



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

MEMORANDUM

From: Jonathan D. Reich, MD
Medical Officer, Pharmacovigilance Branch 2 (PB2)
DPV, OBPV, CBER

To: Adriane Fisher, PhD
RPM, Office of Therapeutic Products (OTP), CBER

Through: Christopher Jason, MD
Branch Chief, PB2, DPV, OBPV

Meghna Alimchandani, MD
Deputy Division Director, DPV, OBPV

Subject: Pharmacovigilance Plan Review of Resubmitted BLA

Applicant: Mesoblast, Inc.

Product: Remestecel-L/Ryoncil

Application: BLA/STN 125706/0/65

Proposed Indication: Ryoncil is indicated for the treatment of Steroid-refractory acute Graft versus Host Disease (SR-aGvHD) in pediatric patients as young as 2 months old.

Submission Date: January 31, 2023

Action Due Date: August 2, 2023

1. Objective

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP) to monitor postmarketing safety for Remestecel-L based on available data on its safety profile. This memo will focus on reviewing new safety data submitted by the applicant since the complete response (CR) of the previous application in 2020, and will address the adequacy of the PVP in light of the new data.

2. Product Information

2.1 Product Description

Remestecel-L is a prepared treatment composed of human mesenchymal stem cells (MSCs). The MSCs are administered intravenously (IV) to patients with SR-aGVHD Grades B to D who had allogeneic human stem cell transplantation (HSCT) and failed to respond to standard treatment.

The dosage consists of: an infusion of 2×10^6 MSCs/kg (actual body weight at screening) twice weekly for 4 consecutive weeks. Infusions are administered at least 3 days apart and no more than 5 days apart. All infusions are administered within 28 days (± 2 days) of the first infusion. *Continued Therapy:* Treatment consisted of 4 once-weekly infusions of remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight at screening. No additional mesenchymal stem cell (MSC) therapy is allowed at any time thereafter.

2.2 Proposed Indication

Ryoncil/Remestecel-L is indicated for the treatment of Steroid-refractory acute Graft versus Host Disease (SR-aGVHD) in pediatric patients as young as 2 months old.

2.3 Pertinent Regulatory History

Ryoncil/Remestecel-L has not been licensed in the US or elsewhere. As noted above, the file was submitted previously and returned to the applicant in September 2020 with the above comments regarding the adequacy of the clinical data.

The file received orphan drug designation in 2017. The IND number under which this product was initially submitted is (b) (4).

The file received a complete response (CR) on September 30, 2020. It was the FDA's determination that the submitted data did not provide confirmatory evidence of efficacy to support a license application. Due to insufficient clinical data to support the application, a recommendation for the file was returned to the applicant detailing a future study which would support a licensing application. A new licensing application for this product was submitted on December 30, 2022. The application contains a new pharmacovigilance plan which includes an assessment of the safety information in two studies. The applicant has submitted the results from a new clinical trial, which is

designated msb-iit015-084 and can be found at 125706/0/65 under 5.3.5.2. The new PVP can be located at BLA: 125706/0/65), 1.16.

Two additional issues were noted in the CR letter. The product lacked an appropriate potency assay and the facility in Singapore where the product was produced required inspection by OCBQ.

2.4 Worldwide Distribution Data and Post-Marketing Exposure

The product is not licensed in any country. Consequently, there are no post-marketing data as of the data lock point of this BLA.

3. Review of Interval Safety Data

3.1 Review of studies presented to the FDA resulting in the CR letter of September 2020

The applicant submitted a number of preliminary studies in their previous marketing application. These studies were single-arm unblinded studies. These results were reviewed by the clinical reviewer at OTP and the conclusion is that these studies, most significantly MSB-GVHD001 were too subjective and unreliable from which to draw clinical conclusions.

3.2 Review of Data Provider from the Expanded Access Single Patient Use Study (MSB-IIT015-084)

In response to the deficiencies in safety data identified in the clinical memo and CR letter, the applicant has submitted additional safety data to support their marketing application. The study referenced above was submitted to the FDA in December 2022 providing patient experiences as of the data lock point of July 2022.

3.2.1 Study Description

A. Study Design: Expanded access, single-patient treatment protocol. Enrolled patients had to have failed a course of systemic steroids and at least one second line treatment for GVHD.

B. Protocol dates: The protocol is on-going. This safety summary is based on a data cutoff point of June 2022. First patient, first treatment: March 24, 2017. Last patient, last treatment: April 06, 2022

C. Objectives: 1. To evaluate the safety of repeated doses, by reports of serious adverse events (SAEs) when MSCs were administered intravenously (IV) to patients with SR-aGVHD Grades B to D who had allogeneic human stem cell transplant (HSCT) and failed to respond to steroid treatment

2. To determine if there were any infusion reactions (a reaction suspected to have been caused by the therapeutic agent, diluent, or delivery vehicle).

D. Endpoints: 1. Serious adverse events (SAEs), 2. Infusion reactions

E. Number of Patients Treated: 43 patients, each from a specific expanded access protocol, are included in this safety synopsis. Enrollment in these Investigator-initiated, single-patient, expanded access protocols is ongoing. This report includes data for the 43 patients who were initiated on remestemcel-L on a compassionate expanded access basis by the cut-off date 07 Jun 2022.

F. Inclusion and Exclusion Criteria: Patients between 2 months and 26 years of age who were experiencing graft vs. host disease refractory to steroids were eligible. Their GVHD grade needed to be B, C, or D, and they had to have received at least 3 days of methylprednisolone without demonstrable benefit. Patients were excluded from the study if they had: 1) alveolar disease, 2) any other medical or psychiatric condition which in the opinion of the investigator rendered them ineligible (for example, heart failure), 3) they had received a stem cell preparation (including human stem cell transfer therapy) as therapy within 30 days of the start of Remestecel-L therapy, or 4) had any of the following specifically mentioned co-morbid conditions: hepatic veno-occlusive disease, encephalopathy, or active HIV/hepatitis B or C infections.

Additional exclusion criteria included: pregnancy, lactation, being a female of childbearing age who refused to use contraception (this included males with a female partner of child bearing age in which there was a similar refusal), patients actively receiving therapy for a solid tumor, patients who had previously received an experimental treatment for GVHD, and patients sensitive to various components of the treatment.

G. Treatment Protocol:

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. Patients received as many as 20 infusions.

No additional mesenchymal stem cell (MSC) therapy was allowed at any time.

H. Endpoints (Evaluation Criteria)

There was no assessment of efficacy performed. Two safety endpoints were evaluated: Serious Adverse Events (SAE) and infusion reactions.

3.2.2 Study Results

A total of 43 patients were enrolled in the study and received treatment. Of these, 38 patients completed the study (88%) and the remaining 5 patients were discontinued early (12%). The mean age of the patients was 12.5 years (\pm 10.6 years (SD)),

Patient demographics (N=43):

Male: 29 (67.4%)

Female: 14 (32.6%)

White: 23 (53.5%)

Black (African-American): 14 (32.6%)

Other: 6 (13.9%)

<18 years of age: 34 (79.1%)

\geq 18 year of age: 9 (20.9%)

The most common indication for HSCT was acute myeloid leukemia (20.6%), followed by acute lymphocytic leukemia (18.6%).

The grading system used in the study to characterize Graft vs. Host Disease is based on histologic activity, more specifically the percentages of apoptotic cells. GVHD is graded A-D with grade A being the most mild.¹ In this study, the most common grade of SR-aGVHD at baseline was Grade D (n=21, [48.8%]), followed by Grade C (n=14, [32.6%]).

Most patients (58.1%) received 12 infusions of remestecel-L. The remainder of the patients received varying amounts based on their clinical status and response to therapy.

Twenty-nine patients (67.4%) reported 79 SAEs. There was no single SAE nor involved organ system that was mentioned in the majority of the reports. The most common SAE reported was sepsis, which was reported in 6 patients (14.0%) and the most common organ system was “infectious” which comprised 13 patients’ complaints (30.2%), followed by “respiratory” which comprised 8 patients (18.2%). For a list of the most common SAEs reported in the applicant’s submitted dataset please see the table below.

Table 2: SAEs, organ system, and number of patients reporting:

SAE	Organ System	Number of Patients (%)
Sepsis	Infectious	6 (14.0%)
Respiratory Failure/Hypoxia	Respiratory	6 (14.0%) ²

GI hemorrhage	Gastrointestinal	4 (9.3%)
Cardiac Arrest	Cardiac	3 (7.1%)
GVHD (in GI tract)	Immune/GI	3 (7.1%)
Acute Kidney Injury	Renal	2 (4.8%)
Microangiopathy	Vascular	2 (4.8%)
Multisystem Organ Failure	Multiple	2 (4.8%)
Pleural Effusion	Respiratory	2 (4.8%)
Hyperbilirubinemia ³	Hepatic	1 (2.4%)
Infusion Reaction ³	Iatrogenic	1 (2.4%)

²MO combined acute respiratory failure, hypoxia, and respiratory failure.

³These two SAEs were adjudicated to be secondary to Remestecel-L.

3.2.3 Deaths

In the submitted dataset, 13 patients (30.2%) died during the treatment period. The age and demographics of the patients who died was not significantly different than of the study population in general. The average time from treatment initiation to death was 39 days. The higher the grade of GVHD the sooner death occurred, for example the time difference was 15 days sooner in patients with grade D GVHD as opposed to grade C.

The 13 deaths are described in table 7 on page 33 of the study report.

Table 3: Demographics and pre-existing status of GVHD in patients who died during the conduct of Study MSB-IIT015-084

Patient Age	Sex/Race	Cause of Death*	Grade of GVHD at time of tx	Days from tx to death	Initial diagnosis/indication for BMT
4 years	Male/White	Adenoviremia	B	79	Pre-B cell ALL
4 years	Male/White	ARF	D	17	LRBA deficiency
6 years	Male/White	Cardiac Arrest	D	43	AML
6 years	Female/White	ARF	B	7	ALL
8 years	Male/White	MSOF	D	34	Fanconi Anemia
10 years	Male/Black	Bacterial sepsis	C	40	Adrenoleukodystrophy
10 years	Male/White	Septic shock	D	36	AML
13 years	Male/Black	Sepsis	D	25	Sickle Cell Anemia
16 years	Female/White	GVHD ⁴	D	81	AML
17 years	Female/White	MSOF	C	93	AML
22 years	Male/White	Cardiac Arrest	D	15	AML
25 years	Male/Black	GI Bleed	D	23	T-cell lymphoma
63 years	Female/White	Liver Failure	C	14	AML

*Cause of death listed as either Graft vs. Host Disease or Progression of Graft vs. Host Disease as either primary or secondary cause of death. Death report examined for specific organ failure leading to patient demise.

⁴No specific organ failure described as cause of death. Patient refused additional care for SR-GVHD and AML and was transferred to hospice care.

GVHD: graft versus host disease. Grading system: see reference 1.

ARF: Acute Respiratory Failure, MSOF: Multi-system organ failure,

Tx: treatment, BMT: bone marrow transplant, ALL: acute lymphocytic leukemia, AML: acute myelogenous leukemia, LRBA: LPS responsive beige-like anchor protein.

The two deaths in patients with class B GVHD (n=8) constitute 25.0% of patients with this class of GVHD. They had an average time between treatment and death of 43 days. The 3 deaths in patients with class C GVHD (n=14) constituted 21.4% of patients with this class of disease. These patients had an average time between treatment and death of 49 days. The 8 deaths recorded in patients who had class D GVHD (n=21) constituted 38.1% of patients with the most severe classification of GVHD. The average time between treatment and death was 34 days.

Reviewer Comments: The reports of death and SAEs in the study are complicated by the multiple comorbidities of the subjects. Given this, the adverse events described above do not describe any unexpected or new safety signals. The clinical profile of patients requiring this therapy would be expected to result in infectious and respiratory complications. Patients with GVHD severe enough to qualify for this therapy would be a population for which this death rate is not excessive.

Although the numbers are small, the largest percentage of patient mortality and the shortest interval between treatment and death was in the patients with the most severe GVHD. It would be reasonable to assume that a major risk factor for patient death after treatment is the pre-treatment morbidity.

3.3 Review of Postmarketing Data in US and Worldwide

There is no post-marketing data for this product.

3.4 Review of Previous OTAT Clinical Memo, submitted August 30, 2020

The clinical memo submitted on August 30, 2020, evaluated the clinical data up to that point for adverse events of concern. This memo reviewed reported adverse events in the integrated safety summary (ISS) which can be found under BLA 125706/0/65, 5.3.5.3.

The ISS contained clinical information on 14 clinical studies which were performed over 20 years. The summary provided clinical information on 1,517 patients. Of these, 1,114 who were treated with Remestecel-L and 403 were treated with placebo.

In the summary, two specific adverse events were noted as worthy of enhanced pharmacovigilance. These two adverse events were: ectopic tissue formation and the development of anti-HLA antibodies. These two adverse events were identified as theoretically possible and not evident, as of the date noted above, in the clinical studies submitted. As a result, the memo states these adverse events warrant neither a Risk Evaluation and Mitigation Strategy (REMS) nor a safety study postmarketing requirement (PMR). The data on the number of patients with ectopic tissue formation and the development of anti-HLA antibodies is provided below.

3.4.1 Ectopic Tissue Formation (ETF):

Ectopic Tissue Formation is defined as the presence of tissue in a location it would not physiologically be located. ETF is diagnosed with a CT scan, most commonly a CT scan of the chest. In the ISS, 530 patients had post-treatment CT scans that could be adequately reviewed (sufficient patient and chronologic identification). Of these scans, 397 (74.9%) were performed in patients who had received treatment with Remestecel-L and the other 133 scans (25.1%) were done in control patients. Although a schedule for follow-up CT scans was in the protocol, not all the patients received CT scans according to the recommended follow-up protocol.

Results: 19 CT scans were read as showing ETF. Of these, 16 positive studies were in Remestecel-L treated patients and 3 were in placebo treated patients. Three treated patients and two placebo patients had no additional information provided on their reading. For two additional treated patients, the ETF was described as “not clinically significant”.

The percentage of treated patients is 73.4% (1,114/1,517). The percentage of treated patients who developed ETF is 84.2% (16/19). If only the patients with findings considered significant according to the radiologic interpretation are evaluated, the percentage of treated patients who developed significant ETF per imaging evaluation = 91.7% (11/12).

For the 12 patients (11 treated, 1 placebo) who had clinically significant ETF and sufficient information, the following results are reported:

Table 4: Ectopic Tissue Formation Clinical Results as Reported by the ISS (N=1,517, (Treated=1,114, Placebo=403)

Study ID Number	Treated/Placebo	Days post-tx CT Scan done	Clinical Information/ Description of ETF
(b) (6)	Remestecel-L	363	Recurrent Lymphoma

(b) (6)

Remestecel-L	781	Progression of Hodgkins Disease
Remestecel-L	742	Calcified right hilar lymph node, large calcified granuloma
Remestecel-L	370	Non-Hodgkins Lymphoma
Remestecel-L	30	New soft tissue nodule-injection or bx site. Decrease in size of soft tissue density behind the left scapula. New soft tissue at biopsy site.
Remestecel-L	14	2 nodules-1 upper lobe, 1 lower lobe
Remestecel-L	111	Pleural thickening, increased abdominal fat
Remestecel-L	95	Two new nodules in left lung, dx as a fungal infxn, responded to anti-fungal tx
Remestecel-L	181	Abnormal, Clinically significant, NOS
Placebo	183	Two lesions identified in the liver
Remestecel-L	102	Multiple bladder calculi and other non-specific findings
Remestecel-L	707	Refractory Non-Hodgkins Lymphoma

Reviewer Comment (ETF): The OTP clinical review memo stated that none of these episodes of ETF were adjudicated to be secondary to the therapy. Certainly, patients with cancer requiring immunosuppression and then developing graft-vs-host disease requiring additional immunosuppression can be expected to develop both neoplasms and ectopic tissue formation independent of the therapeutic intervention (Remestecel-L). However, the frequency of the events in treated patients compared to placebo (both image positive for ETF, and the frequency of imaging of ETF considered of clinical significance (according to the reader of the imaging) is greater than would be expected given the distribution of treated to placebo patients:

Therefore, this medical officer agrees with the assessment of the clinical medical officer that this adverse event warrants enhanced surveillance with expedited reporting under 21 CFR 600.80. Should this product be approved, this would be communicated with the applicant.

3.4.2 Detection of anti-HLA antibodies.

The frequency of the detection of anti-HLA antibodies is addressed in the above-mentioned clinical memo and the data is derived from the same studies and patient population described in the ISS. Of the 14 studies submitted by the applicant, two studies evaluated the presence of anti-HLA antibodies. Both studies consisted of a small sample (N=42 patients treated and N=21 patients receiving placebo) and were limited to populations of patients receiving the therapy with concurrent Crohn's Disease or Type 1 Diabetes. (p.92)

In the 42 patients treated with Remestecel-L, 6 (14%) developed anti-HLA antibodies, and in the 21 patients receiving placebo, 0 (0%) developed anti-HLA antibodies.

Reviewer Comment (anti-HLA antibodies): The patient numbers with anti-HLA antibodies in the studies are small and selected from patients with concurrent morbidities. However, this medical officer concurs with the OTP clinical medical officer that the difference between treated patients and placebo patients developing this AE is large enough to support enhanced pharmacovigilance should this product be approved.

Reviewer Comment (both AEs): The two adverse events of concern according to this memo were discussed by the relevant divisions. The decision regarding additional pharmacovigilance is described in sections 6 and 7.

4 Review of Applicant's Proposed Pharmacovigilance Plan

The applicant submitted an updated PVP as part of STN 125706/0/65 (dated January 30, 2023). This version was compared to the PVP submitted and reviewed in STN 125706/0/3 (dated January 31, 2020). The PVP, including identified risks, potential risks, missing information, and rationale for the proposed action, is summarized in Table 3.

There were differences between the original PVP and the PVP submitted in January 2023. Primarily, there were differences in the identified adverse events. The original

PVP (January 2023) included the following identified adverse events which were not included in the updated PVP: infections, neurologic events, and hypersensitivity to porcine/bovine excipients.

The FDA sent an IR to the applicant on May 31, 2023, requesting the rationale for this change.

The applicant replied to the FDA. (127506/0/84) Their rationale:

- 1) Infections: The applicant contends the infection rate for Remestecel-L is commensurate with the accepted infection rate in patients with GVHD refractory to treatment.

As support, they referred to an FDA Briefing Document for the Oncologic Drugs Advisory Committee (ODAC) on August 13, 2020. This document quoted the established the bacterial, viral, and fungal infection rate for this class of patients as 74%, 65%, and 14% respectively.² The applicant's response was the infection rate in patients treated with Remestecel-L is significantly lower than this with the total infection rate = 25.7%. Furthermore, the applicant notes the cumulative analysis of the treated and control arms was not statistically different. (treated = 25.7%, control = 24.7%)

The applicant established the infection rate for patients treated with this therapy as acceptable as defined by the established baseline infection rates. They thereby justify removing infection as an identified adverse event.

- 2) Neurologic Events: As in the assessment of infections, the applicant contends cumulative incidence of neurologic events in treated vs. control subjects is not statistically significant. (treated=26.9%, control = 29.8%). They use this comparison to justify removing neurologic events as an identified risk.
- 3) Hypersensitivity to porcine/bovine excipients: the applicant points to its labeling, specifically the documentation that the products may contain trace amount of porcine and/or bovine tissue, as an adequate means of making providers aware of risk to facilitate early recognition and prompt treatment of a hypersensitivity reaction.

In particular, the applicant refers to: 1) Section 1.2: Risk Minimization Strategy: The risk of hypersensitivity to porcine/bovine excipients is included as a Risk Minimization Strategy. 2) Section 4: Contraindications: known hypersensitivity to porcine/bovine tissue is labeled as a contraindication, and 3) Section 5: Warnings and Precautions: hypersensitivity reaction to porcine and bovine tissue is clearly labeled as a serious risk.

Reviewer Comment: Given the current plan is to CR this submission, the final recommendations regarding the PVP safety specifications will be deferred until future resubmission of this file.

Table 3: Summary of current Applicant-proposed PVP
(January 30, 2023)

Safety Concern	Identified Adverse Event	Proposed Pharmacovigilance Activities
<i>Important Identified Risks:</i>	1) Acute Infusion reaction 2) Pulmonary Complications 3) Ectopic Tissue Formation 4) Tumorigenicity	RPV + premedicate RPV + for 2,3,4 -- Literature: risks, precaution, treatment
<i>Important Potential Risks:</i>	1) Hypersensitivity to DMSO 2) Transmission of Infectious Agent	RPV + Literature: Risks, treatments

RPV: Routine Pharmacovigilance. Literature: the applicant provides provider and patient with literature: establishing the risk, appropriate precautions, pretreatment if available, and the treatments available should these adverse events occur.

Reviewer Assessment: The proposed PVPs assess potential and identified risks, and recommends management. Other than the discussion provided in sections 6 and 7, no additional changes are recommended.

5 Integrated Risk Assessment

The PVP submitted in STN 125706/0 was previously reviewed and found to be adequate. Safety data accumulated in the interval between the issuance of the Complete Response and the time of this review was consistent with findings documented with the original submission, and does not change the assessment of the overall safety profile of the product.

There were two adverse events of special interest (Anti-HLA antibodies and ectopic tissue formation) noted in OTP and DPVs review of STN 125706/0 necessitating additional pharmacovigilance activities should the product be approved. The review team engaged in preliminary discussions regarding a potential postmarketing study to better characterize the potential adverse event of anti-HLA antibodies. However, the planning for this study was not undertaken due to the complete response for this submission, and will be deferred until future resubmission of this file. For the adverse event ectopic tissue formation, enhanced pharmacovigilance would be indicated should the product be approved. Should this product be resubmitted after completing the deficiencies identified in a complete response letter, this issue for anti-HLA antibodies will be re-assessed and discussed with the review team. At that time enhanced pharmacovigilance strategies and postmarketing safety study(ies) would be further discussed.

6 DPV Recommendations

The decision of the FDA review team, is that the applicant will receive a complete response letter on August 2, 2023 for this submission. At this time, OBPV/DPV will defer final pharmacovigilance recommendations regarding postmarketing safety monitoring, given the CR action.

In the events of resubmission, as discussed in the previous section, DPV will review any updates to the PVP with the resubmission, and discuss a potential safety study for active surveillance of anti-HLA antibodies and enhanced pharmacovigilance (expedited reporting) for ectopic tissue formation.

7. References:

¹[Biol Blood Marrow Transplant. 2017 Sep; 23\(9\): 1573–1579.](#)

²[Garcia-Cardenas, I, et. Al., Bone Marrow Transplant, 2017; 52\(1\):107-113.](#)

Appendix 1: Materials Reviewed

Document Type	Document	Source
Clinical Review Memo	OTAT review of 125706/0	FDA
Risk Management Plan, Module 1.16.1	Updated PVP (January 2023)	applicant
Clinical Study Report, Module 5.3.5.2, seq 65	Safety report (January 2023)	applicant
Risk Management Plan, 125706/0/3	Initial PVP (January 2020)	applicant
Response to IR, 125706/0/84	Discussion of PVP	applicant