

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)**

MEMORANDUM

From: Jonathan D. Reich, MD
Medical Officer, DBPV, OPV, CBER

To: Adriane Fisher, PhD
RPM, OTP, CBER

Through: Christopher Jason, MD
Branch Chief, 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 125706/0/96

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: July 23, 2024

Action Due Date: October 28, 2024

1. Objective

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP) to monitor post-marketing safety for Remestecel-L based on available data on its safety profile. The submission does not contain new safety data, therefore the memorandum reviews previously identified safety concerns and makes PVP recommendations to address them.

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 has been submitted twice previously and returned to the applicant with a Complete Response (CR) letter.

The first submission resulted in the FDA sending a complete response (CR1) letter 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.

The outstanding issues were resolved after a series of FDA meetings resulting in concurrence regarding necessary submissions for approval. (see meeting notes reference in Appendix A). The file received orphan drug designation in 2017. The IND number under which this product was initially submitted is 7939.

The second licensing application for this product was submitted on December 30, 2022. The application contained a new pharmacovigilance plan (125706/0/65, 1.16) which included an assessment of the safety information in two studies. The applicant submitted the results from a new clinical trial, which was designated msb-iit015-084 (125706/0/65 under 5.3.5.2).

The second application resulted in the clinical branch of the Office of Therapeutic Products (OTP) / CBER recommending a second CR letter (CR2) be sent on the basis of the manufacturing issues noted by CMC:

- 1) The product lacked an appropriate potency assay and the facility in Singapore where the product was produced required inspection by OCBQ.
- 2) The executive summary documented deficiencies in clinical trials used to support the submission. Specifically, in reference to study MSB-GVHD001, the clinical memo documented limitations in the statistical analysis plan. In reference to the other studies submitted in support of the application, the memo documented that these studies were not well-controlled nor sufficiently powered to test any hypotheses.

On August 1, 2023, the CR2 letter was sent to the sponsor. This letter detailed deficiencies in the toxicology risk assessment, discrepancies in the analysis methods, questions about the Critical Quality Attributes (necessary to establish analytic compatibility) and proposed a future meeting to discuss the clinical trial design which would answer FDA questions about efficacy and safety. OBPV/DPV submitted a memorandum (CR2 PVP memo) providing its assessment of the pharmacovigilance plan (PVP) contained in the submission 125706/0/65.

The conclusion of this memorandum was no safety signals were identified either in the data submitted by the sponsor nor in an independent FDA analysis of 1,780 subjects either enrolled in clinical trials or treated with this therapy through clinical access protocols. However, there remained concern for the development of antidrug/ antihuman leukocyte antigen (HLA) antibodies and the risk of ectopic tissue formation.

On March 22, 2024, a type C meeting was held with the sponsor. The issue of the inadequacy of the study addressed in the OTP memo was resolved by an FDA determination that the submitted information was adequate for review (see below). On July 8, 2024, the most current submission by the sponsor was received by the FDA.

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 Safety Data

3.1--Update of study MSB-GVHD001 -- previously presented to the FDA.

The study MSB-GVHD001 was determined by OTP to be inadequate in the CR1 and CR2 letters because it was too subjective and therefore the clinical conclusions were deemed unreliable.

However, the FDA reversed its decision and, in the minutes of the Type C sponsor meeting of March 22, 2024, the FDA wrote *“Based upon additional consideration, the available clinical data from Study MSBGVHD001 appears sufficient to support submission of the proposed BLA for remestemcel-L for treatment of pediatric patients with steroid refractory acute graftversus- host disease (SR-aGVHD).”* The FDA also added as part of the response, *“However, as stated above, we have concerns that you will be unable to adequately demonstrate analytical comparability based on your current proposal.”*

No additional studies are provided in this submission.

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

The study protocol and results are described in the PVP memo that was written in the previous submission under STN 125706/0. The reviewer opinion of this study is that the reports of death and SAEs in the study are complicated by the multiple comorbidities of the subjects. However, despite 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.

Taking these factors into consideration, the reviewer’s opinion was the study supported the premise of safety for the therapy.

3.3 Review of Post-marketing Data in US and Worldwide

There is no post-marketing data for this product.

3.4 Discussion of the two clinical safety concerns identified in the OBPV and OTP memorandum⁶ (Ectopic Tissue Formation (ETF) and the generation of HLA antibodies)

3.4.1 ETF:

A review of the 14 studies which assessed the safety of Remestecel demonstrates a total of 1100 patients have been treated. In this patient cohort, 21 patients were identified as possibly having ETF. Three of these patients were excluded from analysis because an alternative source of ETF was identified (lymphoma, calcified LN, injection site nodule). Of the remaining 18 patients, 9 were included in the Integrated Safety Summary (ISS) and 9 were not included in the ISS (also the 3 subjects with an alternative diagnosis were not included in the ISS).

In 9 patients imaging determined the mass preceded the Ryoncil therapy. The remainder of the patients underwent biopsies. The tissue was then subject to DNA analysis to identify the source of the cells. The determination was made that the suspect masses were not ETF secondary to Ryoncil therapy.

3.4.2 Pre-existing and Tx emergent Anti-HLA or anti-donor antibodies

The Integrated Safety Summary contains 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 were treated with Remestecel-L and 403 were treated with placebo. The ISS noted the theoretical possibility of the development of anti-HLA antibodies but did not identify that the presence of anti-HLA or anti-donor antibodies represented a safety concern.

The means of assessing for the possible development of anti-HLA or anti-donor antibodies was evaluation of the ISS for an increase in the incidence of refractory cytopenia (RC). The finding that there was no safety concern was confirmed by a separate evaluation of the patients in the pivotal study who developed RC.

Reviewer Comment: The medical officer recognizes there is no definitive evidence that patients receiving the product are at risk for either of these AEs. However, these AEs have been reported in other first in-class medical therapies of in the category of class (i.e. stem cell therapy).⁷ The new PVP employs enhanced pharmacovigilance in order to surveille for this AE. The MO agrees this is appropriate.

4 Review of Applicant's Proposed Pharmacovigilance Plans

The applicant submitted a PVP as part of STN 125706/0/3 (dated January 31, 2020). The second PVP was submitted as part of 125706/0/65 (dated January 30, 2023). The third and most recent PVP was submitted as part of an IR response on October 10, 2024 (125706/0/105). This PVP included identified risks, potential risks, missing information, and rationale for the proposed action, is summarized in a table compiled by the MO. This summary can be found in Table 3.

Table 3: Summary of current Applicant-proposed PVP
(October 10, 2024) ⁸

Identified Adverse Event	Accumulated Evidence	Proposed Pharmacovigilance
Important Identified Risks		
Acute Infusion Reaction (AIR)	Eight study patients identified	RPV (see description below)*
Important Potential Risks		
Pulmonary Complications	Studies performed - - Rate = 20.4%	RPV, AESI, careful control of drug infusion rate
Donor Specific HLA Antibodies	Based on Literature Derived Risk	EPV (see description below)
Ectopic Tissue Formation	No diagnoses, one negative biopsy	EPV
Suspected Transmission of Infectious Agents	No cases reported	Intensive screening of BM donors, RPV
Hypersensitivity Reaction (HSRxn)	No cases reported	Exclusion of patients previously diagnosed with HSRxn, RPV
Adverse Events due to DMSO	Single patient case reported	Exclusion of patients with HSRxn to DMSO, RPV
New Malignancy	No cases reported	RPV

AESI: Adverse event of special interest

BM: Bone Marrow

DMSO: Dimethyl Sulfoxide

EPV: Enhanced Pharmacovigilance

PV: Pharmacovigilance

RPV: Routine Pharmacovigilance.

* Pharmacovigilance plan for Acute Infusion Reaction: RPV, appropriate prophylaxis as per protocol, and drug product delivered by controlled rate delivery.

4.1 Routine Pharmacovigilance

Per the PVP, RPV has 3 components. The first component acquires and compiles Individual Case Safety Reports (ICSRs). There are four means of collecting ICSRs: the collection of spontaneous adverse event reports, the evaluation of post-market calls, monthly investigations by the safety medical team, and the sponsor's review of their own Internal Safety Database.

Once these 4 sources have compiled the available ICSRs, the second component is an aggregate review of the adverse event data is then compiled and presented in the submission of periodic benefit/risk evaluations (PBRERs). These periodic benefit/risk evaluations will be included in the routine surveillance reports submitted by the sponsor to the FDA at the regulatory required intervals.

The final component is the data is reviewed by the sponsor and the FDA. This data can then be used to change the risk management plan or to edit the PVP as is deemed necessary.

4.2 Enhanced Pharmacovigilance

In an evaluation for AEs under the EPV regime, the components of RPV detailed above remain in effect. In addition, the sponsor must submit expedited (15-day) reports for all ectopic tissue formation and anti-donor antibody events regardless of seriousness of the events. In periodic safety reports, the sponsor must provide aggregate safety assessment (based on interval and cumulative data) for the two AEs which require EPV, i.e., ectopic tissue formation and anti-donor antibody events.

Reviewer Comment: The Reviewer considers the Sponsor's response to the two IRs which specifically amended the PVP (supp. 84 and 105), to be acceptable and has no further queries regarding these adverse events.

5 DPV Conclusions

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. In the CR2 PVP memo (125706/0/65), it was stated that additional pharmacovigilance activities, to better characterize these adverse events (AEs), would be required should the product be approved. The sponsor has agreed to these terms and proposed enhanced pharmacovigilance be the pharmacovigilance strategy for these AEs.

DPV's assessment of the submission, specifically the PVP submitted on October 10, 2024 (125706/0/105), is that a PMR or PMC is not required for these adverse events. This is because the PVP is adequate and there is no definitive evidence patients receiving this therapy are at increased risk of these AEs.

The enhanced pharmacovigilance the sponsor agreed to would allow the FDA to do periodic updated safety evaluations as often as needed. These assessments can determine if additional surveillance is warranted.

This pharmacovigilance strategy complies with the reporting requirements for post-marketing adverse experiences to FDA in accordance with 21 CFR 600.80. The available safety data do not demonstrate a need for a Risk Evaluation and Mitigation Strategy (REMS).

7 DPV Recommendations

Should this submission be approved OBPV/DPV recommends the following for post-marketing safety monitoring of Mesoblast (Ryoncil):

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.
- Enhanced pharmacovigilance in accordance with 21 CFR 600.80, for 3 years following product licensure, as follows:
 - o The Applicant will submit all adverse events of Ectopic tissue formation and pretreatment anti HLA antibody formation, regardless of expectedness or seriousness, as expedited (15-day) reports to FAERS.
 - o In the narrative summary of periodic safety reports, the Applicant will include aggregate analysis and assessment for Ectopic tissue formation and pretreatment anti HLA antibody formation.

The available data do not indicate a safety concern which would require a Risk Evaluation and Mitigation Strategy (REMS). There is no agreed upon postmarketing commitment or postmarketing requirement safety study. Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the applicant for the final agreed-upon language for the label.

References:

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

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

³Two separate inclusion criterion are provided, the ages in the memo are a compilation of both.

⁴Definition of GVHD: Graft-Versus-Host Disease - StatPearls - NCBI Bookshelf (nih.gov)

⁵ Haematologica 2007;92(9):1208-1215

⁷ Centeno CJ, et al. Int Orthop. 2016. PMID: 27026621

Appendix 1: Materials Reviewed

Document Type	Document	Source
Clinical Review Memo	OTP review of 125706/0	FDA
Risk Management Plan, Module 1.16.1	Updated PVP (January 2023)	Sponsor
Clinical Study Report, Module 5.3.5.2, seq 65	Safety report (January 2023)	Sponsor
Risk Management Plan, 125706/0/3	Initial PVP (January 2020)	Sponsor
Response to IR, 125706/0/84	Discussion of PVP	Sponsor
Response to CR, 125706/0/65	Response to CR letter	Sponsor
CR letter, signed by Clinical Acting Director, 8/1/23	Letter from FDA CBER Offices to Sponsor	FDA
⁶ OTAT Clinical Memo, 1/31/2023	Memorandum	FDA
Type C meeting minutes, 3/22/24	Agreement to dispense with an additional clinical study	Joint FDA/sponsor document
EIND study, IND 7939	Protocol and results	Sponsor
DPV Memorandum 125706/0/65 January 31, 2023	Clinical Memorandum	FDA

Document Type	Document	Source
⁸ IR response, 125706/0/105	IR Response, current PVP, 1.16.4	Sponsor