Summary Basis for Regulatory Action

Date:	December 18, 2024
From:	Ileana Marrero-Berrios, PhD, Review Committee Chair, Office of Therapeutic Products (OTP), Office of Cellular Therapy and Human Tissue CMC, Division of Cell Therapy 2/Tissue Engineering Branch 1
BLA STN:	127506/0
Applicant:	Mesoblast, Inc.
Submission Receipt Date:	Original submission: January 31, 2020 Resubmission: January 31, 2023 Resubmission: July 8, 2024
PDUFA Action Due Date:	January 7, 2025
Proper Name:	remestemcel-L-rknd
Proprietary Name:	RYONCIL
Indication:	Steroid-refractory acute graft versus host disease in pediatric patients 2 months of age and older

Abbreviations: CMC, Chemistry, Manufacturing, and Controls; OTP, Office of Therapeutic Products; PDUFA, Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC	
• CMC Product (Product Office and OCBQ/DBSQC)	Ileana Marrero-Berrios, PhD, CBER/OTP/OCTHT Matthew Klinker, PhD, CBER/OTP/OCTHT Heba Degheidy, MD, PhD, CBER/OTP/OCTHT Alyssa Kitchel, PhD, CBER/OTP/OCTHT Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT Bao-Ngoc Nguyen, PhD, CBER/OTP/OCTHT
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Pre-License Inspection	Hector Carrero, CBER/OCBQ/DMPQ Matthew Klinker, PhD, CBER/OTP/OCTHT

Discipline Reviews	Reviewer / Consultant - Office/Division
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• Postmarketing safety Pharmacovigilance review (OBPV/DE)	Jonathan Reich, MD, CBER/OBPV/DPV/PB2
• BIMO	CDR Peter Lenahan, DC, PhD, MPH, CBER/OCBQ/DIS
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• Clinical data (OBPV/DB)	Qianmiao (Ann) Gao, PhD, CBER/OBPV/DBc
Nonclinical/Pharmacology/Toxicology	
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Discipline Reviews	Reviewer / Consultant - Office/Division
Labeling • Promotional (OCBQ/APLB) • Labeling review	Michael Brony, PharmD, CBER/OCBQ/DCM/APLB Afsah Amin, MD, MPH CBER/OTP/OCE
• Carton and container review	Ileana Marrero-Berrios, PhD, CBER/OTP/OCTHT Adriane Fisher, MPH, MBA CBER/OTP/ORMRR
Other Reviews: • Consults	Andrey Sarafanov, PhD CBER/OTP/OPPT Tianjiao Dai, PhD, CBER/OBPV/DB
Advisory Committee Summary	August 13, 2020

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1. Introduction

Mesoblast, Inc. submitted a Biologics License Application (BLA), STN 125706, for licensure of remestemcel-L-rknd with the proprietary name RYONCIL. RYONCIL is indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.

RYONCIL is comprised of allogeneic bone marrow-derived mesenchymal stromal cells (MSCs) cryopreserved in a suspension of Plasma-Lyte A supplement with human serum albumin solution and 10% dimethyl sulfoxide. The drug product (DP) is distributed as a target concentration of 6.68 X 10^6 MSCs per mL in 3.8 mL contained in a 6 mL cryovial and is administered intravenously.

This document summarizes the basis for approval of RYONCIL. A single-arm, prospective study (MSB-GVHD001) provides the primary evidence of safety and effectiveness of RYONCIL for the treatment of SR-aGVHD in pediatric patients 2 month of age and older. The recommendation for approval is based on overall response rate (complete response rate + partial response rate) at Day 28 post initiation of RYONCIL and duration of response. The major risks of RYONCIL include hypersensitivity/acute infusion reactions, transmission of infectious agents and ectopic tissue formation. The risk of anti-donor/anti-HLA antibodies and their impact on clinical outcome is unknown.

The review team recommends traditional approval of this BLA with Chemistry, Manufacturing, and Controls (CMC) Postmarketing Requirement (PMR) related to cumulative leachables and Postmarketing Commitments (PMCs) related to the development of an additional (b) (4) assay(s).

2. Background

Acute graft versus host disease (GVHD) is a serious and life-threatening complication following allogenic hematopoietic stem cell transplantation (HSCT). Donor derived alloreactive T cells play central role in the pathogenesis of GVHD.

Acute GVHD primarily involves three target organs: skin, gastrointestinal tract (GI), and liver. The diagnosis relies on the assessment of these target organs by means of clinical and laboratory analyses with or without biopsy. The severity is graded clinically based on the extent of the involvement of these target organs. Various grading systems are used in assessment of aGVHD.

Upfront treatment includes use of steroids in addition to continuation of drugs used for GVHD prophylaxis and gradual tapering of steroids. About one third of pediatric patients with aGVHD do not respond to upfront steroid therapy. Patients who are steroid refractory (SR-aGVHD) have poor outcomes. Ruxolitinib is the only drug approved for treatment of SR-aGVHD in patients 12 years of age and older. There are no approved therapies in pediatric patients less than 12 years of age.

Regulatory history of RYONCIL development in the United States is provided in Table 1

Table 1. Regulatory History

Regulatory Events / Milestones	Date
IND submission	October 1, 1998
Fast track designation granted	February 28, 2017
Orphan drug designation granted	December 14, 2005

Regulatory Events / Milestones	Date
Pre-BLA meeting	April 5, 2019
BLA 125706/0 submission – final module of rolling BLA received	January 31, 2020
BLA filed (priority review)	March 30, 2020
Mid-cycle communication	June 1, 2020
Late-cycle meeting	July 23, 2020
Pre-license inspection Lonza Bioscience Singapore Pte. Ltd. (LBSS)	May 11-19, 2023
Complete response	CR September 30, 2020 CR August 1, 2023
Type A meeting	December 16, 2020 September 11, 2023
Resubmission after complete response	Resubmission: January 31, 2023 Resubmission: July 8, 2024
Action due date	January 7, 2025

Abbreviations: CR, complete response

3. Chemistry, Manufacturing, and Controls (CMC)

a. Product Quality

The review team concludes that the RYONCIL manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description

RYONCIL is an allogeneic product composed of mesenchymal stromal cells derived from bone marrow aspirate and expanded *in vitro.*

Product Development

Product development began in 2002 under IND 7939 sponsored by Osiris Therapeutics, Inc. (OTI). In 2003, manufacture of the DP (DCB thaw to final DP in the container closure) was transferred to the Lonza Walkersville, Inc. (LWI) facility. In 2007 and 2008, OTI transferred to LWI the role of primary manufacturer of DP and DCB, respectively. In 2013, the RYONCIL development program was acquired by Mesoblast, Inc., including the DCB and DP manufactured at LWI in 2008 and 2009. In 2014, the manufacture of the DP (DCB thaw to final DP in the final container closure) was transferred from LWI to the Lonza Bioscience Singapore Pte. Ltd. (LBSS) facility and the DP manufacturing process at LBSS began in 2015, using the DCB material produced at LWI in 2008.

Manufacturing Summary

To manufacture RYONCIL, mesenchymal stromal cells are isolated from collected bone marrow aspirate and culture expanded (b) (4) passages. The cells are harvested and cryopreserved to establish a donor cell bank (DCB). The contents of a single DCB cryobag are thawed and the cells are expanded an additional three passages. The cells are then harvested, formulated with Plasma-Lyte A supplement with human serum albumin and 10% DMSO to make the drug product, which is then dispensed into 6 mL cryovials with a target concentration of 6.68 X 10^6 MSCs per mL in 3.8 mL and cryopreserved. The product is administered intravenously with a target dose of 2 x 10^6 MSCs/kg.

Manufacturing Controls

The manufacturing control strategy includes: (1) raw material and reagent qualification programs, (2) chain of identity and chain of custody for human/animal-derived materials and cell banks, (3) in-process monitoring and control testing, (4) validation of manufacturing process, and (5) release testing.

The manufacturing control strategy begins with the starting material, bone marrow aspirate, and reagent qualification program consisting of donor screening, eligibility determination, evaluating medical records and testing for relevant communicable agents or diseases (RCDADs), vendor qualification, confirmation of the certification of analysis and independent verification and testing of reagents used in the manufacture of RYONCIL. DCBs and reagents derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents.

Critical process parameters and critical quality attributes are established through process characterization and validation studies. Controls are implemented throughout the manufacturing process to support process consistency. In-process testing includes: sterility, mycoplasma, endotoxin, identity (b) (4) for cell markers), potency (TNFR1 Expression, (b) (4) and IL-2Rα Inhibition), (b) (4) adventitious agent testing.

Lot release testing is performed on the final RYONCIL product after filling into vials, with the exception of mycoplasma testing which is performed on the (b) (4) . Product release testing on the DP includes: sterility, mycoplasma, endotoxin, identity (b) (4) for cell surface markers), potency (inhibition of IL-2Rα and (b) (4) assay), cell viability, cell concentration, appearance (particulates, visual inspection), purity (residual trypsin and bovine serum albumin). While all assays have been validated, additional (b) (4) assay(s) will be evaluated as a PMC.

Process Validation

The Applicant conducted (b) (4) process validation studies for the manufacture of the DS at OTI. The Applicant also conducted validation studies using full-scale manufacturing at LBSS using DCB material derived from (b) (4) different donors. The process validation lots met all prespecified critical process parameters and lot release criteria. Shipping and stability of the final product was established using full scale batches.

Manufacturing Risks, Potential Safety Concerns, and Management

Virus and mycoplasma testing for human and animal-derived reagents are verified with a full Certificate of Analysis (CoA) from the supplier. Certificate of Origin/Certificate of Suitability is required for each lot of animal-derived material coming from manufacturers in acceptable Geographic BSE Risk (GBR) countries or regions. For human-derived materials such as human serum, the documentation requirements cover: (1) Source of material being from an approved licensed blood bank, (2) Donor or reagent testing which verifies no human adventitious agents are present, and (3) Documentation supporting the Plasma Master File. DCB requires a traceable history and testing results for adventitious agents. Transmission of infectious diseases is controlled by reagents and

control of the manufacturing process. The risk of exposure to bovine and/or porcine-derived proteins used during product manufacturing is managed by testing for residuals during drug product lot release testing. Segregation and the prevention of mix-ups are maintained at LBSS by (1) labelling of materials and equipment, (2) spatial segregation of lots, equipment and personnel, and (3) clearance procedures pre- and post-production.

Drug Product Stability and Shelf Life

RYONCIL is supplied as a cellular suspension in a cryovial. The stability of RYONCIL has been determined to be 60 months when stored at ≤-135°C in liquid nitrogen vapor. The post-thaw stability has been determined to be 5 hours at room temperature. The product is shipped in a liquid nitrogen dry shipped maintained at a temperature of ≤-135°C.

CMC PMRs and PMCs

The CMC team recommends one PMR and three PMCs. The rationale for the PMR and PMCs is described below, and the PMR and PMC agreements are detailed in Section 11c of this document.

PMR:

1. Mesoblast, Inc. initiated a cumulative leachables study, but only completed the initial time point (T=0) and first time point (T=6 months). The study must be completed out to the final timepoint (T=(b) (4) months) to assess the cumulative leachables throughout the storage duration. Therefore, the Applicant agreed to a PMR study to complete the cumulative leachables study and to provide the final report and toxicological risk assessment of the overall leachables in the final drug product.

PMCs:

2. The Applicant developed two (b) (4) assays, (b) (4) , for final product release testing. However, based on data the Applicant provided, those (b) (4) assays may not be able to support product or process comparability for any future manufacturing changes. Therefore, the Applicant agreed to a PMC study to develop and validate an additional (b) (4) assay, such as the (b) (4) . The (b) (4) assay should be sufficient for evaluate product and process comparability and be stability-indicating.
3. The Applicant agreed to conduct a PMC study to develop and validate an additional (b) (4) assay (PMC #1). In addition to developing and validating the new (b) (4) assay, the Applicant should demonstrate the (b) (4) assay is suitable to detecting (b) (4) product lots. Therefore, the Applicant agreed to a PMC study to assess the suitability of the (b) (4) assay they will develop to address PMC #1.
4. The Applicant submitted accelerated stability studies that evaluated cell viability post-thaw and demonstrated post-thaw cell viability results passed the acceptance criteria ((b) (4)) regardless of the length of time post-thaw. While cell viability was maintained, other product attributes may be affected following

thawing and formulation of the product by the end user. Therefore, the Applicant agreed to a PMC study to evaluate relevant critical quality attributes of RYONCIL following simulated final drug product formulation at the clinic.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for RYONCIL were found to be adequate for their intended use.

The lot release specifications for RYONCIL are shown below in Table 2

Table 2. Final Product Commercial Release Specifications

Attribute	Test	Methods	Acceptance Criteria
Appearance	Particulates	(b) (4)	(b) (4)
-	Container integrity	(b) (4)	(b) (4)
Identity	CD166$^+$	(b) (4)	(b) (4)
-	CD105$^+$	(b) (4)	(b) (4)
-	CD45$^+$	(b) (4)	(b) (4)
Potency	IL-2Rα inhibition	(b) (4)	(b) (4)
-	(b) (4)	(b) (4)	(b) (4)
-	Cell viability	(b) (4)	(b) (4)
-	Cell concentration	(b) (4)	≥ 6.68 x 106 cells/mL
Purity	Residual BSA	(b) (4)	(b) (4)
-	Residual trypsin	(b) (4)	(b) (4)
Safety	In-process sterility	(b) (4)	Negative
-	Sterility	(b) (4)	Negative
-	Mycoplasma	(b) (4)	Negative
-	Endotoxin	(b) (4)	(b) (4)

Abbreviations: BSA, bovine serum albumin; (b) (4) assay; (b) (4) USP, United States Pharmacopeia

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review/Inspection

Facility information and data provided in this BLA was reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of the product listed in this BLA are listed in the table below. The activities performed and inspectional history are noted in the table and further described in the paragraphs that follow.

Table 3. Facility Inspection Activities

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Results/Justification
Lonza Bioscience Singapore Pte. Ltd. 35 Tuas South Ave 6, 637377 Singapore *Drug Product Manufacture In-Process and Release Testing*	3009725845	936939342	Pre-License Inspection	CBER May 11 – 19, 2023 NAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	CBER (b) (4) VAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) NAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) NAI
(b) (4) *Drug Product Release Testing*	(b) (4)	(b) (4)	Waiver	CDER (b) (4) NAI

Abbreviations: CBER: Center for Biologics Evaluation and Research; DUNS: Data Universal Numbering System; FEI: facility establishment identifier; NAI: no action indicated; OBPO: Office of Biological Products Operations; ORA: Office of Regulatory Affairs; VAI: voluntary action indicated

CBER/DMPQ conducted a pre-license inspection (PLI) of the Lonza Bioscience Singapore Pte. Ltd. facility, May 11 – 19, 2023 for DP manufacturing and QC lab release testing. At the end of the inspection, CBER did not issue a Form FDA 483. The inspection was classified as No Action Indicated (NAI).

CBER performed a PLI inspection of the (b) (4) facility including the testing laboratories from (b) (4), to support the review of a different drug product. All 483 issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA/OBPO performed a surveillance inspection of the (b) (4) facility from (b) (4). The inspection was classified as Voluntary Action Indicated (VAI).

ORA performed a surveillance inspection of the (b) (4) manufacturing facility in (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

ORA performed a surveillance inspection of the (b) (4) manufacturing facility (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

CDER performed a pre-approval inspection of the (b) (4) testing facility in (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

e. Container/Closure System

The DP is filled into 6.0 mL ready-to-fill (b) (4) Closed Vials ((b) (4) Container closure system consists of the cyclo-olefin copolymer (COC) vial, a stopper made of thermoplastic elastomer to allow for (b) (4) filling, and a top ring and cap. Mesoblast conducted the container closure integrity testing, employing (b) (4) (test performed at (b) (4)), and (b) (4) method (test performed at (b) (4)); all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were conducted using human bone marrow-derived culture-expanded MSC (ceMSC) and surrogate animal-derived ceMSC produced using an early manufacturing process. As a result, the completed nonclinical studies provide limited support for RYONCIL.

In vitro studies characterizing the effects of bone marrow-derived ceMSC in co-culture with allogeneic immune cells demonstrated that ceMSC suppressed alloreactive T cell proliferation and can modify the cytokine secretion profile of various immune cells in culture.

A cell distribution study was performed with administration of 10×10^6 (b) (4)-labeled (b) (4) rat ceMSC/kg in (b) (4) rats. Cells were detected in the lung within the first hour following cell administration, followed by distribution to the liver, kidney and spleen within the first 24 hours, and continued to be detected at 240 hours following cell administration.

A GLP safety pharmacology study evaluating pulmonary function in (b) (4) rats was conducted with single IV administration of (b) (4) rat-derived ceMSC at dose levels of 8×10^6, 16×10^6, and 25×10^6 cells/kg via femoral vein catheter at rates of 0.02 - 1.6 mL/min. A high mortality rate was observed, possibly due to cell aggregation, at the highest dose levels at all infusion rates tested and occurred shortly after cell administration. No product-related effects on cardiac function were observed in a cardiac

safety pharmacology study in pigs conducted with single IV infusion of 1×10^6 and 10×10^6 allogeneic pig ceMSC/kg at a constant rate of 2-3 mL/min.

In a 90-day GLP repeat dose toxicity study, (b) (4) rats received 2×10^6, 10×10^6 or 20×10^6 (b) (4) rat ceMSC/kg administered in a 5mL/kg dosing volume by tail vein injection over a two-minute period twice per week for 4 weeks and weekly thereafter for a total of 13 dose administrations. Several unscheduled deaths were observed in the groups administered highest dose levels beginning after the fifth administration. Minimal to moderate findings were observed in the lungs, spermatocytes, and injection site. No toxicities were observed in a six-month GLP study in baboons using (b) (4) labeled allogeneic baboon ceMSC following IV administration of 5×10^6 cells/kg on Day 1 (b) (4)

There was no evidence of neoplastic tissue formation attributable to ceMSC in a six-week tumorigenicity study in athymic mice (b) (4) administered human ceMSC from five separate donors at dose levels up to 50×10^6 cells/kg.

Genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies were not performed for RYONCIL. These studies are not warranted based on the product characteristics and safety profile.

5. Clinical Pharmacology

The mechanism of action for RYONCIL is unclear but may be related to the immunomodulatory activities of ceMSCs. Data from in vitro studies demonstrate that ceMSCs inhibit T cell activation as measured by proliferation and secretion of pro-inflammatory cytokines. Human pharmacodynamic data were obtained from analysis of blood samples in pediatric subjects with SR-aGVHD (n=40; age range 0.6-17 years) following treatment with RYONCIL at a dose of $2x10^6$ cells/kg. At Baseline, elevated levels of tumor necrosis factor receptor type I (TNFR1) and suppressor of tumorigenicity 2 (ST2) were observed consistent with the inflammatory state of aGVHD. Treatment with RYONCIL reduced the levels of TNFR1 and ST2 by 79% and 75%, respectively, at Day 180 as compared to baseline values. Further, the circulating levels of CD3+CD4+CD25+HLA-DR+ T cells, which represent activated T cells, were reduced by 64% at Day 180 following treatment with RYONCIL as compared to the baseline values. Since RYONCIL is an allogenic product, there is a potential for development of anti-drug (donor) antibodies (ADA) or anti-HLA antibodies. Humoral immune response was not characterized in pediatric patients.

No formal pharmacokinetic, clinical dose finding, or dose regimen optimization studies have been performed during the development of RYONCIL for treatment of aGvHD in pediatrics. In early studies, human mesenchymal stromal cells were evaluated to treat steroid-refractory, severe aGvHD with a median dose of 1×10^6 cells/kg for 1-3 infusions. Furthermore, the initial expanded access programs (EAP) included 10 pediatric subjects aged 2-15 years who were infused with allogeneic ceMSC at a dose of $2x10^6$ cells/kg twice a week for 4 weeks. In Study MSBGVHD001/002, treatment with RYONCIL at a dose of $2x10^6$cells/kg, administered by IV infusion twice a week for 4 weeks was generally safe and well-tolerated through Day 180.

6. Clinical/Statistical

The clinical review team recommends granting traditional approval for RYONCIL for the treatment of SR-aGVHD in pediatric patients 2 months of age and older at the requested dosage.

a. Clinical Program

The primary evidence supporting the safety and efficacy assessment in this BLA derives from Study MSB-GVHD001, a single-arm, multicenter trial of RYONCIL in pediatric patients 2 months to 17 years of age. Key eligibility criteria included presence of SR-aGVHD Grades B to D (excluding Grade B skin alone), as per International Blood and Marrow Transplantation Registry Severity Index Criteria (IBMTR) after receiving allogeneic HSCT. Patients received RYONCIL at a dose of 2×10^6 MSCs/kg twice a week for four consecutive weeks, for a total of eight infusions. Patients with partial or mixed response at Day 28 received additional infusions of RYONCIL 2×10^6 MSCs/kg once a week for an additional four consecutive weeks.

Study MSB-GVHD001 enrolled a total of 55 patients, 54 of whom comprised the efficacy analysis population. Among the treated patients (n=54), the demographic characteristics were as follows: median age was 7 years (range: 7 months to 17 years); 36% were females; 56% were White, 19% reported “other” race, 15% were Black, 6% were Asian, 6% American Indian or Alaska Native 33% were Hispanic and 65% were non-Hispanic. Hematologic malignancies (67%) and non-malignant diseases (33%) were the underlying reasons for allogenic HSCT. SR-GvHD severity was as follows at baseline: Grade B (11%), Grade C (43%), Grade D (46%); 72% of patients were categorized at baseline as being high risk by the MacMillan Risk Score. Organ involvement at baseline were as follows: skin alone (26%), lower gastrointestinal tract only (39%), multi-organ involvement (35%). The median duration of prior corticosteroid treatment at baseline was 8 days (range: 2 to 46 days).

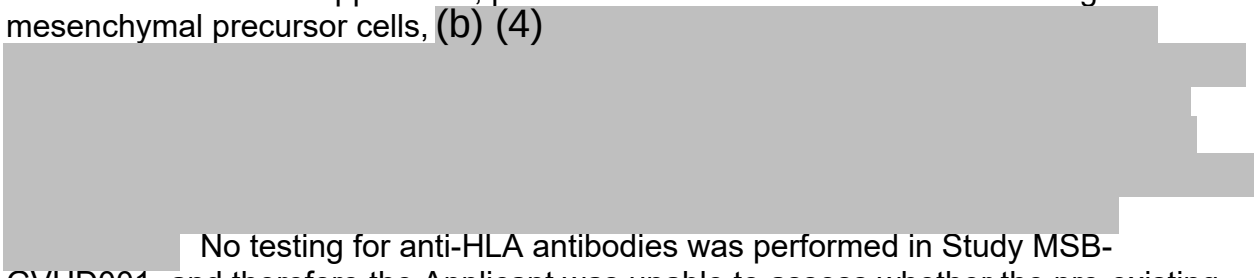
The main efficacy outcome measures were Day-28 overall response rate (ORR comprising of complete response rate, CR and partial response rate, PR) and the duration of response. The DAY-28 ORR was 70.4% (95% CI: 56.4, 82.0), including a CR rate of 29.6% (95% CI: 18.0, 43.6) and a PR rate of 40.7% (95% CI: 27.6, 55.0). Among the 38 responders, the estimated median duration of response (DOR) was 54 days (range: 7, 159+ days). Similarly, among the 38 responders, the median time from Day-28 response to either death or need for new systemic therapy for acute GVHD was 111.5 days (range 9, 182+).

FDA reviewed the safety data for 1,780 patients in clinical trials and EAPs. There were substantial differences between the clinical trials regarding the patient population and treatment plan and the versions of the product used, so no pooling of safety data was performed.
The primary source of safety data was a total of 54 patients treated with remestemcel-L in Study MSB-GVHD001. The most common non-laboratory adverse reactions (incidence ≥20%) are: viral infectious disorders, bacterial infectious disorders, infection – pathogen unspecified, pyrexia, hemorrhage, edema, abdominal pain and hypertension.

Bone marrow derived MSCs have potential for multi-lineage differentiation potential into osteocytes, adipocytes, chondrocytes and skeletal muscle (Moghadam et al. 2014; Okolicsanyi et al. 2015; Wang et al. 2016). Although rare, there are some reports of ectopic tissue formation (ETF) following MSC administration (Prigozhina et al. 2008; Chu et al. 2020; Wu et al. 2020). In the clinical trials of remestemcel-L, 9 patients were identified with possible ETF in the imaging studies. Per Applicant, these scans were evaluated, and it was determined that there were alternative explanations, and none of these patients were considered to have ETF. Biopsies were not performed for any of these cases. The Applicant concluded 'based on the available data, there are no confirmed cases of ETF and there is no evidence that remestemcel-L causes ETF'.

Some patients undergoing alloHSCT may have pre-existing anti-HLA antibodies whereas some may develop these antibodies following HSCT (Detrait et al. 2012; Koclega et al. 2012). These anti-donor/anti-HLA antibodies, if directed against the donor, may be associated with graft failure (Morin-Zorman et al. 2016), and may also increase the risk of refractoriness to platelet transfusions (Solves et al. 2018).

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



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

Based on this information, there remains uncertainty regarding the risk of ETF and anti-donor/anti-HLA antibodies. The review team recommends that the Applicant submit an enhanced pharmacovigilance plan to address these potential safety concerns.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Four Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspections were performed between June 2020 and August 2020 of the pivotal studies, MSB-GVHD-001 and MSB-GVHD-002 at clinical sites: 301; 302; 304; and 323. In view of this previous inspectional history, the review committee decided that additional BIMO inspections are not warranted for this resubmission.

c. Pediatrics

Orphan drug designation was granted to ex-vivo cultured adult human mesenchymal stem cells for treatment of acute graft versus host disease (on December 14, 2005). The primary evidence derives from Study MSB-GVHD001, which enrolled pediatric patients 2 months to 17 years of age. RYONCIL is being approved for treatment of SR-aGVHD in pediatric patients 2 months of age and older.

d. Other Special Populations

Not applicable.

7. Safety and Pharmacovigilance

The Pharmacovigilance Plan (PVP) for MESOBLAST 125706/0.105, received October 10, 2024) includes the Applicant's assessment of important identified risks, important potential risks, and missing information. Important identified risks includes acute infusion reaction. Important potential risks include pulmonary complications, Donor specific HLA antibodies, ectopic tissue formation, suspected transmission of Infectious agents, hypersensitivity reaction, adverse events due to DMSO, and new malignancy.
The Applicant will conduct routine pharmacovigilance, which includes adverse event reporting, in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for ectopic tissue formation and anti-donor antibody events. Enhanced pharmacovigilance will include expedited (15-day) reporting of ectopic tissue formation and anti-donor antibody events. In addition, the Applicant agrees to provide aggregate safety assessments in their periodic safety reports, based on interval and cumulative safety data, for the risk of ectopic tissue formation and anti-donor antibody events.
The proposed pharmacovigilance plan for MESOBLAST is adequate for the labeled indication. The available data do not indicate a safety signal which would require a Risk Evaluation and Mitigation Strategy (REMS) or require a safety-related postmarketing study (postmarketing requirement [PMR]). There is no safety-related study as an agreed-upon postmarketing commitment (PMC) at this time.

8. Labeling

The proposed proprietary name, RYONCIL, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on August 28, 2024 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on September 11, 2024.

APLB reviewed the proposed Prescribing Information and Package and/or container labels on July 10, 2023, and found them acceptable from a promotional and comprehension perspective.

The proposed prescribing information was reviewed and revised by relevant review teams to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

9. Advisory Committee Meeting

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

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

10. Other Relevant Regulatory Issues

There is an extensive regulatory history for this product notable for several cycles of BLA submissions and CR actions as noted in Table 1. Detailed reasons for the regulatory decisions on the preceding BLAs are documented in the respective review documents. Briefly, from the clinical perspective, the primary evidence of efficacy and safety in the initial BLA derived from Study MSB-GVHD001. The primary clinical reviewers (Drs. Kristin Baird and Donna Przepiorka; August 31, 2020) recommended approval, stating the following as reason for approval: "… the efficacy results of Study MSB-GVHD001, which were statistically significant and durable, the unmet medical need, and the favorable safety profile, the clinical reviewer recommends: Approval." The Branch Chief at the time (Dr. Bindu George; September 10, 2020) recommended a CR, stating the following as reasons:

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

On September 30, 2020, FDA issued a CR letter, which included a deficiency that Study MSB-GVHD001 did not constitute an adequate and well-controlled study. The letter also included CMC deficiencies regarding the lack of adequate control of the potency of the commercial product due to either poor assay performance characteristics or the unknown relevance of the attribute measured to the therapeutic activity of the product. The Applicant submitted a complete response (CR) to the BLA on January 31, 2023. In the BLA resubmission, the Applicant proposed to implement a modified version of their established potency assays. Upon resubmission of the BLA on January 31, 2023, the FDA again issued a CR Letter, with the CMC issues including inadequate potency assay suitability for lot release and stability testing and with the clinical reviewers stating that the unresolved chemistry, manufacturing, controls (CMC) deficiencies precluded conclusion review team's conclusion that the trial was adequate and well-controlled. The clinical review memorandum (Drs. Upendra Mahat, Mona Elmacken, Donna Przepiorka, Robert Sokolic, Marc Theoret, and Celia Witten; August 1, 2023), also cited limitations of data deriving from an observational study as being insufficient to provide substantial evidence of effectiveness.

Upon resubmission of the BLA on July 8, 2024, Mesoblast satisfactorily addressed CMC CR letter deficiencies by implementing two complimentary potency assays that can support lot release and shelf-life determination. However, Mesoblast will need to add an additional quantitative potency assay(s) prior (b) (4) Having satisfactorily addressed the CMC deficiencies, and upon consideration of the data submitted in the BLA and FDA's previous assessments of these data (including prior assessments about the adequacy of the design of Study MSB-GVHD001), the clinical

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

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

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

1. Mechanistic/Pharmacodynamic data: Following HSCT, acute GVHD occurs when donor T cells react to differences in the human leukocyte antigens (HLAs) on the recipient's tissue (Ernst Holler et al. 2024). Activation and proliferation of alloreactive T cells plays a central role in the pathogenesis of aGVHD (Malard et al. 2023). The BLA contains *in vivo* pharmacodynamic (PD) studies from patients treated in Study MSB-GVHD001 and Study MSB-GVHD002, which demonstrate the immunomodulatory effects of remestemcel-L. These studies demonstrate the immunomodulatory effects of remestemcel-L relevant to the pathophysiology of

aGVHD. Specifically, treatment with remestemcel-L resulted in a 64% reduction in circulating CD3+CD4+CD25+human leukocyte antigen DR (HLA-DR)+ T cells, compared to baseline, which represents activated T cells. Additionally, two biomarkers—tumor necrosis factor receptor-1 (TNFR1) and suppressor of tumorigenesis 2 (ST2)—have been shown to be released by activated T lymphocytes. Following treatment with remestemcel-L, a decrease in these biomarkers observed at Day 180 (TNFR1 by 79% and ST2 by 75% compared to baseline)—demonstrates the PD activity that leads to a reduced inflammatory state.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends traditional approval of RYONCIL, standardized as to identity, strength, quality, purity, and dosage form, for the treatment of SR-aGVHD in pediatric patients 2 months of age and older based on the Applicant's demonstration of substantial evidence of RYONCIL's safety and effectiveness at the recommended dose and for the indicated population.

b. Benefit/Risk Assessment

SR-aGVHD is a serious and life-threatening disease. Ruxolitinib is the only approved drug in patients 12 years and younger; nothing is approved in pediatric patients younger than 12 years of age.

MSB-GVHD001 represents an adequate and well-controlled investigation that provides substantial evidence of effectiveness of RYONCIL based on Day-28 overall response rate and duration of response in treatment of SR-aGVHD in pediatric patients 2 months of age and older, in the context of acceptable safety profile. Acceptance of ORR at Day 28 as an endpoint denoting clinical benefit was discussed during an open public workshop on "Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation," held May 19, 2009; and also described in the FDA draft guidance, "Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment" (https://www.fda.gov/media/172524/download). The magnitude and durability of response denotes clinical benefit in the indicated population and therefore supports a traditional approval. The mechanistic/pharmacodynamic data included in the BLA, serve as confirmatory evidence in the context of a single adequate and well controlled investigation.

The recommended dosage of RYONCIL is 2×10^6 mesenchymal stromal cell (MSC)/kg body weight per intravenous infusion given twice a week for 4 consecutive weeks for a total of 8 infusions. Administer infusions at least 3 days apart.
Assess response 28 ± 2 days after the first dose

- If complete response: no further treatment with Ryoncil
- If partial or mixed response: repeat administration of remestemcel-L-rknd once a week for additional 4 weeks (4 infusions total)
- No response: consider alternative treatments

- Recurrence of GvHD after complete response: repeat administration of remestemcel-L-rknd twice a week for an additional 4 consecutive weeks (8 infusions total)

c. Recommendation for Postmarketing Activities

The Applicant will conduct routine and enhanced pharmacovigilance activities (with adverse event reporting as required under 21 CFR 600.80).

The Applicant agreed to the following CMC PMR and PMCs:

PMR:

1. Mesoblast will complete the assessment of simulated leachables safety study for remestemcel-L through its manufacturing process and storage. This study must include an assessment of total leachables presented in DP that accumulate throughout the manufacturing process and storage over the shelf-life. Such assessment should be performed in a real-time study using maximal hold times and temperatures at respective steps.

   Please provide a toxicological risk assessment of the overall leachables in the final drug product and final study report.

   Study Completion Date: August 31, 2030

   Final Report Submission: October 31, 2030

PMCs:

2. Mesoblast commits (b) (4) Mesoblast will submit the final study report, which includes the validation report, as a Prior Approval Supplement by December 31, 2027.

   (b) (4) Assay(s) Protocol Submission: December 31, 2025
   Final Study Report Submission: December 31, 2027

3. Mesoblast commits to conduct a (b) (4) assay suitability study to determine the ability of the (b) (4) assays to detect (b) (4) product lots. To conduct this study, Mesoblast will (b) (4) . Mesoblast will submit an interim study report with the current (b) (4) assays by December 31, 2026, and a final study report,

which includes the new (b) (4) assay(s) developed to address PMC #1, by December 31, 2027.

- Interim Study Report Submission: December 31, 2026
- Final Study Report Submission: December 31, 2027

4. Mesoblast commits to conduct an in-use stability study to evaluate relevant critical quality attributes of RYNOCIL following simulated final drug product formulation at the clinic. Mesoblast will submit an interim study report with the current (b) (4) assays by February 28, 2026, and a final study report, which includes the new (b) (4) assay(s) developed to address PMC #1, by December 31, 2027.

- Interim Study Report Submission: February 28, 2026
- Final Study Report Submission: December 31, 2027

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