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A Phase 3, Single-Arm, Prospective Study of Remestemcel-L, Ex Vivo Culture-Expanded Adult Human Mesenchymal Stromal Cells for the Treatment of Pediatric Patients Who Failed to Respond to Steroid Treatment for Acute Graft-versus-Host Disease

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A B S T R A C T

Steroid-refractory acute graft-versus-host disease (SR-aGVHD) following hematopoietic cell transplantation (HSCT) is associated with poor clinical outcomes. Currently, there are no safe and effective therapies approved for use in the pediatric population under the age of 12 years. Accordingly, there is an urgent need for new treatments that are safe, well tolerated, and effective in managing this debilitating and potentially fatal complication of HSCT. In early phase clinical trials, mesenchymal stromal cells (MSCs) have demonstrated efficacy in the treatment of acute GVHD (aGVHD) in pediatric patients. We now report the results of a phase 3, prospective, single-arm, multicenter study (NCT02336230) in 54 children with primary SR-aGVHD who were naive to other immunosuppressant therapies for aGVHD treated with MSC product (remestemcel-L) dosed at 2×10^6 cells/kg twice weekly for 4 weeks. Remestemcel-L therapy significantly improved day 28 overall response rate (OR) compared with the prespecified control OR value of 45% (70.4% versus 45%, $P = .0003$). The statistically significant OR (70.4%) was sustained through day 100, including an increase in complete response from 29.6% at day 28 to 44.4% at day 100. Overall survival was 74.1% at day 100 and 68.5% at day 180. Overall response in all participants at day 28 was highly predictive of improved survival through 180 days, and survival was significantly greater in day 28 responders compared with nonresponders through day 100 (86.8% versus 47.1% for responders and nonresponders, respectively, $P = .0001$) and through day 180 (78.9% versus 43.8%, $P = .003$). Remestemcel-L was well tolerated with no identified infusion-related toxicities or other safety concerns. This study provides robust, prospective evidence of the safety, tolerability, and efficacy of remestemcel-L as first-line therapy after initial steroid failure in pediatric SR-aGVHD.

INTRODUCTION

Acute graft-versus-host disease (aGVHD) is a major obstacle to the overall success of allogeneic hematopoietic stem cell transplantation (HSCT). Although the incidence of aGVHD varies across transplant type and donor sources, severe aGVHD

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(determined by grade C/D, visceral organ and/or multiorgan involvement, or high-risk stratification) is associated with the highest risk of primary treatment failure and highest transplant-related mortality [1,2]. Mortality can reach as high as 90% in adults and children who fail to respond to initial steroid therapy [2-5]. Despite overall improvement in transplantation outcomes [6], the cohort of patients who develop aGVHD and subsequently fail to respond to initial steroid therapy continue to have high morbidity and mortality in large part because there are no effective treatment options for these patients. Two recent reports highlight the poor prognosis and consequent therapeutic gap in the management of pediatric aGVHD, particularly among children who fail to respond to initial steroid therapy and have more severe disease based on organ involvement [7,8]. An exploratory analysis of outcomes in 203 patients with steroid-refractory aGVHD, including 61 children up to 18 years of age, reported a 34% day 28 overall response rate (95% confidence interval, 23% to 48%); overall 2-year survival in this cohort was 32% [7]. In a cohort of 370 pediatric patients with aGVHD, a high-risk subgroup of 42 patients based on Minnesota risk score who failed to respond to steroid therapy the overall response rate (OR) at day 28 was 48% in the high-risk group (based on Minnesota risk score) who failed to respond to steroid therapy and 2-year survival in these subjects was 35% [8]. There are currently no approved therapies specifically indicated for use in steroid-refractory aGVHD in children under the age of 12 years, a patient population with high unmet need and poor prognosis [8-10].

aGVHD is characterized by immune activation with systemic inflammation and tissue injury primarily affecting the gastrointestinal (GI) tract, skin, and liver. HLA disparity between the hematopoietic stem cell (HSC) donor and recipient is a key driver of aGVHD, causing alloreactive donor T cells, contained in the HSC graft, to recognize the patient's tissues as foreign and thereby trigger an immunologic attack [11]. Release of inflammatory cytokines by injured tissues amplifies and sustains the activity of alloreactive donor immune cells, leading to further inflammation and end-organ damage [11]. The biological activity of mesenchymal stem cells (MSCs) provides a mechanistic rationale for their investigational use in aGVHD [12]. Evidence from in vitro studies and animal models indicates that bone marrow-derived MSCs have immunosuppressive and immunomodulatory functions [13-19]. Allogeneic tolerance, inhibition at immune checkpoints, and paracrine signaling are MSC mechanisms particularly relevant to aGVHD [20,21]. Results from initial clinical studies of MSCs have indicated favorable clinical response rates with an acceptable safety profile when used to treat steroid-refractory GVHD (SR-aGVHD) [22-26]. In addition, GVHD therapy with MSCs is associated with reductions in relevant inflammatory biomarkers, including IL-2Ra, tumor necrosis factor receptor 1, IL-8, and hepatocyte growth factor, providing further evidence of the biological basis of the clinical benefit of this therapy in aGVHD [25].

In a multicenter expanded-access protocol using remestemcel-L (Protocol 275, NCT00759018), 241 pediatric patients with SR-aGVHD, the majority of whom were resistant to multiple immunosuppressive therapy (IST) as aGVHD treatment at the time of study enrollment, were treated with remestemcel-L (ex vivo culture-expanded allogeneic adult human MSC) as salvage therapy for SR-aGVHD [26]. Day 28 OR was 65% (95% confidence interval, 58.9% to 70.9%) and responder survival at day 100 in patients with a day 28 OR was significantly greater compared with nonresponders (82% versus 39%, log rank $P < .001$). Infusions were well tolerated with no identified safety concerns. The present phase 3 registration study was designed to confirm previous observations from a pediatric expanded-access program and further evaluate the efficacy and safety of remestemcel-L in children with high-risk SR-aGVHD.

MATERIALS AND METHODS

Study Design

This study (MSB-GVHD001, NCT02336230, IND 7939), a phase 3, single-arm, open-label, prospective, multicenter study conducted at 20 centers in the United States, was designed to evaluate the efficacy and safety of remestemcel-L in pediatric patients with primary SR-aGVHD in the absence of additional IST for aGVHD. It also included a follow-up safety extension study (MSB-GVHD002) to evaluate the safety, survival, and duration of response through 180 days.

The design of the study is shown in Figure 1. Based on ethical and feasibility considerations, the study used a single-arm design with all patients receiving remestemcel-L treatment. Feedback from investigators and key experts in pediatric aGVHD indicated that a randomized, controlled study design would be challenging to enroll and potentially unfeasible because parents might be reluctant to consent to participate in a study in which the child might not receive the active investigational therapy. The study was approved by the institutional review boards of the participating centers and was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines [27]. All participants or legally acceptable representatives provided written informed consent.

Patients

Children 2 months to 17 years of age with steroid-refractory grade B to D aGVHD (excluding skin-only grade B) were enrolled from June 2015 to December 2017. Eligible patients failed to respond to systemic steroid treatment as first-line treatment for aGVHD, as defined by progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/d of methylprednisolone or equivalent. Patients were excluded if they had received any other systemic first-line or any second-line therapy for the treatment of aGVHD prior to screening or treatment with remestemcel-L. Complete inclusion and exclusion criteria are provided in Supplementary Table S1.

Investigational Agent

Remestemcel-L comprises healthy adult volunteer donor human bone marrow-derived MSCs that have been ex vivo cultured and cryopreserved in Plasma-Lyte A supplemented with human serum albumin and dimethyl sulfoxide. Each remestemcel-L dose was stored in the vapor phase of liquid nitrogen, thawed, and reconstituted in Plasma-Lyte A (Baxter International, Inc. USA) immediately prior to administration.

MSCs are nonhematopoietic cells that express low levels of major histocompatibility complex class I, are negative for major histocompatibility complex class II molecules, and are negative for costimulatory molecules CD40, CD80, and CD86. Remestemcel-L cells are $CD105^+$, $CD156^+$, and $CD45^{-/\text{low}}$, express tumor necrosis factor receptor 1; and suppress IL-2Rα expression on activated lymphocytes. Remestemcel-L cells are harvested at passage 5 and then cryopreserved as a final product. In this study, 4 donors and multiple product lots were used. Most patients received infusions from more than 1 lot, and some patients were exposed to cells from more than 1 donor.

Treatment

Treatment with remestemcel-L was administered to patients intravenously at a dose of 2×10^6 MSCs/kg body weight, twice weekly, for 4 consecutive weeks. All initial therapy infusions were completed by day 28 $\pm$ 2 days. Patients could continue treatment with a stable dose of systemic steroid therapy until eligible for steroid taper per treating physician discretion and could continue on an established regimen of baseline prophylactic therapy for GVHD. Per protocol, no other medications for the treatment of SR-aGVHD could be introduced to patients during the initial 28 days of remestemcel-L administration unless disease progression occurred. Addition of other aGVHD therapies prior to day 28 constituted failure to respond, and the patient remained on study for safety follow-up only.

Patients with partial (PR) or mixed response (MR) on day 28 could receive continued therapy of 4 once-weekly infusions of remestemcel-L at the same initial dose of 2×10^6 MSCs/kg, beginning within 1 week after the day 28 assessment. Patients who experienced an aGVHD flare (grade B to D progression after achieving a complete response [CR]) could receive additional therapy at the same dose twice a week for an additional 4 weeks.

Assessments of Efficacy and Safety

aGVHD assessments were performed at baseline and then weekly from day 14 ($\pm$2 days) after the first MSC infusion until day 100 ($\pm$7 days). Weekly assessment visits were conducted at least 24 hours after the most recent remestemcel-L infusion. For patients participating in the follow-up study to day 180, aGVHD assessments were conducted at study visits on days 120,

140, 160, and 180. Severity of aGVHD was evaluated using the Center for International Blood and Marrow Transplant Research grading criteria [28,29].

All untoward medical occurrences after signing of the informed consent were considered adverse events (AEs). Treatment-emergent adverse events (TEAEs) were those adverse events that occurred after the start of treatment. Serious AEs were defined according to International Council for Harmonization E6 standards [27]. Concomitant medication use was assessed at each visit. Occurrence of chronic GVHD and relapse of primary disease were assessed through day 180.

Efficacy Endpoints

Definitions of clinical response endpoints are shown in Table 1. OR at day 28 was the primary efficacy endpoint. Day 28 OR is an early indicator of subsequent longer-term response and is now generally accepted as an appropriate surrogate for clinical outcomes [30]. Patients who were deceased, had missing assessment data, received additional aGVHD IST, or withdrew prior to day 28 were considered or imputed as no response regardless of the responses reported on electronic case report forms. For patients who were enrolled but not treated with remestemcel-L, the day 28 response was also considered no response. For patients who withdrew from the study because of a serious AE or the need for palliative care due to a lack of aGVHD response and had completed a 28 day endpoint assessment, the 28-day assessment was used. The primary study hypothesis was that the primary efficacy endpoint, OR at day 28, is at least 20% greater than the control, standard of care OR of 45%.

Key secondary endpoints were overall and responder survival, as well as rates of PR, CR, and very good partial response (VGPR), defined as an absence

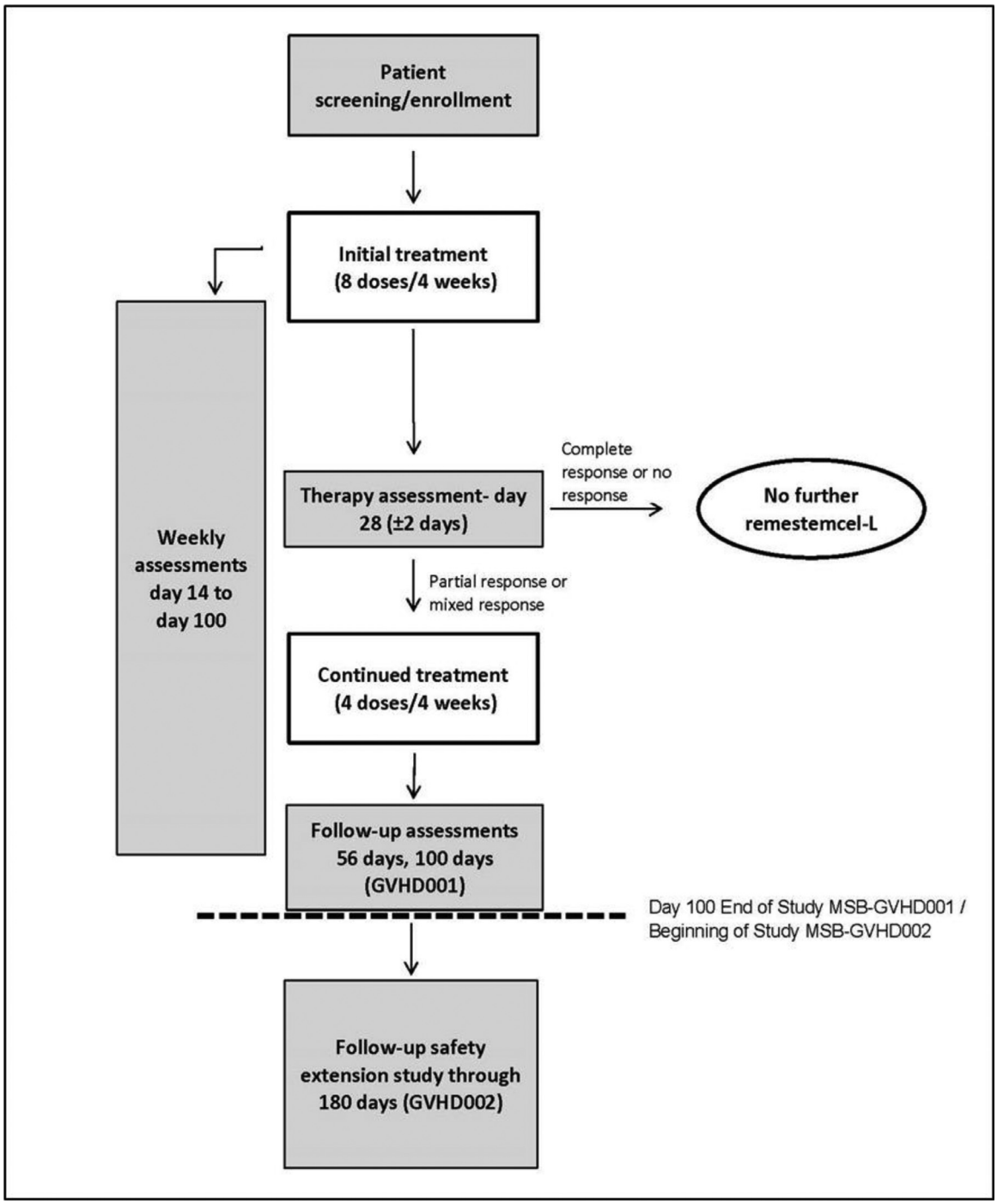

Figure 1. Study design.

Table 1
Clinical Response Definitions

Abbreviation	Definition
CR	Complete response: Resolution of aGVHD in all involved organs
PR	Partial response: Organ improvement of at least 1 stage without worsening of any other organ
OR	Overall response: Includes both CR + PR
VGPR	Very good partial response: Fulfillment of the CR criteria except for 1 or more of the following: Skin: No rash, nonprogressive stage 1 rash, or residual erythematous rash involving <25% of the body surface without bullae (not including residual faint erythema or hyperpigmentation) Liver: Resolving elevations of total serum bilirubin concentration or total serum bilirubin concentration of <2 mg/dL or <25% of baseline at enrollment Gut: Minimal gastrointestinal symptoms, as described below: • Tolerating food or enteral feeding • Predominantly formed stools • No overt GI bleeding or abdominal cramping • No more than occasional nausea or vomiting
MR	Mixed response: Improvement in at least 1 evaluable organ stage with worsening in another
NR	No response: No change in any organ stage in any organ system and no improvement in organ stage
Progression	Deterioration in at least 1 organ system by 1 stage or more with no improvement in any other organ
Responder	Patients who achieve an OR
Nonresponder	Patients who do not achieve OR

of all GVHD symptoms except stage 1 disease in any organ. For all enrolled patients, assessments of vital status through day 100 and day 180 were completed; if vital status was not obtained, the patient was presumed to be deceased for the purpose of survival assessment and analysis.

Statistical Analysis

The primary efficacy objective of this study was to confirm the effect of remestemcel-L on day 28 OR. For the assessment of efficacy, a treatment effect size of 20% (ie, 20 percentage points) was considered clinically meaningful and was used to calculate the null hypothesis. The null hypothesis of 45% OR for standard of care alone was supported by historical age and disease severity-adjusted published findings and internal data showing an approximate 45% day 28 OR rate for aGVHD patients treated with steroids, second-line systemic agents, and supportive symptom management [31,32]. Details regarding the approximate 45% control overall response rate are provided in Supplementary Table S2. Kaplan-Meier curves were used to graphically display the data resulting from time-to-event analyses with a log-rank test used to test for differences across subgroups.

The sample size was determined using East 6.0 software (Waltham, MA). The hypothesis test used a normal approximation to the binomial distribution under the assumption of a symmetric 2-sided, 1-sample test with a significance level of 5% for a single proportion. The minimum sample size required to provide 80% statistical power to demonstrate a 20% treatment difference from a control rate of 45% was 48 patients. To provide power for additional population analyses and account for premature withdrawals, an increase of 10% to 53 patients was planned.

Analysis Populations

The primary endpoint and all other efficacy variables were evaluated for all enrolled patients (n = 55), defined as the Full Analysis Set population. In this article, we present efficacy results on all enrolled patients who received remestemcel-L treatment (n = 54). Safety outcomes were evaluated for all patients who received at least 1 dose of remestemcel-L (n = 54) for MSB-GVHD001 and all patients (n = 32) who continued into MSB-GVHD002, defined as the safety population. Duration of response was evaluated in patients who achieved OR at day 28 in MSB-GVHD001 and patients enrolled in MSB-GVHD002, which was also defined as the duration of the response population. Prespecified subgroup analyses included those defined by age, sex, aGVHD grade at baseline, baseline organ involvement, risk stratification, and transplant characteristics.

Table 2
Protocol GVHD001 Patient Disposition (All Enrolled Patients)

Disposition/Reason	Total Remestemcel-L, No. (%)
Patients enrolled	55 (100)
Patients treated with investigational agent in MSB-GVHD001	
Yes	54 (98.2)
No	1 (1.8)
Patients completed MSB-GVHD001	
Yes	42 (76.4)
No	13 (23.6)
Primary reason for early termination in MSB-GVHD001	
Adverse event	1 (1.8)
Withdrawal of consent	1 (1.8)
Death	9 (16.4)
Other	2 (3.6)
Patients continuing into the MSB-GVHD002 follow-up phase	32 (58.2)
Primary reason for early termination in MSB-GVHD002*	
Death	1 (3.1)

* Percentages based on the number of patients continuing into the MSB-GVHD002 follow-up phase.

RESULTS

Patients

The disposition of patients is shown in Table 2. Fifty-five patients were enrolled in the study and 54 received at least 1 infusion of remestemcel-L. Of the treated patients, 42 completed treatment and 40 were alive and eligible to enroll in the follow-up study on day 100. Of these, 32 patients enrolled and 31 completed the follow-up study to day 180. Thirteen patients died during the primary study and 1 patient was lost to follow-up and presumed deceased. In GVHD002, 3 patients died and 1 patient was lost to follow-up and presumed deceased.

Table 3 shows baseline demographic and disease characteristics. Briefly, the median age of patients was 7 years, 63.6% of patients were male, and 76.4% of patients received an HSCT from an unrelated donor. The source of HSC for transplant was bone marrow (54.5%), peripheral blood stem cells (25.5%), and cord blood in 20% of patients. The median time from onset of aGVHD to first remestemcel-L infusion was 12 days, and median time for establishing onset of steroid failure to first remestemcel-L infusion was 3.5 days. At baseline, 47.3% of patients had grade D aGVHD; 89.1% had severe disease, defined as grade C/D; and 72.7% of patients met the criteria for high-risk disease [33].

Exposure

Patient exposure to remestemcel-L is summarized in Table 4. Thirty patients received more than the initial 8 infusions (25 patients for continued therapy and 5 patients for aGVHD flare [9 to 16 infusions]; see Table 4). Mean duration of infusions was approximately 1 hour. The mean dose of MSCs per infusion was approximately 50×10^6 cells (median weight 25.5 kg). Patients who did not complete the 8 infusions over 28 days were considered nonresponders.

Clinical Response

Clinical response outcomes are summarized in Table 5. OR at day 28 was achieved by 38 of 54 patients (70.4%) with 16 patients (29.6%) and 22 patients (40.7%) achieving CR and PR, respectively. OR at day 28 was statistically superior ($P = .0003$)

Table 3
Demographics, Transplant Characteristics, and Disease Characteristics

Characteristics	Remestemcel-L (n = 55)
Demographic characteristics	
Age, yr	
Mean (SD)	7.3 (5.45)
Median (min, max)	7.0 (0, 17)
Sex, No. (%)	
Male	35 (63.6)
Female	20 (36.4)
Weight, kg	
Mean (SD)	28.8 (18.9)
Median (min, max)	25.5 (4.6, 90.1)
Characteristics, No. (%)	
HLA donor HLA frequency	
Matched/related	6 (10.9)
Mismatched/related	7 (12.7)
Unrelated	42 (76.4)
Type of transplant	
Bone marrow	30 (54.5)
PBSC	14 (25.5)
Cord blood	11 (20.0)
GVHD disease characteristics	
aGVHD grade at baseline, No. (%)	
Grade B	6 (10.9)
Grade C	23 (41.8)
Grade D	26 (47.3)
Organ involvement, No. (%)	
Single organ	35 (63.6)
Lower GI	21 (38.2)
Skin	14 (25.5)
Multiorgan	20 (36.4)
aGVHD risk stratification, No. (%)*	
Standard risk	15 (27.3)
High risk	40 (72.7)
Time from:	
HSCT to onset of aGVHD (days)	
Mean (SD)	50.2 (39.2)
Median (min, max)	35.0 (9, 170)
aGVHD onset to first infusion (days)	
Mean (SD)	18.4 (22.4)
Median (min, max)	12.0 (4, 142)
SR-aGVHD to first infusion (days)	
Mean (SD)	3.9 (2.24)
Median (min, max)	3.5 (1, 10)

PBSC indicates peripheral blood stem cell.
* MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. *Biol Bone Marrow Transplant*. 2015;21:761-767.

to the derived control OR at day 28 of 45%. At day 56, OR was achieved by 32 of 54 patients (59.3%): 17 (31.5%) and 15 (27.8%) CR and PR, respectively. At day 100, OR was achieved by 38 of 54 patients (70.4%), with 24 achieving CR (44.4%) and 14 achieving PR (25.9%). Rates of VGPR, a subset of PR, were consistent throughout the study: 9.3% at day 28, 11.1% at day 56, and 7.4% at day 100. Rates of CR + VGPR improved throughout the study, from 38.9% at day 28 to 42.6% at day 56 to 51.9% at day 100, although this was entirely attributable to an increased CR rate from 29.6% at day 28 to 44.4% at day 100. The median duration of response was 146 days.

Table 4
Exposure to Investigational Agent

Characteristic	Remestemcel-L (n = 54)
Exposure to investigational agent	
Total number of infusions	535
Infusions per patient, No. (%)	
1-4	3 (5.6)
5-8	21 (38.9)
9-12	25 (46.3)
13+	5 (9.3)
Duration of each infusion (min)	
Mean (SD)	62.0 (60.2)
Median (min, max)	61.0 (8.25, 419.7)
Volume administered, each infusion (mL)	
Mean (SD)	45.6 (10.5)
Median (min, max)	47.2 (9, 67)
Total volume administered, all infusions (mL)	
Mean (SD)	453.4 (190.3)
Median (min, max)	482.4 (54, 809)

One interrupted infusion was restarted.

Survival

Overall survival was 74.1% (40/54) through day 100 and 68.5% (37/54) at day 180. Kaplan-Meier survival curves are shown in Figure 2. Survival was statistically superior for day 28 responders compared with nonresponders through 100 days (86.8% versus 47.1%, P = .0001 log rank) and through 180 days (78.9% versus 43.8%, P = .001; Figure 2A).

Table 5
Clinical Response Endpoints

Endpoint	Remestemcel-L (n = 54), No. (%)*
Day 28 response	
Responder (OR = CR + PR)	38 (70.4)
Complete response (CR)	16 (29.6)
Partial response (PR)	22 (40.7)
Very good partial response (VGPR)	5 (9.3)
Nonresponder	17 (31.5)
Mixed mesponse (MR)	5 (9.3)
No response (NR)	8 (14.8)
Progression	4 (7.4)
CR + VGPR	21 (38.9)
Day 56 response	
Responder (OR = CR + PR)	32 (59.3)
Complete response (CR)	17 (31.5)
Partial response (PR)	15 (27.8)
Very good partial response (VGPR)	6 (11.1)
Nonresponder	12 (22.2)
Missing	11 (20.4)
CR + VGPR	23 (42.6)
Day 100 response	
Responder (OR = CR + PR)	38 (70.4)
Complete response (CR)	24 (44.4)
Partial response (PR)	14 (25.9)
Very good partial response (VGPR)	4 (7.4)
Nonresponder	6 (11.1)
Missing	11 (20.4)
CR + VGPR	28 (51.9)

* Responses are based on the number of patients who received remestemcel-L treatment (n = 54).

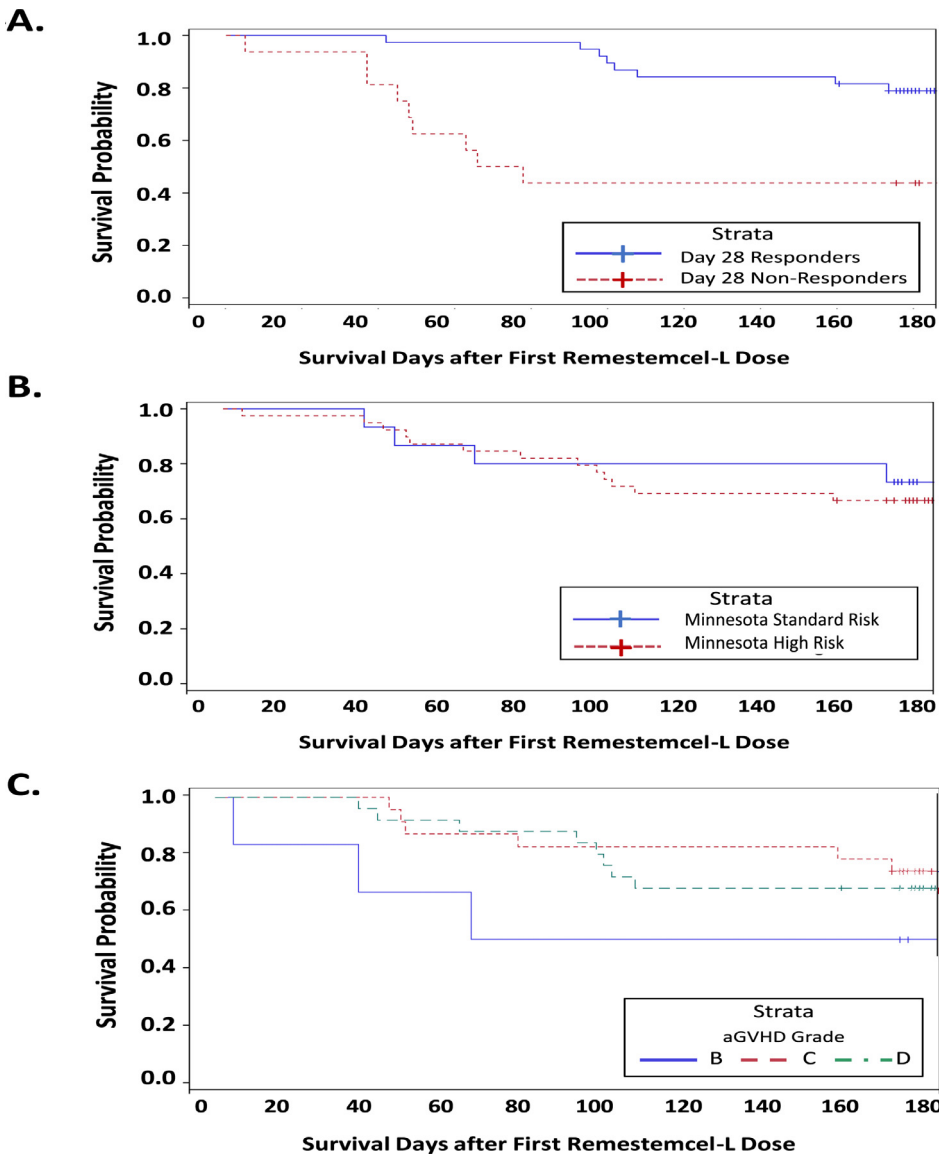

Figure 2. Kaplan-Meier plot of overall survival through day 180 from initiation of remestemcel-L therapy (day 0). (A) Stratified by overall response at day 28 (responders and nonresponders). (B) Stratified by Minnesota risk category (high risk or standard risk). (C) Stratified by baseline aGVHD grade.

This finding indicates the strong predictive value of day 28 response to clinical outcome. Survival through day 180 was comparable in patients stratified by high or standard risk (Figure 2B), suggesting no decrease in the clinical response to remestemcel-L in the high-risk subgroup. Overall survival at day 180 among patients with grade C and grade D aGVHD was 73.9% (17/23) and 68.0% (17/25), respectively (Figure 2C), suggesting a trend for greater efficacy with increasing disease severity.

A total of 30 patients received additional remestemcel-L therapy: 25 patients who were partial or mixed responders at day 28 and 5 patients with GVHD flare following CR. Among the patients who achieved PR (n = 21) or MR (n = 2) at day 28 and received continued therapy after day 28, 16 of 21 (76.2%) and 1 of 2 (50%) achieved OR at day 56. At day 100, 19 (90.5%) patients with PR at day 28 who received continued therapy achieved OR (10 CR plus 9 PR).

The probability of survival at 100 days for patients receiving initial treatment (4 to 8 infusions) and continued treatment (9 to 12 infusions) was comparable, 76.2% and 72%, respectively.

Clinical Response within Subgroups

Clinical responses within subgroups based on demographic and disease characteristics are shown in Table 6. Day 28 OR was consistent across subgroups based on age (0 to 7, 8 to 12, and 13 to 17 years), race (white, nonwhite), and sex (male and female). Day 28 OR of 43% was lower in peripheral blood transplant recipients than in bone marrow and cord blood transplant recipients: 83% and 73%, respectively. In this study, OR in patients with GVHD grade B was 50%; however, grade B skin-only patients were excluded from this study, and the number of grade B patients was small. Overall response rates at day 28 for grades C and D were 69.6% and 76.0%, respectively, and were 86%, 67%, and 63% for skin only, lower GI only, and multiorgan disease, respectively.

Safety

Rates for TEAEs and serious treatment-emergent adverse events (TESAEs) are summarized in Table 7. Adverse events of special interest in this study included infusion-related toxicity and ectopic tissue formation as assessed by computed tomography scans performed at day 180. Infusions were well tolerated with a low incidence of infusion-related events. Three acute infusion reactions were reported in 3 patients. Two of these patients subsequently discontinued infusions and withdrew from the study due to additional TESAEs (somnolence and hypermetabolic syndrome). There was no evidence suggestive of ectopic tissue formation in any patient. During the treatment study MSB-GVHD001, all patients experienced at least 1 TEAE, with a total of 99 TESAEs reported in 35 patients (64.8%). Many of the common TEAEs (occurring in ≥10% of patients) were conditions related to SR-aGVHD, infections due to immunosuppressive agents, or steroid toxicities and were not attributed to the study product.

A total of 16 TEAEs in 9 patients (17%) were assessed by investigators as possibly related to remestemcel-L treatment. Ten of these events were nonserious and expected in this disease population: neutrophil count decreased, neutropenia, thrombocytopenia, platelet count decreased, cytomegalovirus (CMV) infection, nausea, vomiting, pyrexia, allergic transfusion reaction, and hypotension. Six of the possibly related to remestemcel-L treatment TEAEs reported in 5 patients were serious (TESAEs): skin GVHD, adenovirus infection, BK virus infection, hemolytic uremic syndrome, hypermetabolism, and somnolence.

Infections were the most commonly reported TEAEs, occurring in 83.3% of patients, consistent with previous reports of high infection rates and mortality due to infections in aGVHD patients [34]. Serious infections occurred in 17 (31.5%) patients; the most frequent included BK virus (3.7%), staphylococcal infection (5.6%), Epstein-Barr viremia (1.9%), pneumonia (3.7%), and sepsis (3.7%). Two of the serious infection adverse events were considered possibly treatment related (adenovirus infection and BK virus). Aside from infections, as shown in Table 7, other frequently reported TEAEs included GI disorders (57.4%), general disorders (50.0%), metabolic/nutritional disorders (48.1%), laboratory investigations (50.0%), respiratory disorders (48.1%), and immune system disorders (40.7%).

Fourteen deaths were recorded within the initial 100-day (±7) period (13 deaths and 1 patient lost to follow-up and presumed deceased). The primary causes of death were disease relapse (n = 4), aGVHD progression (n = 4), infection (n = 2), multiorgan failure (n = 1), pulmonary hemorrhage (n = 1), and cardiac arrest (n = 1) and lost to follow-up (n = 1). No deaths were causally attributed to remestemcel-L treatment.

Notable shifts in the mean values of monocytes, lymphocytes, neutrophils, bilirubin, and blood glucose were observed over the course of the study. These were expected in a patient population with severe aGVHD requiring multiple supportive medications and not attributed to study product. There were no trends of abnormal safety signals related to other laboratory values.

While events of skin GVHD, Hemolytic uremic syndrome, and infections are expected in this disease population and therefore unlikely causally attributed to remestemcel-L, any potential increase in immune suppression mediated by remestemcel-L could increase the risk of adenovirus and BK virus infections. Overall, steroids were slowly tapered in responding patients, which resulted in a decrease in steroid-related AEs, further supporting the effectiveness of remestemcel-L therapy.

In the MSB-GVHD002 follow-up study, 27 of 32 patients (84.4%) experienced 1 or more TEAEs, and 15 of 32 (46.9%) experienced any TESAE. No TEAEs or TESAEs were considered treatment related. Infections were the most common TESAE, with 8 (25%) experiencing serious infections. Two deaths were recorded between day 100 and day 180: one due to recurrent acute lymphocytic leukemia at day 174, and the other was a patient lost to follow-up and presumed deceased. The patient who was enrolled but not treated died on day 189.

Table 6
Day 28 Overall Response and Day 100 Overall Survival by Subgroups Based on Demographic and Disease Characteristics*

Characteristic	Day 28 OR, No. (%)	Day 100 Overall Survival, No. (%)
Age group, yr		
0-7	20/28 (71)	20/28 (71)
8-12	10/14 (71)	11/14 (79)
13-17	8/12 (67)	9/12 (75)
Sex		
Male	26/35 (74)	27/35 (77)
Female	12/19 (63)	13/19 (68)
Race group		
White	21/30 (70)	24/30 (80)
Nonwhite	17/24 (71)	16/24 (67)
Underlying malignancy at transplant		
Acute myeloid leukemia primary	10/17 (59)	9/17 (53)
Acute lymphoblastic leukemia	9/12 (75)	10/12 (83)
Chronic myeloid leukemia	4/4 (100)	4/4 (100)
Myelodysplastic syndrome	1/2 (50)	2/2 (100)
Hodgkin lymphoma	1/1 (100)	1/1 (100)
Juvenile myelomonocytic leukemia	2/2 (100)	2/2 (100)
Nonmalignant disease	11/16 (69)	12/16 (81)
Conditioning regimen		
Myeloablative	32/46 (70)	35/46 (76)
Reduced intensity	5/6 (83)	4/6 (67)
Nonmyeloablative	0/1 (0)	0/1 (0)
Missing	1/1 (100)	1/1 (100)
Transplant donor		
Related matched	5/6 (83)	3/6 (50)
Related mismatched	4/7 (57)	6/7 (86)
Unrelated	29/41 (71)	31/41 (76)
Type of transplant		
Bone marrow	24/29 (83)	24/29 (83)
Peripheral blood stem cell	6/14 (43)	9/14 (64)
Cord blood	8/11 (73)	7/11 (64)
Grade of aGVHD at baseline		
Grade B	3/6 (50)	3/6 (50)
Grade C	16/23 (70)	19/23 (83)
Grade D	19/25 (76)	18/25 (72)
Organs involved at baseline		
Skin only	12/14 (86)	11/14 (79)
Lower GI only	14/21 (67)	16/21 (76)
Multiple organs	12/19 (63)	13/19 (68)
Minnesota risk score		
Standard risk	11/15 (73)	12/15 (80)
High risk	27/39 (69)	28/39 (72)

* N is based on the number of enrolled patients who received remestemcel-L.

Additional Follow-up to 180 Days

Of the 32 patients followed through 180 days in the follow-up study, 15 (46.9%) discontinued systemic corticosteroid use for GVHD treatment by end of study. In addition, most (n = 28, 87.5%) patients were GVHD IST free by day 180. Chronic GVHD

Table 7
Summary of Safety Outcomes

Characteristic	MSB-GVHD001 through Day 100 (n = 54), No. (%)	MSBGVHD002 through Day 180 (n = 32), No. (%)
Any TEAE*	54 (100)	27 (84.4)
Possibly treatment-related TEAE	9 (16.7)	0 (0)
Any infusion reaction TEAE	3 (5.6)	0 (0)
TEAE leading to study drug discontinuation	8 (14.8)	0 (0)
Any TESAE	35 (64.8)	15 (46.9)
Possibly treatment-related TESAE†	5 (9.3)	0 (0.0)
TESAEs leading to study drug discontinuation	6 (11.1)	0 (0.0)
Deaths	14 (25.9)	3 (9.4)
TEAE by system organ class‡		
Infections and infestations	45 (83.3)	16 (50.0)
Gastrointestinal disorders	31 (57.4)	9 (28.1)
General disorders	27 (50.0)	11 (34.4)
Metabolism and nutrition disorders	26 (48.1)	10 (31.3)
Laboratory investigations	27 (50.0)	9 (28.1)
Respiratory, thoracic, and mediastinal disorders	26 (48.1)	7 (21.9)
Immune system disorders	22 (40.7)	5 (15.6)
TESAE by system organ class‡		
Infections and infestations	17 (31.5)	8 (25.0)
Respiratory, thoracic, and mediastinal disorders	12 (22.2)	0 (0)
General disorders	8 (14.8)	1 (3.1)
Gastrointestinal disorders	7 (13.0)	1 (3.1)
Immune system disorders	6 (11.1)	0 (0)

Values are number (percent) of patients reporting the event. Percentage was calculated using the number of patients in the column heading as the denominator.
* TEAEs are adverse events that started on or after the dose date of study treatment.
† As assessed by the investigator.
‡ Patient may have had more than 1 TEAE or TESAE but is counted only once within a system organ class category.

was reported in 8 patients during the follow-up study; 6 cases were mild, 1 was moderate, and 1 was severe. CMV surveillance testing was conducted during the initial and follow-up study periods. Of all treated patients, 1 experienced CMV disease, 1 experienced sustained reactivation, and 4 experienced transient reactivations considered clinically significant.

There were no infusion-related toxicities and no evidence suggestive of ectopic tissue formation.

DISCUSSION

aGVHD is a major cause of morbidity and mortality in adults and children undergoing HSCT [2,4,7,8]. There is a large unmet need for effective treatment. In previous studies, remestemcel-L treatment showed promising results for the treatment for SR-aGVHD in pediatric patients [26,35,36]. We report here the positive results of a prospective, multicenter, phase 3, pediatric study using remestemcel-L as first-line therapy for SR-aGVHD with long-term follow up through 180 days (MSB-GVHD002). At day 28, remestemcel-L-treated patients achieved statistically superior OR compared with the prespecified control rate (70.4% versus 45%, $P = .0003$, binomial proportion *P*value), demonstrating a clinically meaningful treatment effect greater than a 20 percentage point treatment difference. The high OR was sustained at day 100 (70.4%), meeting study-defined endpoints and confirming previously reported remestemcel-L response rates in SR-aGVHD.

Survival through day 100 was also significantly greater for day 28 responders than nonresponders (86.8% versus 47.1%, $P < .0001$ log rank). Superior survival with remestemcel-L treatment was sustained through day 180 in patients with a day 28 OR, with 78.9% compared with 43.8% for responders and nonresponders, respectively ($P = .001$ log rank). Overall survival through day 100 (74.1%) and day 180 (68.5%) with remestemcel-L treatment is a meaningful increment compared with overall 2-year overall survival of 34% with standard of care in aGVHD patients younger than 18 years as reported by Rashidi et al. [7]. A trend for greater response was observed in aGVHD grades C and D than in grade B patients—in other words, in patients with more severe disease and higher mortality risk. This finding is consistent with a report that the potent anti-inflammatory and immunosuppressive properties of mesenchymal stromal cells are induced by exposure to high levels of specific cytokines [37,38]. Further research may elucidate this hypothesis, which is consistent with our clinical findings of increased rates of OR and overall survival in the presence of more severe aGVHD as defined by risk stratification and aGVHD grade.

The clinical response to remestemcel-L treatment at day 28 was significantly associated with improved survival through day 180, thus demonstrating the strong predictive value of this endpoint for subsequent clinical benefit. The median duration of response for responders who enrolled in the safety follow-up study was 146 days, demonstrating durability of response to remestemcel-L [35]. Our results are also compatible with findings reported in a pediatric subset of patients with SR-aGVHD in a randomized controlled trial of remestemcel-L versus placebo (n = 14 per group) added on to standard of care. In this study, OR at day 28 was 64% and 36% in the remestemcel-L-treated and placebo-treated children, respectively [36].

Overall response and overall survival through day 180 of the follow-up study were consistent across subgroups based on baseline demographic factors: none of these factors substantially influenced overall response rate or overall survival through day 180. Greater overall response was observed in bone marrow and cord blood transplant recipients compared with recipients of peripheral blood stem cell grafts, although the clinical significance of this finding is unclear. Consistent responses were also observed across involved organs.

Results of this study indicate that remestemcel-L is effective, safe, and well tolerated for the treatment of SR-aGVHD in pediatric patients, with the majority of reported adverse events attributable to the patients' underlying disease or its treatment. Adverse events designated by the investigators as possibly related to remestemcel-L were mostly mild to moderate in severity and not clearly related to the study drug. Although a few serious treatment-related events were observed, these generally resolved without sequelae. Complications of aGVHD and/or relapse were the primary causes of death. Relapse was a leading cause of death in nonresponders. Chronic GVHD was reported during the follow-up study, and in most cases, it was mild and did not appear to affect survival through day 180, although this time point is too early to know the impact of remestemcel-L treatment for aGVHD on chronic GVHD. Clinical manifestations of significant CMV viral load were monitored, and most patients remained free of CMV reactivation throughout the study. There were no cases of ectopic tissue formation. Importantly, remestemcel-L did not show hematologic, immunologic, or renal toxicity and therefore does not overlap with known toxicities of other commonly used agents to treat SR-aGVHD.

A number of studies have assessed the safety and efficacy of cell therapies in adults with GVHD, as described in the recent meta-analysis [39]. A number of factors are relevant to the experience reported in adults with aGVHD treated with MSCs, including variations in the type of design (prophylaxis versus treatment of GVHD), type of MSCs (adipose tissue, cord blood, or bone marrow derived cells), specific trial design elements (first line in new-onset GVHD, concomitant corticosteroids and MSCs after GVHD diagnosis, or established steroid refractory), choice of primary efficacy endpoint (the currently established day 28 overall response or durable complete response), choice or comparator, and specific aGVHD patient attributes such as severity of disease and organ involvement. The impact of several of these factors is described by Kebriaei et al. [40]. In this randomized controlled trial of remestemcel-L versus placebo in both adults and children with aGVHD, among high-risk adult patients, remestemcel-L treatment produced significantly higher OR at day 28 compared with placebo (58% versus 37%; $P = .03$) and similarly improved day 28 OR compared with placebo in the pediatric subset (64% versus 23%; $P = .05$) [40].

The present study achieved its primary objectives of demonstrating that remestemcel-L infusions significantly improved overall response in pediatric patients with SR-aGVHD compared with derived historical rates and were well tolerated with no identified safety concerns. In addition, the observed improved response at day 28 was strongly associated with significantly improved survival through day 180. Few patients received additional IST therapy for aGVHD during this study, further evidence of remestemcel-L effectiveness in aGVHD symptom control. Results of this study confirm the overall response, safety, and survival demonstrated in a pediatric expanded-access program study that assessed remestemcel-L in children who failed to respond to steroids and additional immunosuppressive agents for the treatment of aGVHD [26,35]. In conclusion, MSB-GVHD001 and the MSB-GVHD002 follow-up study taken together with positive findings of other remestemcel-L studies in aGVHD [26,36,40] confirm the safety profile and demonstrate the efficacy and durability of remestemcel-L treatment for SR-aGVHD in the pediatric population.

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SUPPLEMENTARY MATERIALS

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