A PHASE I STUDY OF REDUCED INTENSITY CONDITIONING ALLOGENEIC BONE MARROW TRANSPLANT WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR REFRACTORY SYSTEMIC SCLEROSIS

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Table of Contents

PROTOCOL SYNOPSIS

A Phase I Study of reduced intensity conditioning allogeneic bone marrow transplant with post-transplant cyclophosphamide for Refractory Systemic Sclerosis

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Study Design: This is a Phase I, single arm, open label, single center pilot study to assess a reduced-intensity conditioning regimen, bone marrow transplantation with high dose cyclophosphamide (PTCy) in recipients with refractory systemic sclerosis. The trial includes analyses SSc serum biomarkers of CK, aldolase, and troponin over the one-year study period. The trial also includes periodic monitoring of circulating scleroderma autoantibody titers, autoreactive T cells, and flow cytometric signatures over the one-year study period to correlate with response.

Primary Objective: The primary objective of this study is to assess the safety of using a reduced intensity condition (RIC) preparative regimen bone marrow transplant (BMT) with post-transplant cyclophosphamide for GVHD prophylaxis as treatment for patients with scleroderma. Safety events are (i) grade III-IV acute GVHD; (ii) chronic GVHD requiring systemic immune suppression; and (iii) death by any cause that occurs within 1 year of receiving RIC-alloBMT with post-transplant cyclophosphamide.

Secondary Objective: Secondary objectives are to estimate (i) the event-free survival at 12 months, defined as survival without evidence of scleroderma progression or relapse or any end organ failure as defined by the following: pulmonary function decline ([FVC drop ≥10%] OR [≥5 to <10% decline in FVC AND ≥15% decline in DLCO]), new diagnosis of pulmonary hypertension by right heart cardiac catheterization (mean PAP>25 mmHg), new cardiomyopathy (LV function <30% on ECHO), increase in mRSS by 5 points relative to baseline score, or new renal crisis; (ii) Assess immunosuppression-free survival at 1yr; (iii) disease relapse or progression; (iv) rates of grade 3+ infection or other grade 3+ toxicity according to CTCAE v5; (v) donor cell engraftment (failure to engraft); (vi) hematologic recovery (neutrophil and platelet); and (vii) non-relapse mortality without evidence of scleroderma relapse or progression.

Accrual Objective: The accrual goal for this study is 15 eligible donor/ recipient pairs (30 patients).

Accrual Period: We anticipate an accrual period of two and a half years.

Eligibility Criteria: Patients ≥18 years who are eligible for transplantation according to the BMT Policy Manual, meet the 2013 ACR/EULAR Criteria for Systemic Sclerosis and display active diffuse cutaneous disease will be eligible to participation in this clinical trial.

Lack of response to first line therapy including mycophenolate mofetil at maximum tolerated dose (up to 1.5 grams twice a day (BID) after 10 weeks and/or equivalent degree of immunosuppression/ immunomodulatory therapy with methotrexate, cyclophosphamide, IVIG, or rituximab.

Adequate organ function defined as: 1) left ventricular ejection fraction ≥ 45%; 2) serum creatinine clearance ≥ 40 mL/min/1.73m^2;

Treatment Description: All patients ≥ 18 years of age with moderate-to-severe systemic sclerosis (SSc) will be considered for this trial.
The preparative regimen for RIC alloBMT will consist of:
-Thymoglobulin 0.5 mg/kg IV day -9
- Thymoglobulin 2 mg/kg IV Days -8, -7
- Cyclophosphamide (CTX) 14.5 mg/kg IV Days –6,–5
- Fludarabine 30 mg/m2 IV Days –6, –5, -4, -3,-2
- Total body irradiation (TBI) 400cGy
- Day 0 will be the day of infusion of unmanipulated bone marrow

The GVHD prophylaxis regimen for RIC alloBMT will consist of:
- CTX50 mg/kg IV Days 3, 4 (First dose of Cy 48-72 hours after infusion of marrow)
-Tacrolimus (FK-506) (IV or po) beginning Day 5 with dose adjusted to maintain a trough level of 5-15 ng/mL. Sirolimus may be substituted for tacrolimus in cases of unacceptable tacrolimus toxicity or intolerance of the drug or per institutional practice.
- Mycophenolate mofetil (MMF) 15 mg/kg po TID, maximum dose 1 g po TID beginning Day 5 until Day 35
-Filgrastim (G-CSF) 5 µg/kg SQ daily beginning Day 5 until absolute neutrophil (ANC) is greater than 1000/µl over at least 2 days.

Supportive care for RIC allo-BMT transplantation includes:
- Mesna- 10 mg/kg/ IV Day 3, 4
- Patients will receive infection prophylaxis and treatment according to institutional guidelines.

Study Duration: Patients will be followed for one year after transplantation.

TREATMENT SCHEMA

Days -9 Thymoglobulin 0.5 mg/kg IV
↓
Days -8,-7 Thymoglobulin 2 mg/kg IV qd
↓
Days –6, -5 Fludarabine 30 mg/M2 IV qd
Cyclophosphamide (CTX) 14.5 mg/kg IV qd
↓
Days –4, -3-2 Fludarabine 30 mg/M2 IV qd
↓
Day –1 TBI 400 cGy
↓
Day 0 Infuse unmanipulated marrow; begin antimicrobial prophylaxis.
↓
Days 3, 4 CTX 50 mg/kg IV q d Mesna
40 mg/kg IV q d
(First dose of CTX 48-72 hours after infusion of marrow)
↓
Day 5 Begin FK-506 and MMF and G-CSF
↓
Day 30 Assess Chimerism in peripheral blood
↓
Day 35 Discontinue MMF
↓
Day 60 Assess Chimerism in peripheral blood
Evaluate disease
↓
Day 180 Discontinue FK-506
Evaluate disease
Assess Chimerism in peripheral blood
↓
1 yr. Evaluate disease
Assess Chimerism in peripheral blood

1. OBJECTIVES

Primary Objectives

The primary objective of this study is to assess the safety of using a reduced intensity condition (RIC) preparative regimen bone marrow transplant (BMT) with post-transplant cyclophosphamide for GVHD prophylaxis as treatment for patients with scleroderma. Safety events include: (i) grade III-IV acute GVHD; (ii) chronic GVHD requiring systemic immune suppression; and (iii) death by any cause that occurs within 1 year of receiving RIC-alloBMT with post-transplant cyclophosphamide.

Secondary Objectives

Secondary objectives are to estimate (i) event-free survival at 12 months; (ii) immunosuppression-free survival at 12 months; (iii) disease relapse or progression; (iv) rates of grade 3+ infection or other grade 3+ toxicity according to CTCAE v5; (v) donor engraftment (failure to engraft); (vi) hematologic recovery (failure to achieve hematologic recovery); and (vii) non-relapse mortality.

Definitions:

-Event-free survival will be defined as survival without evidence of scleroderma progression or relapse or any end organ failure as defined by the following: pulmonary function decline ([FVC drop ≥10%] OR [≥5 to <10% decline in FVC AND ≥15% decline in DLCO]), new diagnosis of pulmonary hypertension by right heart cardiac catheterization (mean PAP>25 mmHg), new cardiomyopathy (LV function <30% on ECHO), increase in mRSS by 5 points relative to baseline score, or new renal crisis.

-Non-relapse mortality will be defined as any death without evidence of scleroderma relapse or progression.

-Engraftment will be defined as neutrophil recovery with >95% donor $CD3^+$ T cells detected in peripheral blood.

-Hematologic recovery will be defined as both neutrophil recovery (absolute neutrophil count >0.5 cells/µL for 3 consecutive days) and platelet recovery (platelet count greater than 20 x 10^3/µL for 7 days without transfusion).

Tertiary/exploratory Objectives

Additional exploratory objectives are to estimate: (a) To assess the effects of BMT on skeletal and cardiac muscle using serum biomarkers of CK, aldolase, and troponin over the one-year study period; (b) To assess scleroderma autoantibody titers, autoreactive T cells, and flow cytometric signatures over the one-year study period

2.0 BACKGROUND ANDRATIONALE

2.1 Lack of Curative treatments for adults with systemic sclerosis

Systemic sclerosis (scleroderma) is a systemic autoimmune disease associated with high morbidity and mortality, with an estimated prevalence of 50-300 per million persons/year and incidence of 2.3-22.9 per million persons/year[1-2]. Currently there exists no cure for scleroderma, and medical management is entirely off-label, with no FDA approved drugs for this condition. Treatment is based on symptom management focused on the specific organ system affected such as the lung, skin, musculoskeletal, cardiac, renal, or gastrointestinal systems.

High-dose chemotherapy followed by autologous BMT or peripheral blood progenitor transplantation (PBSCT) has been proposed as a novel approach to treat severe autoimmune diseases[3-7]. The stimulus to explore this approach emanates from a variety of autoimmune animal models demonstrating marked improvement or complete eradication of autoimmune disease following allogeneic or autologous BMT.

2.2 BMT is a therapeutic option for systemic sclerosis

Within the past twenty years, several studies have reported on the utility and efficacy of treating systemic sclerosis with bone marrow transplantation. In 1997, the first case report was published in Lancet[8].

Subsequent small case series have been published throughout the years with various conditioning regimens and primary end points[9-12]. In more recent years, three randomized controlled trials have been published examining the role for autologous stem cell transplantation (both myeloablative and non- myeloablative) in systemic sclerosis: The ASSIST Trial[13], ASTIS[14], and SCOT[15]. In 2011, a 19 patient randomized Phase II study on non-myeloablative autologous HSCT in systemic sclerosis was published in the Lancet[14]. Peripheral blood stem cells were mobilized using IV cyclophosphamide 2g/m^2 and 10 ug/kg filgrastim. The conditioning regimen was 200 mg/kg IV cyclophosphamide given over four days in addition to antithymocyte globulin 0.5 mg/kg along with IV methylprednisolone 1000 mg. The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial was a 156-patient randomized control trial comparing autologous myeloablative HSCT to intravenous pulse monthly cyclophosphamide. The primary end-point was event-free survival, which was higher in the HSCT arm in the first year (16.5% vs 10.4%). However, at four years, 15 events (19%) had occurred cumulatively in the HSCT group vs 20 events (26%) in the control group[14]. Autologous CD34+ stem cells were mobilized with IV cyclophosphamide 4g/m^2 with filgrastim 10ug/kg per day. The conditioning regimen consisted of IV cyclophosphamide 200 mg/kg over 4 consecutive days and IV antithymocyte globulin 7.5mg/kg over 3 consecutive days with IV methylprednisolone 1 mg/kg.

Most recently, the SCOT trial, a randomized controlled trial of 75 patients comparing CD34+ selected autologous stem-cell transplantation versus monthly IV cyclophosphamide for 12 months, was published in The New England Journal of Medicine[15]. In intention to treat analysis using a composite global score, transplantation was deemed superior. In per-protocol analysis, the transplantation group had a longer event-free survival at 54 months (79% v 50%), p=0.03) and overall survival (86% vs 51%, p=0.02). Treatment-related mortality in the transplantation group was 3% at 54 months and 6% at 72 months, compared with 0% in the cyclophosphamide group. Autologous CD34+ stem cells were mobilized with G-CSF. The conditioning regimen included patients receiving 800 cGy of total body irradiation with pulmonary and renal shields limiting organ exposure to 200 cGy, cyclophosphamide 120mg/kg, and equine antithymocyte globulin 90mg/kg.

A 2009 *EBMT* report on 900 patients with a variety of severe autoimmune diseases transplanted from autologous PBSCT found the 5-year survival was 85% and the progression-free survival 43%, although the rates varied widely according to the type of autoimmune disease[16]. For SSc, the 5-year progression-free survival was 55% with overall survival 94%. High-dose cyclophosphamide-based, non-myeloablative conditioning regimens were used in over 50% of the HSCT cases reported by EBMT/EULAR and the CIBMT[17-18]. A subset analysis between myeloablative and non-myeloablative conditioning regimens demonstrated that myeloablative regimens were associated with an increase in treatment-related mortality and no clear advantage in terms of remission induction and relapse rate. Hence, most investigators now favor non-myeloablative, immunosuppressive conditioning regimens (usually high-dose cyclophosphamide +/- other non-myeloablative agents such as antithymocyte globulin) for HSCT in patients with autoimmune diseases.

2.3 Allo-BMT for systemic sclerosis- conditioning regimens

Interest in improving response rates and decreasing relapse has turned attention more toward allogeneic stem cell transplantation (allo-BMT). The possibility of maintaining control of autoimmunity by means of mixed chimerism in these autoimmune diseases is quite important as well[19]. These patients may not need full engraftment to have disease modification. There is still concern about the morbidity GVHD for these patients in the allogeneic setting as well as a limited number of donors available in this setting. Towards this end, we have developed an approach to BMT using post-transplant cyclophosphamide (PTCy) that allows us to safely perform allogeneic BMT from matched, mismatched, unrelated or haploidentical donors.

Transplant-related mortality, graft-failure and risk of GVHD have been very low with this approach. Furthermore, this approach allows us to greatly expand the donor pool since any patient shares exactly one HLA haplotype with each biological parent or child and half of siblings, an eligible haploidentical donor can be identified rapidly in nearly all cases. There are excellent published results from Bolanos-Meade et al, 2012, a trial in sickle cell disease (J0676) with PTCy and haploidentical donors[21]. Of 17 transplanted patients, 14 from HLA-haploidentical donors, 11 have engrafted durably. Only one patient developed skin-only acute GVHD that spontaneously resolved. No mortality was seen.

2.4 Utilization of post-transplant cyclophosphamide

As mentioned previously, investigators at Johns Hopkins developed a non-myeloablative conditioning regimen for transplantation of marrow from partially HLA-mismatched, or haploidentical, bone marrow utilizing high dose cyclophosphamide. The regimen's main goal, J9966 , was to titrate the dose of pre- and post-transplantation cyclophosphamide (CY), a potent immunosuppressive drug, given in conjunction with pre-transplantation fludarabine and total body irradiation (TBI), to achieve a regimen that had an acceptably low risk of graft rejection and GVHD, the two major complications of haploidentical bone marrow transplantation (BMT). All patients received mycophenolate mofetil (MMF) and tacrolimus (FK), beginning on day 4 or 5 and terminating on days 35 and 50-180, respectively, to reduce the incidence and severity of GVHD. Of 18 evaluable patients, 13 patients had donor engraftment on day 60, but accrual of patients to this dose level was stopped because 8/13 patients developed severe GVHD, an incidence convincingly in excess of the stopping criterion of 20%. To reduce the incidence of GVHD, a third cohort of patients received an additional dose of CY 50 mg/kg IV on day 4, and MMF dosing was increased from twice a day (BID) to three times a day (TID) , based upon pharmacokinetic data suggesting the need for more frequent dosing. Of the 16 patients who were followed up to 100 days for relapse, 8 relapsed at a median of 64 days (range 24-~100) after transplantation, and 6 patients were alive and disease free at a median of 206 days (range, 100-429 days [as of Feb 8, 2014]) following BMT[21, 25].

The published data from HLA-haploidentical donor transplantation developed by Johns Hopkins that utilizes T-cell replete grafts and post-transplant Cyclophosphamide (Haplo-post-HCT-CY) to control post-transplant allo-reactivity appears to have overcome many of the obstacles historically associated with haploidentical donor transplantation. In particular, treatment related mortality (TRM) rates of <10% are usual and rapid reconstitution of immunity leads to a low rate of post-transplant infections and no post-transplant lymphoproliferative disorders (PTLD), consistent with the hypothesis that post-transplant CY selectively depletes proliferating alloreactive T cells responsible for GVHD and graft rejection while preserving resting memory T cells essential for post-transplant immunologic recovery[26]. This suggests that this treatment regimen can be considered a valid standard-of-care in patients who lack conventional donors and may be as safe as HLA-identical sibling BMT after myeloablative conditioning, and further, may be considered a reasonable treatment option for patients who have severe autoimmune disease like systemic sclerosis. Moreover, as cancer relapse is not a concern in the setting of systemic sclerosis, engraftment with non-myeloablative hematopoietic stem cell transplantation utilizing post-transplant high dose CY could be curative.

These preliminary data from past studies have relied upon the administration of donor marrow in lieu of mobilized peripheral blood stem cells, which is an important consideration in this non-malignant condition. The use of mobilized peripheral blood stem cells for malignant and non-malignant diseases is associated with higher risk of chronic GVHD compared to bone marrow. In this setting, chronic GVHD is known to add to the burden of morbidity and mortality. In particular, for non-malignant diseases where there is not a need for graft versus tumor effect, there are no advantages to transplantation of peripheral blood. In patients with severe aplastic anemia, the most common non-malignant indication for transplantation, chronic GVHD risks are higher after transplantation of peripheral blood compared to bone marrow and mortality risks are higher after transplantation of peripheral blood from HLA-matched sibling and HLA-matched unrelated donors[27].

From these results, we concluded the following:

1) Post-transplantation immunosuppression with high dose cyclophosphamide, tacrolimus, and thrice daily MMF has been associated with an acceptably low incidence of graft rejection, severe acute GVHD, and extensive chronic GVHD, while allowing prompt engraftment.

2) In addition to controlling HLA-haploidentical alloreactivity, there was effective clinical immune reconstitution as demonstrated by the low incidence of severe opportunistic infections.

3) Relapse is the major cause of treatment failure in this population of patients with mostly poor risk hematologic malignancies. A major potential advantage of employing this approach to non-malignant diseases such as systemic sclerosis is that the risk of relapse is exceedingly low. In essence, engraftment without significant GVHD cures the disease.

Given our promising results in the nonmyeloablative haploidentical setting, including a low incidence of engraftment failure, severe acute GVHD, extensive chronic GVHD, and NRM utilizing PTCy, this trial will employ an ATG + fludarabine + cyclophosphamide conditioning along with PTCy on days +3 and +4 for patients with refractory systemic sclerosis (SSc). The purpose of this regimen is to improve the salvage rate for patients with refractory SSc through a reformatting of the immune system.

Given that there are responses of SSc to immunosuppressive therapy in some form, eligible patients will be required to have experienced disease progression despite at least one course of immunosuppressive therapy. In general, this will be defined as progression of skin or lung disease despite optimal courses of therapy or failure to tolerate therapeutic doses of immunosuppressive therapy. A priority will also be placed on male donors over female donors, when both are available. Potential donors will be excluded if they report a history of autoimmunity. The rationale for this comes from the knowledge that gender, a genetically controlled factor, plays a role in the incidence of autoimmune disease[20].

Hypothesis:
For patients with SSc who are considered ineligible for standard therapies, treatment comprising of reduced intensity bone marrow transplantation will significantly increase the percentage of patients who are free from disease progression at 1 year after transplantation.

3.0 DRUG INFORMATION

3.1 Thymoglobulin®

Thymoglobulin is a rabbit preparation of anti-thymocyte globulin (ATG). Common side effects include nausea, fever, chills, diarrhea, rash, dizziness, headache and tiredness. More serious side effects can include severe allergic reaction, serum sickness, easy bleeding/bruising, fast/irregular heartbeat, joint/muscle pain, stomach/abdominal pain, and weakness. Because this drug works by weakening the immune system, it lowers the ability to fight infections. No dose adjustments are required.

3.2 Cyclophosphamide(Cytoxan®)

Cyclophosphamide is commercially available. Cyclophosphamide is an alkylating agent which prevents cell division primarily by cross-linking DNA strands. Cyclophosphamide is cell cycle nonspecific.
Cyclophosphamide for injection is available in 2000 mg vials which are reconstituted with 100 ml sterile water for injection. The concentration of the reconstituted product is 20 mg/ml. The calculated dose will be diluted further in 250-500 ml of Dextrose 5% in water. Each dose will be infused over 1-2 hr (depending on the total volume). Clinical toxicities of cyclophosphamide include alopecia, nausea and vomiting, headache and dizziness, hemorrhagic cystitis, cardiotoxicity, immunosuppression, myelosuppression, pulmonary fibrosis, increased hepatic enzymes and syndrome of inappropriate anti-diuretic hormone (SIADH). Cyclophosphamide will be dispensed by the Oncology Pharmacy and is produced by Mead Johnson Pharmaceuticals.

3.3 Mesna (sodium-2-mercapto ethanesulphonate)

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxasophosphorines (cyclophosphamide and ifosphamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxasophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxasophosphorines. Mesna is available in 200 mg, 400 mg and 1000 mg vials containing a 100 mg/ml solution. Each dose of mesna will be diluted further in 50 ml of normal saline to be infused over 15 min or as per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of mesna is equal to 80% of the total daily dose of cyclophosphamide. At the doses used for uro-protection mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue. Mesna will be dispensed by the Oncology Pharmacy and is produced by Mead Johnson Pharmaceuticals.

3.4 Fludarabine

Fludarabine phosphate is commercially available.
Fludarabine phosphate is purine antimetabolite that, after administration, undergoes rapid conversion in plasma to the nucleoside 2-fluoro ara-A (F-araA). F-araA subsequently enters cells where it is phosphorylated to F-araATP and the monophosphate F-araAMP. Once activated, F-araATP inhibits DNA polymerase and ribonucleotide reductase. The monophosphate F-araAMP, once incorporated into DNA, is an effective DNA chain terminator.
Fludarabine monophosphate, 50 mg/vial, is reconstituted with 2 ml of sterile water, resulting in a 25mg/ml solution. The desired dose is further diluted in normal saline or 5% dextrose (50-100ml) for injection and will be administered by IV infusion over 30 minutes or longer. in a dose of 30 mg/m2/day on days -6 to -2. Fludara® will be dispensed by the Oncology Pharmacy and is produced by Berlex Pharmaceuticals.

Clinical toxicities of fludarabine monophosphate include: myelosuppression, primarily lymphopenia and granulocytopenia, alopecia, rash, dermatitis, nausea, vomiting, anorexia, stomatitis, diarrhea, somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness, hepatocellular toxicity with elevation in serum transaminases, and interstitial pneumonitis. These effects are reversible when the drug is discontinued.
Fludarabine may cause dose-related CNS toxicity, including the posterior reversible encephalopathy syndrome (PRES), acute toxic leukoencephalopathy (ATL) and other leukoencephalopathy conditions (OLE). PRES is usually reversible with supportive care. Typical clinical features include seizures, persistent headache, and vision changes, accompanied by variable mental status alterations. Patients with ATL can

present with cognitive dysfunction, decreased levels of consciousness, and vision changes. Other leukoencephalopathy (OLE) includes patients who behave similar to the ATL group, but with less prominent deep white matter changes on MRI. Both ATL and OLE are less likely to be reversible [29].

3.5 Tacrolimus

Tacrolimus, also known as FK-506, is a macrolide immunosuppressant. It inhibits lymphocytes by forming a complex with FKBP-12, calcium, and calmodulin, leading to the decrease in the phosphatase activity of calcineurin. This drug is used with corticosteroids for prophylaxis of organ rejection in patients receiving allogeneic liver transplants. Its use is also currently being investigated in kidney, bone marrow, cardiac, pancreas, pancreatic islet cell and small bowel transplantation. This drug is well-absorbed orally. It is metabolized in the liver by unknown mechanisms, but demethylation and hydroxylation have been proposed based on *in vitro* studies. Beginning Day 5, tacrolimus (IV or PO) will be dose adjusted to maintain a trough level of 5-15 ng/mL. Sirolimus may be substituted for tacrolimus in cases of unacceptable tacrolimus toxicity or intolerance of the drug or per institutional practice. Nephrotoxic drugs, antifungals, calcium channel blockers, cimetidine, danazol, erythromycin, methyl prednisone and metoclopramide increase the bioavailability of FK-506. In contrast, phenobarbital, phenytoin, rifamycins and carbamazepine decrease FK-506 levels. Adverse reactions include tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction.

3.6 Mycophenolate Mofetil(CellCept®)

Mycophenolate Mofetil (MMF){ is an ester prodrug of the active immunosuppressant mycophenolic acid (MPA) and are used along with tacrolimus as part of GVHD prophylaxis regimen after transplant. This active metabolite is a noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). 15 mg/kg of MMF will be given PO TID, with a maximum dose 1 g po TID beginning Day 4 or 5 until Day 35. Side effect profiles include diarrhea, leukopenia, sepsis, allergic reactions, and vomiting. There is also an increase in certain types of infection mainly from the herpes virus family (CMV, HSV & VZV) and candida. There are no pharmacokinetic interactions with ganciclovir, cotrimoxazole, oral contraceptives and cyclosporine.

3.7 Filgrastim (G-CSF)

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing and the increased expression of some functions associated with cell surface antigens. The product is available in single use vials and prefilled syringes. The single use vials contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 1.0 mL or 1.6 mL, respectively. The single use prefilled syringes contain either 300 mcg or 480 mcg Filgrastim at a fill volume of 0.5 mL or 0.8mL, respectively.

The most common side effects of filgrastim injection are bone pain, muscle pain and headaches. These symptoms can usually be relieved by non-aspirin analgesics such as acetaminophen. Nausea, fatigue and low-grade fevers have been reported. Some patients experience swelling, erythema or itching at the injection site. Rare but serious adverse events associated with filgrastim include splenic rupture and acute respiratory syndrome, both associated with the rapid proliferation of neutrophils. Filgrastim has not been studied in pregnant women and its effect on the developing fetus is unknown.

For further information on the risks associated with filgrastim, please refer to the filgrastim drug label at the following website: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3bc802bd-76b4-4f45-8571-a436ec26228e

3.8 Sirolimus

Sirolimus is an immunosuppressant that inhibits cytokine-stimulated T-cell activation and proliferation, and also inhibits antibody formation. The most common adverse reactions of sirolimus are: peripheral edema, hypertriglyceridemia, hypercholesterolemia, hypertension, increased creatinine, constipation, abdominal pain, nausea, diarrhea, headache, fever, urinary tract infection, anemia, thrombocytopenia, arthralgia, pain.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

Recipient

All patients with moderate-to-severe SSc will be considered for this trial, including women and minorities. SSc is too rare a disease in children for it to be feasible to include them. Patients must meet the following criteria to be eligible for participation in this clinical trial:

1) 2013 ACR/EULAR Criteria for Systemic Sclerosis

2) Active diffuse cutaneous disease with an mRSS ≥ 20 – including increasing skin score, new body areas involved, increased thickening in previously affected body areas, severe pruritus, tendon friction rubs OR concern for active interstitial lung disease (ILD) with FVC<70% of predicted, new fibrosis/GGO on HRCT, and/or falling FVC >10% of predicted

3) Lack of response to first line therapy including mycophenolate mofetil at maximum tolerated dose (up to 1.5 grams BID) after 10 weeks and/or equivalent degree of immunosuppression/immunomodulatory therapy with MTX, CYC, IVIG, or rituximab. Lack of response can include physician judgement based on review of records and patient report.

4) Age ≥18 years and ≤ 65 years

5) Patients should be eligible for transplantation according to the BMT Policy Manual.

6) Female patients (unless postmenopausal for at least 1 year before the screening visit, or surgically sterilized), agree to practice two (2) effective methods of contraception at the same time, or agree to completely abstain from heterosexual intercourse, from the time of signing the informed consent through 12 months post-transplant. Effective birth control is defined as the following:
   - Abstinence
   - Consistently use birth control pills or patch

- Use injectable birth control (for example, Depo-Provera or Norplant)
- Have tubal sterilization
- Have placement of an IUD

7) Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have vaginal sex. Male patients (even if surgically sterilized), of partners of women of childbearing potential must agree to one of the following methods of contraception or abstain from heterosexual intercourse from the time of signing the informed consent through 12 months post-transplant.

   Effective birth control methods include:

   - Abstinence
   - Vasectomy or female partner who had a tubal ligation
   - Use of condoms with contraceptive foam

8) Adequate organ function[a], defined as:
   a. Cardiac: Left ventricular ejection fraction (LVEF) at rest ≥ 45% without evidence of pulmonary arterial hypertension (defined as resting pulmonary arterial systolic pressure [PASP] > 40 mmHg or mean pulmonary arterial pressure [mPAP] > 25 mmHg).
   b. Hepatic: Total bilirubin ≤ 3.0 x the upper limit of normal (ULN) (patients who have been diagnosed with Gilbert's Disease are allowed to exceed this limit) and AST and ALT ≤ 2.0 x ULN (patients with elevated transaminases attributed to skeletal muscle involvement are allowed to exceed this limit).
   c. Renal: estimated creatinine clearance ≥ 40 mL/minute (using the Cockcroft-Gault formula and actual body weight).
      - Cockcroft-Gault formula, based on ideal body weight (IBW):

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{IBW (kg)} \times 0.85 \text{ for females}}{P_{Cr} \times 72}$$

   d. Pulmonary: DLCO (corrected/adjusted for hemoglobin) ≥ 40% **and** FEV1 > 50% predicted (without administration of bronchodilator) **and** FVC ≥ 50% predicted.

   [a]Patients not meeting eligibility for adequate organ function may still be eligible for the study if deemed reasonably safe and clinically appropriate by the investigator following consultation with the appropriate specialist (e.g., cardiology, nephrology, or pulmonology).

9) Karnofsky performance score ≥70%.

10) Patients with a history of hepatitis B virus (HBV) infection must be on suppressive therapy, if indicated, with undetectable HBV viral load within 6 months.

11) Patients with a history of hepatitis C virus (HCV) infection must have received prior treatment or must be receiving treatment currently with undetectable HCV viral load within 6 months.

Donor

1. HLA-matched or -haploidentical relative of the recipient.
   - Donors will be selected to minimize HLA mismatch in the host-versus-graft (HVG) direction.

   In case there are two or more donors with an equiIn case there are two possible donors with an equivalent HLA mismatch in the HVG direction, donors will next be selected based on the most favorable combination of (i) HLA compatibility in cross-match testing and (ii) ABO compatibility:
   - HLA cross matching (in order of priority):
     1. Mutually compatible (no cross-matching antibodies)
     2. Recipient non-cross-reactive with donor, donor cross-reactive with recipient
     3. Mutually cross-reactive
   - ABO compatibility (in order of priority):
     1. Compatible
        2. Minor incompatibility
        3. Major incompatibility
        42. Minor incompatibility
        3. Major incompatibility
        4. Major and minor incompatibility
   - Donor age, donor-recipient CMV serostatus match, donor weight, donor-recipient sex match will also be considered

2. Eligible as per donor selection in FDA 21 CFR Part1271;

3. Meets all requirements for bone marrow donor selection criteria as described in the standard Johns Hopkins BMT Policies and Procedures. Donors who do not meet one or more of the donor screening requirements may donate under urgent medical need as determined by the principal investigators. Medically healthy with no clinically significant findings in the physical examination, medical history, vital signs which, in the judgment of the investigator, would inappropriately jeopardize the safety of the subject, interfere with study assessments, or impact the validity of the study results;

4. No history of any clinically significant immunosuppressive or autoimmune disease including hematologic malignancy or history of solid organ or allogeneic bone marrow transplantation;

5. Ability to understand and provide informed consent for all study procedures including bone marrow harvest.

4.2 Exclusion Criteria

Recipient

1) Pregnant, breast feeding, or considering becoming pregnant during the course of the study;
2) Requiring IV antimicrobial treatment or hospitalization within 7 days prior to study enrollment for known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds);
3) History of human immunodeficiency virus (HIV) infection;
4) Active or unresolved gastric antral vascular ectasia (GAVE) syndrome;
5) Active or unresolved scleroderma renal crisis;
6) Clinically significant pulmonary hypertension, interstitial lung disease, or other cardiopulmonary disease with inadequate organ function as defined above[a];
7) Any illness or condition which, in the judgment of the investigator, would inappropriately jeopardize the safety of the subject, interfere with study assessments, or impact the validity of the study results;
8) Known malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer;
9) Prisoners or subjects who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness;
10) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements or assessment of immunologic endpoints;
11) History of significant allergic reactions, hypersensitivity, or intolerance attributed to compounds of similar chemical or biologic composition to cyclophosphamide or other agents used in the study.

[a]Patients not meeting eligibility for adequate organ function may still be eligible for the study if deemed reasonably safe and clinically appropriate by the investigator following consultation with the appropriate specialist (e.g., cardiology, nephrology, or pulmonology).

4.3 Criteria for donor eligibility

Donors must meet the donor selection criteria as defined by the JHU BMT Policy Manual- Donor Selection Criteria and will be prioritized per current institutional standards. Refer to Appendix 5 for further detail.

Donor approval and consent must be obtained as per the BMT Policy and Procedures- Allogeneic Donor Consent policy which can also be found in Appendix 6.

5.0 TREATMENT PLAN (All patients with refractory systemic sclerosis)

5.1 Indwelling central venouscatheter

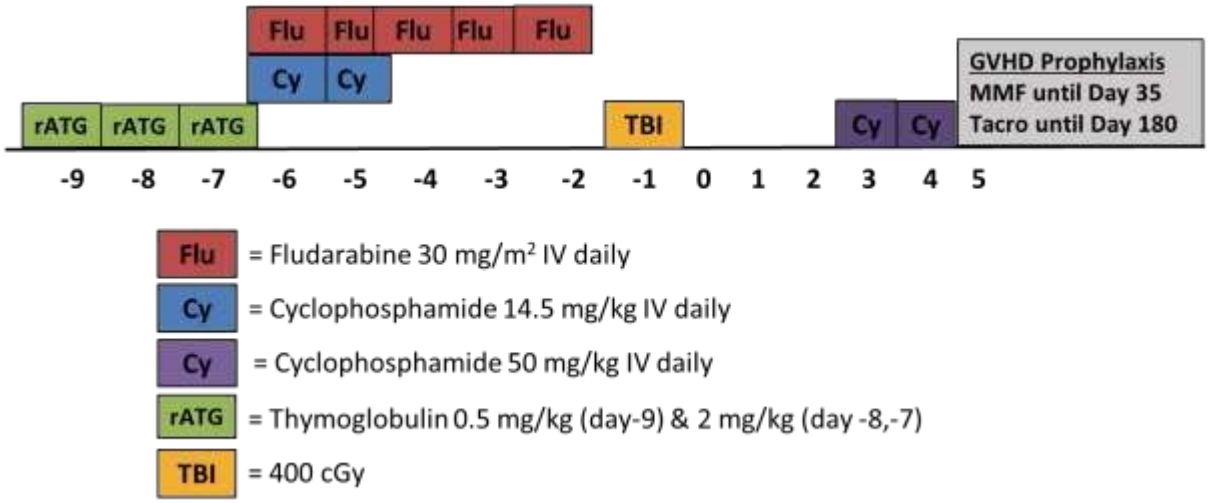
Placement of a double lumen central venous catheter will be required for transplantation and administration of IV medications and transfusion of blood products, as per standard BMT requirements. This catheter may be removed and replaced as clinically indicated

5.2 Pre-treatment Evaluation

All patients will require documentation of a detailed history and physical examination and standard BMT evaluation of cardiac, pulmonary, liver and renal function.

All patients will undergo a bone marrow aspirate and biopsy for morphological, cytogenetic and flow cytometric evaluation.

5.3 Preparative Regimen and GVHD Prophylaxis



5.3.1 Preparative regimen administration

Thymoglobulin® preparation of ATG will be dosed by actual body weight. On day -9, thymoglobulin 0.5 mg/kg is administered and 2 mg/kg on day -8 and day -7. The dose will be 0.5 mg/kg IV on day -9 over 6 hours and 2mg/kg IV on days -8 and -7 over 4 hours. Premedication should follow local institutional practice, but should include a minimum of 1 mg/kg methylprednisolone in children or 100 mg in adults prior to the infusion (equivalent steroid allowed), preferably repeated in 3-4 hours during the infusion.

Fludarabine will be administered by intravenous infusion over 30 min. on D-6 to D-2. The dose will be 30 mg/m2 but may be reduced due to renal impairment per current institutional guidelines.

Cyclophosphamide will be administered as an IV infusion over 1- 2 hr, (depending on volume) on D-6 and D-5. The dose of pre-transplantation cyclophosphamide is 14.5 mg/kg/day. Dose is calculated based on the adjusted ideal body weight or actual body weight whichever is less. (Refer to Appendix 2.) Body weight and height are measured directly. An approximate weight for height would be calculated from a standard table or equations that reflect ideal "values".

Total body irradiation: 400 cGy AP/PA with 4MV or 6MV photons at 8-12 cGy/min at the point of prescription (average separation of measurements at mediastinum, abdomen, hips) will be administered with lung shielding in a single fraction on day -1.

A day of rest may be added after the preparative regimen cyclophosphamide doses and prior to bone marrow infusion depending on donor availability, operating room schedules, and as clinically indicated.

5.3.2 Marrow processing and infusion

Unmanipulated marrow will be infused on Day 0. Guidelines for the infusion of bone marrow have been established and are outlined in the ABO compatible/ minor mismatched allo BMT or the ABO incompatible allo BMT standing orders. The marrow infusion will be done by designated members of the BMT team. The bone marrow graft will not be manipulated to deplete T cells. The donor will be harvested with a target yield of 4 x 10^8 nucleated cells/kg recipient IBW. The lowest acceptable yield is 1.5 x 10^8 nucleated cells/kg. The CD 34+, CD4+, CD8+, and CD3+cell count in the marrow will be quantified by flow cytometry.

5.3.3 Post-transplantation cyclophosphamide

Cyclophosphamide will be given at a dose of 50 mg/kg/day as an IV infusion over 1-2 hrs (depending on volume) on day +3 (between 60 and 72 hours after marrow infusion) and day +4(24 hours after Day 3 cyclophosphamide). Hydration prior to cyclophosphamide may be given according to institutional standard, with patients being instructed to increase fluids overnight before cyclophosphamide administration. Dosing of cyclophosphamide is based on ideal body weight for subjects whose ideal body weight is less than or equal to his/her actual body weight. On occasion, a subject's actual body weight may be less than his/her ideal body weight, in which case cyclophosphamide will be dosed using the subject's actual body weight. Cyclophosphamide [50mg/kg (IBW)] will be given on D+3 post-transplant (within 48-72 hours of marrow infusion) and on D+4 post-transplant. Cyclophosphamide will be given as an IV infusion over 1- 2 hr (depending on volume). Hydration may be administered per current institutional guidelines.

Mesna will be given to prevent hemorrhagic cystitis at 10 mg/kg/dose IV 30 min pre- and at 3, 6, and 8 or 9 hours post-cyclophosphamide. MESNA dose will be based on the cyclophosphamide dose being given. The total daily dose of MESNA is equal to 80% of the total daily dose of cyclophosphamide. Urine output over 2 hr will be checked before administering cyclophosphamide and must be at least 3.0 mL/kg. Urine output must be maintained post cyclophosphamide, as per BMT standards. Urinalysis will be performed to detect evidence of hemorrhagic cystitis,

5.3.4 GVHD prophylaxis

On Day +5, patients will begin prophylaxis with tacrolimus and Mycophenolate Mofetil (MMF) per institutional standard. Tacrolimus dose is adjusted to maintain a serum trough level of 10 – 15 ng/mL, with a minimum acceptable trough level of 5 ng/mL. Serum trough levels should be checked weekly thereafter

and the dose adjusted accordingly to maintain a level of 5-15 ng/ml. Sirolimus may be substituted for tacrolimus in cases of unacceptable tacrolimus toxicity or intolerance of the drug. Tacrolimus prophylaxis will be discontinued after the last dose on Day 180. MMF prophylaxis will be discontinued after the last dose on Day 35.

5.4 Infection prophylaxis and therapy

Patients will receive infection prophylaxis and treatment according to institutional guidelines. Bacterial, fungal, and viral prophylaxis will start on Day 0. Patients will be monitored for viral infections and reactivations per institutional standard.

Post-transplantation immunizations will be given per institutional standard.

5.5 Transfusion support

Platelet and packed red cell transfusions will be given per current institutional recommendations.

5.6 Anti-ovulatory treatment

Females of child bearing potential should be started on an anti-ovulatory agent per institutional practices (recommended agent is Lupron) prior to the initiation of the preparative regimen.

5.8 Management of Slow Engraftment and Graft Failure

Slow engraftment or graft failure shall be managed according to institutional practices, and may include the administration of colony stimulating factors and prophylactic antibiotics.

6.0 DATA MONITORING AND MANAGEMENT

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

This is a high risk study under the SKCCC CRO Data and Safety Monitoring Program (DSMP) version 6.0. External data monitoring of this protocol by the SKCCC CRO QA Department will be prospectively monitored at least annually. Additionally, the protocol will be monitored by the study investigators on a routine basis. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC). The SMC is responsible for continuous, ongoing review of the conduct of all trials, including adherence to study design, documentation of appropriate review, and proper reporting of protocol problems and events as defined in the SKCCC DSMP version 6.0.

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

6.1 Monitoring review plan

The protocol will be monitored internally by the co- principal investigators. The investigators will review data to assure the validity of data, as well as, the safety of the subjects through internal data review. They will also monitor the progress of the trial. The investigators will be responsible for maintaining the clinical protocol.

The principle investigator will be responsible for reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the annual report submitted to the IRB and to the trial monitoring review group.

Content of the annual report at a minimum should include year-to-date and full trial data on accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR reports, response, survival, regulatory compliance, compliance with prearranged statistical goals. The report should be submitted in a timely manner according to the schedule defined by the SKCCC Clinical Research Office. The trial should be placed on hold or closed if there is non-compliance with this reporting. This report serves as the annual report for the IRB.

The Protocol Chair and SMC will periodically review safety data. Enrollment of participants in the trial will be suspended at any time if any of these reviews concludes that there are significant safety concerns.

6.2 Adverse Event Reporting

6.2.1 Overview

The Principal Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE (adverse event) or SAE (serious adverse event) as described in sections 6.2.1.1 and 6.2.1.2 in this protocol. All AEs and SAEs will be recorded in the source documents and on the appropriate electronic CRF(s). All data will be reviewed periodically by the DSMB, which may provide recommendations about withdrawing any participant and/or terminating the study because of safety concerns.

Adverse events that are classified as serious according to the definition of health authorities must be reported promptly and appropriately to the Principal Investigator, the IRB and health authorities. This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording and reporting them. Information in this section complies with 21CFR 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH Guideline E-6: Guidelines for Good Clinical Practice; and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events, Version 5.0 (November 27, 2017**).**

All adverse events will be reported to JHU Institutional Review Board.

6.2.2 Definitions

An AE is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial. An AE for the recipient will be followed until it resolves or until 30 days after the recipient terminates from the study, whichever comes first. An AE for the donor will be followed until it resolves or until 48 hours after the final donor study visit, whichever comes first. All AEs will be reported as specified in section 6.5.2 whether they are or are not related to disease progression or study participation.

6.2.2.1 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

6.2.2.2 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or SAR is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes:

- Death: A death that occurs during the study or that comes to the attention of the Principal Investigator receives the first dose of study medication until 30 days following cessation of treatment must be reported whether it is considered treatment- related or not.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of the Investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2.2.3 Unexpected Adverse Events

A SAR is considered "unexpected" if it is not identified in the package insert and/or drug label, or protocol, or is not listed at the specificity, or severity that has been observed (21 CFR 312.32(a)).

6.3 Collecting and Recording Adverse Events

Methods of Collection

Adverse events for recipients will be collected from the time the participant receives the first dose of study medication until 30 days following cessation of treatment. Adverse events will be followed until the time an event is resolved or until 30 days after the recipient completes or terminates from the study, whichever comes first. The methods for collecting AEs will include:

- Observing the participant.
- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

Adverse Events

All AE grades will be defined per NCI-CTCAE version 5.0 criteria unless otherwise specified.

Recipient

With the following exceptions, all AEs of grade 3 or higher will be collected from the time at which the participant undergoes transplantation until the time the participant completes or prematurely withdraws from the study:

- During the first 30 days post-transplant, expected hematological abnormalities associated with the non-myeloablative conditioning regimen, such as cytopenias, will not be collected as AEs. Neutrophil recovery will be defined as the first day of three consecutive lab values on different days, after the conditioning regimen-induced nadir of blood counts, that the absolute neutrophil count is > 500/µL. Platelet recovery will be defined as the first day of three consecutive lab values on different days, after the conditioning regimen-induced nadir of blood counts, that the platelet count is ≥ 20,000 µL without platelet transfusion support in the seven days prior.

To monitor this, participants will undergo frequent complete blood counts. Delayed hematological recovery will be captured as an AE as follows:

- Hematological abnormalities will be collected as AEs per NCI-CTCAE v. 5.0 criteria once participants have achieved platelet and neutrophil recovery.
- All episodes of allograft rejection as defined in section 6.3 and grade III-IV GVHD as defined in section 6.3 will be collected as AEs.

Donor

Serious Adverse Events

Serious AEs, regardless of grade, will be collected from the time at which the recipient receives the first dose of thymoglobulin until 30 days after the recipient completes, or prematurely terminates, from the study. Serious AEs, regardless of grade, will be collected from the time the donor undergoes donation until 48 hours after the final donor study visit.

6.4 Recording Method

6.4.1 **Adverse Events**

Throughout the study, the Investigator will record AEs on the appropriate eCRF regardless of their relation to study participation. The Investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

6.4.2 **Serious Adverse Events**

Serious AEs will be recorded and health authorities will be notified as outlined in section 6.5.2.

6.5 Grading and Attribution of Adverse Events

6.5.1 Grading Criteria

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 5.0* (published November 27, 2017). This document (referred to herein as the "NCI-CTCAE v. 5.0 manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs.

Severity of adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE v. 5.0 manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.

For additional information and a printable version of the NCI-CTCAE v. 5.0 manual, go to https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Attribution Definitions

Adverse events will be categorized for their relation to one or more of the following:

- Preparative regimen
- Post BMT medication toxicities bone marrow transplantation
- immunosuppression discontinuation including discontinuation of mycophenolate compounds, tacrolimus or sirolimus
- other protocol-directed study procedures

The Principal Investigator will do the initial determination of the relation, or attribution, of an AE to study participation and will record the initial determination on the appropriate eCRF and/or SAE reporting form. The relation of an AE to study participation will be determined using definitions in the Attribution of Adverse Events Table below .

Attribution of Adverse Events Table

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy)
Unrelated Categories		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.

6.5.2 Reporting Serious Adverse Events

The Principal Investigator is required to notify the Institutional Review Board (IRB) of a serious adverse event according to institutional policy. The requirements for IRB Protocol Problem Reporting at Johns Hopkins are can be found at this website:
http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/

From the time of consent through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described below. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described below.

Adverse events that will be reported should include: any mortality within the study period, and all unexpected events as deemed significant by the PIs. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Unexpected, grade 3-5 adverse events (AE) will be reported via an Adverse Event Report form to the

investigators. Unexpected Grade 3 adverse events must be reported within 3 business days of knowledge of the event. Unexpected, grade 4-5 AEs must be reported via an adverse event report form to the PI within one working day of discovery or notification of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 at regular intervals as defined in the patient monitoring section (section 7.0).

Any unexpected, either life threatening or fatal adverse event must be reported within 7 working days to the Johns Hopkins Institutional Review Board (IRB). Otherwise, unexpected serious adverse events must be reported within 15 days. The study staff will assume responsibility for reporting to the CRO and IRB, and to other investigators.

6.5.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol, certain AEs/grades do not require expedited reporting. The following AEs must be reported through the routine reporting mechanism.

Adverse Events	CTCAE v5.0
Anemia	Anemia
Leukopenia	White blood cell decreased
Neutropenic Fever	Febrile neutropenia with or without hospitalization
Infection	Infection with Grade 3 neutrophils with or without hospitalization
Thrombocytopenia	Platelet count decreased

Grades 3 and 4 adverse events (including hospitalization/prolonged hospitalization) of expected events list do not require expedited reporting:

- Progression of the disease should NOT be reported as an AE/SAE unless it is considered to be drug related by the investigator.
- Hospitalization due to signs and symptoms of disease progression does NOT require reporting as an SAE.

6.5.4 Reporting Protocol Deviation

The term "protocol deviation" is not defined by either the HHS human subjects regulations (45 CFR 46) or the FDA human subjects regulations (21 CFR 50). For JHM purposes, a protocol deviation is a minor or administrative departure (see definitions below) from the protocol procedures approved by the IRB that was made by the PI without prior IRB approval. Please note: Eligibility exceptions

for enrollment of a specific individual who does not meet the inclusion/exclusion criteria in the IRB approved protocol are not deviations. Eligibility exceptions are considered changes in research that require IRB review and approval before a subject who does not meet the approved protocol inclusion/exclusion criteria may be enrolled.

Reporting Protocol Deviations to the JHM IRB

There are several types of deviations from protocol procedures recognized by the JHM IRB, and each type has a different IRB reporting requirement:

A. Protocol deviations that constitute unanticipated problems involving risks require prompt reporting to the JHM IRB: A protocol deviation that constitutes an "unanticipated problem involving risks to subjects or to others" (see Policy No. 103.6(b) for the definition of an unanticipated problem) must be reported promptly to the IRB, as follows:

1. *Emergency deviations:* When a deviation occurs in an ***emergency situation*****,** such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The Principal Investigator and the reviewing IRB must be notified as soon as possible, but not later than 5 days after the ***emergency*** situation occurred (21 CFR 812.150(a)(4)).

2. *Major, non-emergent deviations without prior approval:* A planned deviation that is non-emergent and represents a major change in the protocol as approved by the IRB. The JHU Principal Investigator and the IRB must approve the request before the proposed change is implemented. If a major, non-emergent deviation occurs without prior IRB approval the event is considered non-compliance. Non-compliance must be reported to the IRB promptly.

B. Protocol deviations that are only minor or administrative: At JHM, minor or administrative protocol deviations are defined as those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." If a protocol deviation occurs which meets this definition, the deviation should be reported to the JHM IRB at the time the continuing review application is submitted. Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

6.6 Toxicity Monitoring

6.6.1 GVHD

A major toxicity of allogeneic BMT is GVHD. Acute graft-versus-host disease (GVHD) shall be graded clinically according to the criteria developed by the consensus conference on acute GVHD[5] (Appendix 3). All suspected cases of acute GVHD should be confirmed histologically by biopsy of an affected organ (skin, liver, or gastrointestinal tract). Diarrhea and/or hyperbilirubinemia in a patient with histologically documented skin GVHD may be assumed to be a manifestation of visceral GVHD and will be graded as such. All patients with histologically documented, clinical grade >2 acute GVHD should receive initial treatment according to institutional preference. If skin GVHD resolves with treatment but suspected

visceral GVHD does not, biopsy of the affected organ (liver or gastrointestinal tract) should be obtained to rule out other causes of hyperbilirubinemia and/or diarrhea. Steroid refractory acute GVHD will be treated according to institutional preferences. Day 60. GVHD summaries will be taken weekly from the standard histories and physicals performed from Day 14 through Day 60.
The following information shall be collected on all patients with acute GVHD:

- Date of onset (defined as the date of first biopsy confirming GVHD)
- GVHD evaluation form at the time of onset, weekly until GVHD resolves, and Day 60 (see appendix 5)
- Initial overall clinical grade
- Maximum overall clinical grade
- Date of onset of grade III-IV acute GVHD, if any
- Chronic graft-versus-host disease (cGVHD) shall be graded clinically according to the criteria developed by the NIH consensus conference on chronic GVHD48 (Appendix 4).

All suspected cases of chronic GVHD should be confirmed histologically by biopsy of an affected organ whenever possible. Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung), 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. The following information shall be collected on all patients with chronic GVHD:

- Date of onset (defined as the date of first biopsy confirming GVHD, if possible or the first day of onset of clinical symptoms if no biopsy is performed)
- GVHD evaluation form at the time of onset (see appendix 4), until GVHD resolves
- Initial overall clinical score
- Maximum overall clinical score

The occurrence and severity of acute and chronic GVHD after Day 60 will be captured at the patients' six month and annual evaluations.

Treatment of GVHD will be the standard of care on the BMT unit at that time.

6.6.2 Transplant-related mortality (TRM)

Causes of TRM, i.e., death in the absence of disease progression, will be documented as important indicators of procedure-associated toxicity, particularly as these causes relate directly or indirectly to GVHD. Analysis will stratify mortality with respect to the peri-transplant period of 100 days post-BMT or later times post-BMT.

6.7 Data Management

Data will be maintained on case report forms and appropriate Graft Engineering Laboratory spreadsheets. The clinical transplant team will make assessments of GVHD. Hematopoietic engraftment will be assessed by the BMT attending and the investigators. The investigators will be responsible for evaluation of chimerism data and overall toxicities.

7.0 PATIENT MONITORING

The following parameters will be obtained according to this schedule:
(for details of these evaluations, see text sections 7.1-7.3, or additional sections when indicated)

Study Assessments/Testing	Baseline[a]	Day 30 +/-7	Day 60 +/-7	Day 90 +/- 7[h]	Day 180 +/- 21	Day 270 +/- 21[h]	Day 365 +/- 30	Suspected GVHD
History and Physical	X	X	X		X		X	
Performance status	X							
CBC with differential [b]	X	X	X		X		X	
Comprehensive Metabolic Panel [c]	X	X	X		X		X	
Sinus CT	X							
CXR	X		X					
Pregnancy test in women of child bearing age	X							
PT/PTT	X							
ECG	X							
MUGA or ECHO	X						X	
Infectious disease testing [d]	X							
Creatine kinase	X	X	X	X	X	X	X	
Aldolase	X	X	X	X	X	X	X	
Troponin I	X	X	X	X	X	X	X	
Toxicity assessment	X	X	X	X	X		X	
HLA typing/lymphocytotoxic screen	X							
PFTs (Spirometry and DLCO)	X				X[h]		X[h]	
Donor marrow or blood for VNTR or RFLP analysis[i]	X							
Patient blood for baseline VNTR or RFLP analysis[i]	X							
Peripheral blood chimerism, both total leukocyte (unsorted) and T-cell sorted		X	X		X		X	
GVHD and morbidity assessments [e]		X	X	X	X	X	X	
Lymphocyte subsets	X		X					
Skin biopsy [h]	X			X[f]	X[f]	X[f]	X[f]	X

Study Assessments/Testing	Baseline[a]	Day 30 +/-7	Day 60 +/-7	Day 90 +/- 7[h]	Day 180 +/- 21	Day 270 +/- 21[h]	Day 365 +/- 30	Suspected GVHD
Patient research blood [h]	X	X	X	X	X	X	X	
PRO Measures [g,h]	X	X	X	X	X	X	X	
Modified Rodnan Skin Score[e]	X	X	X	X	X	X	X	
Tendon Friction Rub[h]	X	X	X	X	X	X		
CRISS Score[h]	X			X	X	X	X	
Euroline IgG Scleroderma Profile[h]	X	X	X	X	X	X	X	

[a] Baseline evaluations should occur within 30 days before initiation of conditioning therapy, with the exception of the following: cardiac and pulmonary evaluations may occur ≤ 8 weeks prior, and the HLA typing and baseline studies for chimerism determinations may occur at any point prior. Results of evaluations performed before study entry as standard of care may be used for research purposes and to fulfill study requirements.

[b]At minimum, CBC/differential should also be performed twice a week from start of BMT preparative regimen, until ANC is >1000/㎕ over course of 3 days, then weekly until 12 weeks post-BMT, and periodically thereafter; those need not be captured in the CRF.

[c]CMP includes: BUN, creatinine, sodium, potassium, chloride, AST, ALT, total bilirubin, alkaline phosphatase. At minimum, these should be performed weekly until 12 weeks post-transplantation, then periodically until off immunosuppression; those need not be captured in the CRF.

[d]Infectious disease evaluations follow institutional standard of care. Minimum evaluations are CMV IgG, HSV IgG, VZV IgG, hepatitis panel (Hep B surface antigen, Hep B core antibody, Hep C antibody), HIV antibody (unless known to be HIV positive), RPR, EBV IgG.

[e]GVHD and other morbidity assessments are also standardly performed weekly at Johns Hopkins until at least ~Day 60. Results of these and subsequent assessments may be collected for research purposes. Patients may be asked to complete GVHD questionnaires.

[f]If no prior positive GVHD biopsy

[g]Patient-reported outcome (PRO) measures listed in Section 7.1.

[h]Performed by the scleroderma team who process and store these samples at Johns Hopkins Bayview Medical Center.

[I] All samples collected for VNTR or RFLP analysis will be sent to Rheumatic Diseases Resource-based Core Center (RDRCC).

7.1 Scleroderma-specific testing:

a) Pulmonary function testing and echocardiogram: Due to the intrinsic nature of scleroderma, both the heart and lungs are at risk of damage independent of the treatment protocol. Thus, it is our practice to obtain serial PFT and ECHO studies every 6-12months.
b) Skin biopsies: Independent of assessing for GVHD, skin biopsies will be performed for research purposes to study the histopathology and gene expression over time pre- and post-transplant.
c) Patient research blood: An additional amount of blood will be obtained for research purposes for biomarker discovery and development.
d) PRO Measures: Several patient-reported outcome measures (PROMs) will be administered throughout the study period to assess the various organs affected by scleroderma.
e) Modified Rodnan Skin Score (MRSS): An objective outcome measure that is used in the majority of scleroderma clinical trials. It is a score assigned by the treating rheumatologist, ranging from 0-51, with higher numbers corresponding to more severe skin involvement.
f) Tendon Friction Rub: A physical exam finding that has prognostic significance for patients with scleroderma.
g) CRISS Score: A composite outcome score used in some international scleroderma cohorts incorporating FVC% predicted (from PFT), MRSS, HAQ-DI (health-assessment questionnaire), and Patient and Physician Global Assessment.
h) Euroline IgG Scleroderma Profile: This is a line blot immunoassay that evaluates several scleroderma-specific and scleroderma-associated autoantibody specificities. Its use is for research purposes only and will be performed in the Rheumatic Diseases Research Core Center (RDRCC).

7.2. Baseline investigations

All patients will require documentation of a detailed history and physical examination. Baseline investigations include:

a) Scleroderma
    i. Modified Rodnan Skin Score (MRSS)
    ii. Tendon Friction Rub (presence/absence)
    iii. PFT with good or moderate quality with spirometry with DLCO
    iv. ECHO (MUGA)
    v. CRISS (Patient and Physician Global VAS, HAQ-DI)
    vi. Baseline PROs:
        (1) Scleroderma Skin PRO (SSPRO)
        (2) Scleroderma Health Assessment Questionnaire (SHAQ)
        (3) Gastrointestinal tract (GIT)
        (4) BORG Dyspnea Index
        (5) MRC Breathlessness Scale
        (6) UCSD Shortness of Breath Questionnaire
    vii. Euroline IgG Scleroderma Profile
    viii. CK, aldolase, troponin I

b) Hematologic
    i. CBC with platelets, differential
    ii. PT, PTT
    iii. ABO and Rh typing

iv. ESR

c) Hepatic
   i. Serum SGOT/AST
   ii. SGPT/ALT
   iii. Alkaline phosphatase
   iv. total and direct bilirubin

7.3 Pre-transplant Evaluation

These represent the basic baseline studies required on all patients prior to starting their preparative regimen. Additional investigations may be clinically indicated in certain individuals. Other baseline studies may be required for the purposes of non-preparative regimen protocols on which the patient is enrolled. In this case, such requirements will be stipulated in the pertinent protocols.

7.3.1 Complete medical history which should include particular attention to the following details:

a) Previous treatment and response
b) Previous transfusions and transfusion reactions
c) Previous serious infections
d) Allergies
e) Current medications
f) Assessment of performance status

7.3.2 Thorough general medical evaluation which should include:

a) A careful physical examination
b) Evaluation for placement of a central venous access device, if the patient does not already have such a catheter.

7.3.3 Baseline investigations including:

a) Completion of all activity indices and responder indices (CRISS)
b) SSc IgG Euroline Panel
c) Peripheral blood mononuclear cells (PBMCs) and serum for exploratory translational studies
d) Hematologic
   i. CBC with platelets, differential, reticulocyte count
   ii. PT, PTT
   iii. ABO and Rh typing
   iv. Bone marrow aspirate and biopsy
e) Chemistries
   i. Comprehensive chemistry panel
   ii. CK, aldolase
f) Renal
   i. Routine microscopic urinalysis with C&S
   ii. Serum creatinine
g) Cardiac
   i. EKG
   ii. Echocardiogram or MUGA scan with Left Ventricular Ejection Fraction (LVEF)
   iii. Troponin I

h) Pulmonary
   i. Chest X-ray
   ii. Sinus CT scan
   iii. Pulmonary function tests including at least FEV1 and FVC (pediatric patients under the age of 8 are excluded from this test) with spirometry
   iv. High resolution chest CT
i) Immunologic / Infections
   i. HBsAg, anti-HBC, anti-HCV
   ii. RPR
   iii. HIV antibody
   iv. Serology for CMV and HSV (plus VZV – blood samples permitting)
   v. HLA typing/lymphocytotoxic antibody screen
j) RFLP studies will be drawn as a baseline for subsequent engraftment studies when the donor and patient are the same gender.
k) Additional tests (if applicable)
   i. FSH (females)
   ii. Testosterone (males)
   iii. Beta HCG
l) PRO Measures
   i. Scleroderma Skin PRO (SSPRO)
   ii. Scleroderma Health Assessment Questionnaire (SHAQ)
   iii. Gastrointestinal tract (GIT)
   iv. BORG Dyspnea Index, MRC Breathlessness Scale
   v. UCSD Shortness of Breath Questionnaire

7.4 Post-transplant Evaluation

7.4.1 Day 0 through Day 60 (+/- 7 days) evaluation

These represent the minimum required. More frequent determinations and additional investigations may be indicated by the clinical condition of the patient.

a) CBC with differential daily until ANC > 500 for three days consecutive days. Then, CBC weekly with differential.
b) Comprehensive metabolic panel once a week.
c) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum)
   a. Scleroderma research blood will be collected per protocol and a courier will be arranged to take samples to Bayview Medical Center for processing and storage. The trial nurse will coordinate with the scleroderma research staff regarding specific days and times blood is expected.
d) Patients will have evaluations for infectious complications as clinically indicated. Surveillance cultures according to JHOC BMT program standards are recommended.
e) Evaluations by history and physical examination for GVHD will be performed as per hospital standards.

7.4.2 Evaluations on Day 30 (+/-7 days)

a) History and physical examination.
b) Peripheral whole blood and CD3 chimerism.
c) CBC and differential, comprehensive panel.

d) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum).
e) Assess MRSS, tendon friction rubs, patient-reported outcome measures, and Euroline IgG Scleroderma Profile

7.4.3 Evaluations on day 60 (+/-7 days)

a) History and physical examination.
b) Peripheral whole blood and CD3 chimerism.
c) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum).
d) Assess MRSS, tendon friction rubs, patient-reported outcome measures, and Euroline IgG Scleroderma Profile

7.4.4 Evaluations at 3 months (+/-7days)

a) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum)
b) Repeat all testing described in 7.0.1 except ECHO (MUGA)

7.4.5 Evaluations at 6 months(+/-21days)

a) History and physical examination
b) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum)
c) Skin biopsy per Scleroderma Skin Repository Protocol
d) Peripheral whole blood and CD3 chimerism.
e) Repeat all testing described in7.0.1

7.4.6 Evaluations at 9 months(+/-21days)

a) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum)
b) Repeat all testing described in 7.0.1 except ECHO (MUGA)

7.4.7 Evaluations at 12 months(+/- 30days)

a) History and physical examination
b) Scleroderma Research Blood Draw (Peripheral blood mononuclear cells, serum)
c) Skin biopsy per Scleroderma Skin Repository Protocol
d) Peripheral whole blood and CD3 chimerism.
e) Repeat all testing described in7.0.1

8.0 RISKS AND TOXICITIES

8.1 Cyclophosphamide after graft infusion

The risk of treatment-related malignancy in donor cells is difficult to estimate but is likely to be similar to the 1% risk estimated after limited exposure to cyclophosphamide.

8.2 Acute and Chronic GVHD

The second major risk in participating in this research protocol is the risk of developing acute and/or chronic GVHD. Modified Keystone Criteria (See appendix 3) equal to or greater than Overall Grade 2 acute GVHD is considered clinically significant and associated with increased morbidity and non-relapse mortality. The likelihood of surviving severe GVHD is to a large part dependent on the age of the patient and the patient's overall condition. The other risks are the same as for standard BMT for high-risk acute hematologic malignancies, as follows:

8.3 Chemotherapy toxicities

The agents being used in the study are FDA approved. These agents are used extensively in the Bone Marrow Transplant setting and have well defined toxicity profiles. In addition, there are many expected toxicities related to a bone marrow transplant. For these reasons, toxicities will be captured and recorded/graded if the adverse event interferes with the subject's daily function and are considered clinically significant. We will capture and grade all these events structured around the categories of the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for the first 60 days post BMT.

The following is a list of categories that will not be recorded unless the event becomes a grade 4 or meets the criteria of an SAE, as stated in section 6.

- Allergy/Immunology
- Auditory/Hearing
- Cardiovascular (Arrhythmia)
- Cardiovascular (General)
- Coagulation
- Constitutional symptoms
- Dermatology/Skin
- Endocrine
- Hemorrhage
- Hepatic
- Infection/Febrile neutropenia
- Lymphatics
- Metabolic/Laboratory
- Secondary Malignancy
- Sexual/Reproductive Function

The following categories will be recorded only if the event becomes a grade 3 or grade 4 or meets the criteria of a SAE.

- Gastrointestinal
- Musculoskeletal
- Neurology
- Ocular/Visual
- Pain
- Pulmonary
- Renal/Genitourinary

The Blood/Bone Marrow category is captured as endpoints to the study. Thus, for this category, we will not record data according to the NCI Common Toxicity Criteria.

8.4 Thymoglobulin®

Thymoglobulin is a rabbit preparation of anti-thymocyte globulin (ATG). Common side effects include nausea, fever, chills, diarrhea, rash, dizziness, headache and tiredness. More serious side effects can include severe allergic reaction, serum sickness, easy bleeding/bruising, fast/irregular heartbeat, joint/muscle pain, stomach/abdominal pain, and weakness. Because this drug works by weakening the immune system, it lowers the ability to fight infections. No dose adjustments are required.

8.5 Cyclophosphamide(Cytoxan)

A toxicity of cyclophosphamide is hemorrhagic cystitis. Hematuria is not uncommon at this dose level, but is usually not symptomatic or severe unless there is inadequate diuresis. An occasional patient will get severe cystitis despite prophylactic measures.

8.6 Mesna (sodium -2-mercapto ethanesulphonate)

At the doses used for uroprotection, mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue.

8.7 Tacrolimus/sirolimus

Adverse reactions include tremor, headache, diarrhea, hypertension, nausea, cytopenias, pneumonitis, oral ulcers and renal dysfunction.

8.8 MMF

Side effect profiles include diarrhea, leukopenia, sepsis, allergic reactions, and vomiting. There is also an increase in certain types of infection mainly from the herpes virus family.

8.9 Infection

Infection is a major cause of morbidity in allo BMT and is a major concern in these patients.

8.10 Aplasia

Pancytopenia is an expected side effect of allogeneic BMT with the use of myeloablative preparative regimens. Given the previous experience with PTCy in other trials, we would expect the duration of aplasia to be relatively short. Prolonged aplasia can result from the failure of donor BM to engraft.

8.11 Risks Associated with Study Procedures for the Recipient

8.11.1 Bone Marrow Transfusion

The donor bone marrow will be transfused into the recipient through an intravenous catheter in the chest or neck. The risks of transfusion include chills, fever, headache, nausea, vomiting and dyspnea. These side effects can be ameliorated by administration of antihistamine and analgesic pre-medications.

8.11.2 Total Body Irradiation

Recipients will receive a single dose of 400 cGY total body irradiation on Day -1. This is considered a low dose of radiation and thus is not usually associated with side effects common at higher doses such as nausea and vomiting, alopecia and mouth sores. Low dose total body irradiation is associated with minimal to no short term side effects with the exception of possible edema in the radiation field and transient cytopenias. Long term side effects of total body irradiation include infertility. In addition there is an increased risk of lung fibrosis, pericarditis, thyroid disease, and cataracts.

8.11.3 Risk Associated with Immunosuppression Withdrawal

Inherent in the withdrawal of immunosuppression is the increased risk of precipitating graft rejection. This risk will be mitigated by the study design, which includes careful patient selection and close follow-up during and after drug withdrawal. Rejection may occur with a higher frequency or with greater severity than it does with conventional immunosuppression.
The protocol provides for frequent clinical evaluation of participants both during the period of active administration and during follow-up monitoring through approximately 1 year (Day 365) after transplantation.

8.12 Risks Associated with Study Procedures for the Donor

8.12.1 *Bone Marrow Harvest*

Bone marrow harvest will occur under local or general anesthesia per hospital policy as defined in BMT Policy and procedures- Bone Marrow Harvest policy. The risks associated with bone marrow harvest include pain and bleeding at the harvest site, adverse reactions to anesthesia and infection. Rarely, mechanical injury to the underlying bone, nerves, or soft tissue can occur. Factors associated with more complications are use of regional anesthesia, longer duration of harvesting, female gender and older age.

9.0 STUDY PARAMETERS

9.1 Donor chimerism

Donor chimerism will be measured in the peripheral blood around day 30, day 60, day 180, day 365, and day 730. Patients with >5% CD3+ cells of donor origin will be considered as having T-cell engrafted. Chimerism determinations will be made on peripheral blood by a number of different methods depending on the specific patient. Methods may include (i) the usual standard of restriction fragment length polymorphism (RFLP) if the donor and recipient RFLPs are informative, (ii) fluorescence in-situ hybridization (FISH) for Y-chromosome markers on PBMC if the donor is male, (iii) cytogenetic analysis, (iv) flow cytometric analysis of HLA-A, B or DR on lymphocytes in the peripheral blood if haploidentical and suitable reagents exist or (v) PCR analysis of variable nucleotide tandem repeats (VNTR) in PBMC if informative. Mixed donor chimerism will be defined as >5%, but <95% CD3+ cells of donor origin
Complete donor chimerism will be defined as $\geq$95%.

9.2 GVHD

Patients will be followed for development of acute and chronic GVHD using standard criteria. Chronic GVHD usually develops beyond the high-risk, peritransplant period (i.e., >100 d post-BMT, but can occur earlier) and is assessed according to standard criteria (see appendix 4). Treatment of GVHD will follow

the BMT standard of care at that particular time.

9.3 Transplant-related mortality

Transplant-related mortality, which is defined as death in the absence of disease progression, will be characterized at one year after BMT.

9.4 Hematologic toxicity

A secondary endpoint of this Pilot Study is time to recovery of circulating neutrophils and platelets (following chemotherapy). Neutrophil recovery is defined as the first day of three consecutive lab values on different days, after the conditioning regimen-induced nadir of blood counts, that the absolute neutrophil count is > 500/µL. Platelet recovery is defined as the first day of three consecutive lab values on different days, after the conditioning regimen-induced nadir of blood counts, that the platelet count is ≥ 20,000 µL without platelet transfusion support in the seven days prior.

9.5 Cardiotoxicity

The incidence of myocarditis caused by high dose cyclophosphamide (>150 mg/kg) is estimated to be 7 to 25% in adults. Cyclophosphamide-induced hemorrhagic myocarditis is associated with hypertrophy, increased myocardial echogenicity, a decrease in left ventricular ejection fraction, and a normal chamber size[29].

Clinically, cyclophosphamide-related cardiotoxicity presents as a syndrome of CHF or myocarditis or both. The onset is acute, with signs and symptoms occurring within days after the first dose. Loss of QRS voltage associated with significant CHF was observed in at least 50 to 90% of the cases; 25 to 33% may exhibit nonspecific ST segment elevations and T wave inversions. These ECG changes occurred within 1 to 3 days of administering cyclophosphamide, were reversible and returned to baseline in 1 to 7 days. ECG changes may occur even in the absence of clinical cardiotoxicity [30].

The post transplant cyclophosphamide is 50mg/kg on day +3 and day +4. As this is a novel population, we will perform ECG evaluation on each participant on day +10 to screen for ECG changes potentially due to cyclophosphamide-related cardiotoxicity. If ECG changes are found that the investigator determines are either probably or possibly related to cyclophosphamide-related cardiotoxicity, an echocardiogram will be performed.

10.0 Statistical Design and Analysis Plan

The primary objective: The primary objective of this study is to assess the safety of using a reduced intensity condition (RIC) preparative regimen bone marrow transplant (BMT) with post-transplant cyclophosphamide for GVHD prophylaxis as treatment for patients with scleroderma. Safety events include: (i) grade III-IV acute GVHD; (ii) chronic GVHD requiring systemic immune suppression; and (iii) death by any cause within 1 year of receiving RIC-alloBMT with post-transplant cyclophosphamide. This will be a single arm study with a planned follow-up of 1 year.

Secondary Objectives: The secondary objectives are to estimate (i) event-free survival at 12 months; (ii) immunosuppression-free survival at 12 months; (iii) disease relapse or progression; (iv) rates of grade 3+

infection or other grade 3+ toxicity according to CTCAE v5; (v) donor engraftment (failure to engraft); (vi) hematologic recovery (failure to achieve hematologic recovery; and (vii) non-relapse mortality.

Definitions:
-Event-free survival will be defined as survival without evidence of scleroderma progression or relapse or any end organ failure as defined by the following: pulmonary function decline ([FVC drop ≥10%] OR [≥5 to <10% decline in FVC AND ≥15% decline in DLCO]), new diagnosis of pulmonary hypertension by right heart cardiac catheterization (mean PAP>25 mmHg), new cardiomyopathy (LV function <30% on ECHO), increase in mRSS by 5 points relative to baseline score, or new renal crisis.

-Non-relapse mortality will be defined as any death without evidence of scleroderma relapse or progression.

-Engraftment will be defined as neutrophil recovery with >95% donor $CD3^+$ T cells detected in peripheral blood.

-Hematologic recovery will be defined as both neutrophil recovery (absolute neutrophil count >0.5 cells/μL for 3 consecutive days) and platelet recovery (platelet count greater than 20 x 10^3/μL for 7 days without transfusion).

Additional exploratory objectives are to estimate: (a) To assess the effects of BMT on skeletal and cardiac muscle using serum biomarkers of CK, aldolase, and troponin over the one-year study period; (b) To assess scleroderma autoantibody titers, autoreactive T cells, and flow cytometric signatures over the one-year study period.

10.1 Stopping Rules for Safety

The stopping guidelines serve as a trigger for consultation with the Principal Investigator and with the IRB for review. Accrual will be halted during any review. Outcomes will be sequentially monitored for excessive rates mortality as well as for excessive rates of moderate-severe chronic GVHD. Mortality and chronic GVHD are known consequences of alloBMT that are acceptable to some degree in nonmalignant disorders that are otherwise fatal without a successful transplant, but chronic GVHD does not have a direct disease benefit as it would convey in the context of BMT for malignant disorders. The trigger would be met if the posterior probability exceeds 75% that the true rate of mortality is >15% (Table 1). We will accrue three patients, with a minimum of 60 days gap between them in order that we can observe safety for at least 60 days between each of them. If one or none experience either GVHD or mortality, an additional 3 patients will be accrued. We will then observe safety for at least 60 days in all of them before accruing the next 3 patients, and so on as per the schedule shown in Table 1. An Independent rule would monitor for 75% plausibility that the true rate of severe chronic GVHD>15% (Table 2). We assumed the following prior distributions for TRM and severe cGVHD: beta (0.2, 1.8) and beta (0.3, 1.7), respectively.

Table 1: Stopping Boundaries for mortality from any cause

# of patients transplanted	Stop if at least this number experience mortality from any cause
1-3	1
4-6	2
7-11	3
12-15	4

For true TRM rates of 0.2, 0.3, and 0.4, the above design would stop the study with probabilities of 53%, 80% and 94%, and with average sample sizes of 9, 6.4, and 4.5, respectively.

Table 2: Stopping Boundaries for chronic GVHD

# of patients transplanted	Stop if at least this number experience severe cGVHD requiring systemic immunosuppression
1-3	2
4-6	2
7-12	3
13-15	4

For true severe cGVHD rates of 0.2, 0.3, and 0.4, the above design would stop the study with probabilities of 60%, 84%, and 95%, and with average sample sizes of 8.1, 5.5, and 3.7, respectively. The study will be stopped if either of these safety rules is violated. We also note that we will

include severe toxicities observed in the conditioning regimen that would prevent or substantially delay the patient from receiving the transplant.

10.2 Interim Analysis and Stopping Guidelines

There will be no interim analysis for efficacy or futility. Patients will be monitored for key safety endpoints including graft failure and mortality. Study participants will be monitored for grade 3 adverse events including grade III or higher acute GVHD, chronic GVHD requiring systemic immune suppression, disease relapse or progression, or death by any cause that occurs within 1 year of receiving RIC-alloBMT with post-transplant cyclophosphamide.

Mortality will be monitored up to 365 days from the first day of preparative regimen (Day -9) in all patients receiving the conditioning regimen for RIC alloBMT. The rationale for monitoring mortality from the first day of the conditioning regimen is to guard against excessive early mortality including death due to the intervention in patients who never proceed to transplant, although this event is expected to be extremely uncommon, as well as capture adverse events including mortality related to the interventions received as part of the conditioning regimen.

If any of the following occurs during the study, the study will be paused to allow time for DSMB independent review and decision-making regarding attribution, study stopping, study continuation, protocol revision (eligibility criteria, monitoring etc.) and informed consent form revision:

- One death, irrespective of attribution by the investigator
- Any Grade 4 or higher adverse event per CTCAE v5.0 irrespective of attribution by the investigator. Exceptions will be made for the following adverse events which are expected or anticipated events commonly associated with allogeneic BMT: cytopenias, neutropenic fever, CMV reactivation, bacteremia or bacterial pneumonia, nausea, vomiting or non-GVHD diarrhea
- Any Grade 4 or higher hypersensitivity reaction, irrespective of attribution by the investigator
- Two Grade 3 or higher adverse events per CTCAE v5.0 in the same organ class in more than one subject irrespective of attribution by the investigator. Exceptions will be made for the following adverse events which are expected or anticipated events commonly associated with allogeneic BMT: cytopenias, neutropenic fever, CMV reactivation, bacteremia or bacterial pneumonia, nausea, vomiting or non-GVHD diarrhea

Graft failure, GVHD, disease progression and mortality will be monitored so that if rates significantly exceed pre-set thresholds, the DSMB can be advised. Policies and composition of the DSMB are described in the JHU SKCCC DSMP V6.0 02/21/2019. The pausing guidelines serve as a trigger for consultation with the DSMB for additional review and their determination could mandate automatic closure of study enrollment.

10.3 Analysis of Secondary Endpoints

Major secondary endpoints are to estimate:

(i) The event-free survival at 12 months, defined as survival without evidence of scleroderma progression or relapse or any end organ failure as defined by the following: pulmonary function decline ([FVC drop ≥10%] OR [≥5 to <10% decline in FVC AND ≥15% decline in DLCO]), new diagnosis of pulmonary hypertension by right heart cardiac catheterization (mean PAP>25 mmHg), new cardiomyopathy (LV function <30% on ECHO), increase in mRSS by 5 points relative to baseline score, or new renal crisis.

(ii) Assess immunosuppression-free survival at 1yr.

(iii) Disease relapse or progression.

(iv) Rates of grade 3+ infection or other grade 3+ toxicity according to CTCAE v5;
(v) Donor cell engraftment (failure to engraft).
(vi) Hematologic recovery (neutrophils and platelets).
(vii) Non-relapse mortality without evidence of scleroderma relapse or progression.

This will be estimated using the Kaplan-Meier estimator along with 95% confidence intervals. Based on the historical data of 389 Scleroderma patients, the estimated EFS at 2-years was approximately 75%. We would consider allogeneic BMT to be promising if we can achieve an EFS of 85% or greater, although our limited sample size will not give us sufficient power to evaluate this improvement formally.

10.4 Analysis for Exploratory Objectives

We will evaluate the effects of BMT on skeletal and cardiac muscle using serum biomarkers of CK, aldolase, and troponin over the one-year study period. Due to small sample size, we will not be able to conduct inferential analyses. But, we will attempt to characterize the trajectories of these markers over the one-year period using measurements obtained at baseline, days 30, 60, 90, 180, 270, and 365.
These markers are elevated when untreated. We expect them to decrease following BMT. We will quantify the temporal changes using descriptive, as well as using GEE models.
We will also assess scleroderma autoantibody titers, autoreactive T cells, and flow cytometric signatures over a one-year period. Due to small sample size, we will not be able to conduct inferential analyses. But, we will attempt to characterize the trajectories of these markers over the one-year period using measurements obtained at baseline, days 30, 60, 90, 180, 270, and 365. We expect that these markers would decrease. We will quantify the temporal changes using descriptive, as well as using GEE models.

11.0 RISKS AND BENEFITS

11.1 Risks and toxicity

The major toxicity of alloBMT is GVHD. The incidence of severe aGVHD (Grades III-IV)) on the phase I nonmyeloablative haploidentical BMT trial utilizing 2 doses of PTCy, MMF and tacrolimus was approximately 10%. We would not expect a rate of severe GVHD greater than 15%. Another significant risk is failure-to-engraft due to rejection by host lymphocytes. Infection is a major cause of morbidity and mortality in the peritransplant period (#100d post-BMT). However, given current supportive care and the intensive infection prophylaxis of this protocol, we expect the risk to be acceptable. Prolonged neutropenia may increase this risk in the case of graft rejection.

11.2 Benefits

This is a Pilot Study of toxicity in the setting of a reduced intensity conditioning BMT using PTCy to maximize engraftment and minimize GVHD. The potential benefit of this trial is a durable recovery from systemic sclerosis.

12.0 Ethical Considerations and Compliance with Good Clinical Practice

12.1 Statement of Compliance

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines—adopting the principles of the Declaration of Helsinki—and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics review committee or institutional review board (IRB). Any amendments to the protocol or consent materials must also be approved by the Sponsor, the IRB and submitted to FDA before they are implemented.

12.2 Informed Consent

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study, taking any study drugs, and/or undergoing any study-specific procedures. If a participant does not speak and read English, the consent materials must be translated into the appropriate language.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The attending physician, in the presence of a witness, will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason.

Patients eligible for marrow grafting are completely evaluated and presented at group conference. The group's recommendations are discussed with the patient. If the patient is approved for BMT, the marrow processing procedure itself, the risks of the preparative regimen, risks of BMT complications including infection and GVHD and alternate forms of therapy are presented as objectively as possible. Informed consent is obtained from the recipient using the forms approved by the IRB.

12.3 On-study date

A participant will be considered on study upon the date of signed consent.

12.4 Privacy and Confidentiality

A participant’s privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant’s name, will be used to collect, store, and report participant information.

13.0 References

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14.0 APPENDICES

APPENDIX 1- PERFORMANCE STATUS SCALES

ECOG PERFORMANCE STATUS SCALE GRADE DESCRIPTION

0 Fully active, able to carry on all pre-disease activities without restriction.

1 Restricted in physically strenuous activities and able to carry out work of a light or sedentary nature, e.g. light housework, office work.

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 Dead.

KARNOFSKY PERFORMANCE STATUS SCALE

100 Normal no complaints; no evidence of disease

90 Able to carry on normal activity; minor signs or symptoms of disease.
Able to carry on normal activity and to work; no special care needed.

80 Normal activity with effort; some signs or symptoms of disease.

70 Cares for self; unable to carry on normal activity or to do active work.

60 Requires occasional assistance, but is able to care for most of his personal needs. Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.

50 Requires considerable assistance and frequent medical care.

40 Disabled; requires special care and assistance.

30 Severely disabled; hospital admission is indicated although death not imminent.

20 Very sick; hospital admission necessary; active supportive treatment necessary.

10 Moribund; fatal processes progressing rapidly. Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

0 Dead

APPENDIX 2- NCI COMMON TOXICITY CRITERIA

The NCI common toxicity criteria can be accessed and downloaded via the website:
http://ctep.cancer.gov/reporting

APPENDIX 3- NIH CONSENSUS SCORING/EVALUATION FORMS FOR CHRONIC GVHD48

NIH Consensus Scoring/Evaluation Forms for Chronic GVHD48
Organ scoring of chronic GVHD. *AP may be elevated in growing children, and not reflective of liver dysfunction.
+ 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 (LFS) is preferred, but if DLCO is not available, grading using FEV1 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 FEV1 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 = FEV1 score + DLCO score, with a possible range of 2-12. GVHD= graft versus host disease, ECOG=Eastern Cooperative Group, KPS-= Karnofsky Performance Scale; LPS= Lansky Performance Status; BSA= body surface area; ADL=activities of daily living; LFTs = liver function tests; AP= alkaline phosphatase; ALT=alanine aminotransferase; AST= aspartate aminotransferase; ULN=upper limit of normal

Appendix 4 – GVHD EVALUATION FORMS

Acute GVHD Evaluation Note – v6.2001

Date of Evaluation _____

Is this patient's initial GVHD evaluation? No Yes:
GVHD Prophylaxis:_____
SUBJECTIVE
_____
_____
_____
_____
PHYSICAL EXAM
SKIN Rash:_____%
N Y Erythroderma
N Y Bullae
N Y Raised skin
N Y Blanching
N Y Edema
N Y Hyperpigmentation
N Y Hypopigmentation
N Y Abnormal Nails
LIVER T Bili: _____
N Y Jaundice
N Y Hepatomegaly
N Y Hepatic tenderness
N Y Ascites
N Y Weight gain
DB LDH _____
ALT AST_____
AlkPhos _____
GUT Avg Stool Output:_____cc
N Y Nausea
N Y Vomiting
N Y Cramping
N Y Tender to Palpitation
N Y Ileus
S/O from past 3 days:
D-1:_____D-2_____D-3_____
HEMATOLOGY
N Y Upper GI Bleeding
N Y Lower GI Bleeding
N Y GU Bleeding
N Y Pulmonary Bleeding
N Y CNS Bleeding
N Y Oral Bleeding
N Y ENT Bleeding

OPTHALMOLOGICAL

N Y Conjunctival Erythema
N Y Conjunctival Ulceration
N Y Dry Eyes

ORAL

N Y Leucoplacia
N Y Thrush
N Y Erythema
N Y Ulceration
N Y Xerostra

Comments:

_____
_____
_____

Is there evidence of Chronic GVHD? • No • Yes:

Complete Chronic GVHD Evaluation

BIOPSIES SINCE LAST EVALUATION • None
Site:_____• Consistent with GVHD • Not Diagnostic of GVHD Date:
____/_____/_____
Site:_____• Consistent with GVHD • Not Diagnostic of GVHD Date:
____/_____/_____

ACUTE GRAFT VERSUS HOST DISEASE STAGING *(Please circle stage for each organ)*

STAGE SKIN LIVER GUT (adults) ***GUT (children)***

0 No evidence of GVHD Bili <2.0mg/dL < 500 mL diarrhea per day *< 10 ml/kg/day*
1 <25% 2.0 –3.0 mg/dL > 500 mL /day, or persistent nausea with histologic evidence 10-15 ml/kg
2 25-50% 3.1 – 6.0 mg/dL > 1,000 mL diarrhea per day *16-20 ml/kg*
3 >50% 6.1 – 15.0 mg/dL > 1,500 mL diarrhea per day *21-25 ml/kg*
4 W/ bullous formation >15.0 mg/dL Severe abdominal pain w-w/o ileus *>26 ml/kg*

OVERALL GRADE ***(Please circle current overall grade)*** • **Cannot be determined**

GRADE SKIN LIVER GUT

0 None None None
1 Stage 1-2 None None
2 Stage 3, OR Stage 1, OR Stage 1
3 ---------- Stage 2 – 3, OR Stage 2 - 4
4 Stage 4, OR Stage 4 ----------

CURRENT GVHD TREATMENT:

Therapy Name & Dose Start date Stop date Most recent level

OVERALL GVHD ASSESSMENT

□ No current evidence of GVHD □ Symptoms resolved □ Symptoms improved
□ No Changes □ Mixed response □ Symptoms progressing
□ Symptoms questionable for GVHD □ Symptoms suggestive of GVHD

RECOMMENDATIONS

_____
_____
_____
_____
_____ _____ _____ _____

Signature ID# Pager # Date

Appendix 5 – JHU BMT POLICY FOR DONOR SELECTION

The Johns Hopkins BMT Policies and Procedures Manual – Donor Selection Criteria Policy (DON009)

https://hpo.johnshopkins.edu/hopkins/policies/113/9405/policy_9405.pdf?_=0.800089013576

Appendix 6 – JHU BMT POLICY FOR ALLOGENEIC DONOR CONSENT

The Johns Hopkins BMT Policies and Procedures Manual – Allogeneic Donor Consent Policy (DON004)

https://hpo.johnshopkins.edu/hopkins/policies/113/11329/policy_11329.pdf?_=0.114250072162