Application Type	Re-submission addressing CRL
STN	125706/0
CBER Received Date	January 31, 2023
PDUFA Goal Date	August 2, 2023
Division / Office	DCEH/OTP
Committee Chair	Matthew Klinker
Clinical Reviewer(s)	Upendra Mahat
Project Manager	Adriane Fisher
Priority Review	Yes
Reviewer Name(s)	Qianmiao Gao
Review Completion Date / Stamped Date	August 1, 2023
Supervisory Concurrence	Zhenzhen Xu, Ph.D Team Leader, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
	John Scott, Ph.D. Director, FDA/CBER/OBPV/DB
Applicant	Mesoblast, Inc
Established Name	Remestemcel-L, Ex Vivo Cultured Adult Human Mesenchymal Stem Cells (MSCs)
(Proposed) Trade Name	REMESTEMCEL-L
Pharmacologic Class	Ex-vivo cultured adult human mesenchymal stromal cells (MSCs)
Formulation(s), including Adjuvants, etc	Remestemcel-L were formulated in Plasma-Lyte A physiologic electrolyte solution with human serum albumin (HSA) and dimethyl sulfoxide (DMSO).
Dosage Form(s) and Route(s) of Administration	Cell suspension for intravenous infusion in a concentration of 6.68 X 10e6 ce-MSCs per mL in 3.8 mL contained in a 6 mL cryovial.
Dosing Regimen	2 × 10e6 cells/kg body weight
Indication(s) and Intended Population(s)	Pediatric subjects with acute Graft versus Host Disease (aGVHD) following allogeneic hematopoietic stromal cell transplant (HSCT) that has failed to respond to treatment with systemic corticosteroid therapy.

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GLOSSARY

Abbreviation	Definition
aGVHD	Acute Graft versus Host Disease
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	Complete response
FAS	Full analysis set
GVHD	Graft versus Host Disease
HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
IBMTR	International Blood and Marrow Transplant Registry
IMP	Investigational medicinal product
IND	Investigational new drug
ITT	Intent-to-treat
Kg	Kilogram
MAGIC	Mount Sinai Acute GVHD International Consortium
MAP	MAGIC algorithm probability
Max	Maximum
mFAS	Modified full analysis set
Min	Minimum
mITT	Modified intent-to-treat
NR	No response
NRM	Non-relapse mortality
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PP	Per-protocol population
PR	Partial response
SD	Standard deviation
SR-aGVHD	Steroid refractory acute graft versus host disease

1. Executive Summary

This application includes a response to a complete response letter issued by the FDA in 2020. This section of the statistical review memo for the response includes a high-level summary of the statistical review for the original submission (please see attached statistical memo by Dr. Stan Lin), and a summary of the resubmission containing additional efficacy evidence.

This BLA seeks licensure of remestemcel-L for the treatment of steroid-refractory acute graft versus host disease (SR-aGVHD) in pediatric patients, whose aGVHD has failed to respond to treatment with systemic corticosteroids. The original submission was submitted on January 31, 2020. The primary source of evidence on efficacy was a multicenter, single-arm study (MSB-GVHD001). The primary efficacy endpoint of overall response rate (ORR) at Day 28 was analyzed in the Full Analysis Set (FAS)

containing 55 pediatric patients. Study MSB-GVHD001 met its primary efficacy endpoint with an ORR of 69.1%, rejecting the pre-specified null hypothesis of 45% with a one-sided exact p-value of 0.0003 under Binomial distribution. However, considering the limitation of the single-arm study, and the failed outcomes of two previously conducted randomized, double-blind, placebo-controlled, multicenter studies, the FDA held an Oncologic Drugs Advisory Committee (ODAC) meeting on August 13, 2020. Although the Advisory Committee of the FDA voted 9 to 1 in favor of the approval of remestemcel-L, most members recommended that the applicant perform additional adequate and well-controlled studies to confirm the efficacy signal. The Office of Tissues and Advanced Therapies (OTAT) issued a Complete Response Letter (CRL) on September 30, 2020, which commented that the deficiency in the study design of MSB-GVHD001 made the study results highly susceptible to bias and therefore was difficult to interpret. To meet the statutory requirement for a marketing approval, 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.

In the BLA resubmission on January 31, 2023, the applicant provided an additional source of evidence on efficacy. Instead of conducting a randomized, well-controlled study as FDA had recommended, the applicant performed a retrospective analysis by comparing the patients in Study MSB-GVHD001 with an external control group from Mount Sinai Acute GVHD International Consortium (MAGIC) database. In addition, the applicant analyzed the long-term survival data of patients treated with remestemcel-L in Study MSB-GVHD001 conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR).

The two retrospective studies were not adequate or well controlled to assess the efficacy and safety of the investigational product. From the statistical perspective, it is very difficult to interpret overall survival (OS) benefits in an uncontrolled, single-arm study setting. Furthermore, the analyses comparing the patients in MSB-GVHD001 and the external control group from the MAGIC database are subject to bias due to the heterogeneity of the underlying population, selection bias, and unmeasured confounding. Although the applicant claims the control group was a propensity-matched cohort, they did not detail how the control group was matched to the study group according to the estimated propensity score.

Therefore, I conclude that the BLA does not meet the statutory requirement for substantial evidence of effectiveness to support the approval, and recommend that the applicant conduct at least one adequate randomized, well-controlled study to provide evidence of the effectiveness of remestemcel-L in the treatment of SR-aGVHD, as conveyed in the CRL of the original submission.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Acute graft versus host disease (aGVHD) is a life-threatening complication in patients who undergo allogenic hematopoietic stem cell transplantation (HSCT) for various malignant and non-malignant diseases. Acute GVHD occurs when the immunocompetent T cells in the graft recognize recipient cells as foreign and mount an immune attack. Patients with severe aGVHD who fail to respond to first-line steroid therapy (steroid refractory [SR])-aGVHD) have the highest risk of treatment failure.

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

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

Table 1 outlines major Pre- and Post-submission regulatory activities associated with this BLA resubmission.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Dates	Events
January 31, 2020	Initial BLA submission
August 13, 2020	ODAC meeting
September 30, 2020	A Complete response letter was issued
March 31, 2021	Formal Dispute Resolution Request (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 responded to CRL and the BLA was resubmitted
February 13, 2023	Resubmission Kickoff Meeting
June 2, 2023	Mid-Review Meeting
August 2, 2023	FDA Action Letter Due Date

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The datasets for the long-term OS analyses by CIBMTR were not submitted in the resubmission (125706/0.65) but were submitted by CIBMTR via Type V Master File (b) (4), in response to FDA Information Request.

The dataset for the external control group from MAGIC database were not submitted. The applicant explained that the source data and information presented for the MAGIC cohort were collected and analyzed by the consortium at Mt. Sinai and thus were not made available to them due to rules of confidentiality.

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

5.1 Review Strategy

The primary source of evidence to support the efficacy for the indication comes from the CSR of Study MSB-GVHD001 in the original submission. The review for this study is documented in the statistical review memo for the BLA original submission.

In the resubmission, the applicant provides additional information to support efficacy, which consists of (1) CSR of the long-term OS analyses by CIBMTR and (2) CSR of the analysis comparing patients in MSB-GVHD001 and the external control from MAGIC registry database. The statistical review of the resubmission focuses on this additional supportive information.

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

The basis of this statistical memo includes review of CSRs and datasets submitted under module 5 of BLA 125706/0.65; additional datasets submitted under Master File (b) (4) ; and IR response under BLA 125706/0.76 and 0.82.

5.3 Table of Studies/Clinical Trials

The studies pertinent to the pediatric indication were listed in the statistical memo for the original BLA submission.

Table 2 summarizes the two studies reviewed by the statistical team in the BLA resubmission.

Table 2. Studies Reviewed During Evaluation of BLA Resubmission

Study	Design	Study Status	Subject level data submitted
CIBMTR long-term survival study (Module 5.3.4)	Long term survival analyses provided by CIBMTR	Complete	Yes, under MF (b) (4)
MAGIC propensity control study (Module 5.3.4)	External control from MAGIC registry data	Complete	No

(Source: Adapted from BLA125706/0.65 Module 5.3.4)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The supportive evidence for efficacy is summarized in Section 6.1 (long-term OS analysis for Study MSB-GVHD001 conducted by CIBMTR) and 6.2 (analysis comparing subjects in Study MSB-GVHD001 with an external control group from MAGIC database). Please refer to the statistical review memo for the evaluation of the original submission for Study MSB-GVHD001.

6.1 Long-Term OS Analysis for Study MSB-GVHD001 by CIBMTR

6.1.1 Objectives

- To evaluate overall survival post-first remestemcel-L dose at 1, 2, 3 and 4 years
- To determine the cause of death

6.1.2 Design Overview

This study, conducted by CIBMTR, was a retrospective observational cohort study to assess OS up to 4 years for patients who participated in Study MSB-GVHD001. Overall survival (OS) from the first remestemcel-L dose to death due to any cause was the primary endpoint. OS was estimated by the Kaplan-Meier (K-M) method for the overall population and for each IBMTR Severity Index Grade (B, C, and D). Median follow-up of survivors was provided. Survival probabilities with the corresponding 95% confidence intervals (CI) were estimated. A total of 51 subjects participated in this observational study.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The inclusion of patients from Study MSB-GVHD001 to CIBMTR's analysis set is presented in Table 3.

Table 3: Summary of Patient Disposition

Selection Criteria	No. Excluded	No. Patients
Enrolled in MSB-GVHD001	--	55
Excluded patients who did not receive remestemcel-L	1	54
Excluded patients who declined to participate in CIBMTR's Research Database	1	53
Excluded patients who were not approached about participating in CIBMTR's Research Database	2	51

(Source: Adapted from BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.16)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Overall Survival Unstratified

The estimated median duration of follow-up among the patients who participated in CIBMTR analysis was 62 months. The estimated range of follow-up among the 23 survivors was 15-73 months.

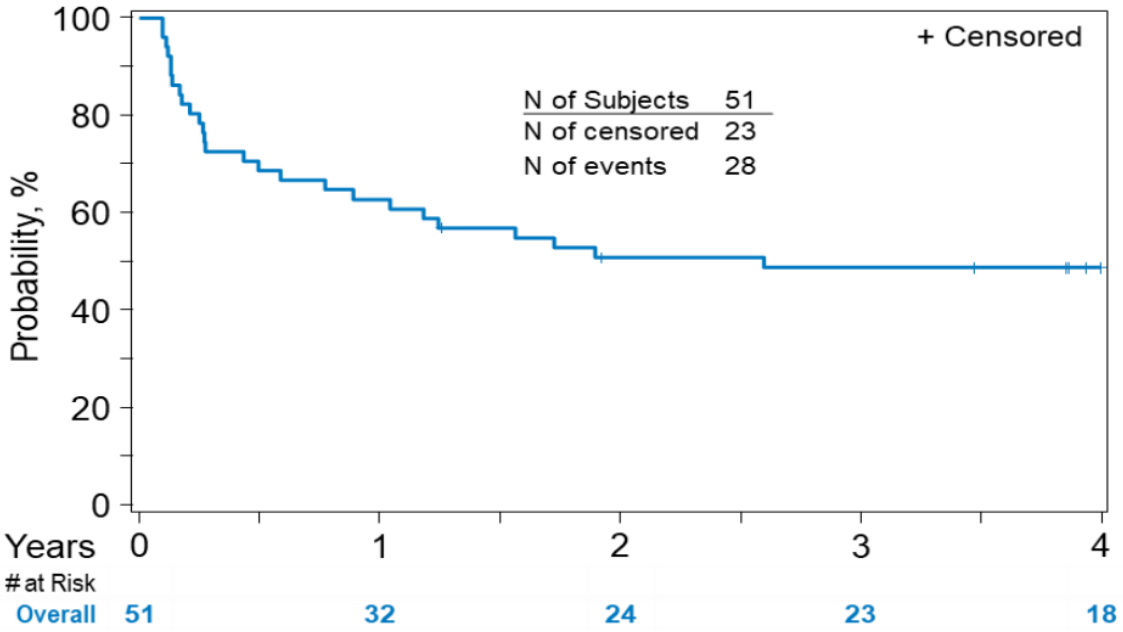
Table 4 shows the K-M estimate of the survival probability and its 95% CI at 1, 2, 3 and 4 years after first Remestemcel-L dose. Figure 1 shows the K-M plot of OS up to 4-years after the first remestemcel-L dose.

Table 4: Kaplan-Meier Estimates for OS at 1, 2, 3 and 4 Years after First Remestemcel-L Dose

Overall Survival	Patients Participated in CIBMTR Analysis (n=51)	
	Kaplan-Meier Estimate of survival probability	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

(Source: Adapted from BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.17)

Figure 1: Kaplan-Meier Estimates for OS up to 4-years after First Remestemcel-L Dose



(Source: BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.17)

<u>Overall Survival Stratified by IBMTR Severity Index Grade</u>

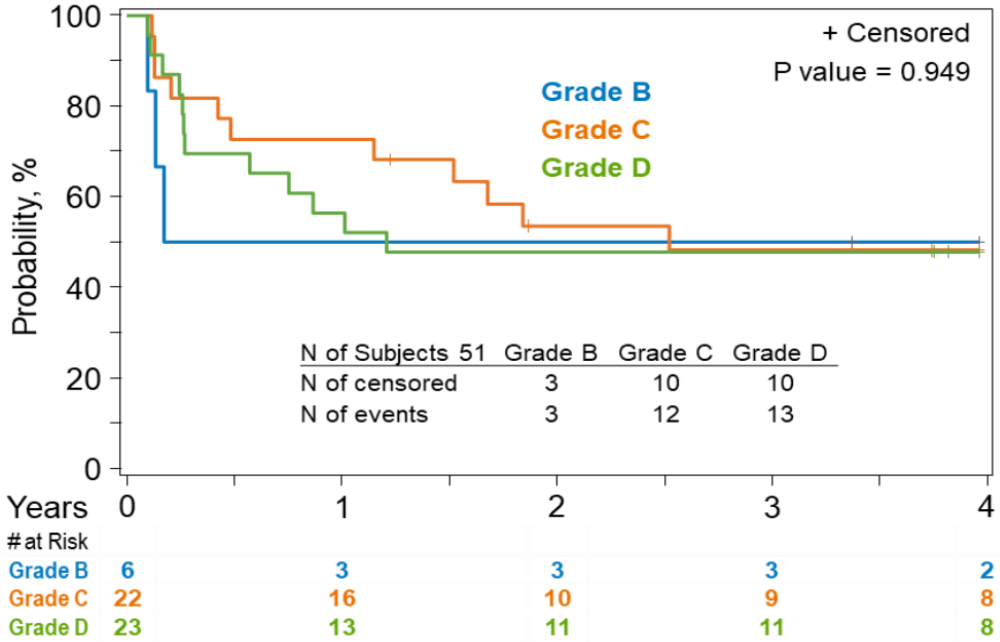
Table 5 shows the K-M estimates of survival probabilities up to 4 years after first remestemcel-L dose by baseline (time of enrollment into MSB-GVHD001) IBMTR Severity Index grade. Figure 2 shows the K-M plot for OS up to 4 years after first dose of remestemcel-L by baseline IBMTR Severity Index Grade.

Table 5: Survival Probabilities up to 4 years after First Remestemcel-L Dose by IBMTR Severity Index Grade

Overall Survival	K-M estimates (95% CI)		
	Grade B (n=6)	Grade C (n=22)	Grade D (n=23)
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 (range) follow-up (months)	56 (42-70)	62 (15-73)	62 (46-73)

(Source: Adapted from BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.18)

Figure 2: Kaplan-Meier Estimates for OS up to 4 years after First Remestemcel-L Dose by Baseline IBMTR Severity Index Grade



(Source: BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.19)

Reviewer comment:
The applicant states that the long-term overall survival analysis indicates a positive outcome for remestemcel-treated patients in MSB-GVHD001, and the effect of remestemcel-L was evident in patients with the most severe form of the disease (Grade C-D). The applicant believes that the observed long-term overall survival virtually eliminates the possibility that the early outcome results previously reported were due to chance. From the statistical perspective, it is very difficult to interpret the clinical benefits on a time-to-event endpoint such as OS under an uncontrolled, single-arm study setting, without a proper comparator arm.

6.1.12 Safety Analyses

For the safety summary of Study MSB-GVHD001, please refer to the statistical memo for the original submission. The safety summary by CIBMTR analysis is summarized in the following sections.

6.1.12.1 Methods

CIBMTR study listed the number and causes of death of the participants.

6.1.12.3 Deaths

Table 6 shows the survival status and causes of deaths for subjects enrolled in Study CIBMTR, for the overall population and by baseline IBMTR Severity Index Grade.

Table 6. 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	3	10	10
Died	28	3	12	13
Organ failure	8	2	1	5
GVHD	7	1	3	3
Primary disease	6	0	3	3
IPn/ARDS	2	0	2	0
Gastrointestinal hemorrhage	1	0	0	1
Graft failure	1	0	1	0
Infection	1	0	1	0
Metabolic acidosis	1	0	0	1
Stroke	1	0	1	0

(Source: Adapted from BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.19)

6.2 Analysis Comparing Subjects in MSB-GVHD001 and An External Control Group from MAGIC Database

The applicant has submitted an ad hoc retrospective study comparing ORR at Day 28 and OS up to 6 months between the patients in MSB-GVHD001 and an external control group from the Mt Sinai acute GVHD international consortium (MAGIC) database. MAGIC is an international GVHD consortium located at Icahn School of Medicine at Mt Sinai in New York. Currently there are 21 active MAGIC centers primarily in the US and Germany.

Reviewer comment:
There was no agreement on any study protocol or SAP between the applicant and the FDA prior to the conduct of this retrospective study. Further, the applicant was unable to provide the dataset from the MAGIC database in the resubmission or upon FDA's information request. Per the applicant, the source data and information presented for the MAGIC cohort were collected and analyzed by the consortium at Mt. Sinai. Due to rules of confidentiality, the source data were not made available to Mesoblast. The CSR presents the results reported directly from Mt. Sinai. Therefore, I just present the study conducted by MAGIC in this section. The data and results cannot be replicated or verified by FDA.

6.2.1 Objectives

To compare the overall response at Day 28 and overall survival up to 6 months in pediatric patients with SR-aGVHD treated with remestemcel-L to a matched cohort from MAGIC database who received best available second line therapy (other than remestemcel-L) stratifying risk for outcomes using (1) the International Bone Marrow Transplant Registry (IBMTR) grading scale, (2) the Minnesota GVHD risk score, and (3) the MAGIC MAP score.

6.2.2 Design Overview

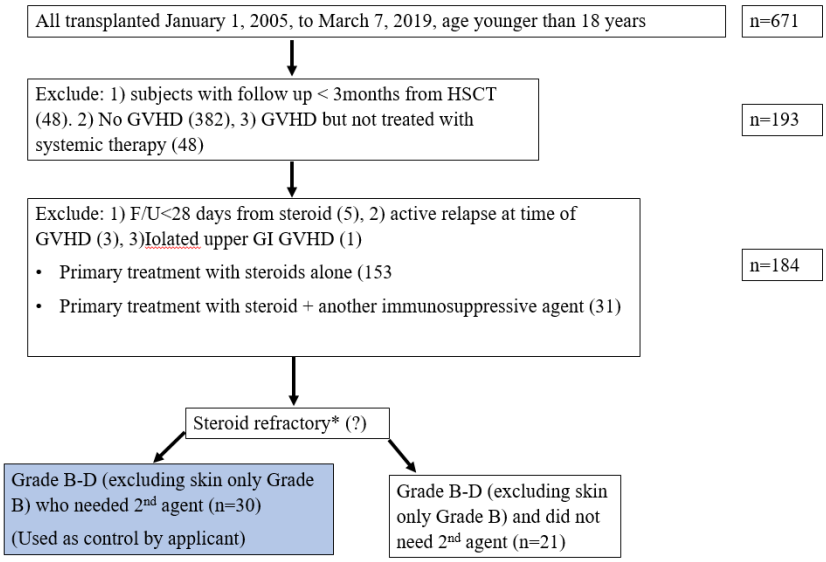
Retrospective study that compares the patients in single-arm MSB-GVHD001 trial and an external control group from MAGIC database.

6.2.3 Population

Population from Study MSB-GVHD001:
Pediatric patients who enrolled in MSB-GVHD001 and received at least one dose of remestemcel-L.

Population from MAGIC database:
Patients in the MAGIC database who matched the key eligibility criteria that was established for MSB-GVHD001. Figure 3 summarizes the methodology used for selection of MAGIC control group. A total of 30 patients were selected as control by the applicant.

Figure 3. Schematic Summary of Methodology Used for Selection of MAGIC Control Group



(Source: Adapted from BLA 125706/0.65 Module 5.3.4; cibmtr-clinical-study-report, p.61)

6.2.8 Endpoints and Criteria for Study Success

- Overall response at Day 28
- Overall survival at Day 180

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations as reported in the CSR are described in the following:

Statistical hypothesis:
Alternate hypothesis: The second line treatment with remestemcel-L is more effective in high-risk patients compared to high-risk patients treated with institutional standard of care second line therapy for SR-aGVHD in pediatric patients.

Reviewer comment:
No study protocol or hypothesis testing method were submitted to or discussed with the FDA prior to the conduct of the study. The analyses were considered exploratory.

Analysis populations:
Two analysis populations were established for this study.

Analyses stratified by IBMTR grade and Minnesota risk score:
MSB-GVHD001 cohort:

Pediatric patients who enrolled in MSB-GVHD001 and received at least 1 dose of remestemcel-L.
MAGIC cohort:
Pediatric patients who did not respond to steroids, received best available second line therapy, and had Grade B to D disease (excluding Grade B skin only).

Analyses stratified by baseline MAP score:
MSB-GVHD001 cohort:
Pediatric patients who enrolled in MSB-GVHD001, received at least 1 dose of remestemcel-L, and had serum samples taken at the time of the first dose of remestemcel-L.
MAGIC cohort:
Pediatric patients who were included in the analysis set for analyses stratified by IBMTR grade and Minnesota risk score, and had serum samples available for measurement of ST2 and REG3α at the time of initiation of second line therapy.

Statistical methods:
The two groups were compared by descriptive statistics.

Stratification:
The applicant stratified patients by three stratification strategies as follows.

- Stratify patients into Grade B, C, vs. D by IBMTR grading scale.[1]
- Stratify patients into standard-risk vs. high-risk patients by the Minnesota GVHD risk score.[2]
- Stratify patients into low vs. high risk of non-response mortality (NRM) based on MAGIC algorithm probability (MAP) biomarker score, by the threshold of MAP <0.29 vs. >=0.29.[3]

Sample size and power calculation:
A total of 30 patients from the MAGIC database and all 54 patients who were enrolled and received at least 1 dose of remestemcel-L in MSB-GVHD001 were included in the analysis stratified by IBMTR grade and Minnesota risk score.

A total of 27 patients in the MAGIC database and 25 patients from MSB-GVHD001 study were included in the analysis stratified by MAP score.

No formal sample size and power calculation were performed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

The median age of the patients in the MAGIC cohort was 6 years (range: 0-17 years) compared to 7.8 years (range: 0.7-18.0 years) in the MSB-GVHD001 study.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Table 7 shows the baseline (at time of initiating second line therapy) characteristics for aGVHD. Table 8 listed the number of patients with the second-line therapies for SR-aGVHD. Table 9 shows the baseline MAP scores.

Table 7. 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: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.33)

Table 8: 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. Note: MSB-GVHD001 patients received remestemcel-L as second line therapy.
(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.34)

Table 9: Baseline MAP Score

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

(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.38)

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoints

No primary analysis was prespecified.

6.2.11.5 Exploratory and Post Hoc Analyses

Outcomes Stratified by IBMTR grade and Minnesota risk score:

Overall Response at Day 28

Table 10 shows the OR at Day 28 by IBMTR grade and Minnesota risk score.

Table 10: Overall Response at Day 28 by IBMTR Grade and Minnesota Risk Score

Outcomes n (%)	**MSB-GVHD001 N=54**	**MAGIC N=30**
Day 28 overall response	38 (70.4)	13 (43.3)
CR	16 (29.6)	7 (23.3)
PR	22 (40.7)	6 (20.0)
Day 28 overall response		
Grade B	3/6 (50.0)	1/6 (16.7)
Grade C	16/23 (69.6)	10/17 (58.8)
Grade D	19/25 (76.0)	2/7 (28.6)
Grade C or D	35/48 (72.9)	12/24 (50.0)
Minnesota risk score		
Standard risk	11/16 (68.8)	7/13 (53.8)
High risk	27/38 (71.1)	6/17 (35.3)

(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.35)

Overall Survival at Day 180

Table 11 presents the OS at Day 180 stratified by IBMTR grade and Minnesota risk score.

Table 11: 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)

(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.35)

Outcomes Stratified by MAP Score:

Overall response at Day 28

Table 12 shows the OR by Day 28 for patients by baseline MAP. For patients with a MAP <0.29, 84.6% of remestemcel-L treated patients and 70.6% of the patients in the MAGIC cohort achieved an overall response by Day 28. For patients with MAP ≥0.29, 66.7% of the remestemcel-L treated patients and 10% of the MAGIC cohort patients achieved an overall response by Day 28.

Table 12: Overall Response at Day 28 Stratified by Baseline MAP

Day 28 Response n (%)	**MSB-GVHD001 (N=25)**		**MAGIC (N=27)**	
Baseline MAP	≥0.29 n=12	<0.29 n=13	≥0.29 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)	5 (18.5)

Abbreviations: CR: complete response; PR: partial response; NR: no response; MAP: MAGIC algorithm probability.
(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.43)

Overall Survival at Day 180

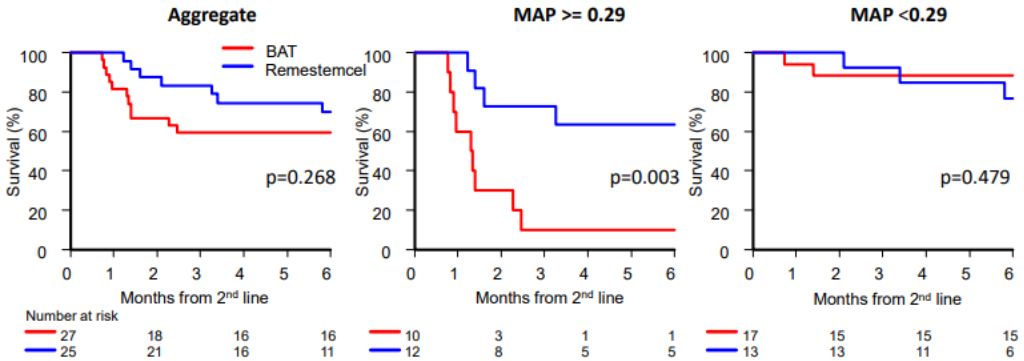
Table 13 shows the Overall Survival at Day 180 stratified by baseline MAP. Figure 4 shows the Kaplan-Meier estimates of 6-month survival probabilities for patients in the overall population, in the strata with a low MAP (<0.29), and the strata with a high MAP (≥0.29), respectively**.**

Table 13: Overall Survival at Day 180 Stratified by Baseline MAP

Outcomes n (%)	**MSB-GVHD001 (N=25)**		**MAGIC (N=27)**	
Baseline MAP	≥0.29 n=12	<0.29 n=13	≥0.29 n=10	<0.29 n=17
OS by Day 180	8 (66.7)	10 (76.9)	1 (10.0)	15 (88.2)

(Source: Adapted from BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.46)

Figure 4: Kaplan-Meier Estimates of 6-month Overall Survival for the Two Patient Cohorts by Baseline MAP



Abbreviations: MAP: MAGIC algorithm probability; BAT: best available therapy.
(Source: BLA125706/0.65, Module 5.3.4; magic-map-clinical-study-report, p.46)

<u>Reviewer comment:</u>
I consider the analyses comparing the patients in MSB-GVHD001 and the external control group from the MAGIC database to be inconclusive, based on the following consideration:

1. *The applicant was unable to provide the dataset from the MAGIC database in the resubmission or upon FDA information request.*
2. *No prespecified study protocol or statistical analysis plan were provided before the analysis or in the resubmission.*
3. *The applicant's selection of the control group was biased, especially due to the exclusion of 21 pediatric patients in MAGIC database who had failed steroids alone and did not receive any second line therapy. Please refer to clinical reviewer's memo for the BLA resubmission for details.*
4. *According to the method of selecting patients for the MAGIC cohort (p. 61 of CSR), the patients in the control group were selected based on baseline demographics and medical experiences (Figure 3). This cannot guarantee the desired baseline covariate balance between treatment groups, because*
    a. *The unmeasured confounding effect cannot be accounted for.*
    b. *Although the applicant states the control group was a propensity-matched cohort, the applicant does not submit the details of the propensity score matching analysis or demonstrate how the control group was matched to the study group according to the estimated propensity score.*
    c. *It is difficult to justify the propensity score is properly estimated as the true propensity score model is unknown.*

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence on efficacy to support the marketing application was a multicenter, single-arm study (MSB-GVHD001) provided in the original submission of this BLA. FDA considers the original submission insufficient to provide statistical evidence to support the applicant's indication for Remestemcel-L in pediatric subjects.

The additional information on efficacy provided in the BLA resubmission consists of (1) an analysis on the long-term survival data of patients treated with remestemcel-L in Study MSB-GVHD001 conducted by CIBMTR, and (2) a retrospective analysis comparing the patients in Study MSB-GVHD001 with an external control group from MAGIC database.

From the statistical perspective, it is very difficult to interpret OS benefits in an uncontrolled, single-arm study setting. Furthermore, the analyses comparing the patients in MSB-GVHD001 and the external control group from the MAGIC database are subject to bias due to the heterogeneity of the underlying population, selection bias, unmeasured confounding, etc. Although the applicant claims the control group was a propensity-matched cohort, they do not demonstrate how the control group was matched to the study group according to the estimated propensity score.

10.2 Conclusions and Recommendations

The BLA does not meet the statutory requirement for the substantial evidence of effectiveness to support an approval. I recommend that the applicant conduct at least one adequate randomized, well-controlled study to provide evidence of the effectiveness of remestemcel-L in the treatment of SR-aGVHD, as conveyed in the CRL of the original submission.

REFERENCES

[1] Rowlings, "IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade," *British Journal of Haematology,* 1997.

[2] MacMillan, "Pediatric acute GVHD: clinical phenotype and response to upfront steroids," *Bone Marrow Transplant,* 2020.

[3] Hartwell, "An early-biomarker algorithm predicts lethal graft-versus-host disease and survival," *Clinical Medicine,* 2017.