PROTOCOL SYNOPSIS

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial of remestemcel-L-rknd added to ruxolitinib for Grade III-IV Steroid-Refractory Acute Graft-Versus-Host Disease

Co-Principal Investigators: John Levine, MD and Iskra Pusic, MD

Study Design: This study is a randomized, double-blind, placebo-controlled, multicenter Phase III trial to compare the efficacy and safety of remestemcel-L-rknd (remestemcel-L), ex-vivo cultured adult human mesenchymal stromal cells (MSC), combined with ruxolitinib vs. ruxolitinib combined with placebo as second-line therapy in adult patients with Grade III-IV steroid-refractory acute graft-versus-host disease (SR-aGVHD).

Primary Objective: The primary objective is to compare the overall response rates (ORR) between the 2 treatment arms, where a response is defined as a partial response (PR) or complete response (CR) on Day 28 post-randomization without new intervening systemic therapy.

Secondary Objectives: Secondary objectives are to compare the 2 treatment arms for the following:

1. Overall survival (OS) through Day 180 post-randomization.
2. Duration of response (DoR), defined as the time from the Day 28 response (CR or PR) to the day of aGVHD recurrence/progression, new systemic therapy for aGVHD, or death from any cause, whichever occurs first.

Exploratory Objectives: Exploratory objectives include describing the following in each treatment arm and compare among arms, where appropriate:

1. Durable ORR at Day 56 defined as the proportion of participants who achieve CR or PR at Day 28 and maintain CR or PR at Day 56.
2. Time to CR and ORR
3. ORR (CR or PR) at Days 14, 56, 100, and 180.
4. Response by involved organ (skin, liver, upper gastrointestinal [GI] and lower GI tract) at Days 7, 14, 28, 56, 100, and 180.
5. Failure-free survival, defined as the time from the date of randomization to the date of non-relapse mortality, or addition of new systemic aGVHD treatment at any time up to Day 180 post-randomization.
6. Steroid dose from randomization until Day 56.
7. Ruxolitinib dose from randomization until Day 56.

8. Proportion of participants free of systemic steroids (e.g., ≤ 8 mg/day of methylprednisolone or equivalent]) by Day 180.
9. Proportion of participants free of any systemic immune suppressive therapy by Day 180.
10. Cumulative incidence of non-relapse mortality (NRM) at Days 100 and 180.
11. Relapse-free survival at Day 180.
12. Acute GVHD-free survival at Days 100 and 180.
13. Cumulative incidence of chronic graft-versus-host disease (cGVHD) at Day 180.
14. Cumulative incidence of underlying disease relapse/progression at Day 180.
15. Incidence and severity of infections using Blood and Marrow Transplant Clinical Trial Network (BMT CTN) criteria.
16. Incidence of adverse events probably or definitely related to remestemcel-L or placebo to match (PTM) based on attribution by treating physician.
17. Levels of soluble and cellular inflammatory biomarkers (to be collected at baseline [Day 0] prior to first infusion and on Days 7, 14, 28, and 56). Soluble biomarkers will include the Mount Sinai Acute Graft-Versus-Host Disease International Consortium (MAGIC) algorithm probability score (MAP, consisting of suppressor of tumorigenicity-2 [ST2] and regenerating islet-derived-3 alpha [Reg3α]) and may include other biomarkers shown to be associated with graft-versus-host disease (GVHD), such as amphiregulin, hepatocyte growth factor (HGF), elafin, soluble interleukin-2 receptor alpha (sIL-2Rα), interleukin-8 (IL-8), and tumor necrosis factor receptor 1 (TNFR1). Cellular biomarkers will include immune cell subsets such as T, B, and natural killer (NK) cells, activated T cells and regulatory T cells. Biomarker levels and longitudinal changes in biomarker levels will be explored. Associations among biomarkers, between biomarkers, clinical response and safety will be explored.
18. Change in functional status from baseline (as assessed with Karnofsky performance scores) to Days 28, 56, 100, and 180.
19. Changes in patient-reported outcomes (PROs) from baseline to Days 100 and 180.
20. ORR at Day 28 measured from the date of the first investigational product infusion.
21. ORR and OS in relevant participant subgroups defined by age (≥ 65 vs. < 65), by biomarker status at baseline (high

risk vs. not as defined by MAP criteria, e.g., Ann Arbor scores 1, 2, and 3), disease risk index (DRI).

Eligibility Criteria:

Inclusion Criteria:

1. Age 18 years or older at the time of enrollment.
2. Able to take oral medications.
3. Have Grade III-IV SR-aGVHD at the time of enrollment, defined as aGVHD resistant to high dose corticosteroids at a dose of ≥ 1 mg/kg/day methylprednisolone (or equivalent), given alone or in combination with GVHD prophylaxis agents such as calcineurin inhibitor (CNI), mammalian target of rapamycin (mTOR) inhibitor, and/or mycophenolate mofetil (MMF).
    a) The minimum time between the initiation of high-dose corticosteroids and enrollment is 3 days if aGVHD has progressed in at least one organ regardless of improvement in other organs, OR
    b) Minimum time of 5 days for aGVHD showing no improvement in GI or liver symptoms, OR
    c) Recurrence of Grade III-IV aGVHD after an initial response to steroid therapy.
4. Prior use of ruxolitinib is permissible in the following cases:
    a) if no more than 2 doses of ruxolitinib were taken for aGVHD treatment prior to enrollment.
    b) if there was prior use of ruxolitinib for GVHD prophylaxis. If aGVHD developed while on ruxolitinib for GVHD prophylaxis or within 3 days of its discontinuation, the patient is not eligible.
5. Evident myeloid and platelet engraftment. Absolute neutrophil count (ANC) ≥ 1000/mm^3 and platelets ≥ 20,000/ mm^3. Use of growth factor supplementation and transfusion support is allowed.
6. Minimum Karnofsky performance score of 30 at the time of study entry.
7. Patient (or legal representative where appropriate) must be capable of providing written informed consent/assent.
8. Female patients of childbearing potential must use a medically accepted method of contraception and must agree to continue use of this method for the entire

duration of study participation. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device, or steroid contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

9. Male patients with partners of childbearing potential must agree to use adequate contraception (barrier method with spermicide or abstinence) for the entire duration of study participation.
10. Willing and able to comply with study requirements, remain at the clinic, and return to the clinic for the follow-up evaluation, as specified in this protocol during the study period.

Exclusion Criteria:

1. Underwent second allogeneic hematopoietic cell transplantation within six months from the first transplant.
2. Received systemic treatment for aGVHD other than corticosteroids +/- agents used for aGVHD prophylaxis (e.g., CNIs, mTOR inhibitor, and/or MMF).
3. Respiratory disease requiring continuous positive pressure ventilation or intubation. Patients who need intermittent continuous positive airway pressure (e.g., during sleep) are eligible.
4. Any underlying or current medical or psychiatric condition that, in the opinion of the investigator, would interfere with the evaluation of the patient.
5. Post-transplant morphologic relapsed malignancy.
6. Donor leukocyte infusion (DLI) for treatment of malignant disease relapse. Patients who received DLI for indications other than relapse, including for treatment of minimal residual disease (MRD) and mixed chimerism, are eligible.
7. Prior treatment with any mesenchymal lineage cells, including remestemcel-L.
8. Active or inadequately treated latent infection with *Mycobacterium tuberculosis* (i.e., tuberculosis).
9. Female patients who are pregnant, lactating, or planning a pregnancy during the expected remestemcel-L treatment period.
10. Concurrently receiving an investigational agent, device or procedure. An investigational agent, device or procedure is defined as having no known Food and Drug Administration (FDA)-approved indications. Any

prior and/or current participation in a clinical trial of an investigational medicinal product (IMP) that is registered and being used off label requires review by the study's Protocol Officer, Protocol Chairs, and Sponsor prior to enrollment.

11. Known hypersensitivity to dimethyl sulfoxide (DMSO) or to porcine or bovine proteins.
12. Requiring vasopressor support.
13. Uncontrolled infections. Infections are considered controlled if appropriate therapy has been instituted and, at the time of enrollment, no signs of progression are present. Persistent fever without other signs or symptoms will not be interpreted as progressing infection. Progression of infection is defined as: hemodynamic instability attributable to sepsis OR new symptoms attributable to infection OR worsening physical signs attributable to infection OR worsening radiographic findings attributable to infection. Patients with radiographic findings attributable to infection within 4 weeks prior to enrollment must have a repeat radiographic exam within one week of enrollment that documents stable or improved findings.
14. Estimated creatinine clearance less than 15 mL/min or those requiring hemodialysis.
15. Clinically significant liver disorders or bilirubin greater than 3 mg/dl not attributable to aGVHD or Gilbert's.
16. Moderate to severe cGVHD that requires systemic treatment. Chronic GVHD that is not requiring systemic therapy is allowed.

Treatment Description:

Eligible participants will be enrolled and randomized 1:1 to receive ruxolitinib and remestemcel-L (Arm A) or ruxolitinib and PTM (Arm B). Consent, enrollment and randomization should occur within 24 hours.

Arm A and B: The day of randomization is designated as Day 0. Following enrollment and randomization, participants will initiate ruxolitinib at a dose of 5 mg twice daily. Treatment with IP (remestemcel-L or PTM) should be initiated within 24 hours of randomization. In the event of a delay in administration of the IP (e.g. due to a weekend or holiday), the infusion must be initiated within 72 hours of randomization. Infusions initiated after 72 hours of randomization will constitute a protocol deviation. An aGVHD assessment performed within 24 hours prior to randomization will serve as the baseline assessment.

An aGVHD assessment will also be performed within 24 hours prior to the initial IP infusion. In the unlikely event that the pre-infusion assessment shows a downgrade from Grade III–IV to Grade II, participants will remain eligible and will proceed with the infusion of the IP as planned.

The ruxolitinib dose may be increased to 10 mg twice daily after 3 days of treatment, provided that the ANC and platelet count have not decreased by ≥50% relative to the first day of ruxolitinib dosing.

Participants who achieve CR, PR, or mixed response (MR) at Day 28 assessment following randomization will continue ruxolitinib through Day 180. After Day 180, a prespecified ruxolitinib taper may be initiated (see section 2.8.3).

Participants with no response at Day 28 assessment, or those who progressed, may discontinue ruxolitinib at any time at investigator's discretion.

Arm A:

Initial Therapy:

Remestemcel-L will be administered as intravenous infusions at a dose of 2×10^6 MSC/kg (based on actual body weight at enrollment) twice weekly for 4 consecutive weeks, for a total of 8 doses. Infusions must be administered at least 3 days apart and no more than 5 days apart. For example, if the cells are infused on Monday, the earliest day for next infusion is Thursday; if infused on Tuesday, the earliest day for next infusion is Friday; if infused on Wednesday, the earliest day is Saturday and the latest day is the following Monday; etc.

Continued Therapy:

Following completion of the initial 4 week treatment period of infusions, eligible participants will receive 4 additional infusions of remestemcel-L at the same dose of 2×10^6 MSC/kg (based on actual body weight at enrollment) administered once weekly (± 3 days) for an additional 4 weeks. Infusions should begin within one week following the Day 28 response assessment.

Eligibility to receive Continued Therapy will be determined based on the participant's response at Day 28 compared with baseline, as follows:

Complete Response (CR): No additional remestemcel-L will be administered.

No Response (NR): No additional remestemcel-L will be administered.

Partial Response (PR): The participant will receive Continued Therapy.

Mixed Response (MR): The participant will receive Continued Therapy.

Arm B:
Initial Therapy:
PTM will be administered as intravenous infusions twice weekly for 4 consecutive weeks of treatment, for a total of 8 doses. Infusions must be administered at least 3 days apart and no more than 5 days apart.

Continued Therapy:
Following completion of the initial 4 weeks treatment period of twice-weekly infusions, eligible participants will receive 4 additional infusions of PTM administered once weekly (± 3 days) for an additional 4 weeks. Infusions should begin within one week following the Day 28 response assessment.

Eligibility to receive Continued Therapy is the same as for Arm A.

Accrual Objective: The target accrual is 180 participants (90 per arm) from at least 35 transplant centers in the United States (US).

Accrual Period: Approximately 36 months is expected for accrual.

Study Duration: Participants will be followed for 6 months after their first dose of remestemcel-L/PTM.

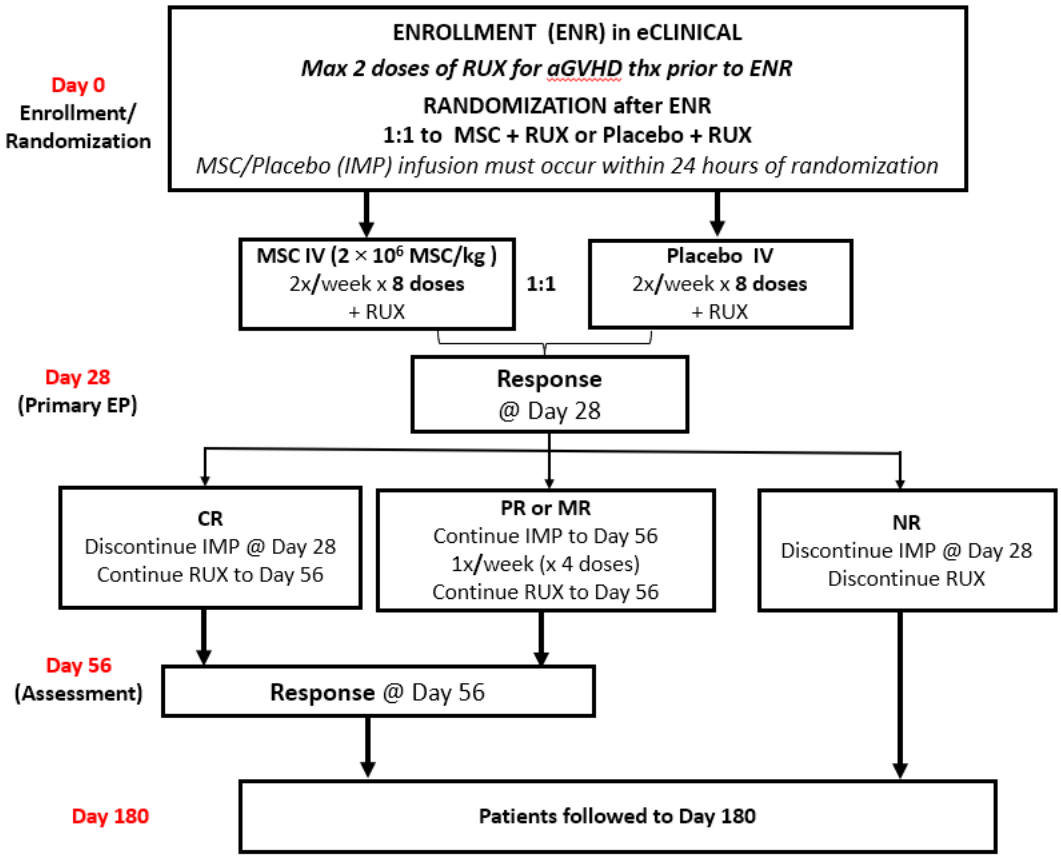
Duration of study participation and treatment:

After eligible patients are consented to the study, they are enrolled and randomized. Participants should start treatment within 24 hours of randomization. Randomization is Day 0. Participants are allowed to have received 2 doses of ruxolitinib for treatment of SR-aGVHD prior to enrollment.

Treatment Period: Day 0 to Day 28; possibility for Continued Therapy for 4 additional weeks through Day 56.

Duration of follow-up: Day 0 to Day 180

STUDY SCHEMA



Abbreviations: aGVHD: acute graft-versus-host disease; CR: complete response; ENR: enrollment; EP: endpoint; IMP: investigational medicinal product; IV: intravenous; MSC: mesenchymal stromal cells; MR: mixed response; NR: no response; RUX: ruxolitinib; thx: treatment