Official Title:	**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**
NCT Number:	NCT02652130
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EXTENSION STUDY PROTOCOL

Protocol Title: 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

IND Number: 07939
Protocol Number: MSB-GVHD002
Clinical Development: Phase 3
Version: 4.0
Protocol Date: 01 December 2016

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INVESTIGATOR'S SIGNATURE

Study Title: 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

I have read and understood the contents of this protocol and the Investigator's Brochure and agree to conduct this study in compliance with the protocol, Good Clinical Practice, and other applicable regulatory requirements. I accept the oversight of the study monitor designated by Mesoblast and the control procedures, including verification by access to source documents, as required by the study monitoring and audit functions of Mesoblast or its designee and the audit functions of regulatory agencies in accordance with Good Clinical Practice.

I understand that any changes to this protocol not associated with procedures necessary for the safety of subjects that are instituted by the Investigator without previous discussion with the Mesoblast Medical Director or designee would constitute a violation of the protocol.

I agree that the investigational agents supplied by Mesoblast will be used solely for the purpose of conducting this investigation.

I will personally conduct the investigation as described herein and in the Mesoblast Clinical Research Agreement.

Agreement Signature:

_____	_____	_____
Principal Investigator (Please print)	Principal Investigator (Signature)	Date

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PROTOCOL SYNOPSIS

Sponsor Mesoblast International Sàrl	**Study Phase** Phase 3	**Protocol number** MSB-GVHD002

Investigational Product
Remestemcel-L (*ex-vivo* cultured adult human mesenchymal stromal cells [MSCs]) cryopreserved in Plasma-Lyte® A supplemented with human serum albumin (5%) and dimethyl sulfoxide (10%). Remestemcel-L is stored and distributed in cryogenic bags (100×10^6 MSCs in 15mL (6.7×10^6 cells/mL)) and vials (25×10^6 MSCs in 3.8 mL (6.25×10^6 cells/mL)).

Protocol Title
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

Indication
Ongoing safety assessment follow up to Protocol MSB-GVHD-001 of remestemcel-L treatment in pediatric subjects with acute Graft versus Host Disease (aGVHD), following allogeneic hematopoietic stem cell transplant (HSCT), that have failed to respond to treatment with systemic corticosteroid therapy .

Objectives
Primary Objective:
To describe the safety through 180 days of remestemcel-L treatment in subjects who participated in Protocol MSB-GVHD001. No additional investigational agent (remestemcel-L) will be administered in this safety follow-up protocol.

Secondary Objectives*:*

1. To assess survival at 180 days
2. To obtain an assessment for GVHD activity to investigational medicinal product (IMP) administered in MSB-GVHD001.
3. To assess the proportion of subjects able to taper steroids by 50% at each time point from Day 100 to Day 180.
4. To assess the time to addition of any second-line GVHD treatment agent
5. To assess the number of days to a GVHD flare
6. To evaluate subjects for evidence of chronic GVHD.

[redacted]

[redacted]

Study Design

This is a safety follow-up study through 180 days of remestemcel-L treatment in subjects who participated in MSB-GVHD001. This study will also explore duration of response over time. Subjects who participated in MSB-GVHD001 and received at least one dose of remestemcel-L as outlined in that protocol will be evaluated at baseline (Day 100) and at Days 120, 140, 160 and 180 for safety endpoints. Subjects who participated in Protocol MSB-GVHD001and received the first 8 doses of remestemcel-L as outlined in that protocol will be evaluated at baseline (Day 100) and at Days 120, 140, 160 and 180 after initial remestemcel-L infusion for evidence of duration of response over time.

Study Population

***Safety population*:** All subjects who participated in Protocol MSB-GVHD001 and received at least one remestemcel-L infusion in that protocol.

Duration of response population: All subjects who participated in Protocol MSB-GVHD001, received the first 8 doses of remestemcel-L as outlined in that protocol, and showed overall response (OR) or very good partial response (VGPR) to remestemcel-L at Day 28.

Inclusion Criteria

Patients are eligible for the study if all of the following criteria are met:

1. Subjects must have participated in Protocol MSB-GVHD001 and have received at least one infusion of remestemcel-L.
2. Subject or subject's authorized representative must be capable of providing written informed consent. Assent, if applicable, must also be collected when required by the IRB/EC.
3. Female subjects of childbearing potential (≥ 10 years of age); (Appendix 7) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for the follow-up time period. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.
4. The subject must be willing and able to comply with study procedures, remain at the clinic as required during the study period, and return to the clinic for the follow-up evaluation as specified in this protocol.

Exclusion Criteria

1. The investigator believes it to be in the best interest of the subject not to participate in the safety follow up study.
2. Subject has participated or is currently participating in any autologous or allogeneic stem cell or gene therapy study for the treatment of aGVHD. Patients participating

in investigative protocols aimed at modification of the transplant graft (such as T cell depletion) or aimed at modification of the conditioning regimen will be allowed in the study.

Assessments

Primary Endpoints

Safety through 180 days of remestemcel-L treatment in subjects who participated in Protocol MSB-GVHD001 and received at least one infusion of remestemcel-L.

Safety

1. Adverse events
2. Serious adverse events
3. Survival through Day 180
4. Ectopic tissue formation

Secondary Endpoints

1. Survival at 180 days for subjects who received the initial therapy through 28 days as outlined in Protocol MSB-GVHD001
2. GVHD activity at time points evenly divided amongst the term, from Day 100 to Day 180 specifically at Days 120, 140, 160 and 180 relative to baseline assessment in MSB-GVHD001.
3. Steroid doses at Days 120, 140, 160 and 180, including proportion of subjects able to taper steroids by 50% by each time point. Guideline for steroid taper is located in Appendix 6.
4. Time to addition of any second-line GVHD treatment agent
5. The number of days to GVHD flares
6. Evidence of chronic GVHD at any time from Day 0 to Day 180. Guidelines for chronic GVHD assessment is located in Appendix 8.

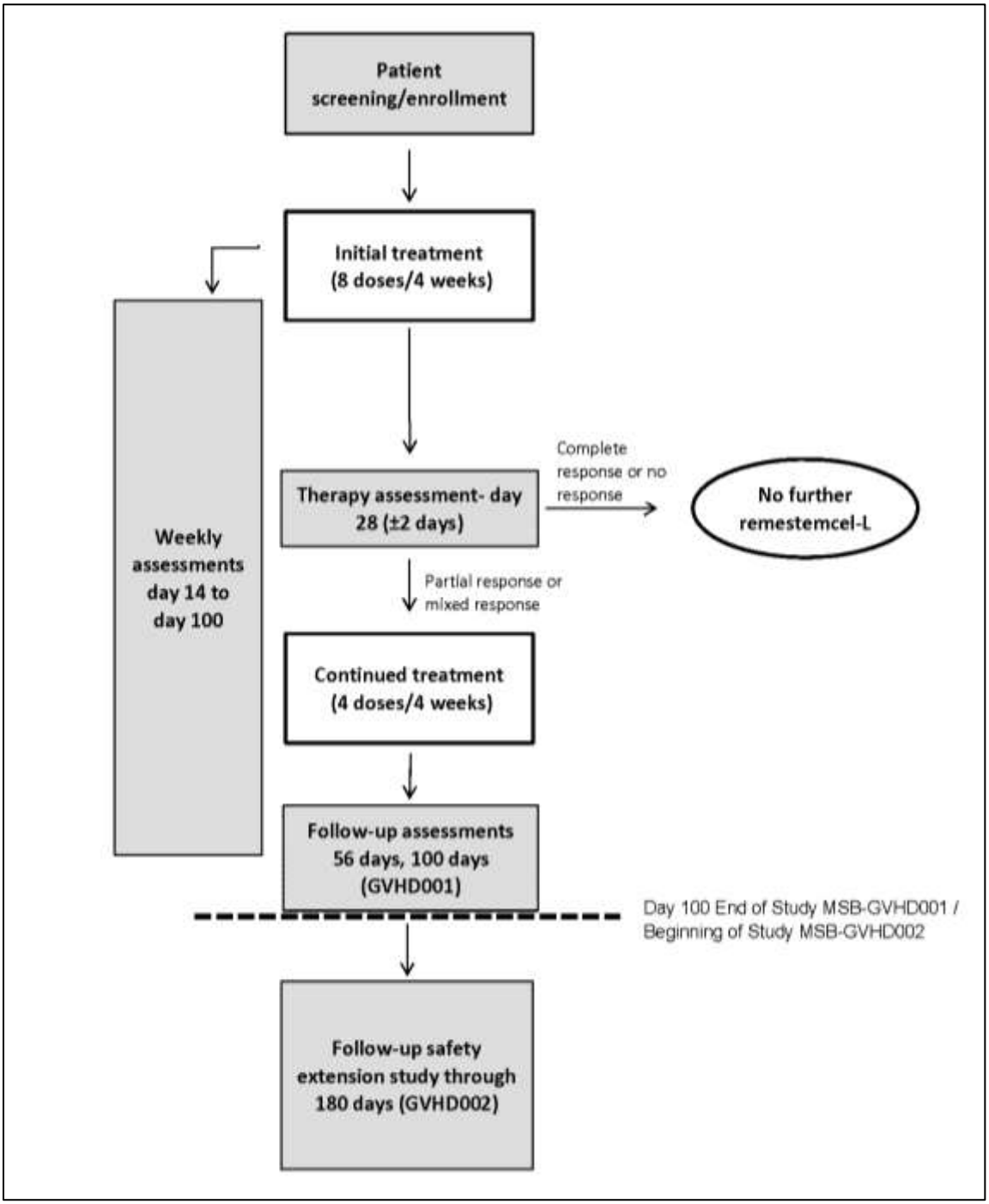
[redacted]

Duration of Study

Subjects who participated in Protocol MSB-GVHD001 will be followed-up for safety, and duration of response through 180 days post initiation of treatment. Total duration of study participation per subject for Protocol MSB-GVHD001 and Protocol MSB-GVHD002 is up to 180 days with the last 80 days being in Protocol MSB-GVHD002.

Statistical Analysis *General* Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Confidence intervals, if presented, will be at the 95% confidence level. The baseline value for a variable is defined as the last non-missing observation prior to or equal to the first dose date of study treatment in MSB-GVHD001. Data collected at unscheduled time points will not be summarized at the unscheduled time points. Study day will be calculated from the first infusion date from MSB-GVHD001, unless otherwise specified. *Analysis Populations* The analysis population for the safety assessment in this study will include all subjects from Protocol MSB-GVHD001 who have signed the Informed Consent form and have received at least one dose of remestemcel-L. The analysis population for the duration of response assessments in this study will include Protocol MSB-GVHD001 subjects with overall response and VGPR to remestemcel-L at Day 28, who have signed the Informed Consent form and have completed treatment for the first 28 days, as prescribed in Protocol MSB-GVHD001. *Safety Analyses* Safety assessments will be summarized with descriptive statistics for subjects in the analysis population. Listings will be provided for adverse events (AEs), serious adverse events (SAEs), 12-lead ECG and ectopic tissue formation. Vital signs will be provided as change from baseline tables by infusion number categories.	
Interim Analysis	No interim analysis is planned for this study

Figure 1: Study Design of MSB-GVHD001 and MSB-GVHD002



[†]Subjects who have a GVHD flare of Grade B-D after achieving a complete response (CR) at Day 28 (following Initial Therapy) or Day 56 (following continued therapy) and before Day 70 may receive additional remestemcel-L treatment per the Initial Treatment plan.

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GLOSSARY OF ABBREVIATIONS

ACR	Albumin-to-creatinine ratio
ADA	American Diabetes Association
ADL	Activities of Daily Living
AE	Adverse event
AEI	Adverse events of interest
aGVHD	Acute Graft versus Host Disease
ALT [SGPT]	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASBMT	American Society for Blood and Marrow Transplant
AST [SGOT]	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
cGVHD	Chronic Graft versus Host Disease
CI	Confidence interval
CK	Creatine kinase
CMV	Cytomegalovirus
CR	Complete response
CRF	Case report form
CRT	Cardiac resynchronization therapy
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DAS28	Disease Activity Score in 28 Joints
DBP	Diastolic blood pressure
DCS	Data collection specification
DLCO	Diffusing capacity for carbon monoxide
DMC	Data monitoring committee
DMSO	Dimethyl sulfoxide
DSMB	Data safety monitoring board
EAC	Events adjudication committee
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
EDC	Electronic data capture
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbant assay
EOT	End of treatment
eGFR	Estimated glomerular filtration rate
eForm	Electronic form (page)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

GLOSSARY OF ABBREVIATIONS

FPG	Fasting plasma glucose
FiO2	Fractional inspired oxygen concentration
GI	Gastrointestinal
γ-GT	Gamma-glutamyl transpeptidase
GCP	Good clinical practice
GMP	Good manufacturing practice
GFR	Glomerular filtration rate
GVHD	Graft versus Host Disease
HbA1c	Glycosylated hemoglobin
Hct	Hematocrit
HDL	High density lipoprotein
[redacted]	[redacted]
HLA	Human leukocyte antigen
HLT	High Level Term
hMSC	Human mesenchymal stem cells
HR	Heart Rate
[redacted]	[redacted]
hsCRP	High sensitivity C-reactive protein
HSCT	Hematopoietic stromal cell transplantation
IB	Investigator's brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
IBMTR	International Bone Marrow Transplant Registry
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
[redacted]	[redacted]
IMP	Investigational medicinal product
IND	Investigational new drug
INN	International non-proprietary name
IRB	Institutional review board
ITT	Intent to treat
IUD	Intrauterine device
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance Imaging
MDRD	Modification of diet in renal disease
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MSC	Mesenchymal Stromal Cells
MR	Mixed Response
NIH	National Institutes of Health
NR	No response

GLOSSARY OF ABBREVIATIONS

O2	Oxygen
OR	Overall response
[redacted]	[redacted]
PFT	Pulmonary function testing
PP	Per protocol population
PR	Partial Response
PRA	Panel reactive antibody
PT	Preferred Term
PT/INR	Prothrombin time/international normalized ratio
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
[redacted]	[redacted]
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SaO_2/SAT	Oxygen (O_2) saturation by pulse oximetry
SAP	Safety analysis population
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
[redacted]	[redacted]
SMBG	Self-monitored blood glucose
SMT	Study management team
SPC	Summary of product characteristics
SOC	System organ class
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
TG	Triglycerides
TNF-α	Tumor necrosis factor-α
ULN	Upper limit of normal
VGPR	Very good partial response
VOD	Veno-occlusive disease
v/v	Volume/volume
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1. BACKGROUND

1.1 Acute Graft-versus Host Disease

Graft versus host disease (GVHD) is a progressive and lethal complication of hematopoietic stromal cell transplantation (HSCT) and donor leukocyte infusion. Two clinically distinct forms of GVHD have been described; acute GVHD, which typically occurs within 100 days of HSCT,[1] and chronic GVHD, which is characterized by later onset.[2] However, this arbitrary temporal distinction between the acute and chronic forms of GVHD has been largely discarded with the recognition of these forms as discrete pathophysiologic conditions defined by separate clinical and diagnostic criteria.[3,4]

Occurrence of acute GVHD (aGVHD) after allogeneic transplantation is fairly common, with Grades II to IV aGVHD reported in approximately 39% of cases involving sibling donors and 59% of cases with unrelated donors.[5] Overall, an estimated 20% to 80% of patients who receive allogeneic HSCT develop acute GVHD, even after prophylaxis with immunosuppressive agents.[6]

While aGVHD is common among patients with allogeneic transplantation, overall, it is a rare disease, affecting about 10,000 individuals per year worldwide, with an estimated 2,000 cases found in children (Table 1). Approximately 5,500 of worldwide aGVHD cases are refractory to steroid,[1] of which 1,000-1,200 are pediatric cases.

Table 1: Worldwide Incidence of Steroid Refractory aGVHD

	All Patients	Pediatric (<18 years)
Allogeneic HSCT	25,000	5,000
aGVHD Requiring systemic treatment (Grades B-D)	10,000	2,000
Refractory aGVHD	5,000-6,000	1,000-1,200

Source: CIBMTR Research Analysis.

In aGvHD, alloreactive T cells present in the donor cell transplant recognize the recipient's tissues as foreign and mount an immunological attack, causing inflammation and tissue damage primarily affecting the gastrointestinal (GI) tract, skin, and liver.[7] Human leukocyte antigen (HLA) disparity between HSC donor and recipient is the key driver of GVHD, causing donor T cells to recognize recipient tissue as foreign.[7]. The severity of the disease is associated with the degree of HLA mismatch between the donor and the recipient, and a greater mismatch will result in more aggressive alloreactivity.[8] Damage to recipient tissue caused by the HSCT conditioning regimen (irradiation or chemo-ablation) creates a cellular and molecular environment that is conducive to GVHD. The tissue damage leads to the increased secretion of

proinflammatory cytokines, which promote donor T cell proliferation and differentiation and interaction with recipient antigen presenting cells. Alloreactive donor T cells traffic to target tissues (skin, gut, liver) and release soluble mediators that mediate cytotoxicity and end organ damage. Other donor immune cells, including natural killer cells, neutrophils and monocytes, are also activated and recruited to target organs and contribute to host tissue destruction.[9] This adverse immune reaction increases over time as the expanding tissue damage mediated by alloreactive immune cells leads to more cytokine production. A vicious cycle ensues: amplification of cytokine expression supports further proliferation and activation of alloreactive immune cells, which in turn leads to further tissue damage.[7.] Consequently, aGVHD potentially involves multiple organ systems, with varying degrees of clinical severity.

Acute GVHD primarily affects the skin, the liver, and the gastrointestinal (GI) tract, though the GVHD reaction targets a number of different host cells, including those of the skin epithelia and mucosa, hair follicles, intestinal crypts, liver bile ducts, bone marrow, and immune system.[1,7] Disease onset often manifests clinically as a pruritic maculopapular rash that first appears on the nape of the neck, shoulders, ears, palms of the hands, and soles of the feet. The liver is the next most commonly affected organ after skin; symptoms of liver involvement include jaundice and increased alkaline phosphatase levels that indicate damage to the bile canaliculi and portend cholestasis. The GI tract is the third organ among the tissues most commonly affected in acute GVHD, frequently presenting as nausea, vomiting, intestinal bleeding, cramping, and diarrhea. GI involvement is often the most severe of the organs affected and can be the most difficult to treat. The large volumes of watery diarrhea common to intestinal involvement in acute GVHD often transitions into bloody diarrhea that prompt the need for frequent transfusions.[7]

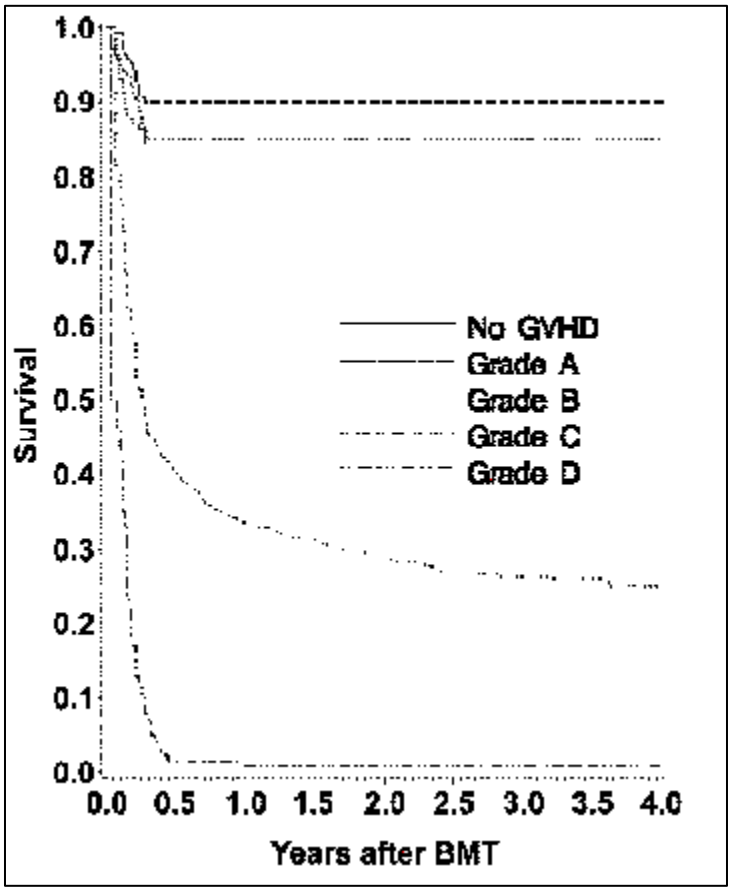
1.2 Current Treatment of aGVHD and Prognosis

Presently, there are no approved therapies for treatment of aGVHD. Available treatment options to prevent aGVHD have historically involved front-line therapy with glucocorticoids along with different combinations of prophylaxis agents such as methotrexate and cyclosporine A.[6,10-12] While many patients who develop aGVHD respond well to first-line corticosteroid treatment, steroids achieve complete response rates in only approximately 50% of cases.[13] Many aGVHD patients display inadequate response to corticosteroid, with approximately 10% to 30% of aGVHD patients progressing to the more severe Glucksberg Grades III or IV GVHD.[5]

As shown by the survival curves in Figure 2, prognosis for patients with the most severe forms of aGVHD (IBMTR Grades C and D) is dismal, primarily because of greater risk for infectious complications, immunosuppression- mediated toxicity, and often incomplete GVHD remission.[14]

Patients that do not respond to steroid therapy have expected one-year survival rates of just 5% to 30%.[6,8,15-19] A wide variety of second-line immunosuppressive agents are commonly used to treat steroid-refractory aGVHD (SR-aGVHD), though there is little evidence to support the efficacy of these drugs as secondary therapy for aGVHD.[6]

Figure 2: Probability of survival according to maximum GVHD grade for a sampling of 607 aGVHD patients from the CIBMTR registry



1.3 Grading of Acute GVHD

Acute GVHD is a heterogeneous set of disease processes that potentially involves multiple organ systems, with varying degrees of severity by organ system. Disease onset typically manifests most commonly in the skin, with the GI tract and liver as the next most common sites involved.[17] Historically, classification systems of aGVHD have been established to segregate aGVHD according to severity. The severity grade of aGVHD has been shown to correspond to overall survival, with increased transplant-related mortality correlating with higher aGVHD grade.[20]

One of the first grading systems, published by Glucksberg and colleagues in 1974,[21] involves assigning a stage of 1 to 4 to each involved organ, as described in Table 2, and combining these stages to yield an overall grade ranging from I to IV (Table 3).

Another grading system, which was devised by the International Bone Marrow Transplant Registry (IBMTR) and used in Protocol MSB-GVHD001, classifies aGVHD severity on a scale of A to D. The selection of the IBMTR was based on the use of this scale in previous programs and studies with remestemcel-L, thereby allowing for use of historical controls from those studies. Table 3 presents a summary of the IBMTR grading systems for aGVHD based on stages of organ severity.[22]

Table 2: GVHD Organ Severity Criteria

Organ	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Maculopapular rash on <25% body surface area	Maculopapular rash ≥25% to ≤50%	Generalized erythroderma	Generalized erythroderma plus bullae and desquamation
GI Tract†	Diarrhea Adult: <500mL/day or <280 mL/m^2 Child: <10 mL/kg/day	Diarrhea Adult: 500- 1000 mL/day or 280-555 mL/m^2 Child: 10-19 mL/kg/day	Diarrhea Adult: 1001- 1500 mL/day or 556-833 mL/m^2 Child: 20-30 mL/kg/day	Diarrhea Adult: >1500 mL/day or >833 mL/m^2 Child: >30 mL/kg/day	Severe abdominal pain with or without ileus or stool with frank blood or melena (regardless of stool volume)
Upper GI Tract	No protracted nausea and vomiting	Persistent nausea, vomiting, or anorexia	–	–	–
Liver‡	Bilirubin <2 mg/dL	Bilirubin 2.1-3.0 mg/dL	Bilirubin 3.1-6.0 mg/dL	Bilirubin 6.1-15 mg/dL	Bilirubin >15 mg/dL

*Sources:

1. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British journal of haematology. 1997;97(4):855-864.
2. Carpenter PA, Macmillan ML. Management of acute graft-versus-host disease in children. Pediatric clinics of North America. 2010;57(1):273-295.
3. Childhood Hematopoietic Cell Transplantation (PDQ®): Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium consensus. National Cancer Institute at the National Institutes of Health; 2014. Available at: ***http://www.cancer.gov/cancertopics/pdq/treatment/childHCT/HealthProfessional/page4***.

†For gastrointestinal (GI) staging, adult stool output values should be used for patients weighing >50 kg. Use 3-day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix.

‡No modification of liver staging for other causes of hyperbilirubinemia.

Table 3: IBMTR and Glucksberg Grades from Organ Stage

IBMTR Grade	Glucksberg Grade	Skin	Intestine	Liver
A	I	1	0	0
B	I	2	0	0
B	II	0-2	1	0-1
B	II	0-2	0-1	1
C	II	3	1	0-1
C	II	3	0-1	1
C	II	3	0	0
B	III	0-2	2	0-2
B	III	0-2	0-2	2
C	III	0-3	0-3	2-3
C	III	3	2-3	0-3
D	III	0-3	0-3	4
D	IV	0-3	4	0-4
D	IV	4	0-4	0-4

Source: Cahn 2005[22]

1.4 Clinical Endpoints for Evaluation of aGVHD Treatment

An important step in evaluating new treatment for aGVHD is to establish meaningful clinical endpoints that would enable effective comparison of clinical benefit between different treatment agents. Until more recently, no formal guidance or recommendations existed regarding the appropriate clinical endpoints for assessing aGVHD treatment.

As with other diseases with grave prognosis, the risk of death associated with aGVHD is considerable. Thus, endpoints for aGVHD trials that indicate clinical benefit would, appropriately, be those related to improvements in survival.[24]

Response to treatment at fixed time points after initiating treatment, including complete response (CR), overall response (OR), partial response (PR) and very good partial response (VGPR), as defined in Table 4, have been shown in several studies to be associated with improvement in mortality up to 2 years post-transplant.[25-28] In particular, OR, as defined in Table 4, to treatment at Day 28 was associated with improved non-relapse mortality at 6 months and 2 years[26,28] and has been supported by a number of different studies as a surrogate endpoint for transplant-related mortality.[25-27]

VGPR, which describes a state of near CR, with a few qualifiers, as described in Table 4, was an endpoint that was also recommended by an expert panel of the American Society for Blood and Marrow Transplant (ASBMT) in 2009 in response to the consensus that CR was too stringent an endpoint, while PR was an inadequate measure of response.[24] This is also an endpoint of interest

to regulators, as endpoints in the field are evolving; by capturing this endpoint MSB will span the whole of the response endpoints currently considered.

Consequently, OR and VGPR will be the endpoints used to evaluate treatment effect in Protocol MSB-GVHD001.

Table 4: Acute GVHD Response Criteria

Abbreviation	Definition
CR	Complete response: resolution of aGVHD in all involved organs
PR	Partial response: organ improvement of at least one stage without worsening of any other organ
OR	Overall Response: Includes both CR + PR
VGPR[†]	Very good partial response: Fulfillment of the CR criteria with the exception of one or more of the following: Skin- No rash, non-progressive 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 one evaluable organ stage with worsening in another
NR	No response: no change in any organ stage or deterioration in at least one organ system by one stage or more with no improvement in any other organ
Progression	Deterioration in at least one organ system by one stage or more with no improvement in any other organ
Responder	Subjects who achieve an OR[§]
Non-Responder	Subjects who do not achieving OR[§]

aGVHD=acute graft versus host disease.

[†] From Martin, 2009 [24]

[§] In summaries of Complete Response, a responder is defined as a subject who achieves a CR and non-responder is a subject who does not achieve a CR.

1.5 Mesenchymal Stromal Cells (MSCs) as Therapy for Acute GVHD

[redacted]

MSCs have been shown to attenuate inflammatory and immunological processes relevant to GVHD. MSCs demonstrate immunosuppressive activity in T cell-driven immune responses in animal models of allogenic skin graft rejection and GVHD.[33,34,35] *In vitro*, MSCs suppress T-cell proliferation in response to allo-antigenic and mitogenic stimulation, and stimulate an increase in the regulatory T cell (Treg) population. [36,37,38] Data suggest that Tregs play an important role in inhibiting allogeneic T cell response and aGVHD.[6,7] In co-culture systems, MSCs alter the cytokine secretion profile of immune cells (dendritic cells, naïve and effector T cells, natural killer cells), decreasing expression of pro-inflammatory cytokines (e.g. IFNγ, TNFα) and increasing secretion of anti-inflammatory cytokines (e.g. IL-4, IL-10).[33] The immunomodulatory effects of MSCs are attributable, at least in part, to secretion of soluble factors such as PGE2.[33] In addition, 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.[39,40,41]

[redacted]

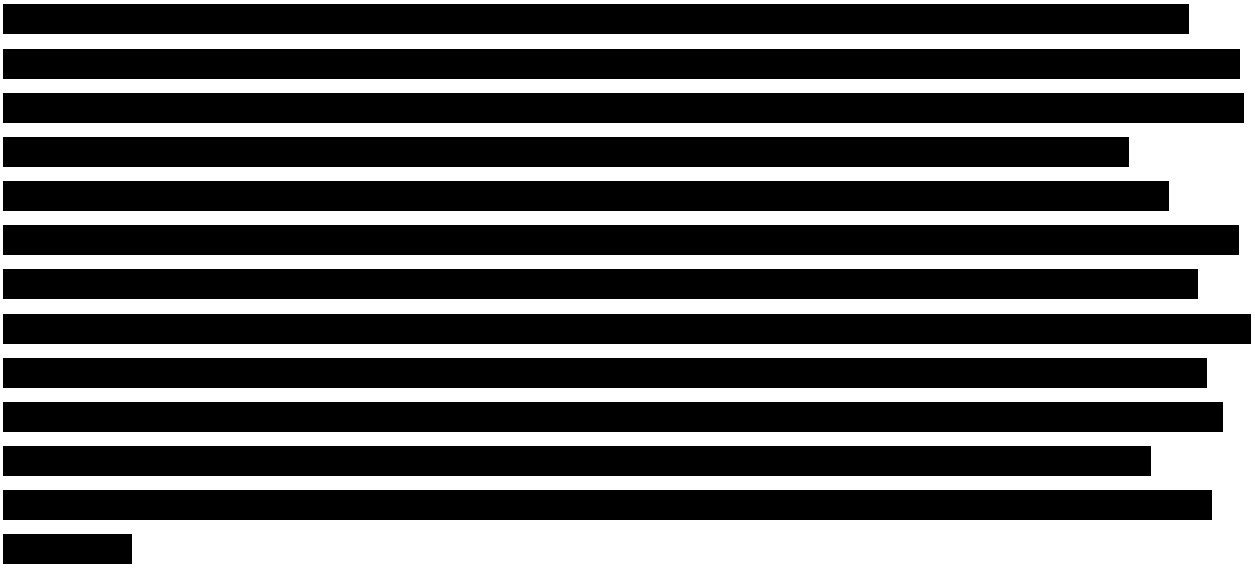
1.8 Clinical Safety of Remestemcel-L

Refer to the remestemcel-L clinical safety as summarized in the MSB-GVHD001 protocol.

1.9 Potential Risks of MSCs

A list of adverse events (AEs) possibly or probably related to remestemcel-L use is found in the Investigator's Brochure (IB) and in Protocol MSB-GVHD001 Section 1.7.8. All AEs were events commonly expected in the treated population, independent of the infusions of hMSCs. The most common adverse events observed for remestemcel-L in clinical trials of pediatric GVHD were infections, gastrointestinal disorders, and respiratory, thoracic and mediastinal disorders.

Due to the known immune modulating effects of hMSCs, there is a risk of immune suppression and increased infection risk. Subjects undergoing treatment for GVHD are typically severely immunocompromised. Treatment with remestemcel-L may lead to further immunosuppression. Therefore, the potential exists for an increased risk of infectious complications. Careful subject monitoring and appropriate anti-infective prophylaxis is recommended.



In theory, cells grown and expanded outside the body have the potential to be contaminated, and infection could be introduced to the subject at the time of infusion. This risk is made negligible by processing cells in a Good Manufacturing Practice (GMP)-compliant production facility, utilizing a closed system, and then by reconstituting them in a cell processing facility immediately prior to administration. The potential risks of introducing a donor-derived

infectious agent are minimized by strict adherence to the 21CFR1271 Subpart C Donor Eligibility and multiple screenings/testing of remestemcel-L for adventitious agents prior to release. The IB contains a full list of donor screening tests performed on all lots of remestemcel-L during production.

[redacted]

There has been no experience with pregnant women receiving infusions of remestemcel-L. The effects of remestemcel-L infusion on the developing fetus have not been established pre-clinically or in clinical trials. Thus, all females of childbearing potential (subjects ≥ 10 years of age) and post-pubescent males with female partners of childbearing potential are to consent to use an effective method of birth control during this treatment protocol in a manner that minimizes risk of failure. Abstinence is an option. Guidelines on childbearing potential and contraceptives are located in Appendix 7.

1.10 Benefits

[redacted]

[redacted]

[redacted]

[redacted]

2. CLINICAL RATIONALE

2.1 Rationale for the Study

There are currently no approved therapies for aGVHD in the US. Standard front-line treatment generally consists of corticosteroid, which produce a complete response in about half of all subjects.[13] Even with the availability of corticosteroids, approximately 10% to 30% of aGVHD subjects develop more severe aGVHD of Glucksberg Grades III or IV.[5] A variety of immunosuppressants are currently used as second-line therapy, though none of these have established efficacy against steroid-refractory aGVHD.[6] The reported one-year survival rate for subjects that do not respond to steroid therapy ranges from 5% to 30%.[6,8,15-19] There is thus a strong need for agents with demonstrated efficacy for treating steroid-refractory aGVHD.

MSB-GVHD001 will provide a series of prescribed doses of remestemcel-L and a follow up period of 100 days. There is a great interest in collecting data regarding treatment of aGVHD with respect to the duration of response, the ability to taper steroid and other secondary treatment and thereby mitigate potential side effects, the development of chronic GVHD after at least partial response to treatment, and any change in quality of life. Accordingly, this study will assess the efficacy and safety of remestemcel-L in pediatric patients with aGVHD refractory to corticosteroid.

2.2 Rationale for Study Design

Overall response, as defined by the response to treatment at Day 28, has been positively associated with non-relapse mortality at 6 months and 2 years.[26,28] Response at Day 28 has been supported guidelines issued by the expert panel of the American Society for Blood and Marrow Transplant (ASBMT) in 2009[24] as well as by subsequent studies.[25,27] Treatment of acute GVHD, which results in response by 28 days, has been shown to correlate well with survival rates at Day

100. Recovery after acute treatment as well as the period after treatment has been associated with an increased incidence of opportunistic infections and many other AEs, some due to the effects of the disease itself and many due to the treatment intervention, particularly with protracted high-dose steroid use. This study will provide safety data through 180 days after treatment of aGVHD. In addition, the present study will also provide information with regard to survival at Day 180, the ability to taper steroid doses and secondary medications and thereby mitigate potential risks, the development of chronic GVHD after at least partial response to treatment, quality of life (QoL), and duration of response. Though validated tools for QoL are limited for pediatric subjects, this study will evaluate several tools and accommodate those subjects too young to answer for themselves.

2.3 Rationale for Subject Population

This study will explore duration of response and evaluate the safety of remestemcel-L in pediatric subjects with aGVHD that has failed to respond to first-line systemic steroid treatment who participated in MSB-GVHD001. The safety population will be comprised of any subject who received at least one infusion of remestemcel-L in MSB-GVHD001. Survival at Day 180 will be evaluated. Additionally, duration of response will be explored in subjects who completed initial therapy of remestemcel-L (first 8 doses) in MSB-GVHD001 and responded to therapy, in order to best assess the impact of a response to treatment of aGVHD.

2.4 Rationale for Dosing Regimen and Treatment Period

There is no treatment intervention in this study; all remestemcel-L dosing will have occurred in the MSB-GVHD001 study.

3. STUDY OBJECTIVES

3.1 Objectives

In clinical studies, MSCs elicited improved clinical response over placebo in subjects with aGVHD, which will have been evaluated in the MSB-GVHD001 study. Here in protocol MSB-GVHD002, we will describe safety for the MSB-GVHD001 population through 180 days of remestemcel-L treatment and explore duration of response of treating aGvHD that has failed to respond to first-line steroid treatment in pediatric subjects.

3.2 Primary Objective

Safety through 180 days of remestemcel-L treatment in subjects who participated in Protocol MSB-GVHD001. No additional investigational agent (remestemcel-L) will be administered in this safety follow-up protocol.

3.3 Secondary Objectives:

1. To assess survival at 180 days
2. To obtain an assessment for GVHD activity to investigational medicinal product (IMP) administered in MSB-GVHD001.
3. To assess proportion of subjects able to taper steroids by 50% at each time point from Day 100 to Day 180.
4. To assess the time to addition of any second-line GVHD treatment agent
5. To assess the number of days to a GVHD flare
6. To evaluate subjects for evidence of chronic GVHD.

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is a 180-day safety follow-up study of MSB-GVHD001, which will also explore duration of response over time. Subjects who participated in MSB-GVHD001 and received at least one remestemcel-L infusion will be evaluated at baseline (Day 100) and at Days 120, 140, 160 and 180 for safety endpoints. Subjects who participated in Protocol MSB-GVHD001and received the first 8 doses of remestemcel-L, as outlined in that protocol, and showed overall response or VGPR at Day 28 will be evaluated at baseline (Day 100) and at Days 120, 140, 160 and 180 after initial remestemcel-L infusion for evidence of duration of response over time.

4.1.1 Primary Endpoints

To describe the safety through 180 days of remestemcel-L treatment in subjects who participated in Protocol MSB-GVHD001 and received at least one infusion of remestemcel-L.

Safety parameters to be assessed include:

1. Adverse events
2. Serious adverse events
3. Survival through Day 180
4. Ectopic tissue formation.

4.1.2 Secondary Endpoints

1. Survival at 180 days for subjects who received the complete initial therapy through 28 days as outlined in Protocol MSB-GVHD001
2. GVHD activity at time points evenly divided amongst the term from Day 100 to Day 180, specifically at Days 120, 140, 160 and 180, relative to baseline assessment in MSB-GVHD001.
3. Steroid doses at Days 120, 140, 160 and 180, including proportion of subjects able to taper steroids by 50% by each time point. Guideline for steroid taper is located in Appendix 6.
4. Time to addition of any second-line GVHD treatment agent
5. The number of days to GVHD flares
6. Evidence of chronic GVHD at any time from Day 0 to Day 180. Guidelines for chronic GVHD assessment are located in Appendix 8.

[redacted]

4.2 Study Duration

In the present study, MSB-GVHD002, subjects who participated in Protocol MSB-GVHD001 will be followed-up for safety and for duration of response from Day 100 through 180 days from MSB-GVHD001 Day 0. Subjects will be assessed in the present study according to the schedule of planned assessments, as summarized in Table 6. Thus, the total duration of study participation per subject for Protocol MSB-GVHD001 and Protocol MSB-GVHD002 will be up to 180 days (± 7 days), with the last 80 of the 180 days under Protocol MSB-GVHD002.

Table 6: Schedule of Assessments and Procedures

	Baseline/ Visit 1	Visit 2	Visit	Visit 4	Visit 5	
Study Days	**Day 100 (same as Day 100 in MSB-GVHD001)**	**Day 120**	**Day 140**	**Day 160**	**End of Study/ Day 180**	
Visit window	**±7 days**	**±5 days**	**±5 days**	**±5 days**	**±7 days**	**Unscheduled**
Inclusion/exclusion criteria/informed consent [a]	X					
Vital signs (HR, BP, Temp, RR, oxygen saturation) [b]		X	X	X	X	X
Height and weight					X	X
Physical examination		X	X	X	X	X
CMV[c]		X	X	X	X	X
Hematology laboratory tests				X	X	X
Chemistry laboratory tests				X	X	X
Urinalysis				X	X	X
Hospitalization[d]						X
[redacted]						
Acute GVHD assessment (Skin, Lower GI, Upper GI, Liver)		X	X	X	X	X
Chronic GVHD assessment		X	X	X	X	X
Concomitant medication[f]		X	X	X	X	X
Transfusion [g]						X
Optional CT scan or MRI (Chest, Abdomen and Pelvis)[I]					X	X
12-Lead ECG					X	X
[redacted]						
Termination/end of study					X	X
Pregnancy test[J]					X	X
Adverse event evaluation [k]		X	X	X	X	X

[a] Informed consent for MSB-GVHD002 may be provided to the subject simultaneously with the informed consent for MSB-GVHD001,or at any visit prior to Day 180 (± 7 days) .

[b] Vital signs include measurements of heart rate (HR), blood pressure (BP), respiratory rate (RR), and temperature (temp).

[c] Investigators should provide standard of care treatment for viral infections as appropriate, including prophylaxis and treatment if there is evidence of viral reactivation and/or infection

[d] Hospitalization with a start date after the visit window of Day 100 (Day 107) will be collected in MSB-GVDH002.
Hospitalization with a start date before the visit window of Day 100 (Day 106) will be collected in MSB-GVDH001.

[redacted]

[f] Concomitant medication with a start date after the visit window of Day 100 (Day 107) will be collected in MSB-GVDH002.
Concomitant medication with a start date before the visit window of Day 100 (Day 106) will be collected in MSB-GVDH001.

[g] Total number of units transfused of blood product will be recorded in the eCRF during study. Transfusion with a start date after the visit window of Day 100 (Day 107) will be collected in MSB-GVDH002. Transfusion with a start date before the visit window of Day 100 (Day 106) will be collected in MSB-GVDH001

[redacted]

[redacted]

[redacted]

[redacted]

[j] Pregnancy test will be performed on all females of childbearing potential (subjects ≥10 years of age). Guidance on childbearing potential and pregnancy testing is located in Appendix 7.

[k] All AEs will be collected in this study. Adverse events with an onset date after the visit window of Day 100 (Day 107 – as allowed in protocol MSB-GVHD001) will be collected in MSB-GVHD002. Adverse events with an onset date before the visit window of Day 100 (Day 106 – as allowed in protocol MSB-GVHD001) will be collected in MSB-GVHD001

[l] CT scans and MRI are optional and may be omitted at the discretion of the Investigator.

4.3 Study Sites

This study will be conducted in approximately 40 different sites.

5. STUDY POPULATION

5.1 Enrollment

The study plans to evaluate only those subjects who participated in Protocol MSB-GVHD001. All subjects who enrolled in Protocol MSB-GVHD001 and who meet the inclusion and exclusion criteria for MSB-GVHD002 will be enrolled in Protocol MSB-GVHD002, using the same subject number they received in MSB-GVHD001. Subjects will be followed through 180 days after initial therapy with remestemcel-L.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

Subjects are eligible for the study if all of the following criteria are met:

1. Subjects must have participated in Protocol MSB-GVHD001 and have received at least one infusion of remestemcel-L.
2. Subject or subject's authorized representative must provide written informed consent. Assent, if applicable, must also be collected when required by the IRB/EC.
3. Female subjects of childbearing potential (≥ 10 years of age) (Appendix 7) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for the follow-up time period. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.
4. The subject must be willing and able to comply with study procedures, remain at the clinic as required during the study protocol, and return to the clinic for the follow-up evaluations as specified in this protocol.

5.2.2 Exclusion Criteria

Subjects are eligible for the study as long as the following criteria are not met:

1. The investigator believes it to be in the best interest of the subject not to participate in the safety follow up study.
2. Subject has participated or is currently participating in any autologous or allogeneic stem cell or gene therapy study for the treatment of aGVHD. Patients participating in investigative protocols aimed at modification of the transplant graft (such as T cell depletion) or aimed at modification of the conditioning regimen will be allowed in the study.

5.3 Premature Subject Withdrawal

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects may be also considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up.

At a minimum, the following should be collected when a subject withdraws:

- The reason the subject discontinued
- The date of the last assessment and/or contact
- Adverse events (AEs) , including concomitant medications used to treat AEs
- Final (end of study) assessments.

5.4 Lost to Follow-Up

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator post randomization after reasonable efforts have been made to contact the subject. The investigator should show “due diligence” by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls or registered letters. The end of participation for a subject lost to follow-up is the date of the last known contact (e.g., visit or telephone contact).

5.5 End of Study

The end of study is defined as any one of the following, whichever occurs first:

- The date of the last scheduled visit for the last subject
- The date of death of the last subject
- The date of withdrawal of the last subject.

Individual subjects will be deemed to have completed study when they have completed all required protocol procedures and assessments. For subjects with ongoing adverse events at the last scheduled visit, the end of study date will be deemed to be the last scheduled visit date.

6. STUDY PROCEDURE

6.1 Visit Schedule and Assessments

Table 6 lists all planned assessments, which are marked with an "X" when the visits are performed. Subjects should be seen for all visits on the designated day or at a time that is as close as possible to the designated day. The study assessment schedule in Table 6 outlines all procedures to be performed on subjects at the scheduled visits.

In order to minimize variability in evaluations, ideally, the same individuals should perform the same tests on all the subjects at a given trial site.
The following assessments and procedures will be performed at study visits:

- Informed consent. Subject may be consented on MSB-GVHD002 simultaneously when being provided with the MSB-GVHD001 consent, or at any visit up through Day 180 (± 7 days). If the IRB/EC has not yet approved the consent for MSB-GVHD002 at Day 100 (MSB-GVHD001), the Investigator should make all efforts to have the IRB/EC approved consent for MSB-GVHD002 presented to the subject no later than Day 180 (± 7 days). See Section 6.3 for additional information about handling of visits from Day 100 through Day 160 when an IRB/EC approved consent is not available.
- Review of inclusion / exclusion criteria
- Physical examination
- Height and weight
- Vital signs (heart rate [HR], blood pressure [BP], temperature, and respiratory rate [RR])
- GVHD assessment (skin, lower GI, upper GI, liver) using the same method as that of MSB-GVHD001
- O_2 saturation by pulse oximetry (SaO_2/SAT)
- Adverse event (AE) assessment
- Incidence of chronic GVHD (cGVHD) (Appendix 8)
- Survival status
- Information on hospitalization status (namely the date of hospitalization)
- Steroid dose(s)
- Prior and concomitant medications

- Laboratory assessments
  - Hematology (including CMV, please see Table 6 for details)
  - Serum chemistry
  - Urinalysis
  - [redacted]
- Optional CT scan or MRI of the chest, abdomen, and pelvis at the discretion of the investigator. Scans may contribute information with regard to baseline disease burden and may also provide baseline for evaluation of future possible ectopic tissue formation. For CT, use intravenous (IV) contrast; if IV is contraindicated for any reason, oral is acceptable even in the presence of GI GVHD.
- 12-Lead ECG

[redacted]

- Serum pregnancy test for female subjects ≥10 years of age (see Appendix 7 for guidance on childbearing potential and pregnancy testing)
- Transfusion (if applicable). Type of transfusion and the number of units will be recorded in the eCRF.

Measurement of all clinical parameters should be performed as described in Table 6. Standard instructions for determining these parameters are provided in the following sections.

6.1.1 Safety Assessments

Many of the study assessments scheduled for Day 100 will be completed during the MSB-GVHD001 protocol and, therefore, will not be completed at the Day 100 visit for this protocol.

6.1.1.1 Physical Examination

A physical examination, including but not limited to, examination for evidence of adverse events, will be performed at Day 120, Day 140, Day 160, the end of study/Day 180, and at unscheduled visits as needed.

Information about physical examinations must be available in the source documentation at the study site. Significant new findings made after the Day 100 visit that meet the definition of an AE or SAE must be recorded on the Adverse Event CRF.

6.1.1.2 Vital Signs

Vital sign measurements should be performed at Days 120, 140, 160, End Of Study/Day 180, and at unscheduled visits as needed.

Measurements of vital signs will include sitting systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), temperature, and respiratory rate (RR).

Vital signs will be measured after approximately 5 minutes of quiet rest with the subject in a sitting position. Ideally, the site should have a dedicated blood pressure machine and use the same machine and blood pressure measurement method for all subjects during the trial.

6.1.1.3 Oxygen Saturation

Concurrent with vital sign measurements, Oxygen saturation (SaO_2/SAT) will be monitored by pulse oximetry. Supplemental oxygen may be administered as needed but should be noted in the source documents

6.1.1.4 Height and Weight

Height and weight measurements should be performed at End of Study/Day 180 or at unscheduled visits as needed.

Measurement of height from a standing position should be performed with the subject's shoes removed, the knees straightened, and head held upright. For infants, height should be measured lying down, and measurements should be recorded as recumbent length.

Measurement of weight should be performed without shoes or extra layers of clothing (e.g., sweater or jacket) during the measurement. Subjects should be weighed on the same scales at all visits.

6.1.1.5 12-Lead Electrocardiogram (ECG)

12-lead electrocardiogram (ECG) will be performed at End of Study/Day 180 or at unscheduled visits as needed, to assess any changes in cardiac physiology from prior measurements performed at Day 0 and Day 100 in MSB-GVHD001. Subjects should be in a supine or semi-supine position for at least 5 minutes prior to the recording. The same recording position (supine or semi-supine) and the same equipment should be used for each subject throughout the study.

All ECG tracings must be (1) reviewed by a medically qualified member of the study team, (2) annotated to indicate any clinical finding, (3) signed and dated by the medically qualified member, and (4) filed with the notes for the subjects. ECG parameters will be entered into the CRF, and if any ECG abnormality is associated with an (S)AE, it must be entered in the (S)AE CRF.

Heart rate (HR), pulse rate (PR), QRS and QT durations should also be noted on the CRF along with the ECG parameters.

6.1.1.6 (Serious) Adverse Events

All (S)AEs, including those considered to have a causal relationship to the IMP, will be collected at each assessment time point. (S)AEs collected will consist of both solicited and events voluntarily reported by the subjects.

6.1.1.7 Pregnancy Tests

A serum pregnancy test may be performed by the site personnel for all females of childbearing potential (subjects ≥10 years of age) Study/Day 180 and at unscheduled visits and at the Investigator's discretion, as needed. Details on pregnancy testing requirements are located in Appendix 7.

6.1.1.8 Laboratory Evaluations

A designated laboratory (or laboratories) will perform the analyses of all specimens collected. Collection, shipment of samples, and reporting of results by the central or local (if needed) laboratory (or laboratories) will be detailed in the laboratory manual provided to the Investigators. If age/weight of the patient does not allow for this additional blood volume, then values from local labs will serve as the Day 160 values used for the present study. The laboratory tests to be performed for subjects in this study are listed in Table 7.

If necessary, laboratory assessments may be performed by a laboratory other than the designated central laboratory. In this case, normal ranges of test values for this laboratory should be provided to the sponsor.

The Investigator at each site is required to review all clinically relevant laboratory results requested in the protocol and to record those results in the CRF. The diagnosis associated with any clinically significant laboratory abnormalities should be recorded as an (S)AE on the CRF.

The reported (S)AE should indicate the underlying abnormality or diagnosis (e.g., renal insufficiency) as opposed to the observed deviation in laboratory results (e.g., elevated creatinine) if in fact the underlying abnormality or diagnosis is known. If there is no apparent underlying abnormality linked to a clinically significant abnormal laboratory value, the observed deviation itself should be reported as the (S)AE.

Table 7: Laboratory Tests

Chemistry	Hematology	Urinalysis
Albumin	Basophils	Blood
Alkaline phosphatase (AP)	Eosinophils	Glucose
ALT (SGPT)	Hematocrit	Ketones
AST (SGOT)	Hemoglobin	Microscopic exam
Bicarbonate	Lymphocytes	pH
Blood urea nitrogen (BUN)	Monocytes	Protein
Calcium	Neutrophils	Specific gravity
Chloride	Platelets	Bilirubin
Creatinine	RBC	Urine pregnancy test
Direct Bilirubin	Total WBC	
Glucose	MCV	
Inorganic phosphorus	MCHC	
LDH	MCH	
Potassium	MPV	
Serum pregnancy test (beta hCG) End of Trial/Day 180 or unscheduled visit	RDW	
Sodium	PTT/INR	
Total Bilirubin	**Special**	**Lipid Panel**
Total protein		
GGT		Total cholesterol
CPK	CMV (local lab only)	HDL
hsCRP		LDL
		Triglycerides
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

6.1.1.9 Assessment of Ectopic Tissue Formation

To detect any ectopic tissue formation, a radiologist and an Investigator at each study site may compare the optional CT scan or MRI performed during screening for MSB-GVHD001with the optional CT scan or MRI performed at end of study/Day 180 or at an unscheduled visit to determine if there is ectopic tissue formation. If applicable, the same method of radiologic scan should be used for both evaluations. If the formation of ectopic tissue is suspected, further evaluation may include MRI or positron-emission tomography (PET) scanning, and possibly biopsy.

[redacted]

6.2 Evaluation Period

Subjects will be evaluated through Day 180 from the date of initial remestemcel-L infusion in MSB-GVHD001.

6.3 Missing or Delayed Study Visits

Every effort should be made to ensure compliance with prescribed study visits. Missing of study visits is generally not permitted. However, in exceptional situations and with the sponsor's approval, visits may be postponed.

Subjects may be consented on MSB-GVHD002 simultaneously when being provided with the MSB-GVHD001 consent, or at any visit up through Day 180 (± 7 days). Due to IRB/EC review times, there may be situations in which there is a delay in the IRB/EC approval for MSB-GVHD002 and the associated informed consent forms. If the IRB/EC approval for MSB-GVHD002 consent form is not available at Day 100, Day 120, Day 140, and/or Day 160, these visits will be marked as missed visits in EDC. Data collection for MSB-GVHD002 will begin once the subject has signed consent for MSB-GVHD002. The Investigator should make every effort to present the IRB/EC approved consent for MSB-GVHD002 to the subject no later than Day 180 (± 7days).

To ensure timely attendance at the required clinic visits, the visit schedule for the entire study period should be arranged and agreed upon with the subject at the baseline visit. The study site should document and notify the sponsor of any visits not completed within the specified time frame or within the allowable window period.

6.4 Background and Prior Second-Line Medication

Background and prior second-line medications will be coded using the most recent WHO Drug Dictionary (WHO-DD)[52] and summarized by ATC code.

6.5 Concomitant Medication and Supportive Therapy

6.5.1 Standard of Care for aGVHD

All enrolled subjects will continue to receive institutionally defined standard of care (i.e., maintenance of steroid treatment and other prophylactic treatment for aGVHD) as described in MSB-GVHD001.

Investigators should provide standard of care treatment for viral infections as appropriate, including prophylaxis and treatment if there is evidence of viral reactivation and/or infection.

6.5.2 Concomitant Medications

Subjects may continue to be treated with systemic steroid therapy and receive any second-line therapy as necessary at the discretion of the Investigator and per institutional guidelines.

Information on all concomitant medications and therapy will be collected for this study. All new pharmacologic and non-pharmacologic treatment used by study subjects from Day 100 to Day 180 should be recorded in the corresponding CRF. Concomitant medications will be coded using the most recent WHO Drug Dictionary (WHO-DD)[52] and summarized by ATC code.

6.5.3 Steroid Taper

If continued steroid therapy is required, the dosing of methylprednisolone or equivalent may be tapered at the discretion of the Investigator. A steroid taper rate of at least 10% of the dose per week but not to exceed 25% of the dose per week is recommended as described in Appendix 6, with the goal of discontinuing steroid by 10 weeks after initiating taper.

6.5.4 Escalating Therapy

Protocol guidelines for escalating therapy of aGVHD for worsening disease include:

1. Worsening of symptoms for at least 3 days, or
2. Grades C-D aGVHD persisting for at least 1 week despite treatment, or
3. Grade B aGVHD persisting for at least 2 weeks despite treatment.

Escalation of therapy does not constitute withdrawal of a subject from the study. If escalation of therapy occurs, the subject is to continue on study and receive all assessments per protocol.

6.5.5 Supportive Care

In addition to prescribed investigational agent plus corticosteroids and prophylactic therapies, all subjects may receive the following:

- Transfusion support per institutional practice. Type of transfusion and the number of units will be recorded in the eCRF.
- Anti-infective prophylaxis directed towards: CMV, gram positive (encapsulated) bacteria, pneumocystis carinii and fungal infections per institutional practice.

7. SAFETY GUIDANCE

7.1 Definitions

7.1.1 Adverse Event

An AE is defined by the International Conference of Harmonization (ICH) guideline for Good Clinical Practice as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening procedures such as biopsies etc.) are to be reported.

Collection of all AEs will begin upon signing of the informed consent form (ICF). Pre-existing conditions that **worsen** during a study are to be reported as AEs.

7.1.2 Serious Adverse Event (SAE) -Immediately Reportable to the Sponsor

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death). This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.1.3 Severity

A clinical determination will be made of the severity of an adverse event. The terms "severe" and "serious" are not synonymous. Severity is a description of the intensity of the manifestation of the AE and is distinct from seriousness, which implies a subject outcome. Severity will be assessed according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[53] scale (Table 8):

Table 8: NIH Common Criteria for Adverse Events (CTCAE) Scale †

AE Severity	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening; urgent intervention indicated.
Grade 5	Death related to AE

† Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. National Cancer Institute. US Department of Health and Human Services. June 14, 2010. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

*Instrumental activities of daily living (ADL) examples include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL includes to bathing, dressing and undressing, feeding self, using the toilet, and taking medications and does not include being bedridden.

7.2 Relationship of Adverse Event to the IMP

A determination will be made of the relationship between an adverse event and the IMP. A causal relationship is present if a determination is made that there is a *reasonable possibility* that the adverse event may have been caused by the IMP. In general, a causal relationship will be assigned when evidence exists to support the causal relationship. As there is no prescribed treatment intervention in this study, relationship would be extrapolated backwards to dosing in protocol MSB-GVHD001.

When assessing a potential relationship between the IMP and an AE, the following parameters should be considered:

- Temporal relationship between IMP and/or protocol-specified procedures and the AE.
- The biological plausibility that the IMP caused the event
- Any underlying/concurrent illness in the subject
- Concomitant medications the subject may have received
- How commonly the event occurs in the study population, independent of treatment.

7.3 Relationship to Study Procedure

For each adverse event, the relationship to the IMP delivery procedure must be recorded as either **related** (there is reasonable possibility of a causal relationship between the event and the study procedure) or **not related** (there is no reasonable possibility of a causal relationship between the event and the study procedure).

8. REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Any adverse event (AE) occurring after a subject has signed the informed consent (or randomization, as appropriate) should be recorded on the appropriate CRF page.

Any SAE (as described in Section 7.1.2) occurring after a subject has signed the informed consent should be immediately reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event. All subjects with an SAE must be followed up and the outcomes reported until the event is resolved or has stabilized.

Upon occurrence of an SAE, the investigator must:

- Immediately notify the sponsor's designee, Quintiles Lifecycle Safety. SAE reporting will originate in the electronic data capture (EDC) system and an email will be sent to

individuals with designated responsibility for safety. The paper SAE form is in place as a back-up in the rare event that EDC is not accessible to the reporter of the SAE:

  - [redacted]
- Provide copy of all relevant source documents, including concomitant medications, as appropriate.

All SAEs that are considered unexpected and related to the study product will be reported by the Sponsor or its designee as a 15-day report to the Regulatory Authorities *as applicable* and to all participating investigators.

SAEs that are considered unexpected, related to the study and are life threatening, or result in death will be reported by the Sponsor or its designee to the appropriate Regulatory Authorities and to all participating investigators as a 7-day report.

Each investigator must notify the IRB/EC responsible for reviewing the study at their site of all 15-day or 7-day safety reports required by local regulations or IRB/EC requirements and shall provide the Sponsor or its designee with written confirmation of said IRB/EC notification.

8.1 Procedures for Reporting Pregnancies

All pregnancies that occur during the study are to be reported immediately to the individual identified in the General Information page of this protocol, and the investigator must provide Sponsor or designee, by facsimile, a Pregnancy Tracking Form. Pregnancies in female partners of male subjects are **not** required to be followed up. All subjects who become pregnant will be monitored to the completion or termination of the pregnancy, including perinatal and neonatal outcome. Monitoring of the subject should continue until conclusion of the pregnancy. If the pregnancy is associated with an SAE (e.g. hemorrhage, spontaneous abortion), then in addition to the Pregnancy Form, a separate SAE form must be provided as described in Section 8.

8.2 Laboratory Test Abnormalities

Laboratory test results will appear on laboratory reports that are submitted directly from the central laboratory. Local laboratory results, if applicable, should be recorded on the CRF.

Any abnormal laboratory result that is clinically significant should be recorded as a single diagnosis in the CRF. An abnormal laboratory result is considered to be clinically significant if it meets one or more of the following conditions:

- Is accompanied by clinical symptoms.
- Requires change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

These conditions will apply to any protocol- and non-protocol- specified safety laboratory results from tests performed after ICF signature that fall outside the laboratory reference range and are considered clinically significant. These conditions will not apply to any abnormal laboratory results that are outside the laboratory reference range, yet does not meet the criteria for clinical significance; these latter results will be analyzed and reported as laboratory abnormalities.
In the event of clinically significant abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or the abnormality is adequately explained or accounted for. If an acceptable explanation is established, it should be recorded on the CRF.

8.3 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

The Sponsor will promptly evaluate all adverse events against cumulative product experience to quickly identify and communicate possible new safety findings to investigators, IRBs, IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- IMP IB
- IMP Development Core Safety Information (DCSI) Document, if applicable.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with a provision for upgrading by the Sponsor as needed.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

9.1 Statistical Analysis Plan

Since this is an extension trial of MSB-GVHD001, data presented for MSB-GVHD002 will be presented in two ways:

1. For the extension period only. This will include assessments beyond Day 100.
2. For the entire period spanning both MSB-GVHD001 and MSB-GVHD002 trials. In particular, this includes time-to-event data (flares and therapy escalation), survival data, incidence of cGVHD, and frequency of flares.

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Confidence intervals, if presented, will have a two-sided 95% confidence level. For time-to-event variables, Kaplan-Meier curves will be presented as appropriate.

In general, the baseline value for a variable is defined as the last non-missing observation prior to or equal to the first dose date of study treatment in MSB-GVHD001. Baseline for analyses of the entire period of MSB-GVHD001 and MSB-GVHD002 will be the same as baseline defined for Protocol MSB-GVHD001. The baseline for the extension period beyond Day 100 will be the same values at the end of study/Day 100 for MSB-GVHD001. Data collected at unscheduled time points will not be summarized at the unscheduled time points.

The actual day relative to start of treatment will be determined from the first dose date in Protocol MSB-GVHD001, which will be considered 'Study Day 0'. Study day will be calculated from the first infusion date in Protocol MSB-GVHD001. A detailed statistical analysis plan (SAP) will be finalized prior to the database lock.

9.2 Analysis Population

The analysis population for safety in this study, the Safety Population, will include all subjects who received at least one dose of the study treatment in study MSB-GVHD001 and entered into study MSB-GVHD002. The population to be evaluated for duration of response will include all subjects who participated in Protocol MSB-GVHD001, received the first 8 doses of remestemcel-L as outlined in that protocol, and showed overall response (OR) or very good partial response (VGPR) to remestemcel-L at Day 28.

9.3 Demographic and Baseline Characteristics

Pre-treatment demographics and subject characteristics will be summarized. Descriptive statistics [e.g., number of subjects, mean, standard deviation (SD), median, minimum, and maximum] will be calculated for continuous variables [e.g. age and weight] and frequency counts will be tabulated for categorical demographic variables [e.g. gender, ethnicity, race, underlying malignancy or leukemic disease at transplant, donor type, donor compatibility, HSCT source, grade of aGVHD at onset, grade of aGVHD at baseline]. Time from HSCT to onset of aGVHD and onset of aGVHD to initiation of study drug will be summarized. Involvement of the skin, lower gastrointestinal (GI) tract, and liver will be summarized by the number of subjects with one organ, two organs, or all three organs involved at baseline.

9.4 Safety Data Analysis

9.4.1 Adverse Events and Serious Adverse Events

All (serious) adverse events in this study will be collected from the time the subject signs the ICF. All (S)AEs will be collected in this study and summarized by treatment, dose, and severity. Numbers and rates of TEAEs and other safety variables will be tabulated by organ system and preferred term.

At each time point, vital signs and safety laboratory parameters will be tabulated. The continuous variables will be summarized by the descriptive statistics – mean, standard deviation, median, minimum and maximum. Additionally, vital signs and laboratory parameters will be assessed for clinically significant abnormalities as well as shifts from baseline.

9.4.2 Survival to Day 180

The number of subjects alive, deceased, lost to follow-up, or withdrawn from Day 0 (Protocol MSB-GVHD001) to Day 180 (Protocol MSB-GVHD002) will be summarized in a Subject Disposition table. For subjects who died, the time to event will be calculated from date of transplant, date of aGVHD onset, and date of treatment initiation. All other subjects will be censored and survival time will be calculated from the date of transplant, date of aGVHD onset, or date of treatment initiation to the date of last contact.

9.4.3 Ectopic Tissue Formation

To detect potential ectopic tissue formation, a radiologist and an Investigator at each study site may compare the CT scan or MRI performed during screening with the CT scan or MRI those performed at study end, if available, to determine if there is ectopic tissue formation. The same method of radiologic scan should be used for both evaluations. If formation of ectopic tissue is suspected, further evaluation may include MRI or positron-emission tomography (PET) scanning, and possibly biopsy.

As noted above, (S)AEs which represent ectopic tissue foci will be summarized by numbers and percentages.

9.4.4 Other

For each applicable time point, key laboratory data, vital signs and safety laboratory parameters will be tabulated. Vital signs and laboratory parameters will be assessed for clinically significant abnormalities and shifts from baseline (baseline as obtained in protocol MSB-GVHD001) will be presented.

9.5 Secondary Endpoints Analysis

9.5.1 Assessment of Survival at Day 180

Survival will be assessed from initial remestemcel-L treatment to the end of study/Day 180. The numbers with percentages for survival, non-survival, or missing, including lost to follow-up, will be summarized at Day 180. For tabulating responders at Day 28 from the MSB-GVHD001 study versus survivors at Day 180 the present study, percentages of survivors and deaths will be based on all subjects, including those with missing survival information for the lost to follow-up or withdrawn subjects. The association between Day 28 OR and survival at Day 180, and between Day 28 VGPR and survival at Day 180, will be tested for statistical significance. First, the associations will be tested using a Cochran–Mantel–Haenszel **(**CMH) test, stratifying by baseline aGVHD grade. Day 180 survival Kaplan-Meier curves will be plotted by Day 28 responder and non-responder groups, and differences between these groups will be tested for any statistically significant difference using the log-rank test. The odds ratio for survival at Day 180, given responder status at Day 28, will be presented and tested for statistical significance (whether statistically significantly greater than 1).

9.5.2 GVHD Activity

GVHD activity will be assessed and summarized at time points evenly divided amongst the term from Day 100 to Day 180, specifically at Days 120, 140, 160 and 180, relative to baseline assessment in MSB-GVHD001.

9.5.3 Steroid Dose

Steroid doses at Days 120, 140, 160 and 180, including proportion of subjects able to taper steroids by 50% by each time point will be summarized. Guideline for steroid taper is located in Appendix 6.

9.5.4 GVHD Flares

The numbers with the percentages of GVHD flares will be summarized and presented. The time to a GVHD flare from the Day 0 and Day 100 will be determined and summarized with a Kaplan-Meier curve.

9.5.5 Second-line Treatment

The number of days to addition of any second-line GVHD treatment agent, from Day 100 in the present study, will be determined and summarized by the mean, standard deviation, median, minimum and maximum. The number of second-line treatments used will also be determined and descriptively summarized.

9.5.6 Chronic GVHD

Subjects will be evaluated for evidence of chronic GVHD at any time from Day 0 to Day 180. The time to first sign of chronic GVHD will be summarized. The number and percentage of subjects developing cGVHD will be tabulated for the overall safety population as well as for the population stratified by baseline GVHD grade, number of infusions received, and Day 28 responder/non-responder categories.

[redacted]

[redacted]

9.8 Interim Analysis

No interim analysis is planned for this study.

9.9 Handling of Missing Values

In general, for safety analyses, observed values will be used, and no imputation will be made for missing values. For specific endpoints and special instances, details for handling missing values will be described in the statistical analysis plan (SAP).

10. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Sponsor's (or designee's) Standard Operational Procedures (SOPs).

Data for this study will be recorded using electronic Case Report Forms (eCRFs).

The site is expected to respond to all SAE queries within 24 hours and to all other queries within 5 business days. A Mesoblast representative or a designee will perform final data review and external data reconciliations prior to all major milestones, including database close and lock.

10.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the CRF (CTCAE terms), using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA)[54] terminology for adverse events and diseases and for treatments and surgical and medical procedures.

11. STUDY COMMITTEES

11.1 Independent Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is a multidisciplinary group that is independent of both the sponsor and CRO, which consists of one biostatistician and physicians with expertise in relevant disciplines, who collectively have experience in the management of clinical trial subject. The DSMB is also knowledgeable in the conduct and monitoring of randomized clinical trials.

The DSMB will meet at regular intervals to review enrollment status, baseline characteristics of the study population, all treatment-emergent safety reports, and status of therapeutic benefit. The chairperson of the DSMB will be notified of all SAEs.

The DSMB will recommend one of the following at each of their meetings:

- Continue the trial
- Modify the trial (amend the protocol)
- Stop enrollment in the trial.

Additional details regarding the specifics of the DSMB operations may be found in the DSMB Charter.

[redacted]

12. LAWS, REGULATIONS, AND ETHICS

12.1 Local Regulations/Declaration of Helsinki

This clinical study shall be conducted in full compliance with current material and relevant laws and regulations and investigators will use best efforts to ensure such compliance. This clinical study will also be conducted in compliance with principles outlined in the "Guideline for Good Clinical Practices" ICH tripartite Guideline[55] and with the ethical principles of the "Declaration of Helsinki"[56] or with the laws and regulations of the country in which the research is conducted, including but not limited to the EU Clinical Trial Directive.[57]

12.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator, if local regulations permit, to obtain signed informed consent from each subject prior to the subject's participation in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For subjects who are not qualified to or are incapable of giving legal consent, written consent must be obtained from a legally acceptable representative. In cases where both the subject and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form would attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the subjects are free to refuse to enter or withdraw from the study at any time and for any reason that a copy of the consent would be provided to the subject, and that the process by which consent is obtained is described in the

source documentation. The CRFs for this study would contain a section for documenting subject informed consent, which must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment, the consent form should be reviewed and updated if necessary. All subjects, including those already being treated, should be informed of the new information, provided with a copy of the revised form, and give their consent to continue in the study in accordance with the IRB/EC requirements.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements (e.g., HIPAA, local Regulatory Agency). Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The Investigator will ensure that study documents forwarded to Mesoblast and any other documents contain no mention of subject names.

12.3 Institutional Review Board/ Ethics Committees (IRB/EC)

This protocol and any modifications, appropriate consent procedures, or accompanying material provided to the subject, such as subject information sheets or descriptions of the study used to obtain informed consent and advertisements or compensation given to the subject, will be reviewed and approved by appropriate Competent Authority and IRBs/ECs.

Before initiation of the trial at each investigational site, approval from the appropriate IRB/EC must be obtained. Written approval must be obtained before a trial site is initiated or the investigational product is released to the investigator.

Any extensions or renewals of IRB/EC approval must be obtained during the course of the study. If required, approvals must also be obtained for any changes to the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

Any new information that may adversely affect the safety of the subjects or the conduct of the study will be reported promptly to the IRB/EC by the Investigator and/or the Sponsor, in accordance with applicable local requirements. Written summaries of the study status will be submitted to the IRB/EC annually, or more frequently if required by the EC/IRB. On completion of the study, the IRB/EC will be notified that the study has ended.

12.4 Protocol Adherence

Investigators will ensure that due diligence is applied in order to avoid protocol deviations. All significant protocol deviations will be reported to the IRB/EC in accordance with IRB/EC requirements. All significant protocol deviations will be recorded and reported in the CSR.

12.5 Protocol Deviation

A protocol deviation is defined as an intentional or unintentional change or non-compliance with a research protocol.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol for ongoing studies will be considered only with consultation between an appropriate representative of the Sponsor and the Investigator. Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the Sponsor.

All protocol modifications must be submitted to the appropriate IRB/EC for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, with the exception of changes necessary to eliminate an immediate hazard to trial subjects, or change(s) involving only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE STUDY

Mesoblast reserves the right to terminate the study at any time under the conditions specified in the Clinical Trial Agreement. In the event the trial is terminated before the planned completion date, action will be taken to assure the protection of the subjects' interests.

14.1 Enrollment Hold and Stopping Rules

Subject safety will be continuously monitored. The investigator site will report all SAEs, including all deaths immediately as outlined in Section 8.

Additionally, all AEs including all deaths will be periodically reported to the DSMB as per the DSMB charter. The DSMB will investigate these complications through a complete safety review. The DSMB will then determine whether enrollment should be continued, suspended, or terminated and their decision will be communicated to the Sponsor.

Further details regarding the role, responsibilities and procedures of the DSMB are provided in the DSMB Charter.

15. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories, consisting of: 1) An Investigator's Study File and 2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments and schedule of assessments, IRB/EC and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae, authorization forms, and other appropriate documents/correspondence. In addition, at the end of the study the Investigator will receive the subject data, including an audit trail containing a complete record of all changes to data, query resolution correspondence, and reasons for changes, in a readable format on CD that must be kept with the Investigator's Study File.

Subject clinical source documents may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, special assessment reports, signed informed consent forms, and consultant letters. The Investigator must keep the Investigator's Study File and subject clinical source documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study, or in accordance with ICH guidelines and local regulations, whichever is of greater duration. After this specified time period, the documents may be destroyed. Study sites must notify the sponsor prior to destroying any trial-related documents.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee compliance with this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these documents in a sealed container(s) outside of the site in order to ensure that they can be returned sealed to the Investigator in the event of a regulatory audit. Where source documents are required for continued care of subjects, appropriate copies should be made for storing outside of the site.

15.2 Source Documents and Background Data

The Investigator shall provide to the Sponsor, upon request, any required background data from the study documentation or clinic records. This is particularly important in cases where errors in data transcription are suspected. In cases of special problems and/or governmental queries or requests for audit inspections, it is also necessary for the Sponsor to have direct access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

Source documents for this trial must be made available by the Investigator to appropriately qualified personnel from the Sponsor's (or designee's) Quality Assurance Unit or its designees or to health authority inspectors, upon appropriate notification. Verification of the CRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

Data for this study will be captured via an Electronic Data Capture (EDC) system using eCRFs. The data will be entered into the EDC system by trained site personnel per the eCRF Completion Guidelines. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change.

An eCRF must be completed for each subject. For each screen-failed subject, the reason for screen failure will be collected in the termination eCRF along with the corresponding screen failure reason. The entire subject casebook of data must be reviewed and electronically signed by the PI or by an authorized delegate from the study staff. This also applies to records for those randomized subjects who fail to complete the study. If a subject withdraws early from the study, the reason must be noted in the termination eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, attempts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

16. MONITORING OF STUDY

The Sponsor's responsible monitor (or designee) will contact and visit the Investigator regularly and will be permitted, upon request, to inspect the trial records, including CRFs and other pertinent data, provided that subject confidentiality is maintained in accordance with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to ensure protocol adherence and that the data entered on the CRFs are complete, consistent, and accurate. The monitor must verify that the subject received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by central randomization system). The monitor will also have access to laboratory test reports and other subject records as applicable needed to verify entries on the CRFs. The Investigator (or deputy) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subject anonymity is maintained and that subject identity is protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should be referenced by an identification code rather than by their names. The Investigator should keep a subject enrollment log showing codes, names and addresses. The Investigator should maintain documents that will not be submitted to the Sponsor (e.g., subjects' written consent forms) in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

18.1 Right to Publish

Subject to the restrictions in this Article 18 and processes described in this Section 19, Investigator may individually communicate, orally present or publish in scientific journals or other scholarly media the Study results. Sponsor retains all right and title to, as well as interest in, the Study data and case report forms. Authorship will be determined by mutual agreement according to guidelines published by the International Committee of Medical Journal Editors (ICMJE).[58]

18.2 Publication Steering Committee

A Publication Steering Committee (the "Committee"), comprised of lead investigators who are appointed by the Sponsor will be responsible for the creation, review, and submission of publications and presentations relating to the Study (e.g., primary manuscript on design, baseline data, mortality, efficacy, and safety data), sub-study, and ancillary analyses after completion of the Study. The Committee will encourage and support other manuscript(s) for publication, content for speaking engagements, abstracts of papers, poster presentations and similar material by the Study Center and/or Investigator as deemed appropriate by the

Committee. Committee review and approval must be obtained prior to submission of any publication or public display of the Study results, alone or in aggregate.

18.3 Procedure

Investigator shall provide Sponsor with a written copy of any proposed publication or other disclosure of the Study results, including disclosures at research seminars, lectures and professional meetings and submission of papers for publication, at least sixty (60) days prior to submission for publication or disclosure so that Sponsor may have a reasonable opportunity to: (i) review and comment on the contents of the proposed publication or disclosure; (ii) identify any trade secrets, proprietary information or Confidential Information (other than the Study results themselves) of Sponsor to be deleted from the proposed publication or disclosure; and (iii) protect proprietary rights to Inventions or products developed or investigated under the Study. Sponsor shall provide, in writing, any comments to Investigator and/or identify any of the Sponsor's trade secrets, proprietary information or Confidential Information (other than the Study results themselves) to be edited from the proposed publication or disclosure within the sixty (60) day period. Upon Sponsor's reasonable request, Investigator shall delay publishing or disclosure for a period not to exceed one hundred twenty (120) days from the date of receipt of such materials by Sponsor to permit the Sponsor to file patent applications or otherwise seek proprietary protection of subject matter disclosed in any proposed publication or other disclosure. In addition, Investigator shall give due regard to Sponsor's legitimate interests, such as manuscript authorship, coordinating and maintaining the proprietary nature of submissions to Regulatory Authorities, and coordinating with other ongoing studies in the same field, and agree to accept Sponsor's reasonable comments and suggestions with respect to such publications or disclosures.

Investigator and Study Center acknowledge that the Study is part of a multicenter study. Accordingly and notwithstanding anything to the contrary herein, Study Center and/or Investigator shall not publish or present the Study results until after the first publication, primary manuscript, or presentation regarding the overall study is completed, the results of the Study from all the sites have been published in a single publication or eighteen (18) months after acceptance of the manuscript or the conclusion of the Study at all Study sites whichever occurs earliest, the. Thereafter, Study Center and/or Investigator may publish or disclose Study results in accordance with the provisions of this Section 18.

19. STUDY COMPLETION

Mesoblast reserves the right to terminate this protocol prematurely for reasonable cause provided that written notices are submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the protocol at his or her site for reasonable cause, after providing written notice to Mesoblast a reasonable time in advance of the intended termination. Advance notice is not required by either party if the protocol is stopped due to safety concerns. If Mesoblast terminates the protocol for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for termination. If the Investigator elects to terminate the study at his or her site, the Investigator will be responsible for returning all investigational products and study-related documents to Mesoblast in a timely manner. Source documents supporting study-related data must be retained by the Investigator as previously described.

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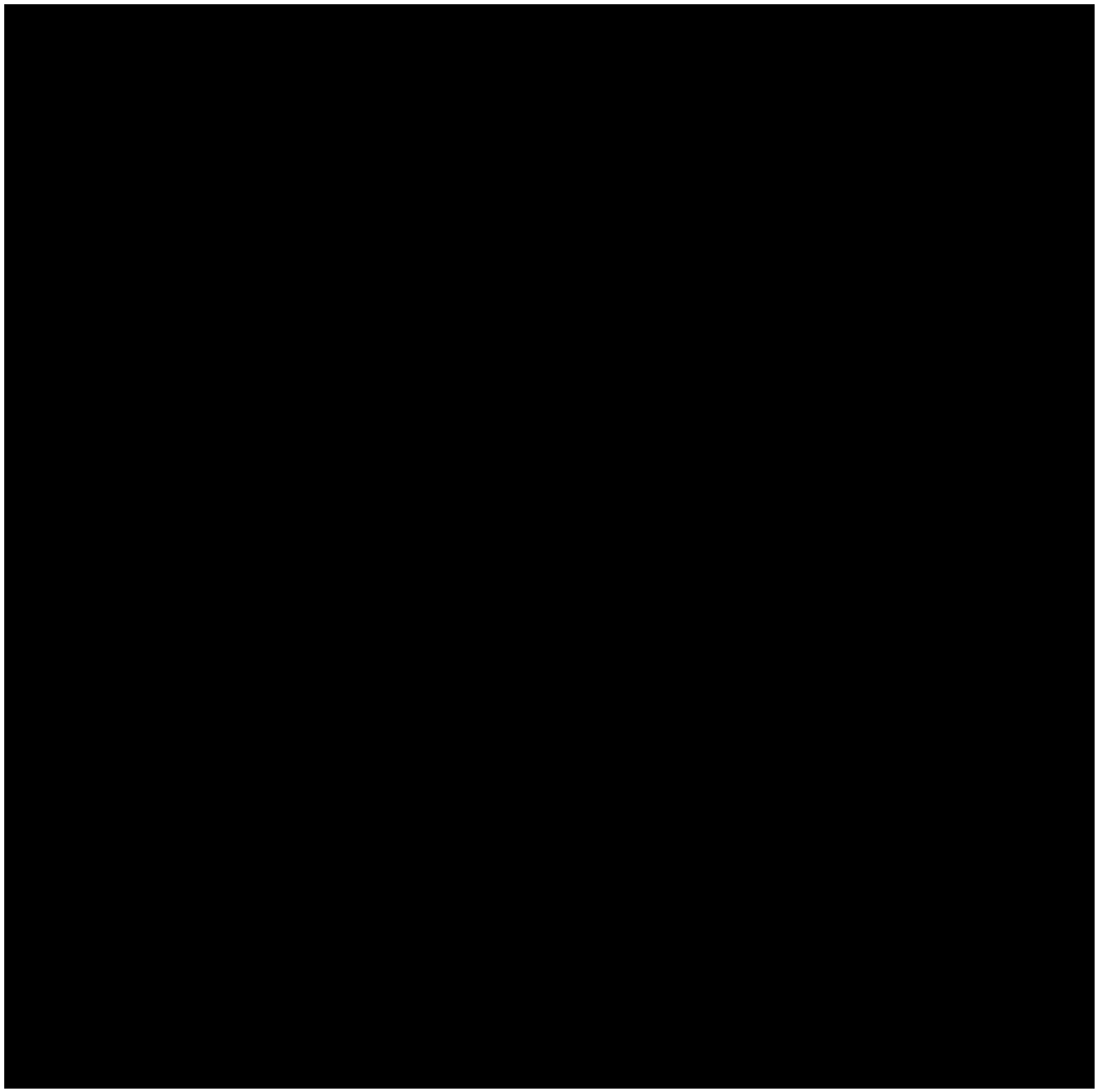

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Appendix 6: Recommended Steroid Taper

Prednisone orally

2.5 mg/kg/day divided in 2-3 doses	Days 0-6
2.5 mg/kg/day once daily	Days 7-13
2 mg/kg/day	Days 14-21
1.4 mg/kg/day	Days 21-28
0.75 mg/kg/day	Days 29-35
0.6 mg/kg/day	Days 36-42
0.4 mg/kg/day	Days 43-49
0.25 mg/kg/day	Days 50-56
0.1 mg/kg/day	Days 57-63
0.1 mg/kg/every **other day**	Days 63-69
Discontinue	Day 70

Methylprednisolone IV

2 mg/kg/day divided in 2-3 doses	Days 0-6
2 mg/kg/day once daily	Days 7-13
1.5 mg/kg/day	Days 14-21
1.0 mg/kg/day	Days 21-28
0.5 mg/kg/day	Days 29-35
0.4 mg/kg/day	Days 36-42
0.3 mg/kg/day	Days 43-49
0.2 mg/kg/day	Days 50-56
0.1 mg/kg/day	Days 57-63
0.1 mg/kg/every **other day**	Days 63-69
Discontinue	Day 70

Appendix 7: Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at Screening. Post-screening, a urine pregnancy test will be performed at Day 56, Day 100, and at any unscheduled visits under protocol MSB-GVHD001. On protocol MSB-GVHD002, a urine pregnancy test will be performed at End of Study/Day 180 and at any unscheduled visit. If the urine pregnancy test is positive, the result must be confirmed by a serum pregnancy test (conducted by the central laboratory).[1]

All female patients are considered to be of childbearing potential **unless** they meet one of the following criteria:

- The patient has been post-menopausal (amenorrheic) for at least 1 year
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy.

Female patients of reproductive or childbearing potential who are unwilling to use a highly effective method of contraception for the duration of the study will be excluded from study participation.[2]

Examples of highly effective contraception include the following:

- Abstinence
- Contraceptive pill or transdermal patch
- Single barrier plus spermicide
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate post-surgical verification of the absence of spermatozoa in the ejaculate.

Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.

1. Study or protocol-specific.
2. IMP-specific and study-specific.

Appendix 8: Chronic GVHD-Specific Measures

Chronic Graft-Versus-Host Disease Scoring Table
Organ Scoring of Chronic Graft-Versus-Host Disease

	Score 0	Score 1	Score 2	Score 3
Performance Score: ☐ **KPS ECOG LPS**	☐Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80- 90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60- 70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
Skin Clinical features: ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement % BSA involved ☐	☐ No Symptoms	☐ <18% BSA with disease signs but NO sclerotic features	0 19-50% BSA OR involvement with superficial sclerotic features “not hidebound” (able to pinch)	☐ >50% BSA OR deep sclerotic features “hidebound” (unable to pinch) OR impaired mobility, ulceration or severe pruritus
Mouth	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs with partial limitation of oral intake	☐ Severe symptoms with disease signs on examination with major limitation of oral intake

Footnotes and abbreviations are provided at the end of the table.

Organ Scoring of Chronic Graft-Versus-Host Disease (Continued)

	Score 0	Score 1	Score 2	Score 3
Eyes Mean tear test (mm): >10 6-10 ≤5 Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eye drops <3xper day) OR asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops >3xper day or punctal plugs), **without** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca
Gastrointestinal tract	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5- 15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs OR esophageal dilation
Liver	☐ Normal LFT	☐ Elevated bilirubin, AP[a], AST or ALT <2xULN	☐ Bilirubin >3 mg/dL or bilirubin, enzymes 2-5xULN	☐ Bilirubin or enzymes >5xULN
Lungs[b] FEV_1 DLCO	☐ No symptoms FEV_1 >80% OR LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) FEV_1 60-79% OR LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) FEV_1 40-59% OR LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 02) FEV_1 <39% OR LFS 10-12
Joints and fascia	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **and** not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)

Footnotes and abbreviations are provided at the end of the table.

Organ Scoring of Chronic Graft-Versus-Host Disease (Continued)

	Score 0	Score 1	Score 2	Score 3
Genital tract	☐ No symptoms	☐ Symptomatic with mild signs on exam **and** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **and** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **with** advanced signs (stricture, labial agglutination or severe ulceration) **and** severe pain with coitus or inability to insert vaginal speculum

[a] AP may be elevated in growing children, and not reflective of liver dysfunction.
[b] Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores, the higher value should be used for final scoring. Scoring using the lung function score (LFS) is preferred, but if DLCO is not available, grading using FEV_1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established. The percent predicted FEV_1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: ≥80%=1; 70-79%=2; 60-69%=3; 50-59%=4; 40-49%=5; <40%=6. The LFS= FEV_1 score+DLCO score, with a possible range of 2-12.

ADL=activities of daily living; ALT=alanine aminotransferase; AP=alkaline phosphatase; AST=aspartate aminotransferase; BSA=body surface area; DLCO=diffusing capacity of the lung for carbon monoxide; ECOG=Eastern Cooperative Oncology Group; FEV_1=forced expiratory volume in 1 second; KPS=Karnofsky Performance Scale; LFS =lung function score; LFTs=liver function tests; LPS=Lansky Performance Scale; ROM=range of motion; ULN=upper limit of the normal range.

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none=0, mild=1, moderate=2, severe=3)

Esophageal stricture or web___
Ascites (serositis)___
Myasthenia gravis___
Polymyositis___
Platelets ≥100 x 10^9/L ___
Pericardial effusion___
Nephrotic syndrome___
Cardiomyopathy___
Cardiac conduction defects___
Progressive onset____
Pleural effusion(s)___
Peripheral neuropathy___
Eosinophilia ≥0.5 x 10^9/L ___
Coronary artery involvement___

Others:
Specify:_____

Based on observations checked in the above table, select the severity of chronic GVHD for this assessment.

☐ None

☐ Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see Note), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites).

☐ Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD.

☐ Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

Note: A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.