Table 9 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
Abbreviations: N, population size

Table 22: Demographics, Patients in the Pharmacodynamic Biomarker Analysis

	FAS	Safety Population[a]	Exploratory Biomarker Subgroup
N	55	54	40
Demographics			
Age			
Mean±SD	7.4±5.4	7.5±5.4	8.5±5.1
Median	7.0	7.0	10
Min-Max	0.6-17.0	0.6-17.0	0.6-17.0
Sex; N (%)			
Male	35 (63.6)	35 (64.8)	28 (70)
Female	20 (36.4)	19 (35.2)	12 (30)
Race; N(%)			
American Indian/Alaska Native	3 (5.5)	3 (5.6)	2 (5)
Asian	3 (5.5)	3 (5.6)	2 (5)
Black/African American	8 (14.5)	8 (14.8)	5 (12.5)
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	31 (56.3)	30 (55.5)	23 (57.5)
Other	10 (18.2)	10 (18.5)	8 (20)
Weight (kg)			
Mean±SD	28.8 (18.9)	29.2±19.0	31.0±17.5
Median	25.5	25.8	30.4
Range	4.6-90.1	4.6-90.1	4.6-73.0

Source: Applicant's Table 7 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; N, population size

Baseline Biomarker Profile

The median levels of soluble biomarkers HGF, IL-8, sIL-2Rα, TNFR1, Reg3α, and ST2 were increased in study patients compared to levels observed in healthy adults, consistent with an inflammatory state characteristic of aGVHD. However, the level of elafin was within the range observed in healthy adults (Table 23). The median MBS was 0.369, with 60% of patients (N=18/29) having a baseline MBS ≥0.291, suggesting that most patients at baseline were Ann Arbor 3 and at high risk for 6 month nonrelapse-related mortality (Table 23).

Table 23: Soluble Biomarkers at Baseline

	N	Mean	SD	Median	Min	Max	Reference Range (a, b)
Soluble Biomarkers(c)							
Elafin	30	3.86	0.54	3.82	3.09	5.03	3.45-4.18
HGF	30	2.64	0.34	2.62	1.80	3.42	1.10-2.45
IL-8	30	1.55	0.42	1.53	1.07	2.53	0.46-1.33(d)
Reg3α	30	4.03	0.50	3.99	2.97	5.67	2.84-3.94
sIL-2rα	30	3.24	0.26	3.19	2.70	3.79	2.34-3.02
TNF-R1	29	3.95	0.31	3.91	3.61	5.31	3.10-3.91
ST2	29	2.33	0.24	2.36	1.82	2.60	1.29-1.72
MAGIC Biomarker Score (MBS)							
MBS	29	0.372	0.163	0.371	0.149	0.762	High Risk: ≥0.291 Low risk: <0.291

Source: Applicant's Table 10 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
a. Reference ranges for soluble biomarkers were determined during assay validation. For elafin, HGF, IL-8, Reg3α, sIL-2R α and TNFR1, data were generated from N=50 healthy adult donors (N=25 males, N=25 females).
b. For ST2, data were generated from N=25 healthy donors (N=13 males; N=12 females).
c. Test results for soluble markers were log10 transformed. For elafin, HGF, IL-8, Reg3α, sIL-2R α and TNFR1, original units = pg/ml. For ST2, original units = ng/ml.
d. Lower level estimated as 0.5xLLOQ; log10(2.905)=0.46.
Abbreviations: HGF, hepatocyte growth factor; IL-8, interleukin-8; MAGIC, Mount Sinai Acute GVHD International Consortium; max, maximum; MBS, Mount Sinai Acute GVHD International Consortium biomarker score; min, minimum; N, population size; Reg3α: regenerating islet-derived protein 3 α; sIL-2rα, soluble interleukin-2 receptor α; ST2, suppressor of tumorigenicity-2; TNF-R1, tumor necrosis factor receptor type I
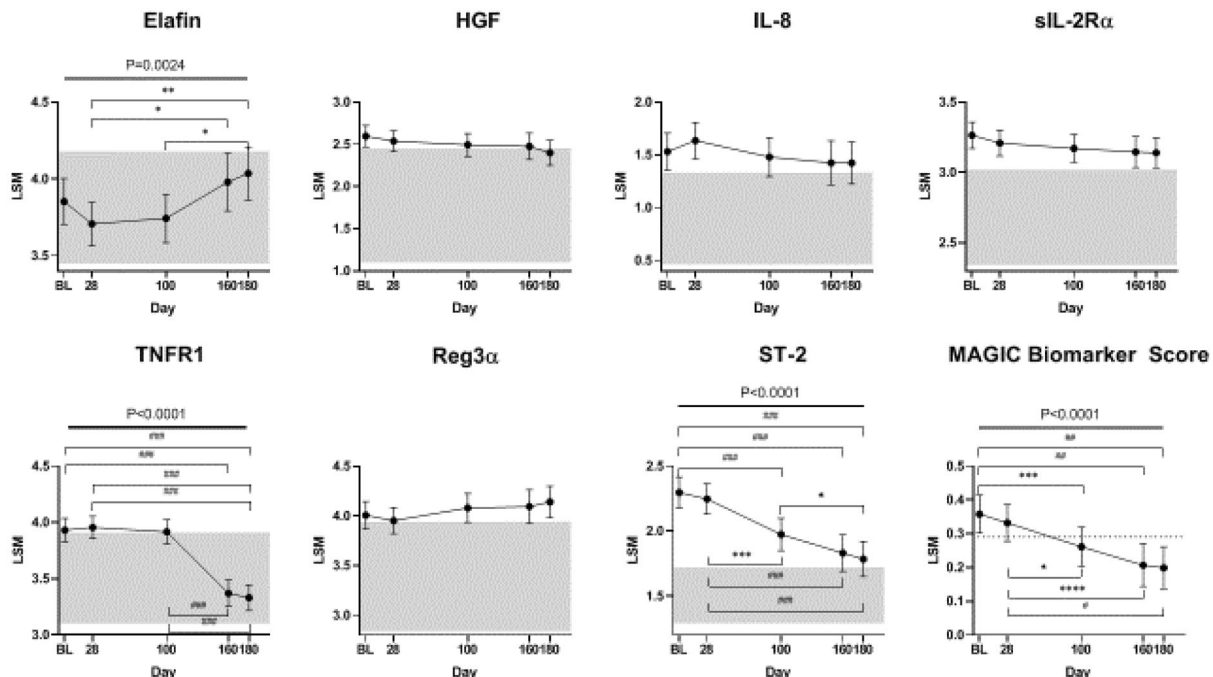
Longitudinal Biomarker Analysis

Figure 1 displays the longitudinal change of soluble PD biomarker levels over the course of Studies MSB-GVHD001 (baseline and Days 28 and 100) and MSB-GVHD002 (Days 160 and 180). There were no significant differences between study timepoints in estimated levels of HGF, IL-8, and sIL-2Rα.

The levels of the following PD biomarker changes from baseline were reported as statistically significant:

- Elafin levels increased at Days 160 and 180 as compared to baseline

- TNFR1 levels decreased at Days 160 and 180 as compared to baseline

ST2 levels steadily and significantly decreased from baseline to Day 180.

Figure 1: Soluble Biomarker Levels at Baseline, Days 28, 100, 160, and 180

Source: Applicant's Figure 1 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
Abbreviations: HGF, hepatocyte growth factor; IL-8, interleukin-8; MAGIC, Mount Sinai Acute GVHD International Consortium; MBS, Mount Sinai Acute GVHD International Consortium biomarker score; Reg3α: regenerating islet-derived protein 3 α; sIL-2rα, soluble interleukin-2 receptor α; ST2, suppressor of tumorigenicity-2; TNF-R1, tumor necrosis factor receptor type I

The circulating levels of activated T cells declined at Day 28 versus baseline for patients in Study MSB-GVHD001 (Table 24). Specifically, the percentage of activated T cells defined by their composite expression of CD3+CD4+HLA-DR+ and CD3+CD4+CD25+HLA-DR+ was significantly reduced at Day 28 relative to levels measured at baseline (%CD3+CD4+HLA-DR+, Day 0 (N=27): 54.55±23.96 vs Day 28 (N=32): 37.38±18.97, P<0.0001; %CD3+CD4+CD25+HLA-DR+, Day 0 (N=28): 27.45±13.31 vs Day 28 (N=31): 18.42±11.5, P=0.0084). CD25 is the alpha chain of the trimeric IL-2 receptor and is upregulated on T cells early following stimulation of the TCR/CD3 complex, while HLA-DR appears later and is considered to be a late-stage marker of activated T cells. Figure 2 displays the estimated frequencies of CD3+CD4+ and CD3+CD8+ T cells expressing the activation markers CD25 and HLA-DR at baseline and Days 28, 100, 160, and 180. The proportion of CD3+CD4+CD25+ HLA-DR+ T cells significantly and progressively declined up to Day 180.

The longitudinal changes of activated T cells by Day 28 in responder group are displayed in Figure 3.

Levels of CD3+CD4+CD25+HLA-DR+ decreased in all groups from baseline to Day 28, then continued to decrease over time through Day 180 in all responder groups. In complete responders, the downward trend resulted in significant differences from baseline (LSM=21.22, 96=5% CI=13.56-28.89) at Day 100 (LSM=8.70, 95% CI=1.07-16.33, P=0.0150) and Day 180 (LSM=9.04, 95%CI=1.45-16.63, P=0.0485). However, the levels of CD3+CD4+CD25+HLA-DR+ were highly variable in the Day 28 nonresponder group.

Table 24: Percentage of Activated T Cells at Screening and Day 28 in the Biomarker Subgroup

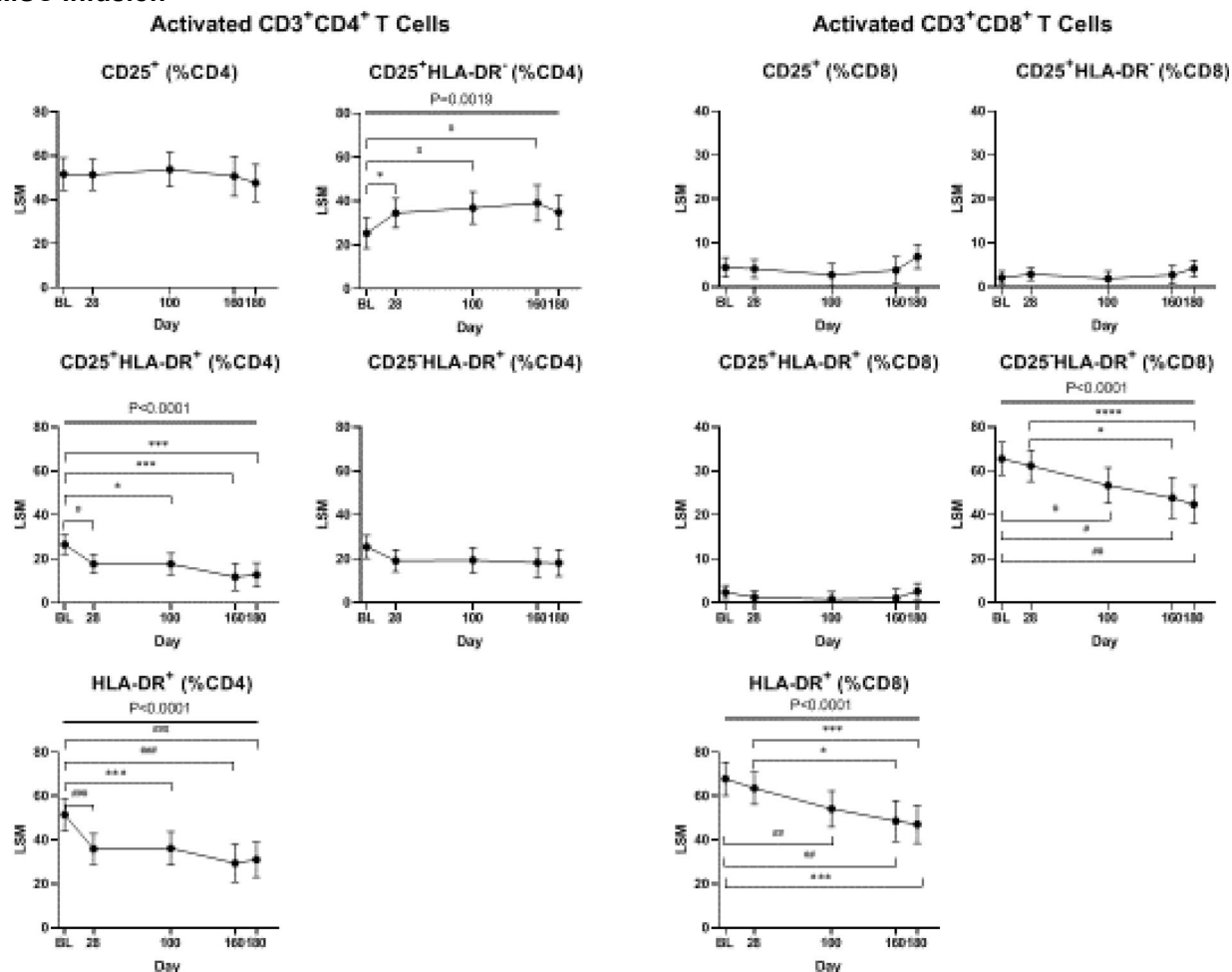| Activated T Cell Phenotype			All Subjects (Biomarker Subgroup) (N=33)	Day 28 Overall Responders (N=22)	Day 28 Non-Responders (N=11)
%(CD4+)	CD3+CD4+CD25+	Screening	53.6±16.2	49.4+16.7	54.9+15.7
		Day 28	51.9+20.5	43.1+16.7	55.3+20.2
	CD3+CD4+HLA-DR+	Screening	54.5+23.5	55.8+27.4	53.8+22.6
		Day 28	37.4+19.0‡	38.0+27.4‡	37.1+19.9*
	CD3+CD4+CD25+HLA-DR+	Screening	28.0+13.4	24.7+14.9	29.0+12.5
		Day 28	18.4+11.5†	14.5+14.9**	20.0+12.7
%(CD8+)	CD3+CD8+CD25+	Screening	4.3+5.0	5.0+4.9	4.1+5.3
		Day 28	4.2+4.0	3.6+4.9	4.5+4.2
	CD3+CD8+HLA-DR+	Screening	71.3+22.6	74.9+25.9	67.9+20.8
		Day 28	64.8+21.0	74.0+25.9	61.1+20.1
	CD3+CD8+CD25+HLA-DR+	Screening	68.9+22.0	2.9+4.5	2.2+4.1
		Day 28	63.5+20.9	1.2+4.5	1.3+1.6

Source: Applicant's Table 29 from Module 3.2.S.3.1
N shown indicates the number of patients in the biomarker sub-study for whom there are results from the activated T cell [(b) (4)] panel. Data represented as Mean ± SD. For the overall biomarker group and each responder sub-group, the mean % of each phenotype at screening and Day 28 were compared using Tukey's HSD test. *p<0.02; **p<0.01; †p<0.001; ‡p<0.0001.
Abbreviations: HSD, Honestly Significant Difference; N, population size

The percentage and absolute counts of CD4+CD25+CD127-/Lo regulatory T cells are displayed in Figure 4. Like the overall trend in the CD3+CD4+ population, the concentration of regulatory T cells tended to decrease from baseline to Day 28 then increased from Day 28 through Day 180. There were no significant differences in regulatory T cell numbers between overall response versus NR groups at baseline. At Day 28, the percentage of CD4+CD25+CD127-/lo regulatory T cells was significantly increased in overall response (15.37 ± 10.99) compared to NR (8.69 ± 6.28).
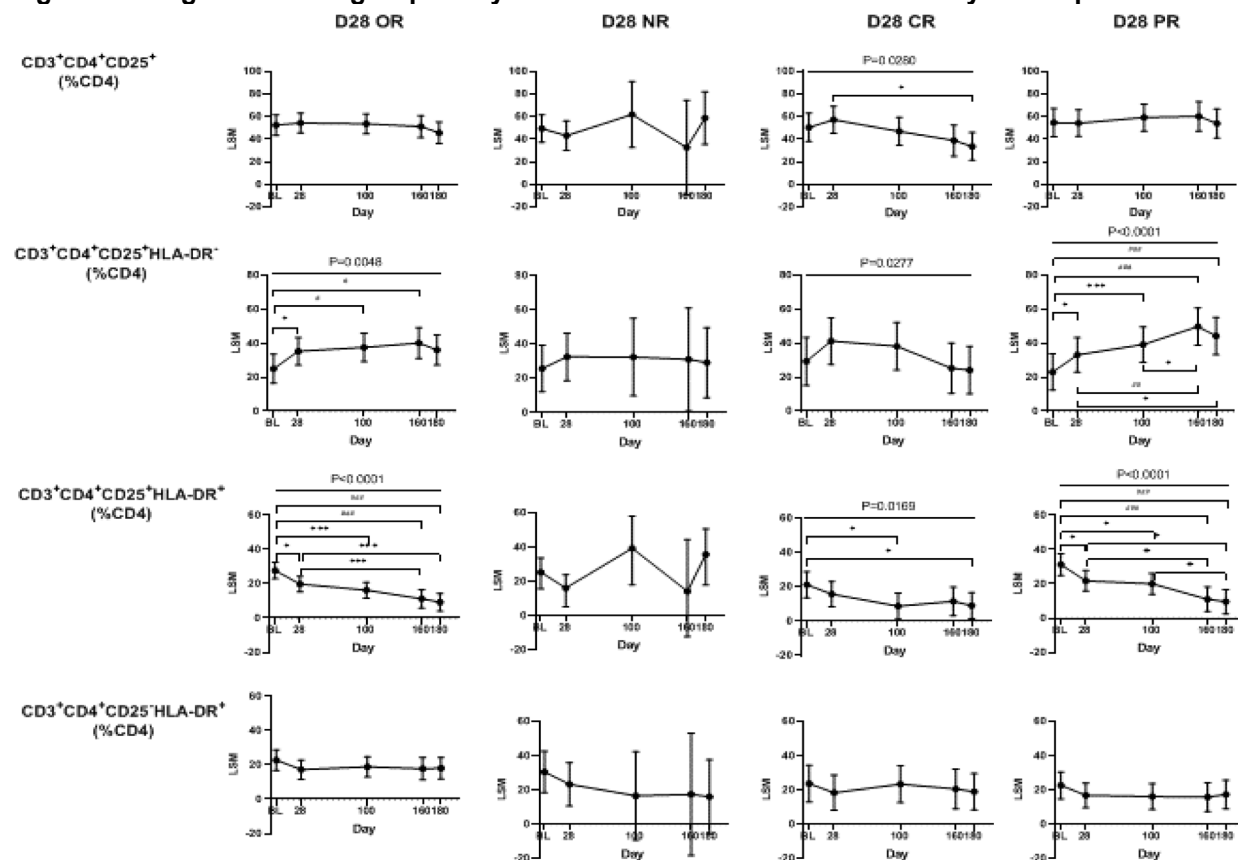
Figure 2: Activated T Cells at Baseline, Days 28, 100, 160, and 180 Following Culture-Expanded MSC Infusion

Source: Applicant's Figure 3 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
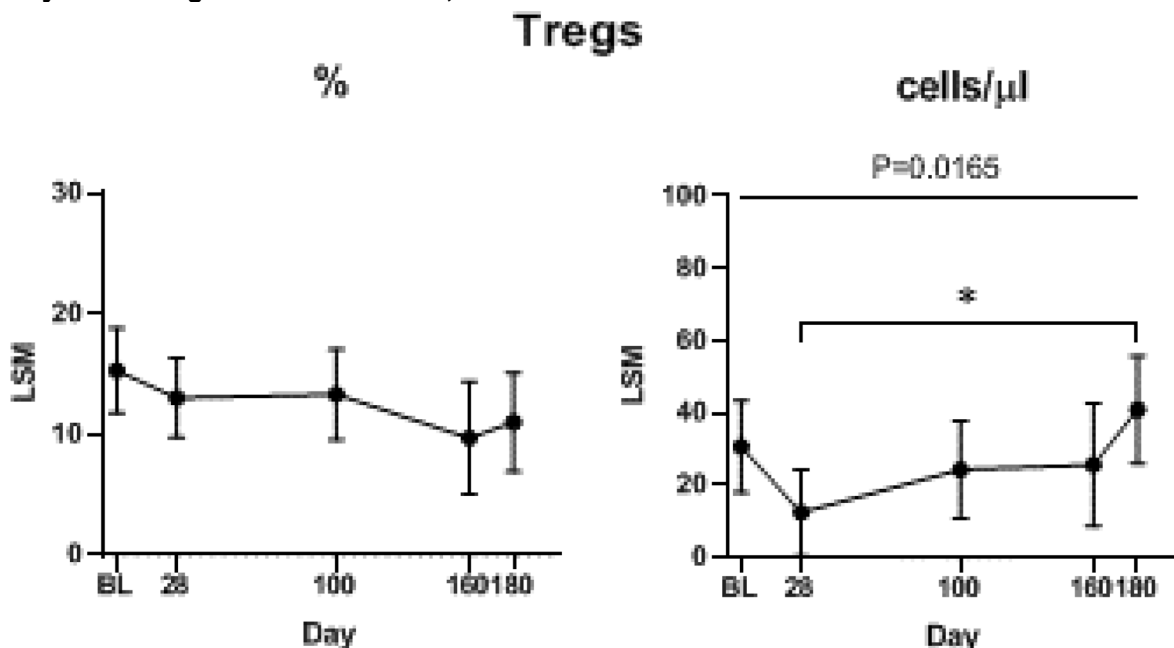Abbreviations: MSC, mesenchymal stromal cell

Figure 3: Longitudinal Subgroup Analysis of Activated T Cells Based on Day 28 Response

Source: Applicant's Figure 20 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
Abbreviations: CR, complete response; HLA-DR, human leukocyte antigen-DR; NR, no response; OR, overall response; PR, partial response

Figure 4: CD4+CD25+CD127-/Lo Regulatory T Cell Levels at Baseline and at Days 28, 100, 160, and 180 Days Following First MSC Infusion, All Patients

Source: Applicant's Figure 4 from Study MSB-GVHD001/002 Biomarkers Final Analysis Report
Abbreviations: BL, baseline; LSM, least squares mean; MSC, mesenchymal stromal cell; Tregs, regulatory T cells

***Clinical Pharmacology Reviewer Comment**: Treatment with remestemcel-L reduced TNFR1 and ST2 levels by 79% and 75 %, respectively, at Day 180 as compared to the baseline levels. Both TNFR1 and ST2 have been shown to be released by activated T lymphocytes, and their steady decrease upon treatment with remestemcel-L demonstrate PD activity resulting in a reduced inflammatory state. Further, the circulating levels of CD3+CD4+CD25+HLA-DR+ T cells, which represent fully activated T cells, were reduced by 64% at Day 180 following treatment with remestemcel-L as compared to the baseline values. Overall, the reduction in levels of secreted factors (TNFR1 and ST2) and activated T cells provide clinical pharmacology evidence of the immunomodulatory PD effects of remestemcel-L in pediatric patients with SR-aGVHD. These results are in part further justified by in vitro PD characterization. However, the sample size was too small to fully understand how the levels vary between responder and nonresponders.*

Pharmacokinetics

Since remestemcel-L is administered via an IV route, clearance and distribution are the most relevant PK parameters. The Applicant indicated a major methodological hurdle is that current methods for assessing the distribution of cell-based therapies require either modification of cells to introduce a label and/or in vivo tissue sampling that is practically limited in humans. The Applicant provided data on the distribution characteristics of culture-expanded MSC based on nonclinical animal studies. We conducted preliminary qualitative matching analysis of the Applicant-submitted nonclinical versus published exploratory clinical studies on the biodistribution of MSC following IV infusion (Table 25). The qualitative matching analysis indicates rapid clearance from the circulation and potential distribution to mechanistically relevant organ (e.g., GIT, lymph nodes). Several intrinsic and extrinsic factors are expected to influence the clearance and distribution of MSC, and it is difficult to extrapolate the nonclinical

results to humans with the existing data. Future studies are needed to address the knowledge gaps in elucidating the in vivo fate of infused MSC in humans to better characterize the mechanism of action, efficacy, and safety. The results of the available published exploratory biodistribution clinical studies indicate the feasibility of developing and optimizing methods (e.g., polymerase chain reaction or whole-body imaging) for human PK assessments.

Table 25: Qualitative Matching of Non-Human Primate Model Versus Human Studies on Biodistribution of MSC Following Intravenous Infusion

Category	Intravenous MSC Dose (×10⁶ Cells/kg)	Sampling Time After MSC Infusion	MSC Quantification Method	Tissue With Detectable Level of MSC
Applicant nonhuman primate model; TBI & HSCT	18.5	9 months	PCR	Bone marrow, GIT, Liver, Kidney, Spleen, Lymph nodes, Lung, Skin
Applicant pivotal clinical trial; aGVHD	2 and twice per week	ND	ND	ND
Human clinical ((Ringdén et al. 2006); aGVHD	1.3	9 days	PCR	GIT, Lymph nodes
Human clinical (von Bahr et al. 2012); aGVHD	1.9	7 days	PCR	Bone marrow, GIT, Liver, Kidney, Spleen, Lymph nodes, Lung
Human clinical (von Bahr et al. 2012); aGVHD	0.7 and 1.4	24 days	PCR	GIT, Lymph nodes
Human clinical (Gholamrezanezhad et al. 2011); liver cirrhosis	3.5-6	Serial imaging at 2, 4, 6, 24 hours and at 2, 7 and 10 days	Planar whole-body acquisitions	Lung (~33.5% at 2hour vs. ~2% at Day 10), Spleen (~30-40% at Day 10), Liver (~13-17% at Day 10)

Source: Reviewer Analysis
Abbreviations: GIT, gastrointestinal tract; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MSC, mesenchymal stromal cell; ND, not determined; PCR, polymerase chain reaction; TBI, total body irradiation

10. CONCLUSIONS

Study MSB-GVHD001 provided evidence of effectiveness for remestemcel-L in treatment of SR-aGVHD in pediatric patients. The Day-28 ORR in the treated population (n=54) was 70.4% (95% CI: 56.4, 82.0). The median duration of response calculated from Day-28 response to either progression (worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment), new systemic therapy for aGVHD or death from any cause was 54 days (range 7, 159+). Alternative measure of durability calculated from Day-28 response to either death or need for new systemic therapy for aGVHD was 111.5 days (range 9, 182+).

The safety profile in the intended population appears favorable and there were no safety signals of concern.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

SR-aGVHD is a serious condition with high mortality. Ruxolitinib is the only drug approved for treatment of SR-aGVHD in patients 12 years and older. No therapies are approved in children below 12 years of age.

See Table 26 for FDA's benefit-risk assessment.

Clinical Reviewer: Upendra Mahat, MD
Clinical Pharmacology Reviewer: Million Tegenge, PhD
STN: BLA 125706/0

Table 26: Risk and Benefit Assessments

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The most common life-threatening complication of allogeneic HSCT is GVHD. • Given the number of allogeneic HSCTs performed, approximately 5000 patients/year develop aGVHD in the United States; of those, approximately 300-400 are pediatric patients. • Despite prophylaxis with immunosuppressants, aGVHD may still occur; among all patients undergoing allogeneic HSCT, 30 to 50% have aGVHD (Grades 1-4) and 14% have severe aGVHD (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.	• SR-aGVHD is a serious and life-threatening condition. It is a major cause of morbidity and mortality post allogenic HSCT.
Unmet Medical Need	• 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 NCCN guidelines as "suggested" systemic agents for treatment of SR-aGVHD. Ruxolitinib is listed as Category 1; all other are stated to have only Category 2A evidence. There is not sufficient data to recommend use of one agent over others.	• There is an unmet medical need for the treatment of SR-aGVHD. No approved therapies exit in pediatric patients below 12 years of age. Current treatment includes various savage chemotherapies with limited clinical benefit and significant toxicities.
Clinical Benefit	• 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 in the Treated population was 70.4% (95% CI: 56.4, 82.0), and the median duration of response was 54 days (range: 7, 159+)	• The magnitude of ORR and durability of response to treatment demonstrate that remestemcel-L is active in this disease.
Risk	• The incidence of infections was not higher than expected for this population. • Infusion reactions were rare. • There remains some uncertainty about the risk of ectopic tissue and the impact of pre-existing and treatment-emergent anti-HLA antibodies for this treatment.	• The safety profile is acceptable for the intended population.
Risk Management	• The premedications and safety monitoring plan in Study MSB-GVHD001 were effective in mitigating serious potential toxicities.	• If remestemcel-L were approved for children, routine measures, such as

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
		the labeling, would be sufficient to mitigate risks. • Enhanced pharmacovigilance is recommended to address the potential risks of ectopic tissue formation and anti-donor/anti-HLA antibodies.

Abbreviations: ADA, antidrug antibodies; aGVHD, acute graft-versus-host disease; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; SR-aGVHD, steroid-refractory acute graft-versus-host disease

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 outweighs the risks for treatment of SR-aGVHD 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 traditional approval.

SR-aGVHD is a serious and life-threatening disease. There are 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, a single-arm multicenter prospective trial provided the primary evidence in support of this BLA. Study MSB-GVHD001 study met its primary objective; the Day-28 ORR was 70.4% (95% CI: 56.4, 82.0) in the treated population. The primary endpoint results in Study MSB-GVHD001 were statistically significant, the measured response was durable (median 54 days), and the results were consistent across subpopulations and secondary efficacy endpoints. These results denote clinical benefit in pediatric patients with SR-aGVHD.

Having satisfactorily addressed the CMC deficiencies, and upon consideration of the data submitted in the BLA and FDA's previous assessments of these data (including prior assessments about the adequacy of the design of Study MSB-GVHD001), the clinical review team concludes that Study MSB-GVHD001 represents an adequate and well-controlled trial. There is extensive FDA precedent for basing approvals on single-arm trials that evaluate response rate including the approval of ruxolitinib, the only other drug approved for SR-aGVHD for patients who are 12 years of age and older, which was based on a single-arm trial evaluating ORR at Day 28. The study protocol for Study MSB-GVHD001 specified study objectives, enrollment criteria, outcome measures, and an analysis plan to evaluate outcomes, which help inform FDA's determination that the characteristics of an adequate and well-controlled study are present in Study MSB-GVHD001. The study population enrolled in Study MSB-GVHD001 had no available therapies and was refractory to steroids. In this clinical setting, withdrawal of steroids would not be appropriate in the absence of alternative effective therapeutic options. In this clinical setting, use of salvage therapies or referral to clinical trials is the SOC. However, given the high ORR and favorable safety profile observed with remestemcel-L in Study MSB-GVHD001, a trial that would randomize pediatric patients to a control arm comprising unapproved salvage therapy would be unnecessary; additionally, such a trial would likely be infeasible to conduct due to a high risk of patient dropout from the control arm. As such, a single-arm trial is acceptable and sufficient to demonstrate the effectiveness of remestemcel-L.

Although cross-trial comparisons should be interpreted with caution, the effects of remestemcel-L observed in Study MSB-GVHD001 were compared to a historical ORR benchmark of 45% at Day 28. While some of the reviews in the administrative record question the selection of 45% as the cutoff for the lower bound of the 95% CI, we note the effectiveness of ruxolitinib characterized by an ORR of 57.1% (95% CI:42.2, 71.2), albeit in older patients. Additionally, notwithstanding the targeted effect (65%) and lower bound of 95% CI (45%) in Study MSB-GVHD001, a magnitude of ORR of 70.4% (95% CI: 56.4, 82.0) is a clinically meaningful benefit in patients with SR-aGVHD. We note that an Oncologic Drugs Advisory Committee meeting to

discuss this BLA was held on August 13, 2020. The Committee voted 9 to 1 that the available data support the efficacy of remestemcel-L in pediatric patients with SR-aGVHD.

In this request for approval, FDA assessed additional data in the BLA to substantiate the results of Study MSB-GVHD001, as the sole adequate and well-controlled clinical investigation submitted to support the Applicant's claims of effectiveness for the proposed indication; as described in FDA draft guidance: Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence [(December 2019) https://www.fda.gov/media/172166/download], data drawn from one or more sources (e.g., clinical data, mechanistic data, animal data, etc.) may serve as the confirmatory evidence for this purpose. While there is regulatory precedence in oncology for a single, multicenter, adequate and well-controlled investigation to be sufficient to demonstrate the effectiveness of a product, mechanistic/pharmacodynamic data as described below further substantiates the evidence of effectiveness provided by Study MSB-GVHD001:

1. Mechanistic/Pharmacodynamic data: Following allogenic HSCT, acute GVHD occurs when donor T cells react to differences in the HLAs on the recipient's tissue (Ernst Holler et al. 2024). Activation and proliferation of alloreactive T cells plays a central role in the pathogenesis of aGVHD (Malard et al. 2023). The BLA contains in vivo pharmacodynamic (PD) studies from patients treated in Study MSB-GVHD001 and Study MSB-GVHD002, which demonstrate the immunomodulatory effects of remestemcel-L. These studies demonstrate the immunomodulatory effects of remestemcel-L relevant to the pathophysiology of aGVHD. Specifically, treatment with remestemcel-L resulted in a 64% reduction in circulating CD3+CD4+CD25+HLA-DR+ T cells, compared to baseline, which represents activated T cells. Additionally, two biomarkers—TNFR1 and ST2—have been shown to be released by activated T lymphocytes. Following treatment with remestemcel-L, a decrease in these biomarkers observed at Day 180 (TNFR1 by 79% and ST2 by 75% compared to baseline)—demonstrates the PD activity that leads to a reduced inflammatory state.

The safety profile of remestemcel-L is manageable with no safety signal of concern. This is in stark contrast to SOC therapies, which are highly immunosuppressive and lead to increased infection-related mortality in this already vulnerable population.

11.4 Recommendations on Regulatory Actions

The clinical data submitted support traditional approval of remestemcel-L for the treatment of SR-aGVHD in pediatric patients 2 months of age and older, at the requested recommended dosage. The clinical and clinical pharmacology review team recommends traditional approval.

The BLA contains substantial evidence of effectiveness from one adequate and well controlled investigation evaluating the ORR at Day 28 of remestemcel-L in pediatric patients 2 months or age or older, with SR-aGVHD. Acceptance of ORR at Day 28 as an endpoint denoting clinical benefit in acute GVHD was discussed during an open public workshop on "Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation," held May 19, 2009 (Food and Drug Administration and National Institutes of Health 2009; December 2018); FDA recommendations on the use of this endpoint are also described in the FDA draft guidance, "Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment" (September 2023). The mechanistic/ pharmacodynamic data included in the BLA, serve as confirmatory evidence in the context of a one adequate and well controlled investigation.

11.5 Labeling Review and Recommendations

During Initial BLA Review in 2020

Labeling revisions were suspended on 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 to 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 package insert

During Review of BLA Resubmission in 2024

Several revisions were made to the Applicant's proposed United States Prescribing Information. Please see Table 27 below for a summary of significant changes to the United States Prescribing Information.

Table 27: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	For the treatment of steroid refractory acute graft versus host disease (SR-aGVHD) in pediatric patients.	Revised to include the pediatric age range: For the treatment of steroid refractory acute graft versus host disease (SR-aGVHD) in pediatric patients 2 months of age and older.
Section 2: Dosage and Administration	-	Section 2.1: A table with recommended treatment based on Day 28 response was added. Section 2.2: Revised to include subheadings of receipt and storage, preparation, and administration. Information was reorganized using bullets to improve readability.
Section 5: Warnings and Precautions	Pulmonary Complications	Subsection on pulmonary complications was removed as there is currently insufficient data to support the risk with RYONCIL administration.
	Transmission of Infectious Agents: Donor testing was not specified.	Transmission of Infectious Agents: Information about donor testing was added.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	Tumor Development/Malignancy included	Subsection on Tumor Development/Malignancy was removed since there was no data to support the risk.
Section 6 Adverse Reactions (Safety)	-	The information in this section was revised based on the current labeling practice for concise presentation of data and to remove redundant information.
Section 7: Drug Interactions	Included with no known drug interactions with RYONCIL	Section was omitted as it was not informative.
Section 8: Use in Specific Populations	No background risk of major birth defects and miscarriage specified in the risk summary.	Revised to include information about the background risk of major birth defects and miscarriage in the U.S. general population.
Section 12: Clinical Pharmacology	MOA of RYONCIL with possible immunomodulatory activity was specified.	Revised to state that the MOA of RYONCIL is not clear but may be related to immunomodulatory effects.
	PK/PD: Included non-clinical data	PK/PD: Non-clinical data was omitted as it was not generated from the current or comparable version of the product.
Section 14: Clinical Studies	Included pooled data from Study MSB-GVHD001, Study MSB-GVHD002, and Protocol 275.	Revised to include the efficacy data from only Study MSB-GVHD001 which used the current version of the product.
Section 17: Patient Counseling Information	-	This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).

Source: Created by FDA Associate Director of Labeling
Abbreviations: MOA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics; SR-aGVHD, steroid-refractory acute graft-versus-host disease; U.S., United States

11.6 Recommendations on Postmarketing Actions

The following postmarketing requirement is recommended as enhanced pharmacovigilance plan:

Enhanced pharmacovigilance for ectopic tissue formation and anti-donor antibodies for 3 years following approval. This pharmacovigilance should include:

- Submission of expedited (15-day) reports for all ectopic tissue formation and anti-donor antibody events regardless of seriousness or label status for the events

- In periodic safety reports, submission of aggregate safety assessment (based on interval and cumulative data) for ectopic tissue formation and ADA events

The Applicant has agreed with the above recommendations.

12. CLINICAL AND CLINICAL PHARMACOLOGY REVIEW TEAM

Upendra Mahat, MD
Primary Clinical Reviewer

Donna Przepiorka, MD, PhD
OCE MORE Team Lead

Million Tegenge, PhD
Primary Clinical Pharmacology Reviewer

13. BRANCH CHIEF, MALIGNANT HEMATOLOGY BRANCH

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'Lola Fashoyin-Aje, MD, MPH

14. DIVISION DIRECTOR (DCEH)

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'Lola Fashoyin-Aje, MD, MPH

15. ONCOLOGY CENTER OF EXCELLENCE (OCE) SIGNATORY

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application.

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Marc R. Theoret, MD

Clinical Reviewer: Upendra Mahat, MD
Clinical Pharmacology Reviewer: Million Tegenge, PhD
STN: BLA 125706/0

16. DIRECTOR, OFFICE OF CLINICAL EVALUATION (OCE)

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'Lola Fashoyin-Aje, MD, MPH