



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

Pharmacovigilance Plan Review Memorandum

From: Wenyu Sun, MD, MPH
Medical Officer, Pharmacovigilance Branch (PVB)
Division of Epidemiology (DE)

Through: Meghna Alimchandani, MD
Deputy Director, DE

To: Matthew Klinker, PhD
Committee Chair

Subject: Pharmacovigilance Plan Review Memorandum – Remestemcel-L
Ex Vivo Cultured Adult Human Mesenchymal Stem Cells

Applicant: Mesoblast Inc.

Proprietary Name: RYONCIL™ (Remestemcel-L)

Established/Proper Name: Ex Vivo Cultured Adult Human Mesenchymal Stem Cells

BLA Submission: 125706/0

Proposed Indication: Remestemcel-L is indicated for the treatment of acute graft versus host disease (aGVHD) in pediatric patients when the aGVHD has failed to treatment with systemic corticosteroids.

Submission Date: January 31, 2020

Action Due Date: September 30, 2020

1. Introduction

1.1 Objectives/Scope

This memorandum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by Mesoblast Inc. for the original BLA 125706, Ex Vivo Cultured Adult Human Mesenchymal Stem Cells. The sponsor is seeking approval for the indication of acute graft versus host disease (aGVHD) in pediatric patients when the aGVHD has been refractory to treatment with systemic corticosteroid therapy (i.e., steroid-refractory aGVHD [SR-aGVHD]). The purpose of this review is to assess the adequacy of the submitted pharmacovigilance plan and to identify potential safety issues that may need to be addressed through post-marketing safety surveillance, post-market studies, or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved.

1.2 Product Information

Product description: Remestemcel-L is an allogeneic cell product comprised of culture-expanded mesenchymal stromal cells (ceMSC) isolated from the bone marrow of healthy adult donors. The bone marrow cells are expanded through cell culture, washed, and formulated into a suspension, then cryopreserved. The final product is composed of ceMSC formulated in Plasma-Lyte A (70%), dimethyl sulfoxide (DMSO, 10%) and human serum albumin (HSA) solution (20%, comprising 5% HAS and 15% buffer) at a concentration of 6.68×10^6 viable cells/mL. Remestemcel-L is provided as a frozen cell suspension in a cryogenic vial. The product is stored at $\leq -135^\circ\text{C}$ in the vapor phase liquid nitrogen until use. The product is thawed and resuspended in Plasma-Lyte A prior to intravenous administration.

Proposed dosing regimens: Remestemcel-L is administered by intravenous (IV) infusion at a dose of 2×10^6 cells/kg per infusion. As initial therapy, Remestemcel-L is administered twice a week, at least 3 days apart, for 4 consecutive weeks for a total of 8 doses. Based on the response to initial therapy and the severity of residual symptoms, Remestemcel-L may be administered once a week for another 4 weeks as continued therapy.

Proposed mechanism of action:¹ Mesenchymal stromal cells (MSC) have been shown to attenuate inflammatory and immunological process relevant to aGVHD through the following putative mechanism of action:

- Data from in vitro studies demonstrate that MSCs suppress T-proliferation in response to alloantigenic and mitogenic stimulation and stimulate an increase in the regulatory T-cell (Treg) population. Data suggest Tregs play an important role in inhibiting allogeneic T-cell response and aGVHD.
- MSCs alter the cytokine secretion profile of immune cells (dendritic cells, naïve and effector T cells, natural killer[NK] cells) by decreasing expression of proinflammatory cytokines and increasing secretion of anti-inflammatory cytokines.
- The immunomodulatory effects of MSCs are attributable, at least in part, to secretion of soluble factors such as prostaglandin E2.
- MSCs may mediate tissue protection and repair at sites of injury in GVHD by secretion of soluble factors that are known to mediate processes such as inhibition of apoptotic cell death, recruitment of endogenous stem cell populations, and angiogenesis.

1.3 Background

Acute GVHD is a progressive multisystem disorder and a potentially fatal complication of allogeneic hematopoietic cell transplantation (HCT). Despite prophylactic treatment with immunosuppressive agents, 20% to 80% of recipients develop aGVHD after allogeneic HCT.² Acute GVHD can involve skin, gastrointestinal tract, and liver. It occurs more frequently and is more severe after HCT from HLA-non-identical or unrelated donors as compared with

¹ The sponsor's Document 5.3.5.3 Integrated Summary of Safety, Page 23

² Martin PJ, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012;18(8):1150-1163.

HLA-matched sibling donors. Systemic corticosteroid therapy is the standard first-line treatment for aGVHD. However, response to corticosteroids is seen in approximately 50% of patients, and those who fail initial therapy have mortality rates as high as 95%.³ Most patients who fail to respond to first-line steroid therapy require a second-line therapy added to steroids. The only FDA-approved therapy for SR-aGVHD is Jakafi (ruxolitinib), and its approval is limited to SR-aGVHD patients at least 12-years old.

1.4 Pertinent Regulatory History

This is an original BLA for licensure of Ex Vivo Cultured Adult Human Mesenchymal Stem Cells, STN125706. The proposed proprietary name is “RYONCIL™ (Remestemcel-L)”. RYONCIL™ (Remestemcel-L) has not been previously licensed in the United States. Remestemcel-L under the brand name Prochymal was conditionally approved for SR-aGVHD in pediatric subjects in Canada and New Zealand in 2012, however marketing has not begun.

2. Materials Reviewed

Document Reviewed	Source
1.11.3 Clinical Information Amendment Fda-info-request-rfi35-msb-reponse-24july2020 1.14.1.3 Draft Labeling Text 1.16.1 Risk Management (Pharmacovigilance Plan) 1.16.1 Risk Management (Non-REMS Justification) 2.5 Clinical Overview 2.7.4 Summary of Clinical Safety 5.2 Tabular Listing of all Clinical Studies 5.3.5.1 Study Report of msb-gvhd001 5.3.5.1 Study Report of msb-gvhd002 5.3.5.2 Study Report of msb-gvhd275 5.3.5.2 Study Report of msb-gvhd280-ped 5.3.5.3 Integrated Summary of Safety	BLA 125706.0
Input from BLA review team	Review team discussions with CBER staff; draft clinical review memo

Pertinent published literature was also reviewed and is referenced in this memo. There are no post-licensure data for review, as this product has not been marketed in any country.

3. Clinical Safety Database

3.1 Pediatric SR-aGVHD Studies

The clinical studies to support the safety of remestemcel-L in pediatric aGVHD subjects includes data from the pivotal phase 3 study MSB-GVHD001 (and the extension study MSB-GVHD002), the expanded access protocol (EAP) Protocol 275 and Protocol 280.

³ Westin JR et al. Steroid-refractory acute GVHD: predictors and outcomes. *Advances in Hematology*. 2011 (8):601953.

3.1.1 Review of MSB-GVHD001: A Single-arm, Prospective Study of Remestemcel-L, Ex-vivo Culture-Expanded Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients who Have Failed to Respond to Steroid treatment for Acute GVHD

Study Objective

The stated safety objective was to “gather additional information on the safety of remestemcel-L in pediatric subjects with Grades B-D aGVHD who have failed to respond to steroid treatment post allogeneic HSCT”.

Study Design

This was a phase 3, prospective, single-arm, open-label, multicenter study to evaluate the efficacy and safety of remestemcel-L in pediatric subjects with aGVHD who failed to respond to first-line treatment with systemic steroids.

Study Population

This study included male and female subjects between the ages of 2 months and 17 years with aGVHD following allogeneic HSCT that had failed to respond to first-line treatment with systemic steroids. Failure to respond to systemic corticosteroid therapy was defined as any Grades B-D (IBMTR grading) aGVHD that showed progression within 3 days or no improvement within 7 days of consecutive treatment with 2mg/kg/day of methylprednisolone or equivalent.

Treatment Plan

Subjects were administered intravenous (IV) remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight at screening, twice per week for each of the first 4 consecutive weeks (Initial Therapy). Subjects with partial or mixed response were eligible to receive an additional 4 once-weekly infusions of remestemcel-L (Continued Therapy) at a dose of 2×10^6 MSCs/kg actual body weight at screening, which began within 1 week after the Day 28 assessment. Before Day 70 post remestemcel-L initiation, subjects experiencing a flare after achieving a complete response were permitted to receive GVHD Flare Therapy, which consisted of twice-weekly infusions of remestemcel-L for an additional 4 weeks at the Initial therapy dose of 2×10^6 MSCs/kg actual body weight at screening. Subjects were followed for up to 100 days following the introduction of Initial Therapy.

Exposure and Subject Disposition

Fifty-five subjects were enrolled, 54 (98%) enrolled subjects received at least 1 infusion of remestemcel-L. A total of 535 infusions were administered to 54 subjects, resulting in a mean (SD) of 9.9 (3.28) infusion per subject. A total of 46 (85%) subjects received 5 to 12 infusions. Five (9.3%) subjects had at least 13 infusions; the maximum number of infusions was 16.

Forty-two (76%) subjects completed the study. Among 13 (24%) subjects not completing the study, the primary reason for early termination was death in 9 (16%) subjects, an adverse event in 1 (1.8%) subject, withdrawal of consent in 1 (1.8%) subject, delay in shipment of remestemcel-L and worsening conditions in 1 (1.8%) subject, and investigator decision not to continue with remestemcel-L infusion in 1 (1.8%) subject.

Safety Results

Common Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that started or worsened after the first dose of remestemcel-L. All 54 subjects in the safety population experienced at least 1 TEAE during the study. Infections and infestations were the most frequently reported AEs (83% of subjects), followed by gastrointestinal disorders (57% of subjects), and metabolic and respiratory disorders (42% of subjects). The most common TEAEs (occurring in $\geq 10\%$ of subjects) were listed in the Table 1.

Table 1: TEAEs with Preferred Term (PT) Incidence $\geq 10\%$ (MSB-GVHD001 Safety Population)

Preferred Term	Total Remestemcel-L N=54 n (%)
Pyrexia	18 (33.3)
Abdominal pain	11 (20.4)
Adenovirus infection	11 (20.4)
Vomiting	10 (18.5)
Hypertension	10 (18.5)
Epstein-Barr viremia	8 (14.8)
Hyperglycemia	8 (14.8)
Arthralgia	8 (14.8)
Hypotension	8 (14.8)
Diarrhea	7 (13.0)
Edema peripheral	7 (13.0)
BK virus infection	7 (13.0)
Hypokalemia	7 (13.0)
Cough	7 (13.0)
Chronic graft-versus-host disease	6 (11.1)
Hypogammaglobulinemia	6 (11.1)
Hypomagnesemia	6 (11.1)

See Module 2.7.4, Table 5

Serious Adverse Events (SAEs)

Thirty five of 54 subjects (65%) reported at least one SAE. Infections and infestations were the most frequently reported SAEs (32% of subjects), followed by respiratory disorders (22% of subjects). Table 2 summarizes SAE with a PT incidence of $\geq 5\%$ in the safety population.

Table 2: SAEs with PT Incidence $\geq 5\%$ (MSB-GVHD001 Safety Population)

Preferred Term	Total Remestemcel-L N=54 n (%)
Pyrexia	5 (9.3)
Respiratory failure	5 (9.3)
Pneumatosis intestinalis	4 (7.4)
aGVHD	3 (5.6)
Staphylococcal infection	3 (5.6)

See Module 2.7.4, Table 7

AEs Leading to Study Drug Discontinuation

Eight subjects (15% of safety population) discontinued remestemcel-L treatment due to an AE during one of the infusion periods. Four of these 8 subjects experienced a fatal outcome. Among the remaining 4 subjects who experienced an AE that lead to study drug discontinuation, one experienced grade 3 dyspnea leading to interruption of the infusion. The subject recovered from the infusion reaction and received additional remestemcel-L infusions that were well tolerated. Another subject experienced life-threatening hypermetabolism. One subject experienced moderately severe somnolence. The last subject experienced mild norovirus gastroenteritis that led to discontinuation of study drug.

Deaths

A summary of the 11 subjects (20%) who experienced TEAEs leading to death are presented in Table 3. In addition, there were 2 subjects who were terminated early from the study and later found to have died within the Day 100 window. One subject died from multiple organ failure related to aGVHD, and the other subject died from a pulmonary hemorrhage and respiratory failure.

Table 3: TAES Leading to Death by PT (MSB-GVHD001 Safety Population)

Preferred Term	Total Remestemcel-L N=54 n (%)
Acute myeloid leukemia	2 (3.7)
Acute respiratory distress syndrome	2 (3.7)
Respiratory failure	2 (3.7)
Cardiac arrest	1 (1.9)
Cardiac failure	1 (1.9)
Multiple organ dysfunction syndrome	1 (1.9)
aGVHD	1 (1.9)
Fungal infection, NEC	1 (1.9)
Pneumonia	1 (1.9)
Metabolic acidosis	1 (1.9)

See Module 2.7.4, Table 10

Adverse Events of Special Interest (AESI)

AESI specified in the protocol included the following: acute infusion reactions, serious infections, serious pulmonary complications, pneumatosis intestinalis, serious neurological events, and ectopic tissue formation.

Acute Infusion Reactions: Acute infusion reactions were defined as adverse reactions temporally associated with remestemcel-L administration during a 2-hour observation window. Three acute infusion reactions were reported in 3 subjects (5.6% of 54 subjects; 3 of 535 injections [0.56%]): somnolence (1), dyspnea (1), and worsening of hypotension (1).

Serious Infections: A total of 17 subjects (32%) experienced 26 serious events of infection. Twelve subject (22%) experienced serious bacterial infection, 6 subjects (11%) experienced serious viral infections, 2 subjects (3.7%) experienced serious fungal infections, and 4 subjects (7%) experienced serious infections caused by unidentified pathogens (eg, pneumonia, sepsis). According to the investigator, two subjects (3.7%) experienced a serious infection considered possibly related to remestemcel-L; all other serious infections were considered not related to remestemcel-L.

Serious Pulmonary Complications: A total of 11 subjects (20%) experienced 12 serious pulmonary complications, including hypoxia (1), acute respiratory distress syndrome (ARDS) (2), respiratory distress (2), and acute respiratory failure (7). None of these serious respiratory events was considered related to remestemcel-L by the investigators.

Pneumatosis Intestinalis: Pneumatosis intestinalis is an expected event (about 10%) in pediatric stem cell transplant recipients.⁴ Four subjects (7%) experienced pneumatosis intestinalis during this study.

Serious Neurological Events: Three serious neurological events were reported in the study: 1 event of somnolence and 2 events of posterior reversible encephalopathy syndrome (PRES) reported in 2 subjects.

⁴ Korhonen K, et al. Incidence, risk factors, and outcome of pneumatosis intestinalis in pediatric stem cell transplant recipients. *Pediatr Blood Cancer*. 2012 Apr;58(4):616-20.

Ectopic Tissue Formation: One subject was reported with a finding of ectopic tissue formation. However, a review of the computed tomography (CT) scan on Day 100 identified 3 abnormal findings but no compelling evidence for ectopic tissue formation. These abnormal CT findings are expected in this disease population. Therefore, there was no evidence suggesting ectopic tissue formation in the CT scan reports.

3.1.2 Review of MSB-GVHD002: Safety Follow-up through 180 Days of Treatment with Remestemcel-L in Study MSB-GVHD001 in Pediatric Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD

Study Objective

The primary objective was to evaluate safety through 180 days of remestemcel-L treatment in subjects who participated in Study MSB-GVHD001.

Study Design

This was a phase 3, open-label, follow-up safety study of MSB-GVHD001 participant. The study evaluated only those subjects who received at least one dose of remestemcel-L in MSB-GVHD 001. Of the 42 subjects who completed MSB-GVHD001, 32 subjects were enrolled in MSB-GVHD002. No study drug was administered during this follow-up study. Safety data were collected at baseline (Day 100) and at Days 120, 140, 160, and Day 180 (End of Study) visit.

Safety Results

Common AEs

Twenty-seven of 32 subjects (84%) were reported with 1 or more TEAEs during the MSB-GVHD002 study period. The most common TEAEs by System Organ Class (SOC) were Infections and infestations (50% of subjects). The most frequently reported TEAEs by PT were pyrexia, hypokalemia, and pain in extremity, each occurring in 4 subjects (12.5%).

SAEs

A total of 15 subjects (47%) were reported with 1 or more SAEs during the MSB-GVHD002 study period. The most common SAEs by SOC were Infections and infestations which were reported in 8 subjects (25%); all other SOC and all PTs were reported in either 1 or 2 subjects.

Deaths

One subject died of recurrent acute lymphoblastic leukemia during the MSB-GVHD002 study period (Day 174). This subject had received 8 remestemcel-L infusions and achieved a complete response.

AESI

No subjects experienced acute infusion reactions since no infusions of remestemcel-L took place during the MSB-GVHD002 study period. And no subjects experienced serous pulmonary complications or serious neurological events. No subjects had evidence of ectopic tissue formation, based on CT scan or MRI, during the MSB-GVHD002 study period.

Serious Infections: Eight subjects (25%) experienced a total of 12 serious infections by PT: pneumonia (2), septic shock (2), bacteremia (1), bronchopulmonary aspergillosis (1), enterococcal infection (1), nocardiosis (1), acute osteomyelitis (1), pneumococcal pneumonia (1), pseudomonas infection (1), and vulval abscess (1).

Pneumatosis Intestinalis: One subject (3%) was reported with pneumatosis intestinalis during the MSB-GVHD002 study period.

3.1.3 Review of MSB-GVHD275: Expanded Access of Prochymal (Ex-vivo Cultured Adult Human Mesenchymal Stem Cells) Infusion for the Treatment of Pediatric Patients Who Have Failed to Respond to Steroid Treatment for aGVHD

Study Objective

The stated safety objective was to document the safety profile and tolerability of remestemcel-L for the pediatric population for the given dosing regimen.

Study Design

This was a single-arm, multi-center study for pediatric subjects with Grades B-D aGVHD secondary to allogeneic HCT or donor lymphocyte infusion (DLI) who failed to respond to steroid treatment.

Study Population

This study included male and female subjects between the ages of 2 months and 17 years (inclusive) with aGVHD following allogeneic HSCT who had failed to respond to first-line treatment with systemic steroids. Failure to respond to steroid therapy was defined as any Grades B-D (IBMTR grading) aGVHD that was not improving after at least 3 days of methylprednisolone ($\geq 1\text{mg/kg/day}$) or equivalent. Subjects were evaluated for efficacy and safety at Day 28, and until death, withdrawal or 100 days post first infusion (Day 0), whichever occurred first.

Treatment Plan

Subjects were administered intravenous (IV) remestemcel-L at a dose of 2×10^6 MSCs/kg (actual body weight) at screening, twice per week for each of the first 4 consecutive weeks prior to Day 28 (Initial Therapy). Infusions were administered at least 3 days apart. All enrolled subjects were allowed to receive institutionally defined standard of care therapy for the treatment of SR-aGVHD in addition to remestemcel-L therapy.

A therapy assessment was performed on Day 28 (± 2 days) post first infusion to determine whether continued treatment was indicated. Subjects with partial or mixed response were eligible to receive infusions of remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight once per week for an additional 4 weeks (Continued Therapy).

Before Day 72 post remestemcel-L initiation, subjects experiencing a flare after achieving a complete response were eligible to be treated with aGVHD Flare Therapy, which consisted of twice-weekly infusions of remestemcel-L for an additional 4 weeks at the initial therapy dose of 2×10^6 MSCs/kg actual body weight at screening. Subjects were followed for up to 100 days following the introduction of Initial Therapy.

Exposure and Subject Disposition

A total of 242 subjects were enrolled into this pediatric expanded access protocol. One adult subject was excluded from all analyses. Of the 241 pediatric subjects enrolled, the median extent of exposure was 46 days, and the median number of infusion received was 11 (range: 1 to 24). One hundred and three (43%) subjects received ≤ 8 infusions, 113 (47%) subjects received 8 to 12 infusions, and 25 (10%) subjects received > 12 infusions.

Of the 241 pediatric subjects, 232 (96.3%) subjects completed participation in the protocol. Because this was an expanded access treatment protocol providing rescue or salvage therapy to patients who had failed to respond to prior treatment, patients who died during the protocol were considered to have completed the protocol. A total of 81 subjects (34%) died during the 100-day treatment and follow-up period.

Information regarding the disposition of one subject is not available. Of the other eight (3.3%) subjects who did not complete the protocol, four subjects (1.7%) discontinued due to a single SAE: recurrent ALL (1 subject), acute respiratory distress (1 subject), and aGVHD (2 subjects). Four subjects (1.7%) did not complete the protocol for

other reasons: one subject withdrew from the protocol because the investigator suspected respiratory distress secondary to transplant, consent was withdrawn for one subject, and two subjects withdrew upon transfer to palliative care.

Safety Results

Common AEs

Only SAEs were collected for this protocol.

SAEs

Of 241 subjects receiving at least 1 dose of remestemcel-L in the study, 131 (54%) experienced at least one SAE. By SOC, 22% of subjects developed infections or infestations, 15% developed respiratory, thoracic, and mediastinal disorders, 11% developed general disorders, and 9% developed GI disorders.

The most frequent SAEs reported by PT were multi-organ failure (7.1%), respiratory failure (7.1%), GI hemorrhage (4.1%), GVHD (3.3%), convulsion (2.9%), hypertension (2.9%), renal failure (2.9%), sepsis (2.9%) and pneumonia (2.5%).

AEs Leading to Study Drug Discontinuation

Twenty-six subjects (11% of safety population) discontinued remestemcel-L treatment due to a total of 38 SAEs. Of these 26 subjects, four subjects had events attributed to remestemcel-L treatment by the investigator: neutropenia (1), infusion reaction (1), hypertension (1), and pulmonary hemorrhage (1).

Deaths

Seventy-seven subjects (32% of safety population) died during the protocol up to Day 100. The most frequently reported SAEs leading to death by SOC were respiratory disorder (9.1%), general disorders and administration site conditions (7.5%), infections and infestations (6.6%), immune system disorders (3.3%), gastrointestinal disorders (2.1%), neoplasms benign and malignant (1.2%), and cardiac disorder (1.2%).

Adverse Events of Special Interest (AESI)

Acute Infusion Reactions:

One 14-year-old female subject with a history of enterococcal sepsis requiring intubation and pressor support experienced two infusion-related reactions. The first infusion reaction occurred on Day 7. One hour after the 3rd remestemcel-L infusion, the subject experienced a low-grade fever and increased work of breathing, which resolved without sequelae. Five days following the first event (Day 12), two hours after completing the 4th remestemcel-L dose, the subject experienced a second infusion reaction characterized by fever of 38.8, decreased blood pressure and tachypnea. The event later resolved without sequelae. Remestemcel-L was permanently discontinued for this subject.

Ectopic Tissue Formation:

Two subjects had CT scan findings initially suggestive of potential ectopic tissue formation after starting treatment with remestemcel-L. One subject had findings in the chest, abdomen, and pelvic on Day 110 that initially appeared consistent with ectopic tissue formation but later were attributed to increased thickening of intra-abdominal fat tissue over time. The second subject had two new nodules in the left lung identified by CT scan on Day 94; however, these were later considered a sign of fungal infection. The findings of ectopic tissue foci for both subjects were assessed to be unrelated to remestemcel-L and not clinically significant by the investigator.

3.1.4 Review of MSB-GVHD280-PED: Statistical Analysis of a Pediatric Patient Subpopulation Enrolled in Osiris Protocol 280: A Phase III, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Prochymal (Ex-vivo Cultured Adult Human Mesenchymal Stem Cells) Infusion for the Treatment of Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD

Study Objective:

The safety objective was to gather additional information on the safety of remestemcel-Lin subjects with Grades B-D aGVHD who have failed to respond to steroid treatment.

Study Design:

This was a phase 3, randomized, double-blind study of patients with Grades B-D aGVHD who had failed to respond to steroid treatment and secondary to allogeneic hematopoietic stem cell transplant (HSCT) or donor leukocyte infusion (DLI). Subjects were randomized in a 2:1 ratio (remestemcel-L to placebo). Subjects were evaluated for efficacy and safety until death, withdrawal or 180 days post first infusion, whichever occurred first.

Study Population

The total study population consisted of male and female subjects between the ages of 6 months and 70 years (inclusive) with Grades B-D aGVHD secondary to allogeneic HSCT or DLI who have failed to respond to steroid treatment. Failure to respond to steroid treatment was defined as any Grades B-D (IBMTR grading) aGVHD that showed no improvement after 3 days and a duration of no greater than 2 weeks, while receiving treatment with methylprednisolone (≥ 1 mg/kg/day) or equivalent.

Treatment Plan

Subjects assigned to the active treatment group were administered remestemcel-L at a dose of 2×10^6 MSCs/kg actual body weight, while those assigned to the placebo group received a physiologic electrolyte solution. Study drug (remestemcel-L or placebo) was to be infused twice per week for each of the first 4 consecutive weeks (Initial Therapy). Infusions were administered at least 3 days apart. Both active and placebo treatment groups received institutionally defined standard of care (e.g., a second-line therapy in addition to continued steroid treatment). Subjects were to have received all 8 infusions in the initial treatment plan by Study Day 28. Subjects with partial or mixed response on Study Day 32 (± 2 days) were eligible to receive an additional 4, once-weekly infusions of remestemcel-L (Continued Therapy) at a dose of 2×10^6 MSCs/kg actual body weight.

Subjects who experienced a flare after achieving a complete response and before Study Day 72 were permitted to receive additional infusions that consisted of twice-weekly remestemcel-L for an additional 4 weeks at the Initial therapy dose of 2×10^6 MSCs/kg actual body weight. Subjects were followed for up to 100 days following the introduction of Initial Therapy.

Exposure and Subject Disposition

Of 260 subjects (both adult and pediatric) enrolled in Protocol 280, all (100%) were randomized to receive study treatment (remestemcel-L or placebo). A total of 223 (85.8%) subjects completed the study. Of 28 pediatric subjects (< 18 years of age) enrolled, 27 (96%) received study treatment (14 remestemcel-L and 13 placebo) and 25 (89%) completed the study. Ten subjects (36%) who died on study were considered to have completed the study. Two subjects were discontinued from the study participation prematurely due to withdrawal from the study.

Regarding study drug exposure in pediatric SR-aGVHD subjects in Protocol 280, the majority (79%) of subjects in the remestemcel-L group received 5-12 study drug infusions.

Safety Results (From Pediatric Subjects Only):**Common AEs**

All patients (both remestemcel-L and placebo groups) had at least 1 TEAE. The number of TEAEs was 121 for the remestemcel-L group and 102 for the placebo group. By SOC, the most commonly reported TEAEs were:

- Infections and infestations: 79% of patients in the remestemcel-L group and 69% of patients in the placebo group.
- Gastrointestinal disorders: 64% of patients in the remestemcel-L group and 46% of patients in the placebo group.
- Respiratory, thoracic, and mediastinal disorders: 50% of patients in the remestemcel-L group and 54% in the placebo group.

There was no difference between the remestemcel-L and placebo treatments overall or by SOC, HLT, or PT for the following TEAE analyses:

- The percentage of patients who experienced TEAEs that were deemed related to the Investigational Agent was 29% for the remestemcel-L group and 23% for the placebo group.
- In the remestemcel-L group, 5 patients (36%) had a TEAE that resulted in death. In the placebo group, 6 patients (46%) had a TEAE that resulted in death.
- One patient in the remestemcel-L group and 1 patient in the placebo group discontinued study medication due to a TEAE.

Serious Adverse Events (SAEs)

Table 4 summarizes SAEs with a PT incidence $\geq 3\%$ and involving at least 2 subjects in either treatment group. The numbers of SAEs reported in the two groups were similar. Although nearly 90% of subjects in the study experienced an SAE, none of the SAEs were experienced by more than 2 subjects in a treatment group.

Table 4: SAEs with PT Incidence $\geq 3\%$ of Subjects in Either Treatment Group (Protocol 280 Safety Population, Pediatric Subjects Only)

System Organ Class Preferred Term	Protocol 280 (Peds) N=27	
	Rem-L N=14 n (%)	Placebo N=13 n (%)
Any SAE	12 (85.7)	12 (92.3)
Immune system disorders	2 (14.3)	3 (23.1)
Graft versus host disease	2 (14.3)	2 (15.4)
Metabolism and nutrition disorders	3 (21.4)	0 (0.0)
Dehydration	2 (14.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	5 (35.7)	4 (30.8)
Respiratory distress	2 (14.3)	1 (7.7)
Respiratory failure	2 (14.3)	2 (15.4)

Source: Module 2.7.4, Table 32

AEs Leading to Study Drug Discontinuation

A single remestemcel-L-treated patient was discontinued due to intracranial hemorrhage and a single placebo-treated patient was discontinued due to gastrointestinal hemorrhage, hypotension, and depressed level of consciousness.

Deaths

A summary of the 11 subjects (5 from the remestemcel-L group and 6 from the placebo group) who experienced TEAEs leading to death are presented in Table 5.

Table 5: SAEs Leading to Death (Protocol 280 Safety Population, Pediatric Subjects Only)

System Organ Class Preferred Term	Protocol 280 (Peds) N=27	
	Rem-L N=14 n (%)	Placebo N=13 n (%)
Any SAE leading to death	5 (35.7)	6 (46.2)
Gastrointestinal disorders	0 (0.0)	1 (7.7)
Gastrointestinal hemorrhage	0 (0.0)	1 (7.7)
Immune system disorders	1 (7.1)	1 (7.7)
Graft versus host disease	1 (7.1)	1 (7.7)
Infections and infestations	2 (14.3)	1 (7.7)
Adenovirus infection	1 (7.1)	1 (7.7)

Cytomegalovirus infection	1 (7.1)	0 (0.0)
Pneumocystis jiroveci pneumonia	1 (7.1)	0 (0.0)
Nervous system disorders	1 (7.1)	0 (0.0)
Hemorrhage intracranial	1 (7.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	2 (14.3)	3 (23.1)
Acute respiratory distress syndrome	1 (7.1)	0 (0.0)
Pulmonary hemorrhage	0 (0.0)	1 (7.7)
Respiratory distress	0 (0.0)	1 (7.7)
Respiratory failure	1 (7.1)	1 (7.7)

Source: Module 2.7.4, Table 35

Adverse Events of Special Interest (AESI)

There were no reported cases of infusion toxicity, ectopic tissue formation, or relapse of underlying disease in pediatric subjects in this study.

3.2 Integrated Summary of Safety

As of December 5, 2018 (data cut-off for this application), a total of 1,517 subjects worldwide have participated in studies involving the use of remestemcel-L. Besides GVHD indication, remestemcel-L has been studied in 4 non-GVHD indications including acute myocardial infarction (AMI), Crohn's disease, chronic obstructive pulmonary disease (COPD), and type 1 diabetes mellitus. Across all studies, 1,114 subjects have been exposed to remestemcel-L, and 403 have received placebo. In the aGVHD studies, 654 (333 pediatric and 321 adult) subjects have received remestemcel-L and 173 (13 pediatric and 160 adult) subjects received placebo. Remestemcel-L doses ranged from 0.5 million cells/kg to over 24 million cells/kg in the treatment of aGVHD and from 0.5 million cells/kg weight-based dosing to a total of 2.5 billion cells in non-GVHD indication.

Integrated safety analysis used pooled results across all aGVHD studies. This study population was further analyzed across separate safety cohorts. Data analysis results were prepared with emphasis on the following study populations:

- Cohort A: Pediatrics with SR-aGVHD (Protocols MSB-GVHD001/002, 275, 280-Ped)
- Cohort A + B: Pediatrics and adults with SR-aGVHD (Protocols MSB-GVHD001/002, 275, 280)
- All subjects who received at least 1 infusion of remestemcel-L
- All subjects who received at least 1 infusion of placebo (controls)

Overview of AEs

The number and severity of AEs experienced in remestemcel-L across all indications was similar to the control population. Of 804 subjects who received remestemcel-L across all indications, 93% subjects experienced 9,721 AEs. Similarly, 94% of 403 control subjects experienced 4,243 AEs. Most AEs were moderate (all remestemcel-L 28%, controls 33%) or severe (all remestemcel-L 32%, controls 27%). A similar proportion of subjects had an AE considered related to study drug in the remestemcel-L (23%) and control (19%) groups across all indications by the investigators. Note that some protocols are not included in AE summaries since only SAEs were collected in those protocols.

The most commonly occurring AEs in all remestemcel-L subjects included: peripheral edema (17%), nausea (13%), pyrexia (13%), abdominal pain (13%), fatigue (13%), diarrhea (11%), and hypertension (11%). The most common AEs that occurred in SR-aGVHD subjects (Cohort A + B) included: peripheral edema (30%), pyrexia (24%), abdominal pain (22%), hypokalemia (20%), diarrhea (20%), hyperglycemia (18%), hypertension (18%), thrombocytopenia (17%), hypotension (16%) and GVHD (16%).

Overview of SAEs

The incidence of SAEs was similar between all subjects exposed to remestemcel-L (57%) and control (54%). Fewer SR-aGVHD subjects (Cohort A + B) who received remestemcel-L experienced an SAE (70%) compared to control (88%). In the Cohort A + B remestemcel-L group, the most common SAEs were GVHD (7.2% remestemcel-L vs

11.1% control), respiratory failure (7.0% remestemcel-L vs 6.2% control), sepsis (5.5% remestemcel-L vs 7.4% control), gastrointestinal hemorrhage (4.8% remestemcel-L vs 6.2% control), multiple organ dysfunction syndrome (5.0% remestemcel-L vs 7.4% control), renal failure (4.1% remestemcel-L vs 4.9% control), pneumonia (3.9% remestemcel-L vs 4.9% control), pyrexia (3.5% remestemcel-L vs 3.7% control) and bacteremia (2.8% remestemcel-L vs 3.7% control).

AEs/SAEs leading to treatment discontinuation

Overall, 9.2% of SR-aGVHD subjects (cohort A + B) receiving remestemcel-L compared to 12.3% of SR-aGVHD controls, and 4.8% of subjects across all indications receiving remestemcel-L compared to 3.2% in all controls, experienced an SAE that led to treatment discontinuation. Infection was the most frequent AE and SAE that led to treatment discontinuation. Seven (0.9%) remestemcel-L subjects experienced an infection AE and 15 (1.3%) remestemcel-L subjects experienced an infection SAE that led to treatment discontinuation. No control subjects had an infection AE/SAE leading to treatment discontinuation.

Deaths

According to the sponsor's response to OBE/DE information request, across all indications, 335 (30%) subjects exposed to remestemcel-L died during the study and study follow-up period compared to 87 (22%) control subjects. In the SR-aGVHD (Cohort A + B) subjects, 226 (49%) subjects exposed to remestemcel-L died during the study and study follow-up period compared to 45 (56%) control subjects.

AESI

The following AESIs were examined in integrated pooled analysis: Acute infusion reaction, Serious infections, Tumorigenicity, and Ectopic tissue formation.

Acute Infusion Reaction:

The incidence of acute infusion reaction was similar between all remestemcel-L (n=165, 21%) and control subjects (n=83, 21%). Remestemcel-L subjects experienced acute infusion reaction at a rate of 0.205 per subject-year compared to 0.182 per subject-year in the control group. Acute infusion reaction was a composite endpoint of 4 categories. For each, the incidence was comparable between remestemcel-L and control groups including: pulmonary circulatory disorder (9.2% vs 9.7%), hypersensitivity (8.5% vs 7.4%), intravascular hemolysis (6.6% vs 6.7%), and local circulatory disorder due to cellular embolism and thrombogenesis (1.7% vs 1.5%).

Remestemcel-L subjects with SR-aGVHD (Cohort A + B) experienced 190 acute infusion reaction events across 103 (48%) subjects compared to 52 events in 33 (41%) control subjects.

Serious Infections:

The incidence of serious infection was similar between all remestemcel-L (24%) and control subjects (23%). Remestemcel-L subjects experienced serious infections at a rate of 0.300 per subject-year, similar to the control group (0.199 per subject-year). The most common serious infections occurring in the remestemcel-L group included: sepsis (3.6% vs 3.0% control), pneumonia (3.1% vs 2.5% control), bacteremia (2.1% vs 1.0% control), septic shock (1.5% vs 1.2%), staphylococcal bacteremia (1.3% vs 1.2% control) and adenovirus infection (1.2% vs 0.5% control).

In SR-aGVHD subjects (Cohort A + B), the incidence of serious infections was higher in the control group (51%) compared to the remestemcel-L group (32%) and the incidence of serious infections was similar across all remestemcel-L dose cohorts.

Tumorigenicity:

Tumorigenicity included benign, malignant, and unspecified neoplasms (exclude cysts). One adult subject with new-onset of aGVHD experienced tumor associated fever. However, there were no definitive cases of malignancy in any subjects receiving remestemcel-L.

Ectopic Tissue Formation:

There were no definitive cases of ectopic tissue formation in any subjects receiving remestemcel-L.

4. Summary of Sponsor-Submitted Pharmacovigilance Plan (PVP)

A summary of the sponsor's PVP is provided in Table 5 below.

Table 5. PVP

SAFETY CONCERN	PROPOSED INTERVENTION
Important Identified Risk	
Acute Infusion Reaction	Drug product delivered by controlled rate delivery Routine pharmacovigilance
Infections	Routine pharmacovigilance
Pulmonary Complications	Drug product delivered by controlled rate delivery Routine pharmacovigilance
Neurological Events	Routine pharmacovigilance
Important Potential Risk	
Ectopic Tissue Formation	Routine pharmacovigilance
Suspected transmission of infectious agents	Routine pharmacovigilance
Hypersensitivity to porcine/bovine excipients	Routine pharmacovigilance
Potential adverse effects with dimethyl sulfoxide (DMSO)	Routine pharmacovigilance In order to minimize potential allergic reaction due to DMSO, premedication with diphenhydramine and hydrocortisone is recommended prior to infusion of remestemcel-L.
New malignancy	Routine pharmacovigilance
Missing Information	
Use during pregnancy	Routine pharmacovigilance methods for the monitoring and follow-up of pregnancy

Should the product be approved, the sponsor proposes routine pharmacovigilance activities in accordance with 21 CFR 600.80 to monitor remestemcel-L safety during the post-marketing period. In addition to the collection and analysis of individual case safety reports (ICSRs) according to regional and international regulations and guidelines, the sponsor proposes review of aggregate adverse event data and periodic benefit-risk evaluation report (PBRER) to evaluate safety signals. The sponsor states that new safety signals will be evaluated for potential inclusion in the adverse reactions section of the US Prescribing Information for Remestemcel-L as well as for potential risk communication to consumers, health care providers and health authorities.

5. Post-Marketing Data

Remestemcel-L under the brand name Prochymal was conditionally approved for SR-aGVHD in pediatric subjects in Canada and New Zealand in 2012, however marketing has not begun. Similar mesenchymal cell therapy products have not been approved in the United States. Since Remestemcel-L has not been marketed in any country, there is no available post-marketing data.

6. Integrated Risk Assessment

The pivotal study MSB-GVHD001/002 submitted by the sponsor in support of this BLA was a single-arm prospective study to evaluate the efficacy and safety of remestemcel-L in pediatric subjects with aGVHD who had failed to respond to systemic steroid treatment. There was no blinding or randomization in the study, and no placebo or a comparator product was used in the study. Instead, Mount Sinai aGVHD international consortium dataset served as an external control. The major disadvantage of an externally controlled trial is its susceptibility to patient, observer, and analyst bias. It is well documented that externally controlled trials tend to overestimate efficacy of test therapies. Hence, the use of external control design is generally restricted in situations which the effect of treatment is dramatic and the usual course of the disease highly predictable.⁵ With regard to safety evaluation, an externally controlled trial is less ideal because generally placebo-controlled trials provide the maximum ability to distinguish adverse effects caused by a drug from those events caused by underlying conditions. Study 280 is the only clinical study in the exposure database that included a control arm and enrolled pediatric subjects with SR-aGVHD. However, small sample size in pediatric study population posed significant analytical problems as the number of pediatric subjects receiving remestemcel-L was only 14 and the number of subjects receiving a placebo control was 13.

The sponsor has identified the following important identified and potential risks as well as the missing information in its pharmacovigilance plan:

Acute infusion reaction: Three acute infusion reactions (Grade 2 somnolence, Grade 3 hypotension, and Grade 3 dyspnea) from three subjects (5.6%) have been reported in study MSB-GVHD001. No fatal infusion reaction events have been reported in any of remestemcel-L studies. Hypersensitivity reaction can occur with infusion of remestemcel-L. Premedication with antihistamine and corticosteroids may reduce the incidence and intensity of infusion reaction. It's proposed in the label that vital signs and oxygen including O₂-saturation should be monitored from the start of infusion to two hours after starting infusion. The sponsor also proposed labeling hypersensitivity reactions and acute infusion reactions in Section 5 "Warnings and Precautions".

Infections: Due to the immune modulating effects of MSC, there is a theoretical risk of increased risk of infection. Subjects within the aGVHD disease population are particularly at high risk of serious infections due to their primary medical conditions as well as the transplantation procedures and immunosuppression therapy.⁶ A total of 17 (32%) subjects experienced 26 serious infection events in study MSB-GVHD001. Infections have been reported as the most frequent SAEs from remestemcel-L studies. Nevertheless, overall, the incidence of serious infection was similar between all remestemcel-L (24%) and control subjects (23%).

Pulmonary complications: In the pivotal study MSB-GVHD001, a total of 11 (20%) subjects experienced 12 events of serious pulmonary complication including hypoxia (1), ARDS (2), respiratory distress (2), and respiratory failure (7). A review of possible causes by the investigators determined that multiple factors might contribute to pulmonary

⁵ Guidance for Industry, E 10 choice of control group and related issues in clinical trials, U.S. Food and Drug Administration, May 2001

⁶ Miller HK, et al. Infectious risk following allogeneic hematopoietic cell transplant complicated by acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2017 March; 23(3): 522-28.

complications, including progression of aGVHD, infections, relapse of primary medical condition (e.g. AML), fluid overload, and hypovolemic shock. None of the serous pulmonary complications were assessed to be related to remestemcel-L by the investigators.

Neurological events: In study MSB-GVHD001, two subject experienced posterior reversible encephalopathy syndrome (PRES) and one subject experienced somnolence. The investigators considered these neurological events were unlikely related to remestemcel-L due to more plausible alternate causes exist (predisposing factors of GVHD and hypertension, concomitant drug cyclosporine). Medical officer agrees with the assessment.

With respect to important potential risks with remestemcel-L treatment, ectopic tissue formation and tumor development are of special interest and theoretical risks for mesenchymal stromal cells (MSCs) due to the ability of MSCs to differentiate into mesenchymal lineage cells, such as bone, cartilage and fat cells, under specific conditions in the laboratory.⁷ According to the sponsor, among 1114 subjects that have been exposed to remestemcel-L with some subjects that were followed for up to 2 years, there have been no confirmed ectopic tissue formation that have been assessed to be causally related to remestemcel-L. Similarly, tumor formation attributable to remestemcel-L has not been observed among the 1114 subjects with remestemcel-L exposure. While short-term data on ectopic tissue formation /tumor development appear reassuring, long-term safety from remestemcel-L is not available at this time.

Other listed important potential risks for remestemcel-L, including suspected transmission of infectious agents, hypersensitivity to porcine/bovine excipients, and potential adverse effects with DMSO, are believed to be extremely low due to extensive screening and testing during manufacturing and release process. There have been no reported donor-derived infections or adverse events indicating a hypersensitivity to the porcine/bovine excipients in remestemcel-L. However, one case of Grade 2 somnolence has been reported that it was possibly due to DMSO. The sponsor proposed that premedication with glucocorticoids and antihistamines to minimize potential allergic reactions due to DMSO. These potential hypersensitivities will be included in the Warning and Precautions section of the proposed labeling.

There are no safety data on the use of remestemcel-L during pregnancy. It is not known if remestemcel-L has the potential to be transferred to the fetus. Therefore, remestemcel-L is not recommended for women who are pregnancy. Routine pharmacovigilance for the monitoring and follow-up of pregnancy are considered adequate since the proposed indication in this application is to treat SR-aGVHD in pediatric patients.

This is the first BLA for a culture expanded adult human mesenchymal stromal cell (ce-MSC) in the United States. Remestemcel-L has been studied as a treatment for a variety of target indications including acute myocardial infarction, COPD, type 1 diabetes mellitus, and Crohn's disease. And there are many other diseases where MSCs have been considered as a potential therapy. The possibility of unauthorized off-label use is always present as stem cell businesses or "stem cell clinics" promote their products as treatments for a wide range of conditions. FDA has recognized the promise of stem cell therapy and the growing risk posed by unauthorized use of stem cell therapies.⁸

Note: Remestemcel-L was discussed during August 13, 2020 Oncologic Drugs Advisory Committee (ODAC) Meeting. There was no new information pertaining to postmarket safety monitoring during this meeting.

7. DE Recommendations

Should the product be approved, the Risk Management Plan (pharmacovigilance plan) submitted under the original BLA 125706/0 is adequate for the postmarketing safety monitoring for RYONCIL™ (Remestemcel-L) with routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80. The reviewed safety data do not

⁷ Krampera M et al. Mesenchymal Stem Cells: from Biology to Clinical Use. Blood Transfusion. 2007 Jul;5(3):120-129.

⁸ FDA Warns About Stem Cell Therapies (2019). Available at <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>. Accessed 21 July 2020.

indicate the need for a Risk Evaluation and Mitigation Strategy (REMS), a safety post-marketing requirement (PMR) study, or a safety post-marketing commitment (PMC) study.