

BLA Resubmission Clinical Review Memorandum

BLA Application Type	BLA125706/0
CBER Received Date	January 31, 2023
PDUFA Goal Date	August 2, 2023
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Applicant	Mesoblast, Inc.
Established Name	Remestemcel-L-rknd, Ex Vivo Cultured Adult Human Mesenchymal Stem Cells (MSCs)
Trade Name	REMESTEMCEL-L-rknd
Pharmacologic Class	Undetermined
Formulation(s), including Adjuvants, etc.	REMESTEMCEL-L is provided as a frozen cell suspension in cryogenic vials. The active ingredient in REMESTEMCEL-L is comprised of culture-expanded mesenchymal stromal cells (ce-MSK) isolated from the bone marrow of healthy adult human donors. Each cryovial contains nominally 25×10^6 ce-MSKs 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 is available as a cell suspension for intravenous infusion in a concentration of 6.68×10^6 ce-MSCs per mL in 3.8 mL contained in a 6 mL cryovial.
Dosing Regimen	The recommended dose of REMESTEMCEL-L is 2×10^6 ce-MSC/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 (CR), treatment may be repeated.
Indication(s) and Intended Population(s)	Treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

aGVHD	acute graft-versus-host disease
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	chemistry, manufacturing, and controls
CR	complete response
CSR	clinical study report
DCEH	division of clinical evaluation hematology
DOR	duration of response
FAS	full analysis set
FDA	Food and Drug Administration
FDRR	formal dispute resolution request
GI	gastrointestinal
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
MAGIC	Mount Sinai Acute GVHD International Consortium
MAP	MAGIC algorithm probability
MOA	mechanism of action
OCE	Oncology Center of Excellence
ODAC	Oncologic Drugs Advisory Committee
ORR	overall response rate
OS	overall survival
PR	partial response
RCT	randomized controlled trials
RWE	Real World Evidence
SAP	statistical analysis plan
SR-aGVHD	steroid-refractory acute graft-versus-host
TEAE	treatment-emergent adverse event

1. EXECUTIVE SUMMARY

1.1. Recommended Regulatory Action

The clinical review team recommends issuance of a Complete Response Letter to the Biologics License Applicant of remestemcel-L for treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients, submitted under section 351(a) of the Public Health Service Act, on the basis of lack of outstanding chemistry, manufacturing, and controls (CMC) information that would be required to conclude that the clinical data obtained from Study MSB-GVHD001 were generated with a product that was standardized in accordance with 21 CFR 314.126(d).

This executive summary highlights the key findings from the initial review (BLA [biologics license application] 125706.0 clinical review memorandum dated August 31, 2020). Further, the executive summary describes a review of additional data/clinical information submitted by the Applicant with this resubmission, and the basis for Food and Drug Administration's (FDA's) regulatory decision.

1.2. Basis for the Recommendation

The Applicant is seeking approval of remestemcel-L for the indication of "Treatment of SR-aGVHD in pediatric patients." There are no drugs approved for treatment of SR-aGVHD in patients less than 12 years. BLA125706 was first submitted on January 31, 2020. The Applicant submitted the results of Study MSB-GVHD001 as the primary evidence of efficacy to support the marketing application for the proposed indication. The Applicant also provided safety and/or efficacy information from 14 prospective trials of remestemcel-L for treatment of acute graft-versus-host disease (aGVHD), acute myocardial infarction, chronic obstructive pulmonary disease, diabetes mellitus, or Crohn's disease conducted over more than 20 years.

Study MSB-GVHD001 was a multicenter, single-arm study of remestemcel-L for treatment of pediatric patients with SR-aGVHD grades B-D (excluding grade B, skin alone). The primary endpoint was the Day-28 overall response rate (ORR) defined as the proportion of subjects in the full analysis set (FAS) with complete response (CR) and partial response (PR). The study was designed to determine if the Day-28 ORR exceeded a null rate of 45%. The FAS used for primary analysis of Day-28 ORR consisted of 55 pediatric subjects enrolled on Study MSB-GVHD001 between 2015 and 2017 in the United States. The Day-28 ORR was 69.1% (95% confidence interval [CI] of 55.2-80.9), and the median duration of response was 54 days. The results were consistent across subpopulations and secondary efficacy endpoints. However, the main limitation of the statistical analysis plan was the method with which the null rate was determined. Specifically, the null rate was derived from the Applicant's own data from the

previous studies of remestemcel-L, rather than from the historical literature of the disease response. For further details, refer to BLA125706/0 clinical review memo dated August 31, 2020.

Additionally, the Applicant provided the results of two randomized, double-blind, placebo-controlled trials of remestemcel-L for treatment of aGVHD in pediatric and adult patients. Study 280 was a comparison of standard salvage regimens with or without remestemcel-L for treatment of SR-aGVHD (this study was conducted primarily in adult patients with SR-aGVHD, but also included a small pediatric cohort with 14 patients in remestemcel-L arm and 13 patients in placebo arm); and Study 265 was a comparison of standard steroids with or without remestemcel-L for treatment of newly diagnosed aGVHD in adults. Both studies failed to meet their primary objective to demonstrate an improvement in the rate of CR>28 days duration, and no treatment effect was detected even when these studies were reanalyzed using a Day-28 ORR endpoint. The Applicant also submitted results for Study 275, an expanded-access study of remestemcel-L plus physician's choice of therapy for treatment of pediatric patients with SR-aGVHD, which enrolled and treated 241 pediatric subjects, showing a Day-28 ORR of 65%. Of note, Study 275 was not an adequate or well-controlled study and was not designed or powered to test any statistical hypothesis.

FDA reviewed the safety data for 1,780 subjects in clinical trials and expanded-access protocols. In general, no safety signals of concern were identified. However, there remained some uncertainty regarding the risk of antidrug/anti-human leukocyte antigen (HLA) antibodies and the risk of ectopic tissue formation in patients treated with remestemcel-L. Refer to BLA125706/0 clinical review memo dated August 31, 2020, for details about these issues.

A major issue during the initial review of the BLA was how to consider the positive outcome of one single-arm study in the setting of the historical data to serve as an external control in the choice of a null hypothesis, the limitations with minimizing bias, impact of confounding factors and history of failed randomized controlled trials (RCTs) of remestemcel-L in aGVHD trials. All these issues raised concerns and uncertainties associated with interpreting the observed efficacy outcomes between studies. An Oncologic Drugs Advisory Committee (ODAC) meeting to discuss manufacturing as well as clinical issues, was held on August 13, 2020. The committee voted nine to one that the available data supports the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD.

Although the primary clinical review team considered study MSB-GVHD001 as adequate and well controlled, the Clinical Hematology Branch as well as the statistical reviewer considered the study not adequate and well controlled and hence did not recommend approval. The Oncology Center of Excellence (OCE) concluded that MSB-GVHD001 was an adequate and well controlled trial and the recommendation on the clinical portion of the application was an approval.

Ultimately, the Office of Tissues and Advanced Therapies (OTAT) director concluded that the study was not adequate and well controlled to meet the statutory requirement for a marketing approval, and a Complete Response Letter was issued on September 30, 2020. To meet this requirement, in addition to addressing outstanding CMC deficiencies, the FDA recommended that the Applicant conduct at least one randomized, well-controlled study in adults and/or pediatric subjects to provide evidence of the effectiveness of remestemcel-L in the treatment of SR-aGVHD.

The Applicant filed a formal dispute resolution request (FDRR) concerning the Complete Response Letter on March 31, 2021. In the FDRR, the Applicant noted that the appeal was submitted “on the narrow issue of whether the clinical data contained in the BLA provide substantial evidence of the effectiveness of remestemcel-L for the treatment of SR-aGVHD in pediatric patients.” Additionally, the Applicant noted in their FDRR that they did not dispute the two CMC deficiencies in the Complete Response Letter. The FDA responded to the Applicant’s FDRR on May 28, 2021, and noted that “*it was premature to adjudicate the Applicant’s request in the absence of certain outstanding CMC information needed to address the deficiencies regarding the current potency assay matrix. Such outstanding information includes information that would be needed to conclude that the clinical data obtained from Study MSB-GVHD001 were generated with a product that was standardized in accordance with 21 CFR 314.126(d).*”

During the November 2021 CMC Type C Teleconference meeting between the FDA and the Applicant, the FDA’s CMC and clinical teams advised the Applicant that an additional clinical study will be necessary to establish the validity of a potency assay for remestemcel-L. Although no clinical questions were specifically asked by the Applicant during the Type C CMC meeting, the clinical team reiterated their recommendation to conduct at least one randomized controlled study in adults and/or pediatric subjects to provide evidence of effectiveness of remestemcel-L in treatment of SR-aGVHD.

With the BLA resubmission on January 31, 2023, the Applicant responded to clinical deficiencies in the Complete Response Letter by submitting new clinical information that included a clinical study report (CSR) from a retrospective propensity control study from the Mount Sinai Acute GVHD International Consortium (MAGIC) database (Module 5.3.4.2), and a CSR from a long-term survival registry study of patients treated with remestemcel-L conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) (Module 5.3.4.2).

These retrospective studies were not adequate or well controlled. During the review of the initial BLA submission in 2020, the MAGIC external control study was reviewed by the FDA and was considered inconclusive. On the Applicant’s

behalf, the CIBMTR submitted survival data on 51 subjects from Study MSB-GVHD001, which shows a 4-year overall survival (OS) estimate of 48%. Although this reviewer acknowledges that the OS appears higher compared to survival in patients with SR-aGVHD reported in limited historical literature, such time-to-event survival data observed in a single-arm study derived from an ad hoc analysis of a patient population (post-hematopoietic stem cell transplantation [HSCT]) with several competing causes for death, cannot support an efficacy claim for a regulatory consideration. Furthermore, additional epidemiology review by the Oncology Center of Excellence Real World Evidence (OCE RWE) team also agreed with the clinical reviewers that the results of these studies cannot serve as an adequate and well-controlled study to support approval of remestemcel-L and do not provide sufficiently evaluable clinical information beyond the initial BLA 125706 submission. Because the studies are not adequate and well controlled, they cannot be used to establish substantial evidence of effectiveness. See Appendix 2 (OCE RWE Review) for the basis of this recommendation including outstanding concerns including, and not limited to, potential for confounding, outcome measurement, matching, and misclassification.

This reviewer acknowledges that SR-aGVHD is a highly morbid and serious condition, and there is no approved therapy in children younger than 12 years. This reviewer further acknowledges the high Day-28 ORR seen in Study MSB-GVHD001. However, there are significant concerns with the efficacy data. Notably, the evidence of effectiveness is based on ORR seen in one single-arm study of a new therapy with unclear mechanism of action (MOA) which has a history of failed RCTs for the same disease. It should be noted that the subjects enrolled in study MSB-GVHD001 were permitted to continue immunosuppression that was initiated as prophylaxis against graft versus host disease (GVHD). Subjects were also allowed to continue steroids used as front-line therapy of aGVHD. These concurrent immunosuppressive therapies may have confounded the treatment effect of the investigational agent:-

During the review of this resubmission, the FDA CMC team identified significant deficiencies related to the new potency assay proposed by the Applicant and recommended a CR. Considering the life-threatening nature of the disease and the lack of available therapies, the clinical review team acknowledges the magnitude of unmet need for treatment of the proposed indication. However, the CMC deficiencies related to product potency/attributes and the lack of adequate efficacy data raise serious questions regarding the efficacy of remestemcel-L for the treatment of the proposed indication.

In summary, as noted in 21 CFR 314.126 (d), *“for an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.”* Therefore, the lack of a valid

potency assay for the product used during Study MSB-GVHD001 precludes use of data from that trial to substantiate a claim of effectiveness. Additionally, no new data were submitted from an adequate and well-controlled trial. Therefore, the clinical team concludes that the BLA does not meet the statutory requirement for the substantial evidence of effectiveness to support an approval. To meet this requirement, the Applicant will need to provide data from at least one adequate and well-controlled study in adults and/or pediatric subjects using an adequately characterized product identical or comparable to the to-be-marketed form.

1.3. Letter Ready Comments

Clinical Deficiency Comment

- You have not provided substantial evidence of effectiveness from an adequate and well-controlled trial of remestemcel-L for treatment of SR-aGVHD in pediatric patients.
 - As noted in 21 CFR 314.126 (d), “for an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.” With the lack of a valid potency assay for the product used during the MSB-GVHD001 study, the study cannot be considered an adequate study for the purpose of demonstration of substantial evidence of effectiveness required for a marketing approval.
 - You submitted a retrospective ad hoc analysis of Study MSB-GVHD001 results compared to an external control from the MAGIC and a long-term CIBMTR survival analysis of subjects treated in Study MSB-GVHD001. Note that these retrospective analyses are not considered adequate and well-controlled trials, and as such, the results do not provide substantial evidence of effectiveness.

To address this deficiency, in addition to addressing the CMC deficiencies, please submit the results of an adequate and well-controlled randomized controlled trial of remestemcel-L for treatment of aGVHD in adults and/or pediatric subjects using an adequately characterized product identical or comparable to the to-be-marketed form.

Additional Clinical Comments

- We recommend that you request a meeting with the FDA to discuss the trial design and statistical analysis plan (SAP) before conducting such study with registrational intent.

2. CLINICAL AND REGULATORY BACKGROUND

2.1. Disease or Health-Related Condition(s) Studied

aGVHD is a life-threatening complication in patients who undergo allogeneic HSCT for various malignant and non-malignant diseases. When the immunocompetent cells in the graft recognize recipient cells as foreign and mount an immune attack against host cells, aGVHD occurs. The risk of developing GVHD is dependent on many factors, including the stem cell source, the age of the patient, conditioning, and GVHD prophylaxis used. Clinically, aGVHD presents with involvement of different organ systems, mainly skin (maculopapular rash), gastrointestinal tract (nausea, vomiting, diarrhea), and liver (hyperbilirubinemia with jaundice). The diagnosis of aGVHD relies on the assessment of target organs by means of clinical and laboratory analyses with or without biopsy. The severity is graded clinically by tabulating the extent of the involvement of the three main target organs: the skin, the gastrointestinal tract, and the liver.

Upfront treatment of aGVHD involves continuation of drugs used for GVHD prophylaxis (often a combination of a calcineurin inhibitor and methotrexate or mycophenolate) and addition of corticosteroids. About 60% of patients respond to corticosteroids. Patients who progress or are not improved after steroid therapy have poor outcomes and they often get salvage (second-line) immunosuppressive therapy. Historically, outcomes of SR-aGVHD are poor, with an OS rate of only 5 to 30% (Zeiser and Blazar 2017).

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 therapy for the treatment of SR-aGVHD, and the intended population is limited to adults and pediatric patients 12 years and older. Ruxolitinib was approved (traditional approval) based on an open-label, single-arm, multicenter study consisting of 49 patients with SR-aGVHD. The efficacy was based on day-28 ORR (CR, very good partial response, or PR as per CIBMTR criteria) and the duration of response. The Day-28 ORR was 57.1%, 95% CI 42.2, 71.2, and the median duration of response was 16 days, 95% CI 9, 83 (Przepiorka et al. 2020).

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

2.3. Safety and Efficacy of Pharmacologically Related Products

Remestemcel-L is the first product of this class. There are no approved mesenchymal stromal cell products.

2.4. Previous Human Experience With the Product (Including Foreign Experience)

Not applicable.

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

outlines key milestones pertinent to this BLA resubmission. Please see BLA125706/0 clinical review memorandum dated August 31, 2020, for details prior to initial BLA submission.

Table 1. Summary of Key Regulatory Events

Dates	Events
January 31, 2020	Initial BLA submission
August 13, 2020	ODAC meeting
September 30, 2020	A CRL was issued
March 31, 2021	FDRR submitted by the Applicant
April 28, 2021	Meeting between FDA and the Applicant to discuss FDRR
May 28, 2021	FDA Responded to Applicant's FDRR
November 2021	CMC Type C meeting
January 31, 2023	Applicant submitted response to CRL

Abbreviations: BLA, biologics license application; CMC chemistry, manufacturing, and controls; CRL, Complete Response Letter; FDA, Food and Drug Administration; FDRR, formal dispute resolution request; ODAC, Oncologic Drugs Advisory Committee

2.6. Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1. Submission Quality and Completeness

In the initial resubmission, the Applicant provided two CSRs: one for a MAGIC propensity-matched control study and one for a CIBMTR long-term survival study. Of note, both studies were retrospective ad hoc analyses, and they were not discussed with and agreed upon by the Applicant and the FDA before they were conducted. The FDA previously reviewed the results of the MAGIC external control study and concluded that the results were inconclusive. With this resubmission, the clinical study protocol/SAP and subject-level data for these studies were not provided. Subsequently, the CIBMTR submitted deidentified subject-level data from the long-term survival study on behalf of the Applicant in the form of a master file.

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, NC), 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). The inspection reviews of all four sites have been completed and revealed: *No Action Indicated*.

3.3. Financial Disclosures

Refer to BLA125706/0 clinical review memo dated August 31, 2020.

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

4.1. Chemistry, Manufacturing, and Controls

Please refer to the CMC review memo for details.

4.2. Assay Validation

Please refer to the CMC review memo for details regarding deficiency related to the potency assay.

4.3. Nonclinical Pharmacology/Toxicology

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

4.4. Clinical Pharmacology

No new clinical pharmacology data were submitted with this resubmission.

4.5. Statistical

The primary data for study MSB-GVHD-001 were reviewed by the statistical review team. The CIBMTR long-term survival data, submitted with this resubmission, were analyzed by the statistical reviewer, and the Kaplan-Meier estimates for survival were verified.

4.6. Pharmacovigilance

- There are two uncertainties based on the safety data provided with this BLA.
- There remains some uncertainty about the risk of ectopic tissue formation. The clinical significance of anti-drug/donor antibodies or anti-HLA antibodies following treatment with remestemcel-L is not fully understood. A substantial proportion of patients undergoing HSCT have anti-HLA antibodies (Koclega et al. 2012), and when directed against the donor, they are associated with graft rejection (Morin-Zorman et al. 2016); anti-HLA antibodies are also a risk

factor for refractoriness to platelet transfusions in this population (Solves et al. 2018). Additional information is needed to determine whether pre-existing anti-HLA antibodies impact the efficacy of remestemcel-L, and whether patients in this population develop anti-drug/donor antibodies that might result in refractoriness to platelet transfusions.

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

5.1. Review Strategy

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 BLA125706/0 clinical review memorandum dated August 31, 2020.

With the resubmission, the Applicant has provided additional CMC information related to potency assay along with the following additional supportive clinical information:

- 1) MAGIC registry study
- 2) CIBMTR long-term survival study
- 3) Final analysis report of Study MSB-GVHD001/GVHD002 Exploratory Biomarkers Study

The clinical review of the resubmission focused on review of this additional supportive clinical information.

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

[Table 2](#) shows the new clinical information that was reviewed during this BLA resubmission.

Table 2. BLA Documents Reviewed

Study Number	Description	Study Documents	Location
1	Applicant's response to CRL	CRL-response-28Jan23.pdf	125706/0.65 (Module 1.11.14)
2	MAGIC Propensity Control Study	magic-map-clinical-study-report.pdf	125706/0.65 (Module 5.3.4.2)
3	CIBMTR Long Term Survival Study	cibmtr-clinical-study-report.pdf deidentified subject level data submitted by CIBMTR	125706/0.65 (Module 5.3.4.2) MF5-(b) (4)
4	Final Analysis Report of Exploratory Biomarker Study	Exploratory-biomarkers-final-analysis-report.pdf	125706/0.65 (Module 5.3.4.2)

Abbreviations: BLA, biologics license application; CIBMTR, Center for International Blood and Marrow Transplant Research; CRL, Complete Response Letter; MAGIC, Mount Sinai Acute GVHD International Consortium

5.3. Table of Studies/Clinical Trials

Nineteen clinical studies, including studies in subjects with GVHD and other diseases, were conducted: 14 prospective treatment trials and five follow-up safety trials, in addition to several individual subject-expanded access protocols under IND #007939 and multiple emergency compassionate use investigator-initiated trials. A total of 1,780 subjects have participated in studies worldwide involving the use of remestemcel-L. Across all studies, a total of 1,270 subjects have been exposed to remestemcel-L, and 510 have received placebo. In aGVHD studies, 678 (352 pediatric and 326 adult) subjects have received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. Study MSB-GVHD001/002 is the main efficacy study in support of this BLA application. See BLA clinical review memorandum dated August 31, 2020.

[Table 3](#) shows additional clinical information that was reviewed during this BLA resubmission:

Table 3. Studies Reviewed During Evaluation of BLA Resubmission

Study	Design	Subject-Level Data Submitted	Reviewed During Initial BLA Submission	Reviewed During This Resubmission
MAGIC propensity control study (Module 5.3.4)	External control study from MAGIC registry data	No	Yes, and inconclusive	Yes, and data inconclusive and control not appropriate or fit for purpose
CIBMTR LongTerm Survival Study (Module 5.3.4)	Long-term survival data provided by CIBMTR	Yes, under MF5-(b) (4)	No	Yes; inconclusive
Exploratory biomarkers: final analysis report (Module 5.3.4)	Exploratory data from MSB-GVHD001 study	No	Yes (initial analysis); only exploratory with multiple limitations	Yes; inconclusive; only exploratory

Abbreviations: BLA, biologics license application; CIBMTR, Center for International Blood and Marrow Transplant Research; MAGIC, Mount Sinai Acute GVHD International Consortium

5.4. Consultations

5.4.1. Advisory Committee Meeting (if applicable)

An ODAC meeting was held on August 13, 2020, during the review of the initial BLA. This Complete Response Letter response was not reviewed by an Advisory Committee.

5.4.2. External Consults/Collaborations

None.

5.5. Literature Reviewed

Cahn, JY, JP Klein, SJ Lee, N Milpied, D Blaise, JH Antin, V Leblond, N Ifrah, JP Jouet, F Loberiza, O Ringden, AJ Barrett, MM Horowitz, G Socie, C Societe Francaise de Greffe de Moelle et Therapie, I Dana Farber Cancer, and R International Bone Marrow Transplant, 2005, Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study, *Blood*, 106(4):1495-1500.

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Zeiser, R and BR Blazar, 2017, Acute Graft-versus-Host Disease - Biologic Process, Prevention, and Therapy, *N Engl J Med*, 377(22):2167-2179.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Study MSB-GVHD001 is the main efficacy study in support of remestemcel-L in treatment of proposed indication. (See BLA 125706/0 clinical review memorandum dated August 31, 2020.)

The following additional clinical information/analyses were reviewed with the BLA resubmission.

6.1. MAGIC Propensity Matched Controlled Study

6.1.1. Objectives

The primary objective of the MAGIC control study was to compare the Day 28 overall response and OS up to 6 months in pediatric subjects with SR-aGVHD treated with remestemcel-L compared to a matched cohort from the MAGIC database who received best available second-line therapy (other than remestemcel-L) stratifying risk for outcomes using the CIBMTR grading scale, the Minnesota GVHD risk score, and the MAGIC algorithm probability (MAP) score.

6.1.2. Design Overview

MAGIC is an international GVHD consortium, currently located at the Icahn School of Medicine at Mt Sinai in New York. The consortium was initially established in 2001 at the University of Michigan. Currently, there are 21 active MAGIC centers, primarily in the United States and Germany.

The Applicant has submitted an ad hoc retrospective study comparing Day-28 ORR and OS up to 6 months between the subjects in the MSB-GVHD001 study and a propensity-matched control group of 30 subjects from the MAGIC database. Of note, prior to the conduct of this study, there was no discussion or agreement on the study protocol or SAP between the Applicant and the FDA. Further, these data were previously reviewed by the FDA, and were found to be inconclusive. A summary of the methodology used, and the main results, are presented below.

6.1.3. Population

A control group of 30 subjects 0 to 17 years was selected from the database using entry criteria from the MSB-GVHD001 Protocol. Subjects selected had:

- 1) Received an HSCT between 2005 and 2019 at one of 21 participating transplant centers
- 2) Developed aGVHD that required treatment with systemic steroids alone
- 3) Failed to respond to steroid treatment alone (using the steroid failure definition from the GVHD001 Protocol)
- 4) Received second-line treatment for SR-aGVHD (alemtuzumab, basiliximab, etanercept, infliximab, mycophenolate, ruxolitinib, tocilizumab, antithymocyte globulin, and extracorporeal photopheresis [ECP])

6.1.4. Study Treatments or Agents Mandated by the Protocol

Not applicable.

6.1.5. Directions for Use

Not applicable.

6.1.6. Sites and Centers

As of October 2019, there were 21 active MAGIC centers located primarily in the United States and Germany but there are also centers in Thailand, Italy, and Canada. Two centers (University of Michigan and Technical University, Dresden, Germany) were moved to an inactive status in 2016 but both inactive centers respond to any data queries.

6.1.7. Surveillance/Monitoring

Not applicable.

6.1.8. Endpoints and Criteria for Study Success

The study endpoints are the following:

- Overall response at Day 28 – In MSB-GVHD001, Day 28 response was determined by assessing severity of GVHD symptoms in the skin, gastrointestinal (GI) tract, and liver using the CIBMTR criteria (Cahn et al. 2005).
- Overall survival at Day 100 and at Day 180
- Relapse at Day 100 and at Day 180
- Non-relapse mortality at Day 100 and at Day 180

6.1.9. Statistical Considerations & Statistical Analysis Plan

No formal sample size estimates were performed.

Two analysis populations were established for this study. The first analysis set compared the 54 subjects in MSB-GVHD001 to 30 subjects from the MAGIC database who matched the eligibility criteria for MSB-GHVD001.

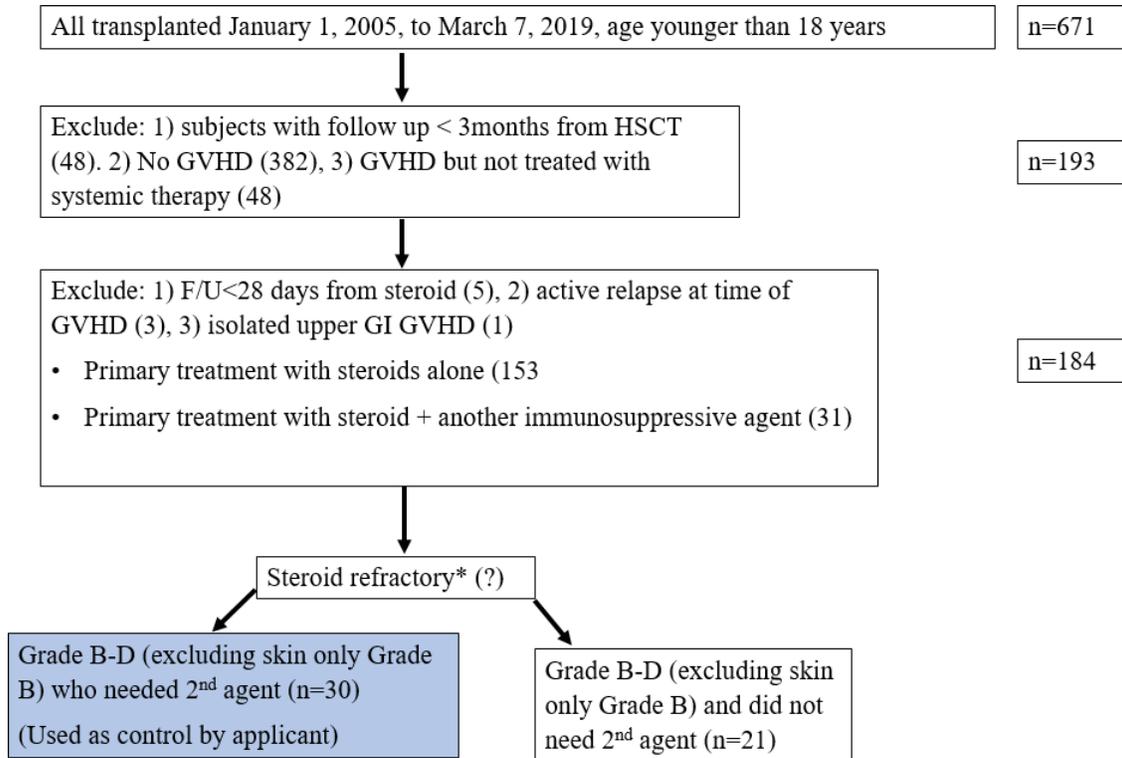
The second analysis set included all subjects who met the entry criteria and had serum samples available for the measurement of ST2 and REG3a at the time of development of SR-aGVHD. A total of 25 subjects from MSB-GVHD001 and 27 subjects from the MAGIC database were included in this analysis.

The planned analysis consisted of descriptive statistical analyses. No formal hypothesis testing was planned.

6.1.10. Study Population and Disposition

A total of 30 control subjects with SR-aGVHD were selected from the MAGIC database as shown in [Figure 1](#).

Figure 1. Schematic Summary of Methodology Used for Selection of MAGIC Control Group



Abbreviations: GI, gastrointestinal; GVHD, graft-versus-host disease; F/U, follow-up; HSCT, hematopoietic stem cell transplantation

The Applicant stated that a total of 21 pediatric subjects were also identified who had failed steroids alone. However, these subjects did not receive any second-line therapy and were therefore not included in the analysis. Compared to the cohort of SR-aGVHD pediatric subjects who received second-line therapy, these subjects had received a lower mean dose of steroids, had milder disease, and responded well with continued steroids. Further, the Applicant states that this is not the intended patient population for treatment with remestemcel-L.

6.1.11. Efficacy Analyses

The median age of subjects in the MAGIC cohort was 6 years (range: 0 to 17 years) compared to 7.8 years (range: 0.7 to 18 years) in Study MSB-GVHD001. [Table 4](#) summarizes the baseline disease characteristics of subjects included in the MAGIC Propensity control study compared with the MSB-GVHD001 study subjects. [Table 5](#) summarizes second-line therapies for SR-aGVHD; [Table 6](#) shows aGVHD response comparison of MSB-GVHD001 versus MAGIC Controls; and [Table 7](#) shows OS at Day 180 by IBMTR Grade and Minnesota Risk Score.

Table 4. Summary of Baseline aGVHD Characteristics

aGVHD Characteristics n (%)	MSB-GVHD001 N=54	MAGIC N=30
IBMTR Grade		
B	6 (11.1)	6 (20.0)
C	23 (42.6)	17 (56.7)
D	25 (46.3)	7 (23.3)
C-D	48 (88.9)	24 (80.0)
Multi-organ involvement	19 (35.2)	12 (40.0)
Skin stage		
0	25 (46.3)	12 (40.0)
1	3 (5.6)	6 (20.0)
2	2 (3.7)	2 (6.7)
3	14 (25.9)	10 (33.3)
4	10 (18.5)	0 (0.0)
Liver stage		
0	44 (81.5)	23 (76.7)
1	7 (13.0)	1 (3.3)
2	3 (5.6)	4 (13.3)
3	0 (0.0)	2 (6.7)
4	0 (0.0)	0 (0.0)
Lower GI stage		
0	14 (25.9)	10 (33.3)
1	5 (9.3)	5 (16.7)
2	6 (11.1)	1 (3.3)
3	13 (24.1)	7 (23.3)
4	16 (29.6)	7 (23.3)
Minnesota risk score		
Standard risk	16 (29.6)	13 (43.3)
High risk	38 (70.4)	17 (56.7)

Source: MSB-GVHD001 Table 14.1.5.1

Abbreviations: aGVHD, acute graft-versus-host disease; GI, gastrointestinal; IBMTR, International Bone Marrow Transplant Registry; MAGIC, Mt Sinai Acute GVHD International Consortium

Table 5. Second-Line Therapies for SR-aGVHD

Second-line therapies n (%)	MSB-GVHD001 (N=54)	MAGIC (N=30)
Alemtuzumab	Not Applicable	2 (6.7)
ATG		2 (6.7)
Basiliximab		1 (3.3)
ECP		5 (16.7)
Etanercept		5 (16.7)
Etanercept + ECP		1 (3.3)
Infliximab		5 (16.7)
Infliximab + ECP		2 (6.7)
Mycophenolate		2 (6.7)
Mycophenolate + ECP		1 (3.3)
Ruxolitinib		3 (10.0)
Tocilizumab		1 (3.3)

Abbreviations: ATG, anti-thymocyte globulin; ECP, extracorporeal photopheresis; MAGIC, Mt. Sinai Acute GVHD Consortium; SR-aGVHD, steroid-refractory acute graft-versus-host disease.

Table 6. aGVHD Response Comparison of MSB-GVHD001 Versus MAGIC Controls

Response	MAGIC, Steroid Refractory Treated With Second-Line Therapy Grade B-D (No Skin Only Grade B) (N=30)	MAGIC, Steroid Refractory No Second-Line Grade B-D (No Skin Only Grade B) (N=21)	MAGIC, Steroid Refractory (n=51)	MSB-GVHD001, Steroid Refractory Grade B-D (No Skin Only Grade B) (n=54)
Day 28 ORR	13 (43%)	18 (86%)	31 (60.78%)	38 (70%)
CR	7 (23%)	15 (71%)	22 (43.13%)	16 (29.6%)
PR	6 (20%)	3 (14.5%)	9 (17.64%)	22 (40.7%)

Abbreviations: CR, complete response; MAGIC, Mt. Sinai Acute GVHD Consortium; ORR, overall response rate; PR, partial response

Table 7. Overall Survival at Day 180 by IBMTR Grade and Minnesota Risk Score

Day 180 Overall Survival, n (%)	MSB-GVHD001 (N=54)	MAGIC (N=30)
IBMTR grade		
B	3/6 (50.0)	4/6 (66.7)
C	17/23 (73.9)	13/17 (76.5)
D	17/25 (68.0)	1/7 (14.3)
C-D	34/48 (70.8)	14/24 (58.3)
Minnesota risk score		
Standard risk	11/16 (68.8)	10/13 (76.9)
High risk	26/38 (68.4)	8/17 (47.1)

Abbreviations: IBMTR, International Bone Marrow Transplant Registry; MAGIC, Mt. Sinai Acute GVHD Consortium

Outcome Stratified by MAGIC Algorithm Probability Score

The MAP, derived from two biomarkers (ST2 and REG3a), measures damage to crypts in the GI tract during GVHD. MAP measured before and after treatment of

aGVHD is a response biomarker that has been shown to predict long-term outcomes.

Twenty-five out of 54 (46%) subjects in study MSB-GVHD001 had serum samples for measurement of ST2 and REG3a at the beginning of treatment and were included in the analysis. Twenty-seven out of 30 (90%) MAGIC control subjects met the eligibility criteria and had serum samples available when second-line therapy was initiated.

In MSB-GVHD001, samples for analysis of biomarkers were obtained at baseline (Day -4 to -1), Day 28, and end of study (Day 100). MAGIC subjects provided blood samples for biorepository 7 days after initiation of corticosteroid treatment for newly diagnosed aGVHD.

Key characteristics (underlying disease, HSCT, GVHD prophylaxis, and grade and staging of aGVHD) of the two populations were comparable, as shown in [Table 8](#).

Table 8. Baseline MAGIC Algorithm Probability

Baseline MAP	MSB-GVHD001 (N=25)	MAGIC (N=27)
Mean (SD)	0.283 (0.166)	0.262 (0.197)
Median	0.287	0.247
Min, max	0.088-0.653	0.0193-0.742
20.29, n (%)	12 (48.0)	10 (37.0)
<0.29, n (%)	13 (52.0)	17 (63.0)

Source: for GVHD data, MSB-GVHD001 CSR

Abbreviations: MAGIC, Mt. Sinai Acute GVHD Consortium; MAP, MAGIC algorithm probability; max, maximum; min, minimum.

[Table 9](#) shows that subjects with high MAP scores treated with remestemcel-L achieved high ORR.

Table 9. Overall Response at Day-28 Stratified by Baseline MAP

Day 28 Response n (%)	MSB- GVHD001 (N=25)	MSB-GVHD001 (N=25)	MAGIC (N=27)	MAGIC (N=27)
Baseline MAP	20.29 n=12	<0.29 n=13	20.29 n=10	<0.29 n=17
Overall response	8 (66.7)	11 (84.6)	1 (10.0)	12 (70.6)
CR	2 (16.7)	4 (30.8)	1 (10.0)	6 (35.3)
PR	6 (50.0)	7 (53.8)	0 (0.0)	6 (35.3)
NR	4 (33.3)	2 (15.4)	9 (90.0)	6 (18.5)

Source: for GVHD data, MSB-GVHD001 CSR

Abbreviations: CR, complete response; MAGIC, Mt. Sinai Acute GVHD Consortium; MAP, MAGIC algorithm probability; NR, no response; PR, partial response.

Overall survival relapsed and Non-relapse Mortality at day 100 and at day 180 are shown in [Table 10](#), below.

Table 10. Overall Survival, Relapse and Non-Relapse Mortality at Day 100 and 180 Stratified by Baseline MAP

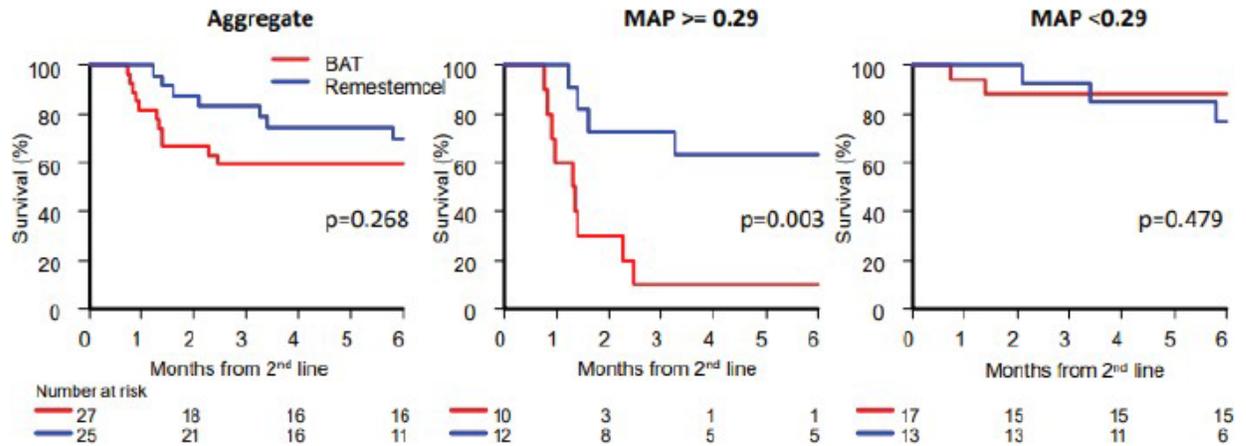
Outcomes n (%)	MSB-GVHD001 (N=25) n=12	MSB-GVHD001 (N=25) n=13	MAGIC (N=27) n=10	MAGIC (N=27) n=17
Baseline MAP	20.29	<0.29	20.29	<0.29
Day 100				
NRM	3 (25.0)	1 (7.7)	9 (90.0)	2 (11.8)
Relapse	1 (8.3)	0 (0.0)	0 (0.0)	1 (5.9)
OS	8 (66.7)	12 (92.3)	1 (10.0)	15 (88.2)
Day 180				
NRM	3 (25.0)	2 (15.4)	9 (90.0)	2 (11.8)
Relapse ¹	1 (8.3)	1 (7.7)	0 (0.0)	4 (23.5)
OS	8 (66.7)	10 (76.9)	1 (10.0)	15 (88.2)

Source: for GVHD data, MSB-GVHD001 CSR

1. For MSB-GVHD001, relapse only includes fatal relapses. For MAGIC, relapse includes death and second transplant. Abbreviations: NRM non-relapse related mortality; OS, overall survival; MAGIC, Mt. Sinai Acute GVHD Consortium; MAP, MAGIC algorithm probability

Figure 2 shows the Kaplan Meier estimates of 6-month OS for the two subject cohorts by baseline MAP score.

Figure 2. Kaplan-Meier Estimate of 6-month Overall Survival for the Two Subject Cohorts by Baseline MAP



Abbreviations: BAT, best available therapy; MAP, MAGIC algorithm probability

6.1.12. Safety Analyses

No comparative safety analyses were provided in the MAGIC control study.

6.1.13. Study Summary and Conclusions

In summary, the MAGIC study is a retrospectively performed ad hoc analysis of outcomes of propensity-matched control subjects with SR-aGVHD obtained from MAGIC registry database with the subjects treated with remestemcel-L in Study MSB-GVHD001. The selection of control appears biased and not fit for purpose. Specifically, the Applicant stated that a total of 21 pediatric subjects were also identified who had failed steroids alone. However, these subjects did not receive

any second-line therapy and were therefore not included in the analysis. Compared to the cohort of SR-aGVHD pediatric subjects who received second-line therapy, these subjects had received a lower mean dose of steroids, had milder disease, and responded well with continued steroids. Further, the Applicant states that this is not the intended patient population for treatment with remestemcel-L. This reviewer does not agree with the Applicant's approach in selecting the control group. Since the subjects enrolled in MSB-GVHD001 study only had steroid refractory disease, and no certainty that they would be treated with a second agent if not enrolled in the study, the appropriate control group should be all pediatric subjects (n=51) who have the matched demographic and disease attributes and meet the criteria for steroid refractoriness.

Although these data show improved outcome in subjects treated with remestemcel-L compared to MAGIC control group including subjects with a high MAP score, there are several limitations to the results of this propensity-matched control study. The study is an ad hoc retrospective analysis, performed without a prespecified statistical analysis plan a priori and without prior discussion and agreement with the FDA. The selection of a control group is biased, not fit for purpose, and not acceptable, and there are several confounders. For example, all subjects in the MSB-GVHD001 study were treated between 2015 and 2017, whereas MAGIC control groups were selected from 2005 to 2019, key data including data on disease prognostic factors, concomitant medications used by subjects in this external control group, and biomarker data were missing. Therefore, this study is not an adequate and well-controlled study and cannot be used for a regulatory decision making.

6.2. Center for International Blood and Marrow Transplant Research (CIBMTR) Long-Term Survival Study

6.2.1. Objectives

The objectives of this study were the following:

- To evaluate OS after the first remestemcel-L dose at 1, 2, 3, and 4 years
- To evaluate relapse/progression after the first remestemcel-L dose at 1, 2, 3, and 4 years
- To determine the cause of death

6.2.2. Design Overview

Study MSB-GVHD001 enrolled pediatric subjects with steroid-refractory aGVHD. Study MSB-GVHD002 was an extension protocol that followed subjects out to Day 180. Overall survival at Day 100 was 74.1% (40/54 subjects) and 68.5% at Day 180.

The CIBMTR database collects longitudinal survival information of patients in the United States who have undergone allogeneic or autologous HSCT. As per the

Applicant, upon their request, the CIBMTR has 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 subjects who participated in MSB-GVHD001/002 study ([Table 11](#)).

Table 11. Brief Overview of CIBMTR Long-Term Survival Study

Design	Registry Analysis
Primary objectives	To evaluate overall survival post-first remestemcel-L dose at 1, 2, 3, and 4 years To evaluate relapse/progression post-first remestemcel-L dose at 1, 2, 3, and 4 years To determine the cause of death
Primary endpoints	OS
Inclusion criteria	Subject enrolled in MSB-GVHD001 study Subject received at least one dose of remestemcel-L Subject had data reported to the CIBMTR including the CIBMTR Research ID, the first date of remestemcel-L infusion, and the IBMTR Severity Index Grade of aGVHD at the time subject was enrolled into Mesoblast’s clinical trial.
Key exclusion criteria	Subject did not provide consent to the CIBMTR’s research database

Source: CIBMTR-clinical-study-report (Module 5.3.4.2)

Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research;

GVHD, graft-versus-host disease; IBMTR, International Bone Marrow Transplant Registry; OS, overall survival.

6.2.3. Population

The population consisted of subjects enrolled in Study MSB-GVHD001 and treated with remestemcel-L.

6.2.4. Study Treatments or Agents Mandated by the Protocol

The subjects enrolled in this study were the subjects enrolled and treated with remestemcel-L in Study MSB-GVHD001.

6.2.5. Directions for Use

Not applicable.

6.2.6. Sites and Centers

Not applicable.

6.2.7. Surveillance/Monitoring

Not applicable.

6.2.8. Endpoints and Criteria for Study Success

Primary Endpoint

- Overall survival (OS): Event was defined as death due to any cause. In the absence of confirmation of death, OS was censored at the date the subject

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 subjects with adequate follow-up.

Secondary Endpoint

Cause of death: overall and by IBMTR Severity Index Grade

6.2.9. Statistical Considerations & Statistical Analysis Plan

This was a retrospective, observational cohort study. No formal sample size estimates were performed. Descriptive statistical analysis was planned, and no formal hypothesis testing was performed.

6.2.10. Study Population and Disposition

Out of 54 subjects treated in study MSB-GVHD001, a total of 51 subjects were included in this analysis. One subject did not consent to participate in the CIBMTR research database, and two subjects were not approached about participating in this database study.

6.2.11. Efficacy Analyses

Overall Survival

[Table 12](#) shows OS of subjects treated in the registry study. The median duration of follow-up of subjects enrolled in this registry study was 62 months (range 15 to 73 months). Note that, as per the Applicant, the median duration of follow-up was calculated from the reverse Kaplan-Meier method. Using this method, the median was estimated with the meaning of the status indicator reversed, so that censoring becomes the event of interest (23 censored becomes 23 events), and death becomes the censoring event (28 death events becomes 28 censored). Therefore, the median calculated by the reverse Kaplan-Meier method is no longer the median of survival, instead is the median of follow-up.

Table 12. Overall Survival of Subjects Treated in MSB-GVHD001 Study

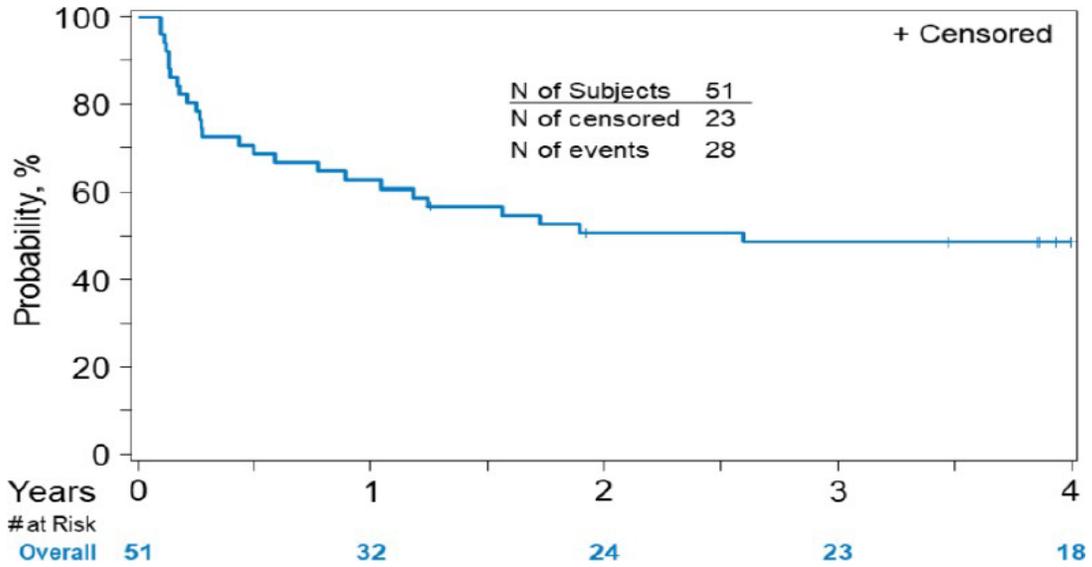
Overall Survival	%OS: KM Estimate of Survival (95% CI) ¹
1-year	62.7 (49.2, 75.4)
2-year	50.8 (37.1, 64.3)
3-year	48.7 (35.1, 62.3)
4-year	48.7 (35.1, 62.3)

Source: CIBMTR-clinical-study-report (Module 5.3.4.2).

1. N=51

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

Figure 3. Kaplan-Meier Estimate of Overall Survival of MSB-GVHD001 Subjects Based on IBMTR Grade



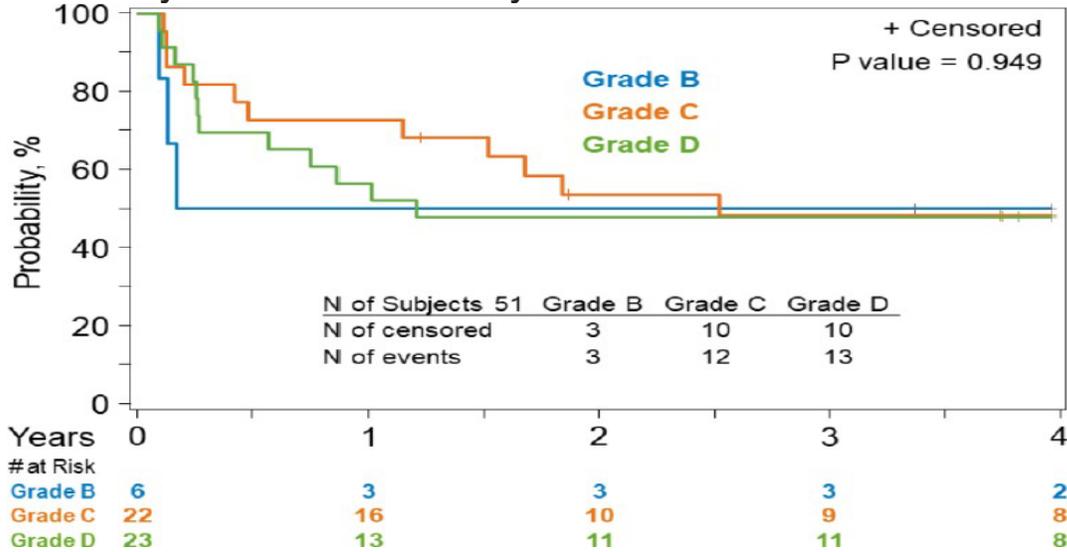
Abbreviations: IBMTR, International Bone Marrow Transplant Registry

Table 13. Overall Survival of MSB-GVHD001 Subjects Based on IBMTR Grade

Overall Survival	Grade B (n=6) KM Estimate (95% CI)	Grade C (n=22) KM Estimate (95% CI)	Grade D (n=23) KM Estimate (95% CI)
1-year	50.0% (14.1-85.9)	72.7% (52.7-88.8)	56.5% (36.3-75.7)
2-year	50.0% (14.1-85.9)	53.6% (32.7-73.8)	47.8% (28.2-67.9)
3-year	50.0% (14.1-85.9)	48.2% (27.5-69.2)	47.8% (28.2-67.9)
4-year	50.0% (14.1-85.9)	48.2% (27.5-69.2)	47.8% (28.2-67.9)
Median follow-up, range (months)	56 (42-70)	62 (15-73)	62 (46-73)

Abbreviations: CI, confidence interval; IBMTR, International Bone Marrow Transplant Registry; KM, Kaplan-Meier

Figure 4. Kaplan-Meier Estimate of OS up to 4 Years After First Remestemcel-L Treatment by Baseline IBMTR Severity Grade



Abbreviations: IBMTR, International Bone Marrow Transplant Registry

The OS at 4 years was 50.0% for subjects with Grade B disease, 48.2% for subjects with Grade C, and 47.8% for subjects with Grade D aGVHD ([Table 13](#)).

Cause of deaths: [Table 14](#) shows the survival status and cause of death of subjects enrolled in CIBMTR long term survival study

Table 14. Survival Status and Causes of Deaths for Subjects Enrolled in CIBMTR Study

Cause of Death	Overall, N=51 (%)	Grade B, n=6 (%)	Grade C, n=22 (%)	Grade D, n=23 (%)
Alive	23 (45%)	3 (50%)	10 (45%)	10 (43%)
Died	28	3 (50%)	12 (55%)	13 (57%)
Organ failure	8 (16%)	2 (33%)	1 (5%)	5 (22%)
GVHD	7 (14%)	1 (17%)	3 (14%)	3 (13%)
Primary disease	6 (12%)	0 (0%)	3 (14%)	3 (13%)
IPn/ARDS	2 (4%)	0 (0%)	2 (9%)	0 (0%)
Gastrointestinal hemorrhage	1 (2%)	0 (0%)	0 (0%)	1 (4%)
Graft failure	1 (2%)	0 (0%)	1 (5%)	0 (0%)
Infection	1 (2%)	0 (0%)	1 (5%)	0 (0%)
Metabolic acidosis	1 (2%)	0 (0%)	0 (0%)	1 (4%)
Stroke	1 (2%)	0 (0%)	1 (5%)	0 (0%)

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

6.2.12. Safety Analyses

No additional safety information was submitted in the CIBMTR Long Term Survival study report.

6.2.13. Study Summary and Conclusions

This observational study was performed by the CIBMTR on behalf of the Applicant. The study design and the SAP were not previously discussed with the FDA. The clinical study protocol, SAP, and the subject-level datasets were not included in the resubmission. After further advice by the FDA, the Applicant made arrangements for CIBMTR to submit subject-level data in the form of a master file cross-referencing this BLA. The deidentified data were submitted by CIBMTR under MF5-(b) (4).

The OS data for 51 subjects treated in Study MSB-GVHD001 were submitted in the CIBMTR long-term survival study report. Of note, there was no control arm in this long-term survival study. The study reported an OS estimate of 48.7% (91% CI 35.1, 62.3) after 4 years from the first dose of remestemcel-L treatment. Out of the 28 deaths that occurred in those 51 subjects, seven (14%) deaths were due to GVHD.

The time-to-event survival results observed in a single-arm study derived from an ad hoc analysis for a patient population (post-HSCT) who have several competing causes of death (as shown in [Table 14](#)), are inconclusive and cannot support an efficacy claim for a regulatory consideration.

7. INTEGRATED SUMMARY OF EFFICACY

7.1. Indication: Steroid Refractory Acute Graft Versus Host Disease (SR-aGVHD)

The main efficacy claim of remestemcel-L for treatment of the proposed indication is based on the Day-28 ORR observed in Study MSB-GVHD001 (see Section [16.1](#), Appendix 1).

Two additional study reports were submitted by the Applicant to support the efficacy results seen in Study MSB-GVHD001.

The MAGIC propensity-controlled study is a retrospectively performed ad hoc analysis of outcomes of control subjects with SR-aGVHD obtained from the MAGIC registry database compared with the outcomes of subjects treated with remestemcel-L in Study MSB-GVHD001. Although the study report presented superior outcomes (Day-28 ORR) in subjects treated with remestemcel-L compared to propensity-matched controls from the MAGIC registry, the design of the study and the selection of controls was flawed and biased. Additionally, there were many missing data including key demographic and disease characteristics, lack of information about concomitant medications, and missing biomarker data in more than half of the subjects. Therefore, this study does not meet the criteria for an adequate and well-controlled study, and hence the results are not interpretable.

The CIBMTR long-term survival study provided OS data for 51 subjects treated in Study MSB-GVHD001. Of note, there was no control arm in this long-term survival study. The study reported an OS estimate of 48.7%, 91% CI 35.1, 62.3 after 4 years from the first dose of remestemcel-L. Of the 28 deaths that occurred in those 51 subjects, only seven (14%) deaths were due to GVHD.

The time-to-event survival results observed in a single-arm study derived from an ad hoc analysis for a patient population (post-HSCT) who have several competing causes of death are inconclusive and cannot support an efficacy claim for a regulatory consideration.

These two studies are retrospectively performed ad hoc analyses. There are several heterogeneities in the study design and analyses. No conclusion can be drawn from these studies to support an efficacy claim. No integrated analysis of efficacy results was performed.

8. INTEGRATED OVERVIEW OF SAFETY

With this resubmission, the Applicant has provided safety data for 1,780 subjects treated with remestemcel-L. Across all studies, 1,270 subjects have been exposed to remestemcel-L via infusion, and 510 have received placebo. In aGVHD studies, 678 (352 pediatric and 326 adult) subjects have received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. No new safety signals have been reported. See Section [16.1.3.1](#), Appendix 1 for summary of safety results.

9. ADDITIONAL CLINICAL ISSUES

9.1. Special Populations

No additional study results from special populations such as pregnant or geriatric subjects were provided in this BLA resubmission.

9.2. Aspects of the Clinical Evaluation Not Previously Covered

Study MSB-GVHD001 and MSB-GVHD002 included an exploratory biomarker substudy. These studies were designed (1) to characterize the immune profile of subjects enrolled in MSB-GVHD001; (2) to monitor changes in immune cell subsets and inflammatory molecules associated with aGVHD and thereby examine mesenchymal stromal cell bioactivity in vivo; and (3) to evaluate relationships between biomarkers and clinical outcomes.

With this BLA resubmission, the Applicant submitted a final study report of the biomarker data on 40 out of 55 subjects from study GVHD-001. The FDA review team previously determined that these data were descriptive and exploratory. Further, there was no reliable quantification of certain biomarker data, due to

capping of upper limits. Therefore, the review team considers these data as exploratory and not informative for regulatory decision making.

10. CONCLUSIONS

The review of this BLA resubmission focused on the evaluation of additional clinical information and data submitted as a response to the deficiencies noted in the Complete Response Letter dated September 30, 2020.

The MAGIC propensity control study is a retrospective ad hoc analysis, performed without a prespecified statistical analysis plan a priori and without prior discussion or agreement with the FDA; the selection of the control group is biased, not fit-for-purpose and not acceptable; and there are several confounders. For example, all subjects in Study MSB-GVHD001 were treated between 2015 and 2017, whereas subjects for the MAGIC control groups were transplanted between 2005 and 2019. Various key data, including data on disease prognostic factors, concomitant medications used by subjects in this external control group, and biomarker data were missing. Therefore, this study is not an adequate and well-controlled study and cannot be used for regulatory decision making.

The OS data for 51 subjects treated in Study MSB-GVHD001 were submitted in the CIBMTR long-term survival study report. The time-to-event survival results observed in this single-arm study derived from an ad hoc analysis for a patient population (post-HSCT) who have several competing causes of death, are inconclusive and cannot support an efficacy claim for a regulatory consideration. The final analysis of the biomarker data collected during MSB-GVHD001 is only exploratory.

The results of the primary efficacy study MSB-GVHD001 were adjudicated by the FDA during the review of initial BLA submission. The study met its primary endpoint; the Day-28 ORR was 69.1%, 95% CI 55.2, 80.9 in the FAS, excluding the null hypothesis of 45%, and the measured response was durable (median 54 days). The results were consistent across subpopulations and secondary efficacy endpoints. The observed safety profile revealed no safety signal of concern. However, it should be noted that there are several limitations to the single-arm study design, which includes lack of a control group and randomization, the risk of bias in subject selection, baseline assessment, outcome assessment, and a lack of blinding, which may introduce bias in concomitant treatment or endpoint assessments.

During the review of this resubmission, CMC colleagues identified a significant deficiency related to the potency of the product used during Study MSB-GVHD001. Lack of potency data for an investigational product used to generate clinical data limits the relevance and interpretability of the clinical efficacy results in the treatment of the proposed indication.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1. Risk-Benefit Considerations

Disease

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. Ruxolitinib is approved for this indication in patients 12 years and older.

Efficacy

The Applicant submitted results of two retrospectively performed studies to support the efficacy claim for remestemcel-L in treatment of SR-aGVHD. The MAGIC propensity control study compared the Day-28 ORR and the overall OS at Month 6 in subjects treated with remestemcel-L in Study MSB-GVHD001 with a propensity-matched control group from the MAGIC registry. The CIBMTR long-term survival study reported OS of 51 subjects treated with remestemcel-L in Study MSB-GVHD001. Both studies are not considered adequate or well controlled, and the results of these analyses are inconclusive.

Of note, during the initial BLA submission, the Applicant submitted results of Study MSB-GVHD001 to support the efficacy claim for the proposed indication. During the review of the original submission, a major CMC deficiency related to the potency of the product used during Study MSB-GVHD001 was identified, which raises concerns regarding the validity and relevance of results of the study. Those CMC deficiencies remain unresolved at this time.

Safety

There is no safety signal of concern. Uncertainties exist with the risk of ectopic tissue formation and antidrug/anti-HLA antibodies.

Recommendations

In view of the deficiencies associated with the potency assay of the products used in study MSB-GVHD001 as noted in CMC review, along with limitations of the clinical data, there remain significant concerns and uncertainties associated with the efficacy of remestemcel-L in the treatment of the proposed disease. The additional clinical data submitted during the BLA resubmission (the MAGIC control study and the CIBMTR long-term survival study) are inconclusive, and hence do not support the efficacy claim.

Therefore, this BLA does not meet the statutory requirement for substantial evidence of effectiveness. To meet this requirement, in addition to addressing the CMC deficiencies, the clinical review team recommends that the Applicant conduct at least one adequate randomized, well-controlled study in adults and/or pediatric subjects to provide evidence of the effectiveness of remestemcel-L.

11.2. Risk-Benefit Summary and Assessment

Please see [Table 15](#).

Table 15. Risk and Benefit Assessments

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	<p>The most common life-threatening complication of alloHSCT is GVHD. Despite prophylaxis with immunosuppressants, aGVHD may still occur; among all patients undergoing alloHSCT, 30% to 50% have aGVHD (grades 1-4) and 14% have severe aGVHD (grades 3-4). Only ~50 of aGVHD responds to steroid therapy. Those refractory to steroid therapy have poor outcomes. Due to life threatening nature of SR-aGVHD, the natural history is ill-defined. High-grade SR-aGVHD is usually fatal if left untreated.</p>	<p>SR-aGVHD is a difficult-to-treat, serious and life-threatening illness.</p>
Unmet medical need	<p>Currently, ruxolitinib is the only FDA-approved therapy for the treatment of SR-aGVHD in patients 12 years or older. There are no drugs approved for treatment of SR-aGVHD in patients less than 12 years. There are 13 drugs listed in the NCCN guidelines as “suggested” systemic agents for treatment of SR-aGVHD. All, except ruxolitinib (Category 1) are stated to have only Category 2A evidence.</p>	<p>In children younger than 12 years, there is an unmet medical need for the treatment of steroid-refractory aGVHD.</p>
Clinical benefit	<p>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, and 54 were treated with remestemcel-L monotherapy. The Day-28 ORR was 69.1% (95% CI 55.2, 80.9), and the median duration of response was 54 days. It is noted that the product has unclear MOA, has no validated potency attribute, and has history of failed RCTs in previous trials of acute GVHD (both newly diagnosed and SR-aGVHD), and very benign safety profile. With BLA resubmission, results from two additional retrospective studies were provided, MAGIC propensity-matched control study and the CIBMTR long-term survival study.</p>	<p>In this one single-arm study, the magnitude of ORR and durability of response to treatment were consistent with activity of remestemcel-L in this disease. The MAGIC control study and the CIBMTR long-term survival studies are not adequate or well-controlled studies, and the results are inconclusive. There remains uncertainty regarding substantial evidence of effectiveness required to support a marketing application.</p>
Risk	<p>There were no fatal adverse reactions, and the withdrawal rate was 13%. 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 formation and the impact of pre-existing and treatment-emergent anti-HLA antibodies for this treatment.</p>	<p>The safety profile is acceptable for the intended population. However, uncertainties remain regarding the risk of ectopic tissue formation and ADA/anti-HLA antibodies.</p>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk management	The premedication and safety monitoring plan in Study MSB-GVHD001 were effective in mitigating serious potential toxicities.	Although the safety profile is mostly benign, the data remain unclear regarding the risk of ectopic tissue formation and ADA/anti-HLA antibodies.

Abbreviations: ADA, anti-drug/donor antibodies; aGVHD, acute graft-versus-host disease; alloHCT, allogeneic hematopoietic stem cell transplantation; BLA, biologics license application; CIBMTR, Center for International Blood and Marrow Transplant Research; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; MAGIC, Mount Sinai Acute GVHD International Consortium; MOA, mechanism of action; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial; SR-aGVHD, steroid-refractory acute graft-versus-host disease.

11.3. Discussion of Regulatory Options

With the BLA resubmission, the Applicant provided additional clinical information/data to support the marketing Applicant of remestemcel-L for the treatment of pediatric SR-aGVHD.

The efficacy of remestemcel-L observed in Study MSB-GVHD001 for the treatment of SR-aGVHD formed the basis for the initial BLA submission. Although Study MSB-GVHD001 met its primary endpoint with Day-28 ORR of 69% and the response was durable (median duration of response [DOR] of 54 days), there remain concerns about the clinical data. Aside from the limitations of the single-arm nature of the study, the product (remestemcel-L) has history of failed RCTs in acute GVHD clinical studies (Study 275 and 280) and has shown a very benign safety profile, which may indicate lack of activity. The product's MOA remains unclear, and the FDA CMC team has recommended Complete Response due to deficiency related to product potency.

The results of the MAGIC propensity control study and the CIBMTR long-term survival study are inconclusive, and these studies are not considered adequate and well-controlled studies. The final study report from the biomarker analysis (performed as an exploratory part in Study MSB-GVHD) is also inconclusive and considered exploratory.

Considering the life-threatening nature of the disease and the lack of available therapies for the proposed indication, the clinical review team considered possible regulatory options. However, the CMC deficiencies related to product potency/attributes along with concerns with the single-arm study design and the efficacy data raises serious questions regarding the relevance of study MSB-GVHD001 results and the activity of remestemcel-L for the treatment of the proposed indication. As noted in 21 CFR 314.126 (d), "*for an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.*" With the lack of a valid potency assay for the product used during MSB-GVHD001, the study cannot be considered an adequate study for the purpose of demonstration of substantial evidence of effectiveness required for a marketing approval, and hence this BLA does not meet the statutory requirement for the substantial evidence of effectiveness to support an approval. The additional clinical data provided with the BLA resubmission are inconclusive, and do not support an efficacy claim for regulatory considerations.

11.4. Recommendations on Regulatory Actions

The clinical team recommends issuing a Complete Response Letter to the BLA of remestemcel-L for treatment of steroid-refractory acute GVHD in pediatric patients. To address the deficiency, in addition to addressing the CMC

deficiencies, the clinical review team recommends that the Applicant conduct at least one adequate and well-controlled study in adults and/or pediatric subjects using a well-characterized product to provide evidence of the effectiveness of remestemcel-L in the treatment of SR-aGVHD. Due to the uncertainties with the mechanism of action and the challenges that have been encountered with identifying an appropriate potency assay, it would be in the Applicant's best interest to conduct a randomized trial designed using an adequately characterized product identical or comparable to the to-be-marketed form, in a fashion to ensure that the results are robust and unquestionable.

11.5. Labeling Review and Recommendations

No labeling reviews were performed during the review of this resubmission since a Complete Response was decided.

11.6. Recommendations on Post-marketing Actions

Not applicable.

13. BRANCH CHIEF, MALIGNANT HEMATOLOGY BRANCH, DCEH

Robert Sokolic, MD

Robert A. Sokolic Digitally signed by Robert A. Sokolic -S
Date: 2023.08.01 10:49:44 -04'00'

14. 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 indicates that I have considered the assessments and recommendations included in this Clinical Review in determining the OCE recommendation to the application signatory for issuance of a complete response letter.

Marc Theoret, MD

Marc R.
X Theoret -S

Digitally signed by Marc
R. Theoret -S
Date: 2023.08.01
13:05:45 -04'00'

15. DIVISION DIRECTOR (DCEH)

Celia Witten, PhD, MD, Director

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16. APPENDICES

16.1. Appendix 1: Summary of Main Efficacy Study MSB-GVHD001

Study MSB-GVHD001 is a single-arm, prospective study of remestemcel-L, for the treatment of SR-aGVHD in pediatric subjects (see [Table 16](#)).

16.1.1. Study Overview

Table 16. Study MSB-GVHD001

Design	Prospective, Multi-Center, Single Arm
Primary objectives	Evaluate the efficacy of remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT Gather additional information on the safety of remestemcel-L in pediatric subjects with Grades B-D SR-aGVHD
Secondary objectives	Determine the correlation between response to remestemcel-L at Day 28 and survival at Day 100 Obtain QOL data on remestemcel-L-treated subjects via the Pediatric Quality of Life Inventory (PedsQL™); and the pediatric global HRQOL Parent Proxy Report Measure the functional status of remestemcel-L-treated subjects using the Karnofsky/Lansky scale
Exploratory objectives	To capture and analyze biomarker expression by remestemcel-L-treated subjects
Primary endpoints	ORR, defined as CR or PR, at 28 days post initiation of remestemcel-L
Secondary endpoints	OS at Day 100 post initiation of remestemcel-L therapy OS at Day 100 post initiation of remestemcel-L therapy, stratified by responder status at Day 28 (responder versus non-responder) OS at Day 100 post initiation of remestemcel-L therapy, stratified by baseline aGVHD grade and organ involvement Rate of VGPR at Day 28 post initiation of remestemcel-L therapy ORR and rates of CR + VGPR at Day 56 and Day 100 post initiation of remestemcel-L therapy ORR and rates of CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by organ involvement ORR and rates of CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by individual subject organ involvement and MacMillan risk score at baseline ORR and rates of CR + VGPR at Days 28, 56, and 100 post initiation of remestemcel-L therapy, stratified by baseline GVHD grade Rate of aGVHD progression requiring additional GVHD medications/therapy through Day 100 post initiation of remestemcel-L therapy Effect of additional remestemcel-L therapy after Day 28 on ORR and CR + VGPR at Days 56 and 100 post initiation of remestemcel-L therapy Assessment of change in organ involvement and organ staging, from baseline to Day 28 post initiation of remestemcel-L therapy
Sites/centers	Opened at 27 centers in the U.S., and 20 centers enrolled subjects

Design	Prospective, Multi-Center, Single Arm
Key inclusion criteria	Subjects between the ages of 2 months and 17 years inclusive, with aGVHD following alloHSCT that has failed to respond to treatment with systemic corticosteroid therapy. Steroid refractory: any Grade B-D (IBMTR grading) aGVHD that shows progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day of methylprednisolone or equivalent
Key exclusion criteria	Diffuse alveolar hemorrhage or other active pulmonary disease Subjects who have received HSCT for a solid tumor Prior treatment with experimental GVHD therapy
Study treatment	Initial Treatment: 2×10^6 MSCs/kg body weight at screening twice weekly for 4 consecutive weeks Infusions were administered at least 3 days apart and no more than 5 days apart. All subsequent infusions were administered within 28 days (± 2 days) of the first infusion. Continued Treatment (if indicated): 2×10^6 MSCs/kg once each week for 4 weeks, beginning within 1 week of the end of initial treatment. Infusions were administered once weekly (± 2 days). All infusions were to be administered within 28 days (± 2 days) of the first continued-therapy infusion. One subject (b) (6) received a total of 20 infusions, as was allowed in the individual treatment protocol for this subject. No additional MSC therapy was allowed at any time.

Abbreviations: CR, complete response; GVHD, graft-versus-host disease; HRQOL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; IBMTR, International Bone Marrow Transplant Registry; MSC, mesenchymal stem cells; OS, overall survival; ORR, overall response rate; PR, partial response; QOL, quality of life; VGPR, very good partial response

16.1.2. Study MSB-GVHD001 Population

The FAS included 55 enrolled subjects with median age of 7.75 years (range 7 months to 17.9 years); 63.6% were male; 56.4% were white, and 67.0% were non-Hispanic or Latino. Over 67% (67.27%) had a history of malignant conditions (the most common being acute myeloid leukemia, 32.7%), and 32.7% had a history of non-malignant disorders. Seventy-six (76.4) percent had received HSCT from an unrelated donor.

Ninety (90.9) percent of subjects had IBMTR Grade C and D acute GVHD at steroid refractory diagnosis, and 72.7% had high MacMillan risk score (high-risk acute GVHD).

16.1.3. Summary of Results

16.1.3.1. Safety

During the initial review of this BLA, the FDA reviewed the safety data for 1,517 subjects in clinical trials and expanded-access protocols. These included 1,114 subjects treated with remestemcel-L and 403 treated with placebo. As noted in the clinical review memorandum, there were substantial differences between the clinical trials regarding the patient populations and treatment plans, so there was no pooling of data. FDA's review of the safety profile of remestemcel-L focused

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

With this resubmission, the Applicant has provided safety data for 1,780 subjects treated with remestemcel-L. Across all studies, 1,270 subjects have been exposed to remestemcel-L via infusion, and 510 have received placebo. In aGVHD) studies, 678 (352 pediatric and 326 adult) subjects have received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. No new safety signals have been reported.

Key Safety Results

Deaths

There were 422 deaths reported in the integrated safety database; 229 occurred within 30 days of the last dose of remestemcel-L. In the randomized trials, there was no apparent difference between the remestemcel-L and placebo arms in the incidence of deaths. Given the complicated course of patients with acute GVHD, there are multiple potential causes of death. The non-GVHD studies provide for a clean assessment of the risk of fatal adverse reactions. The lack of any fatal adverse reaction among the 460 subjects treated with remestemcel-L in the non-GVHD studies suggests that the risk is low. However, there is still a need to assess the population-specific risk.

In Study MSB-GVHD001, there were 14 deaths reported among the 54 treated subjects; seven deaths (50% of deaths) occurred within 30 days of the last dose of remestemcel-L ([Table 17](#)).

Table 17. Study GVHD001- FDA-Adjudicated Root Cause of Death

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

Source: FDA reviewer-generated table from ADAE/ADSL datasets, GVHD001/002 CSR and patient narratives

1. accident

Abbreviations: GVHD, graft-versus-host disease

Serious Adverse Events

In Study MSB-GVHD001, an SAE was reported for 42 subjects (77.8%). The most common System Organ Class for SAEs was infections and infestations (37%).

Common Adverse Events

The Applicant reports that all 54 subjects in the safety population experienced at least one treatment-emergent adverse event (TEAE) during the study.

The most common treatment emergent AEs were viral infections (56%), bacterial infections (43%), infection (39%), pyrexia (35%), and hemorrhage (33%).

Note that patients with aGVHD following alloH SCT have high rates of infection, and this safety is consistent with literature reports of treatments used for GVHD.

[Table 18](#) summarizes the Grade 2-3 TEAEs using FDA grouped terms (see Appendix 3).

Table 18. Grade 2-3 TEAE Occurring in >5% of Subjects (N=54)

Preferred Term	Number of Subjects	Proportion (%)
Bacterial infection	10	19
Infection	8	15
Viral infection	8	15
Hemorrhage	7	13
Hypokalemia	6	11
Respiratory failure	5	9
Abdominal pain	4	7
Hypertension	4	7
Hyperglycemia	3	6
Hypersensitivity	3	6
Neutropenia	3	6
Vomiting	3	6

Source: FDA analysis

Note: Includes FDA grouped terms

Abbreviations: TEAE, treatment-emergent adverse events

In general, the analyses of safety data in studies of remestemcel-L showed a mild and manageable safety profile.

16.1.3.2. Efficacy

Analyses of Primary Endpoint(s)

[Table 19](#) shows primary endpoint analysis of MSB-GVHD001.

Table 19. MSB-GVHD001 - Primary Endpoint Analysis (Day-28 ORR)

Analysis Set	N	Day-28 CR n (%)	Day-28 PR n (%)	Day 28 ORR n (%)	Day 28 ORR 95% CI
Full analysis set ¹	55	16 (29.1)	22 (40.0)	38 (69.1)	(55.2, 80.9)
Treated set ²	54	16 (29.6)	22 (40.7)	38 (70.4)	(56.3, 82.0)
Sensitivity set 1 ³	45	15 (33.3)	19 (42.2)	34 (75.6)	(60.5, 87.1)
Sensitivity set 2 ⁴	55	15 (27.3)	19 (34.5)	34 (61.8)	(47.8, 74.6)

Source: Modified from Table 14 FDA clinical review memorandum

1. Treated Set: Subjects who received at least one treatment with remestemcel-L

2. Sensitivity analysis: Sensitivity analysis was performed by excluding a total of 10 subjects: nine subjects who had confounders for determination of ORR at Day 28 (one subject who withdrew, six subjects who received concomitant medications that could potentially impact the Day 28 primary endpoint analysis, and four subjects who had active aGVHD but did have aGVHD symptoms that improved by one grade in the interval between the determination of steroid refractoriness and the baseline aGVHD evaluation). One subject was excluded for both reasons; therefore, the total number excluded in the sensitivity analysis was 10 subjects.

3. Sensitivity set 1: These 10 subjects were removed from the analysis.

4. Sensitivity set 2: Ten excluded subjects were analyzed as treatment failures.

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

Analyses of Secondary Endpoints

[Table 20](#) summarizes the secondary endpoints as adjudicated by the FDA review team.

Table 20. Summary of Secondary Endpoint Outcomes

Secondary Endpoint	% (n/total)
OS at Day 100	74.5% (41/55)
OS at Day 100, stratified by responder status at Day 28	
Responder	86.6% (33/38)
Nonresponder	47.1% (8/17)
OS at Day 100, stratified by baseline aGVHD grade and organ involvement	
Grade B	50% (3/6)
Grade C	82.6% (19/23)
Grade D	73.1% (19/26)

Abbreviations: GVHD, graft-versus-host disease; OS, overall survival.

Subpopulation Analyses

The FDA confirmed the Applicant's subpopulation analysis of Day-28 ORR. The response rates were consistent in these subpopulation analyses including in subjects with higher grade aGVHD (Grade C and D) and subjects with high-risk aGVHD (high MacMillan risk score).

Duration of Response

DOR is a key metric in a single-arm study. [Table 21](#) below summarizes the DOR results based on the approaches used by the Applicant and the FDA.

Table 21. MSB-GVHD001 - Duration of Day-28 ORR

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 ¹	70.5	1, 171	N/A	N/A	N/A	N/A
FDA-defined DOR ²	54	7, 159+	50.5	10, 158+	57.5	7, 159+
FDA-defined alternative measure of durability ³	111.5	9, 182+	112+	16, 172+	111.5	9, 182+

Source: Table 19, BLA125706/0 Clinical Review Memo dated August 31, 2020

1. Applicant-defined DOR: the number of weeks that Day 28 response was maintained

2. FDA-defined DOR: The interval from the Day-28 response to progression, new systemic therapy for acute GVHD or death from any cause. Progression is defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment (i.e., progression from nadir). New therapy is defined as a new systemic treatment for aGVHD or an increase in the dose of corticosteroids to methylprednisolone 2 mg/kg (+/- 10%) equivalent.

3. FDA-defined alternative measure of durability: The interval calculated from Day-28 response to either death or need for new therapy for acute GVHD.

Abbreviations: CR, complete response; DOR, duration of response; N/A, not available; ORR overall response rate; PR, partial response

16.2. Appendix 2: OCE RWE Review

Regulatory Question(s):

- Question 1: Does the Agency agree that the use of a propensity-matched external control from the MAGIC consortium registry as a comparator to efficacy observed in an uncontrolled single-arm study is appropriate to establish evidence for substantial effectiveness in treatment of pediatric patients with SR-aGVHD?
- Question 2: Does the Agency agree that the propensity-matched control from an established observational registry such as the MAGIC consortium registry, sufficiently address and allay the risk of bias encountered with establishing an acceptable control in diseases like SR-aGVHD where there is potential for bias at multiple levels such as subject selection, disease staging, concomitant treatments as well as response assessment.

Real World Data (RWD) Proposal Key Elements

Cancer Grouping	Pediatrics
Cancer site	Rare Cancers
Indication	Treatment of pediatric patients with steroid-refractory acute graft-versus-host disease (SR-aGVHD)
Review documents	<ol style="list-style-type: none"> 1) Final Study Report: Prospective, Controlled Study Assessing Outcomes Using the Magic Algorithm Probability in Pediatric Patients with Steroid Refractory Acute Graft Versus Host Disease Treated with Remestemcel-L Compared to a Matched Cohort (MAGIC-MAP). Protocol Number MSB-GVHD001. Report Release Date November 1, 2022. 2) Final Study Report: Long-Term Clinical Outcomes of Pediatric Patients Treated with Remestemcel-L for Steroid-Refractory Acute Graft Versus Host Disease. Protocol Number MSB-GVHD001. Report Release Date December 6, 2022.
Study design	<ol style="list-style-type: none"> A) Externally controlled single-arm trial B) Long-term follow-up using registry data
Data source type/dataset	<ol style="list-style-type: none"> A) Mount Sinai Acute GVHD International Consortium Cohort B) Center for International Center for International Blood & Marrow Transplant Research Registry t
Primary real world outcome(s)	Objective response rate at day 28 Overall survival
Secondary real world outcome(s)	Relapse and non-relapse mortality (NRM) at Day 100 and 180 Cause of Death

Summary Review

- We concur with the clinical and CMC reviews that the information included in this new package does not address the potency issues outlined in the Complete Response letter and is therefore incomplete.
- The ability of these additional studies incorporating RWD to support a BLA cannot be determined based on the insufficient information provided. A complete submission would additionally include a prespecified protocol and SAP for each study.
 - FDA guidance recommends that protocols and SAPs for externally controlled trials should be pre-specified and discussed with the FDA early, prior to study initiation and analysis.¹

¹ U.S. FDA Draft Guidance. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Feb 2023. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products> (Accessed 2 June 2023).

- Note that the ability of a RWD study to support substantial evidence of effectiveness would be a review issue pending detailed interdisciplinary review of all study materials (i.e., protocol, SAP, and final study report), and clear and transparent presentation of all study results as pre-specified in the protocol and SAP.

Question 1: Does the Agency agree that the use of a propensity-matched external control from the MAGIC consortium registry as a comparator to efficacy observed in an uncontrolled single-arm study is appropriate to establish evidence for substantial effectiveness in treatment of pediatric patients with SR-aGVHD?

Answer: No, OCE RWE agrees with the Office of Oncologic Diseases that the results of this study cannot serve as an adequate and well-controlled study to support approval of remestemcel-L and do not provide sufficiently evaluable clinical information beyond the initial BLA 125706 submission. Because the study is not adequate and well-controlled, it cannot be used to establish substantial evidence of effectiveness. We note the following deficiencies based on review of the study report:

- **Pre-specification:** FDA guidance recommends that Applicants submit a protocol and SAP for FDA review prior to conducting any analyses for real-world data.² Good pharmacoepidemiology practice states that all analyses, including sensitivity analyses, should be pre-specified.³
- **Confounding:** There may be important differences in baseline characteristics between the MAGIC study participants and patients in Trial MSB-GVHD001, both measured and unmeasured (e.g., performance status, biomarker score data) that may impact the study results. There are key differences across treatment groups in measured covariates, including underlying disease type, donor type, HLA match, time from transplant to aGVHD diagnosis, IBMTR grade, Minnesota risk score.
- **Matching:** Based on the description of the methods in the final study report, it is unclear that propensity-score matching or matching of any kind was performed. The term “match” seems to be used here colloquially and incorrectly to describe alignment of the study selection criteria between the clinical trial and the MAGIC registry. If propensity score matching was performed, it is standard practice to report all diagnostics to ensure ability to evaluate matching adequacy.
- **Outcome measurement:** There is inadequate detail to determine if measurement of ORR outcomes in the MAGIC study is sufficiently

² See Reference 1.

³ Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf.* 2016 Jan;25(1):2-10.

comparable to measurement in the trial. This includes lack of information on dealing with competing risks, evaluating potential misclassification, or providing operational definitions.

- Additionally, blinded independent central review is generally considered best practice to eliminate evaluator bias, given that the study investigators know the patient treatment status.
- **Misclassification:** The potential misclassification of real-world covariates, including the stratification factors, may lead to unreliable study results. This is especially true given the very small sample sizes in certain strata.
 - Misclassification may be due to recording errors or recording differences across study sites.
- **Results:** The results for this study appear to be inconsistently presented; the lack of systematic presentation of results makes it challenging to interpret stratified results where the overall results are not presented concurrently or with rationale for combination of categories, which should be justified and clinically meaningful.
 - The reliance on such stratified analyses without prespecified plans, given these findings will not inform the indication and these analyses were not pre-specified, is a cause for concern about potential cherry-picking of results.
- **Analysis:** It is unclear whether other analytic approaches were considered.
 - Direct comparison of subjects in the trial compared to subjects in the MAGIC study using a weighted propensity score approach may be able to better account for potential confounding, while maximizing sample size.
 - Auditing is another aspect if a RWD study is supporting substantial evidence of effectiveness. The Applicant did not submit the real-world datasets and stated that they do not have right of reference or ability to provide the data.

Question 2: Does the Agency agree that the propensity-matched control from an established observational registry such as the MAGIC consortium registry sufficiently addresses and allays the risk of bias encountered with establishing an acceptable control in diseases like SR-aGVHD where there is potential for bias at multiple levels such as subject selection, disease staging, concomitant treatments as well as response assessment.

Answer: No. Please see above the description of outstanding concerns related, and not limited to, potential for confounding, outcome measurement, matching, and misclassification.

Additional Comments Regarding Real-World Data

Regarding the clinical study evaluating extended follow-up of Trial MSB-GVHD001 using data from the CIMBTR registry, we noted the following deficiencies based on the study report:

- Interpretability: Time-to-event endpoints such as OS cannot be interpreted in the context of a single-arm trial.
- Endpoint Ascertainment: There is little information on how follow-up is conducted in CIMBTR, and whether additional data sources are used to verify mortality.
- Important key clinical covariates may also not be available in the data for this study.

Detailed Observational Study Evaluation of MAGIC Study

Objective	Compare the Day 28 overall response and overall survival up to 6 months in pediatric subjects with SR-aGVHD treated with remestemcel-L compared to a matched cohort from the MAGIC database who received best-available second-line therapy (other than remestemcel-L), stratifying risk for outcomes using the IBMTR grading scale, the Minnesota GVHD risk score, and the MAGIC MAP score.	
Study design	Externally controlled trial	
Data sources	Trial MSB-GVHD001: Main trial Trial MSB-GVHD002: Additional follow-up of main trial	MAGIC Registry : MAGIC Database and Repository that was originally established in 2001 at the University of Michigan. In 2015, the database and biorepository relocated to the Icahn School of Medicine at Mount Sinai in New York
Study cohort/population	Patients at 20 study sites in the United States	21 active MAGIC centers located primarily in the United States and Germany but there are also centers in Thailand, Italy, and Canada. Two centers (University of Michigan and Technical University, Dresden, Germany) were moved to an inactive status in 2016, but both inactive centers respond to any data queries
Study period	Receipt of remestemcel-L followed until 100 +/- 7 days (001) or day 180 (002)	Receipt of 2L aGVHD therapy through day 180
Time zero	Receipt of remestemcel-L	Receipt of 2L aGVHD therapy (best available second-line therapy)
Study eligibility criteria	IBMTR Grades C and D aGVHD involving the skin, liver, and/or GI tract, or had Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease. Detailed inclusion and exclusion criteria available at clinicaltrials.gov	<ul style="list-style-type: none"> • Age less than 18 years • Transplanted from 2005 to 2019 • Related or unrelated donor • Any stem cell source • Any conditioning regimen • Any HLA-match • aGVHD initially treated with systemic steroids that met the criteria for SR-aGVHD (progression within 3 days or failure to improve within 7 days) and received second-line therapy • Grade B to D aGVHD, excluding patients with Grade B skin aGVHD only at the time of development of SR-aGVHD

Exposure	IV remestemcel-L at a dose of 2 × 106 MSCs/kg actual body weight at screening, twice per week for each of 4 consecutive weeks (initial therapy).	Patients received institutional standard of care for the prevention and treatment of aGVHD. Eligible patients had to have received systemic steroids with progression within 3 days of treatment or failure to improve within 7 days of treatment (to match the eligibility criteria for MSB-GVHD001) and received institutional standard of care second-line therapy
Primary endpoint/ outcome measures	ORR (CR + PR) at Day 28. If they died before Day 28, classified as a non-responder. Patients with data at Day 28 (incl. missing assessments or missing stage data) classified as non-responders.	
Other or exploratory outcomes	Overall survival (OS) day 100 and 180. Assessed from initial 2L therapy to end-of-study period, death, loss to follow-up (whatever occurred first). Non-relapse mortality treated relapse and second transplants as competing risks. Relapse at Day 100/180. Cumulative incidence of relapse, treating death or transplants as competing risks.	
Key clinical covariates	Stratification factors: IBMTR grading scale, the Minnesota GVHD risk score, and the MAGIC MAP score	
Estimated sample size	54 total; 25 had serum samples to calculate MAP score	30 total; 27 had serum samples to calculate MAP score
Analysis	Descriptive analysis by key clinical covariates at baseline across trial and ECA. Efficacy endpoints evaluated for each study arm; no formal statistical comparisons conducted. Results presented stratified by IBMTR Grade, Minnesota Risk Score, and MAP Score	
Data missingness and plan	Not described	

<p>Summary of preliminary results, if available</p>	<p>Descriptive, FAS: differences across treatment group in underlying disease, donor type, HLA match, time from transplant to aGVHD diagnosis, IBMTR grade, Minnesota risk score. Most common 2L therapies in MAGIC study were etanercept, ECP, and infliximab.</p> <p>ORR: overall 70.4% (trial) vs. 43.3% (MAGIC) Grade C/D 72.9% (trial) vs. 50% (MAGIC) High Minnesota Risk 71.1% (trial) vs. 35.5% (MAGIC)</p> <p>180 Day OS: Overall not presented Grade C/D 70.8% (trial) vs. 58.3 (MAGIC) Grade C 73% (trial) vs. 76.5% (MAGIC) High Minnesota Risk 68.4% (trial) vs. 47.1% (MAGIC) Standard Minnesota Risk 68.6% trial vs. 76.9% (MAGIC)</p> <p>100 Day OS: Not presented</p> <p>NRM: not presented</p> <p>Stratified by MAP Score (cut-off 0.29) 48% of trial patients and 37% of MAGIC patients classified as high-risk by MAP 0.29+.</p> <p>ORR: Low MAP 84% (trial) vs. 70.6% (MAGIC) High MAP 66% (trial) vs. 10% (MAGIC)</p> <p>100 Day OS: Low MAP 92% (trial) vs. 88% (MAGIC) High MAP 67% (trial) vs. 10% (MAGIC)</p> <p>180 day OS: Low MAP 77% (trial) vs. 88% (MAGIC) High MAP 67% (trial) vs. 10% (MAGIC)</p>
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Detailed Observational Study Evaluation CIMBTR Study

<p>Study objective</p>	<ul style="list-style-type: none"> To evaluate overall survival post-first remestemcel-L dose at 1, 2, 3 and 4 years To evaluate relapse/progression post-first remestemcel-L dose at 1, 2, 3, and 4 years To determine the cause of death
<p>Study design</p>	<p>Trial matched to registry for long-term follow-up</p>
<p>Data sources</p>	<p>Trial MSB-GVHD001: Main trial Trial MSB-GVHD002: Additional follow-up of main trial</p> <p>The CIMBTR collects transplant data on two levels, using a Transplant Essential Data (TED) form and a Comprehensive Report Form (CRF). The CIMBTR collects TED data on all patients. TED data are an internationally accepted standard data set that includes hundreds of details about patients' demographics, disease, treatment, response, side effects, and long-term outcomes</p>
<p>Study cohort/population</p>	<p>Patients at 20 study sites in the US who were also participating in the CIMBTR registry</p>

Study period	Receipt of remestemcel-L followed until 100 +/- 7 days (001) or day 180 (002)																		
Time zero	Receipt of remestemcel-L																		
Study eligibility criteria	<p>IBMTR Grades C and D aGVHD involving the skin, liver, and/or GI tract, or had Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease.</p> <p>Detailed inclusion and exclusion criteria available at clinicaltrials.gov</p> <p><u>Inclusion:</u></p> <ul style="list-style-type: none"> • Patient was enrolled in Mesoblast's Phase 3 clinical trial (MSB-GVHD001, NCT02336230). • Patient received at least one dose of remestemcel-L. • Patient had data reported to the CIBMTR, including CIBMTR Research ID, first date of remestemcel-L infusion, and International Bone and Marrow Transplant Research (IBMTR) Severity Index Grade of aGVHD at time patient was enrolled into Mesoblast's clinical trial. <p><u>Exclusion:</u> Patient did not provide consent to the CIBMTR's research database.</p>																		
Exposure	IV remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight at screening, twice per week for each of 4 consecutive weeks (initial therapy).																		
Primary endpoint/ outcome measures	Overall survival (OS): Event was defined as death due to any cause. In the absence of confirmation of death, post-first remestemcel-L dose OS was censored at the date the patient was last known to be alive. OS was described at 1, 2, 3 and 4 years following the first remestemcel-L dose by IBMTR Severity Index Grade in patients with adequate follow-up.																		
Other or exploratory outcomes	Cause of death: overall and by IBMTR Severity Index Grade																		
Key clinical covariates	IBMTR (stratification)																		
Estimated sample size	51 patients																		
Analysis	Kaplan-Meier estimates and 95% CIs of OS at 1, 2, 3, and 4 years were calculated. OS results were stratified by IBMTR Severity Index Grade. Cause of death was evaluated descriptively overall and stratified by IBMTR grade																		
Data missingness and plan	Not described																		
Summary of preliminary results, if available	<table border="1"> <thead> <tr> <th rowspan="2">Overall Survival</th> <th colspan="2">All Patients (n=51)</th> </tr> <tr> <th>Kaplan-Meier Estimate</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>1-year</td> <td>62.7%</td> <td>49.2, 75.4</td> </tr> <tr> <td>2-year</td> <td>50.8%</td> <td>37.1, 64.3</td> </tr> <tr> <td>3-year</td> <td>48.7%</td> <td>35.1, 62.3</td> </tr> <tr> <td>4-year</td> <td>48.7%</td> <td>35.1, 62.3</td> </tr> </tbody> </table>		Overall Survival	All Patients (n=51)		Kaplan-Meier Estimate	95% CI	1-year	62.7%	49.2, 75.4	2-year	50.8%	37.1, 64.3	3-year	48.7%	35.1, 62.3	4-year	48.7%	35.1, 62.3
Overall Survival	All Patients (n=51)																		
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Overall Survival	Grade B (n=6)	Grade C (n=22)	Grade D (n=23)
	K-M estimate (95% CI)	K-M estimate (95% CI)	K-M estimate (95% CI)
1-year	50.0% (14.1, 85.9)	72.7% (52.7, 88.8)	56.5% (36.3, 75.7)
2-year	50.0% (14.1, 85.9)	53.6% (32.7, 73.8)	47.8% (28.2, 67.5)
3-year	50.0% (14.1, 85.9)	48.2% (27.5, 69.2)	47.8% (28.2, 67.5)
4-year	50.0% (14.1, 85.9)	48.2% (27.5, 69.2)	47.8% (28.2, 67.5)
Median (range) follow-up (months)	56 (42-70)	62 (15-73)	62 (46-73)

The most frequent causes of death were organ failure (15.7%), acute GVHD (11.8%) and relapse of primary disease (11.8%). Only one patient died due to an infection as the primary cause of death.

16.3. Appendix 3: Acute GVHD Grading

Table 22. Criteria for IBMTR Severity Index for Acute GVHD

Index*	Skin involvement		Liver involvement		Gastrointestinal involvement	
	Stage (max.)	Extent of rash	Stage (max.)	Total bilirubin (µmol/l)	Stage (max.)	Volume of diarrhoea (ml/d)
A	1	< 25%	0	< 34	0	< 500
B	2	25–50%	or 1–2	34–102	or 1–2	550–1500
C	3	> 50%	or 3	103–255	or 3	> 1500
D	4	Bullae	or 4	> 255	or 4	Severe pain and ileus

*Assign Index based on maximum involvement in an individual organ system.

(Rowlings et al. 1997)

16.4. Appendix 4: List of FDA Group Terms and Preferred Terms

Table 23. List of FDA Group Terms and Preferred Terms Used in This Review

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

Abbreviations: HLGT, high-level group terms; HLT, high-level terms; PT, preferred term; SMQ, Standardised MedDRA Queries; NEC, not elsewhere classifiable.