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Protocol Title:
A Phase I/II Study of Nonmyeloablative Conditioning and Transplantation of HLA-matched, Partially HLA-mismatched, HLA-haploidentical or matched unrelated Bone Marrow for Patients with Refractory Systemic Lupus Erythematosus

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TREATMENT SCHEMA

Days -9 Thymoglobulin 0.5 mg/kg IV with pre-meds
Start steroid taper
↓
Days -8,-7 Thymoglobulin 2 mg/kg IV qd with pre-meds
↓
Days –6, -5 Fludarabine 30 mg/M2 iv qd
Cyclophosphamide (CTX) 14.5 mg/kg IV qd*
Begin antibiotic prophylaxis (except antifungals)
↓
Days –4 -2 Fludarabine 30 mg/M2 iv qd
↓
Day –1 TBI 200 cGy ↓
Day 0 Infuse marrow
↓
Days 3, 4 CTX 50 mg/kg iv q d
Mesna 40 mg/kg iv q d**
(First dose of CTX must be administered 60-72hr after infusion of marrow)
↓
Day 5 Begin FK-506 1mg iv/po bid** and
MMF 15 mg/kg po tid with maximum daily dose 3 gm/d
Begin antifungal prophylaxis
↓
Day 30 Assess Chimerism in peripheral blood
↓
Day 35 Discontinue MMF
↓
Day 60 Assess Chimerism in peripheral blood
↓
Day 180 Evaluate disease
Assess Chimerism in peripheral blood
↓
Day 180 Discontinue FK-506
Evaluate disease
Assess Chimerism in peripheral blood
↓
1 yr, 2 yrs Evaluate disease
Assess Chimerism in peripheral blood

1.0 OBJECTIVES

Primary Objectives

1.1 The primary endpoint of this study will be the feasibility of non-myeloablative conditioning regimen and post transplantation cyclophosphamide in refractory SLE patients with donors having various degrees of matching.

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Secondary Objectives

1.1 To estimate the improvement in the RIFLE (Responder index in Lupus Erythematosus) score with the goal as target organ complete response with no worsening in any other organ at 12 months.

1.2 Of the patients with an initial SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) of 4 points or higher, estimate the proportion of patients that have an improvement of 4 points.

1.3 Estimate the proportion of patients with an improvement in PGA (Physician's Global Assessment) to 0.5 or less

1.4 To estimate the overall survival (OS) and event-free survival (EFS) at 1 year.

1.5 To estimate the cumulative incidence of full donor chimerism by day 60

1.6 To estimate the cumulative incidence of non–relapse-related mortality following transplant.

1.7 To estimate the incidences of primary and secondary graft failure following transplant.

1.8 To estimate the cumulative incidences of grade II-IV and grade III-IV graft versus-host disease (GVHD).

1.9 To estimate the cumulative incidence of chronic graft versus-host disease (GVHD).

1.10 Summarize all hematologic and non-hematologic toxicities.

2.0 BACKGROUND AND RATIONALE

Systemic lupus erythematosus is a devastating systemic autoimmune disease that predominantly affects young women, is more common in African-Americans than in whites, and results in poor quality of life.(1) Lupus has no cure, and up to 90% of patients require corticosteroids for disease control. More than half of patients with lupus have permanent organ damage, much of which is either directly due to or increased by corticosteroids.(2) Mortality is increased in patients with systemic lupus erythematosus, with accelerated atherosclerosis the most important contributing factor, although the risk of cancer is also increased. (3) Ultimately, to satisfactorily manage moderate-to-severe SLE, we need effective treatments that will allow corticosteroid-sparing.

Although the precise etiology of SLE remains unclear, genetic predisposition, hormonal, and environmental factors play a role in the pathophysiology of SLE. If one member of a pair of identical twins develops SLE, there is a 14-60% chance that the other member of the pair will acquire the disease; thus, susceptibility to develop SLE involves more than genetics alone(4). SLE has a female to male prevalence of 9:1 and occurs more frequently in African-Americans than in whites(5). The highly skewed prevalence in women is felt, in part, to be secondary to hormonal factors. For example, in (NZBxNZW) F1 mice (a murine model of SLE) the onset of disease is delayed in males compared to females, while castration of males makes the onset of the disease similar to that in untreated female mice of the same strain. Similarly, ovariectomy of female (NZBxNZW) F1 mice delays the onset of disease making it similar to that in untreated males of this strain(6). However, recent studies suggest that hormonal differences alone may not be enough to explain the female predominance in SLE. In fact, having two X chromosomes may predispose to SLE. Although one X chromosome is randomly inactivated, it is now known that the Lyonized X chromosome is only partly inactivated in women; about 10-15% of genes can be expressed by both X chromosomes in female cells(7). To directly study the role of the X chromosome in autoimmunity, investigators established mice which had different compliments of sex chromosomes (XX or XY) but possess the same gonads (ovaries or testes)(8). Gonadectomy of such mice allowed for direct assessment of the role of sex chromosomes in the immune response and susceptibility to autoimmune diseases. The authors tested two independent models of induced autoimmune disease, EAE and pristine-induced lupus. Possession of an XX, as opposed to an XY sex

chromosome complement conferred greater disease severity in both models. Moreover, cytokine analysis revealed that T cells from the XY mice produced increased amounts of Th2 cytokines such as IL-4, IL-5, IL-13, than have a protective effect in autoimmunity(9). These data suggest that the X chromosome complement may directly contribute to the female bias of autoimmune diseases such as lupus.

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(10-13). 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. SLE is considered the paradigm of autoimmune diseases and the murine models are known to be curable by means of hematopoietic stem cell transplantation.(14;15)

Allogeneic BMT is not currently utilized for the routine treatment of SLE because of the significant morbidity (GVHD) and mortality associated with the procedure. 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). The most common autoimmune diseases treated, accounting for roughly 50% of the cases, were multiple sclerosis and systemic sclerosis. High-dose cyclophosphamide-based, non-myeloablative conditioning regimens were used in over 50% of the HSCT cases reported by EBMT/EULAR and the CIBMTR.(17-19). 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(3,5,9). 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.

Due to concern of reinfusing autoreactive lymphocytes with the autograft, our group performed an evaluation of high dose cyclophosphamide without stem cell support for SLE patients as part of a trial of high dose cyclophosphamide versus monthly intravenous cyclophosphamide for patients with SLE.(20) Of the total 40 patients treated, 16 had highly refractory disease and were treated on an open-label study; 24 were treated as part of a randomized trial comparing high-dose cyclophosphamide to monthly intravenous cyclophosphamide in a cohort of patients who were less heavily pretreated. In the randomized study, six of seven patients with neurologic manifestations of their SLE had a complete response; in the patients with renal manifestations only four of ten patients responded to high-dose cyclophosphamide (2 complete and 2 partial responses). Patients on this randomized trial who did not respond to intravenous pulse-dose cyclophosphamide were eligible to cross over to the high dose arm. Interestingly, of the six patients who crossed over to high dose cyclophosphamide, three achieved a complete response(20). Our data suggest that high dose cyclophosphamide is not superior to monthly pulse dose cyclophosphamide and we do not recommend the use of high dose cyclophosphamide as front-line therapy in SLE.

Similar to autologous BMT, most patients with SLE relapse within a few years after HiCy therapy. Since no autograft is given and the dose of cyclophosphamide with HiCy (50mg/kg/d x 4 days) is equivalent that used for autologous BMT, our data suggest that either the conditioning regimen is inadequate to eradicate the autoimmunity or, similar to the genetic mouse models of autoimmunity, that allogeneic BMT may be required to eradicate disease in lupus. Interest in improving response rates and decreasing relapse has turned attention more toward allogeneic stem cell transplantation. There are already case reports of patients transplanted for other indications whose SLE was cured with allogeneic stem cell transplantation.(21;22)

Despite the improved survival achieved in recent years in these patients suffering from SLE, some of them continue to have severe morbidity and mortality from their disease particularly if patients do not respond to their therapy and have immunosuppressant refractory disease.(24-28). In fact, patients with SLE with renal or

hematologic manifestations have a sevenfold increase on mortality and those with heterogeneous clinical presentation have a 25% increase in mortality(29). Therefore they are the ideal candidates to proceed with experimental therapies. Allogeneic bone marrow transplant is one of them. Allogeneic BMT has not historically been used for the treating SLE because of perceived morbidity and mortality and the lack of suitable HLA-matched donors. However, recent experience using non-myeloablative BMT in patients with non-malignant conditions (sickle cell disease and hemoglobinopathies) has shown that these transplants can be done safely, with low incidence of graft versus host disease, low transplant related mortality, and high efficacy utilizing both HLA matched or haploidentical donors(30-32). Therefore the traditional toxicities encountered with BMT employing high dose chemotherapy are avoided and the procedure becomes safer to patients.

The possibility of maintaining control of autoimmunity by means of mixed chimerism in these autoimmune diseases is quite important as well. (33) These patients may not need full engraftment to have disease modification.

From these results, we concluded the following:

1) Post-transplantation immunosuppression with high dose CY, tacrolimus, and thrice daily MMF was associated with an acceptably low incidence of graft rejection, severe acute GVHD, and extensive chronic GVHD, while allowing reasonably 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 lupus erythematosus is that the risk of relapse is exceedingly low. In essence, engraftment without significant GVHD cures the disease.

Recently, a 25 yo female patient with SLE who received a non-myeloablative HLA-haploidentical bone marrow transplant from her brother for the indication of sickle cell disease(32). Pretransplant, her anti-DNA screen for lupus was positive, her C3 was 53 mg/dl, her C4 was 14mg/dl and her dRVVT was prolonged. She is now 3 months post BMT with full donor chimerism from her HLA-haploidentical brother. Currently, her anti-DNA screen is negative, her C3 is 141 mg/dl, her C4 is 33 mg/dl, her dRVVT is normal, and her urine protein has decreased from 859 mg/dl to 395 mg/dl.

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 post-transplantation Cy, and our promising results in the myeloablative matched related and unrelated setting, this trial will employ a fludarabine + cyclophosphamide conditioning along with posttransplantation Cy on days +3 and +4 for patients with refractory SLE. The purpose of this trial is to improve the salvage rate for patients with refractory SLE through a reformatting of the immune system.

Given that there are responses of SLE to immunosuppressive therapy in some form, eligible patients will be required to have failed at least one course of immunosuppressive therapy. The priority of donors will be as follows: HLA-matched sibling donor > HLA-haploidentical donor > matched unrelated donor. A priority will also be placed on male donors over female donors, when both are available. The rationale for this comes from the knowledge that gender, a genetically controlled factor, plays a role in the incidence of autoimmune disease. SLE occurs much more frequently in females than males. (34) The genetic difference in the donation of a male allograft to the SLE recipient could influence the recipient's chance of cure.

3.0 DRUG INFORMATION

3.1 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.

3.2 Mesna (sodium-2-mercapto ethane sulphonate)

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 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. Mesna will be dispensed by the Oncology Pharmacy and is produced by Mead Johnson Pharmaceuticals.

3.3 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 to concentrations of 0.04-1 mg/ml in normal saline or 5% dextrose (50-100ml) for injection and will be administered by IV infusion over 30 minutes or longer.
Following IV administration, the drug is metabolized to 2-F-araA and widely distributed in tissues. 2-F-araA is excreted primarily in urine and has a terminal elimination half-life of 7 to 12 hours.
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 will be administered by IV infusion over 30 minutes 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.

3.4 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. The metabolized products are excreted in the urine. Nephrotoxic drugs, antifungals, calcium channel blockers, cimetidine, danazol, erythromycin, methylprednisone and metoclopramide increase the bioavailabilty 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.

3.5 Mycophenolic Acid Mofetil (Cellcept®)
Mycophenolate Mofetil is an ester prodrug of the active immunosuppressant mycophenolic acid (MPA). This active metabolite is a noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). There are no pharmacokinetic interactions with ganciclovir, cotrimoxazole, oral contraceptives and cyclosporine. 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.

3.6 Rabbit antithymocyte globulin (ATG)
Thymoglobulin® [Anti-thymocyte Globulin (Rabbit)] is a purified, pasteurized, gamma immune globulin, obtained by immunization of rabbits with human thymocytes. This immunosuppressive product contains cytotoxic antibodies directed against antigens expressed on human T-lymphocytes. This drug is commonly used to treat graft rejection in kidney transplantation. It is also commonly used in bone marrow transplantation as part of the conditioning regimen to avoid graft failure and to prevent graft-versus-host disease.

Thymoglobulin is a sterile, freeze-dried product for intravenous administration after reconstitution with Sterile Water for Injection, USP (SWFI). Each 10 mL vial contains 25 mg anti-thymocyte globulin (rabbit) as well as 50 mg glycine, 50 mg mannitol, and 10 mg sodium chloride. After reconstitution with 5 mL SWFI, each vial of reconstituted product contains approximately 5 mg/mL of Thymoglobulin, of which >90% is rabbit gamma immune globulin (IgG). The reconstituted solution has a pH of 7.0 ± 0.4. Human red blood cells are used in the manufacturing process to deplete cross-reactive antibodies to non-T-cell antigens. The manufacturing process is validated to remove or inactivate potential exogenous viruses. All human red blood cells are from US registered or FDA licensed blood banks. A viral inactivation step (pasteurization, i.e., heat treatment of active ingredient at 60°C/10 hr) is performed for each lot. Each Thymoglobulin lot is released following potency testing (lymphocytotoxicity and E-rosette inhibition assays), and cross-reactive antibody testing (hemagglutination, platelet agglutination, anti-human serum protein antibody, antiglomerular

Adverse side effects include immunodeficiency, infusion related toxicities such as hypertension, chills, rigors, tachycardia, capillary leak syndrome, hyperglycemia, cytopenias, transient hepatitis, anaphylaxis, serum sickness, myalgias, sensory changes including hearing loss, headaches, renal toxicity, dyspnea and bronchial spasm, fevers. The drug is potentially teratogenic and is unknown if it can be passed to children in breastfeeding.

Thymoglobulin will be dispensed by the Oncology Pharmacy and is produced by Genzyme. ATG–rabbit must be infused through a 0.22 micro filter with premedications: acetaminophen 650 mg orally and diphenhydramine 25mg orally as well as a steroid taper (see Section 6.3). The dose to be used is 0.5 mg/kg on day -9 and 2 mg/kg/day on days -8 and -7. Note: Keep anaphylaxis kit at bedside during ATG administration. ATG should not be administered during the weekend.

4.0 PATIENT SELECTION

4.1 Inclusions Criteria

All patients with moderate-to-severe SLE will be considered for this trial, including women and minorities. SLE 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) Four or more ACR criteria as revised by Hochberg(35)for the classification of SLE or 4 or more of the SLICE criteria(36)

2) Involvement of one or more of the following organ systems (renal, neurologic, hematologic, cardiac, pulmonary, gastrointestinal) of moderate-to-severe severity as indicated by an "A" or 2 B score on the BILAG, a 2 or higher on the Physician Global Assessment, or severe enough to require hospitalization if the organ involvement was not "captured" on either the BILAG or SLAM instruments~~,~~.

3) Patients must have failed at least two forms of immunosuppression:
   a) moderate-to-high dose corticosteroids (***0.5-***1mg/kg/day*******, ***and/***or IV pulse methylprednisolone)
   b) azathioprine, methotrexate, cyclosporine, tacrolimus, belimumab, rituximab, or mycophenolate mofetil,

   In the case of severe and ongoing hemolytic anemia and/or thrombocytopenia, failure of intravenous immunoglobulin treatment will count as the second treatment.

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

****When cyclophosphamide is the accepted standard of care (renal and neurologic), the maximally tolerated dose of prednisone will be sufficient to meet the corticosteroid criterion.***

4.2 Exclusion Criteria:

1) Age less than 18 years and over 75 years.
2) Any risk of pregnancy – ALL female patients must have an effective means of birth control or be infertile due to hysterectomy, fallopian tube surgery, or menopause.
3) Active, life threatening or clinically significant uncontrolled systemic infection, known HIV-related illness, Hep B or Hep C infection.

4.3 Criteria for donor eligibility

4.3.1 Age >18 yr

4.3.2 Donors must meet the selection criteria as defined by the BMT Policy Manual.

4.3.3 Donors will be selected to minimize HLA mismatch in the host-versus-graft Direction.

4.3.4 In case there are two or more 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

4. Major and minor incompatibility

5.0 TREATMENT PLAN (All patients with refractory systemic lupus erythematosus)

Days -9 Thymoglobulin 0.5 mg/kg IV with pre-meds
Start steroid taper
↓
Days -8,-7 Thymoglobulin 2 mg/kg IV qd with pre-meds
↓
Days -6, -5 Fludarabine 30 mg/M2 iv qd
Cyclophosphamide (CTX) 14.5 mg/kg IV qd*
Begin antibiotic prophylaxis (except antifungals)
↓
Days -4 to -2 Fludarabine 30 mg/M2 iv qd
↓
Day –1 TBI 200 cGy
↓
Day 0 Infuse marrow
↓
Days 3, 4 CTX 50 mg/kg iv q d
Mesna 40 mg/kg iv q d**
(First dose of CTX must be administered 60-72hr after infusion of marrow)
↓

Day 5 Begin FK-506 1mg iv/po bid** and
MMF 15 mg/kg IV or po as tolerated tid with maximum daily dose 3 gm/d
Begin antifungal prophylaxis
↓
Day 30 Assess Chimerism in peripheral blood
↓
Day 35 Discontinue MMF
↓
Day 60 Assess Chimerism in peripheral blood
↓
Day 180 Evaluate disease
Assess Chimerism in peripheral blood
↓
Day 180 Discontinue FK-506
Evaluate disease
Assess Chimerism in peripheral blood
↓
1 yr, 2 yrs Evaluate disease
Assess Chimerism in peripheral blood

5.1 Indwelling central venous catheter
Placement of a double lumen central venous catheter will be required for administration of IV medications and transfusion of blood products, as per standard BMT requirements.

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 administration
Fludarabine will be administered by intravenous infusion over 30 min. on D-6 to D-2. The dose will be 30 mg/m2.

For decreased creatinine clearance (< 61 ml/min) determined by the Cockcroft Formula:

$$CCr = \frac{(140 - age) \times IBW\ (kg)}{PCr \times 72} \times 0.85 \text{ (for women)}$$

Fludarabine dosage should be reduced as follows:

C_{Cr} 46-60 ml/min, fludarabine = 24 mg/m^2
C_{Cr} 31-45 ml/min, fludarabine = 22.5 mg/m^2
C_{Cr} 21-30 ml/min, fludarabine = 19.5 mg/m^2
C_{Cr} <20 ml/min, fludarabine = 15 mg/m^2

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. (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”.

Note: Mesna will be utilized for the Day 3 and Day 4 post BMT cyclophosphamide doses, not for the pre-BMT cyclophosphamide doses.

Total body irradiation: 200 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 in a single fraction on day -1.

Cyclophosphamide will be given in two blocks. The first one on days -6 and -5 at a dose of 14.5 mg/kg and the second block will be given at a dose of 50 mg/kg/day IV over 1-2 hrs x 2 days on day +3 and day +4. Dosing of cyclophosphamide is based on ideal body weight for all subjects. 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. Intravenous hydration with appropriate fluids will be started at least 2 hr prior to cyclophosphamide and continued for at least 8 hr post-cyclophosphamide.

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, a known complication of high-dose Cy therapy.

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

5.4 Marrow processing and infusion

Bone Marrow will be harvested and infused on day 0.

Donor bone marrow will be harvested with a target yield of 4 x 10^8 nucleated cells/kg recipient IBW. Major incompatible ABO graft will have red blood cell depleted by buffy coat preparation. Minor ABO incompatible graft will have plasma removed. 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.

Major incompatible ABO graft will have red blood cell depleted by buffy coat preparation. Minor ABO incompatible graft will have plasma removed. 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.

5.5 Post-transplantation cyclophosphamide

Cyclophosphamide [50mg/kg (IBW)] will be given on D+3 post-transplant (within 60-72hr of marrow infusion) and on D+4 post-transplant. Cyclophosphamide will be given as an iv infusion over 1- 2 hr (depending on volume). Patients will follow institutional standards for uroprotection.

It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes steroids as antiemetics.

5.6 GVHD prophylaxis

On Day +5, patients will begin prophylaxis with Tacrolimus and Mycophenolic Mofetil (MMF). Tacrolimus will be given at a dose of 1mg IV over 4 hours(adults). Serum trough levels of tacrolimus should be measured around Day+7 and the dose should be adjusted based on this level to maintain a level of 5-15 ng/ml.

Tacrolimus should be converted to oral dosing on Day 14. For adults, the oral dosing is 1mg po bid, or 3 times the IV dose. Serum trough levels should be checked again on Day 16, or 2 days after conversion from IV to po. Patients may continue on IV dosing if they are not tolerating po. It is not a protocol violation to switch tacrolimus from IV to po earlier then Day 14.
Serum trough levels should be checked weekly thereafter and the dose adjusted accordingly to maintain a level of 10-15 ng/ml. Mycophenolic acid mofetil will be given at a dose of 15 mg/kg IV or po as tolerated TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g TID).MMF prophylaxis will be discontinued after the last dose on D35 and tacrolimus prophylaxis will be discontinued after the last dose around Day 180.

5.7 Infection prophylaxis and therapy
All infection prophylaxis and therapy will be administered and discontinued as per institutional standards. During pre-transplant evaluation patients will be screened for respiratory syncitial virus, influenza A, B and parainfluenza viruses if symptomatic. Assays of these viruses must be negative for symptomatic patients to be admitted for transplant. Strong consideration should be given to institution of ribavirin or cidofovir therapy if positive for adenovirus or nalidixic acid if positive for BK virus. Oral hygiene will be maintained according to institutional standards. Prophylactic antimicrobial therapy will be started during the preparative regimen, per institutional guidelines.

An oral antibiotic for gastrointestinal decontamination will be administered according to institutional preference at least until the ANC is >500 following BMT. Antifungal prophylaxis will be administered according to institutional preference. The prophylactic anti-fungal drug will be discontinued if the patient is started on amphotericin B or other anti-fungal therapy empirically while neutropenic or for treatment of documented fungal infection. ***Pneumocystis jiroveci*** **pneumonia (PCP) prophylaxis will be administered with dapsone and should continue for the first year following BMT.** Patients intolerant of dapsone will receive either atovaquone, or pentamidine as PCP prophylaxis. Viral prophylaxis for HSV will be administered according to institutional preference. For adults at SKCCC, viral prophylaxis will consist of valacyclovir or acyclovir per institutional protocol. Although not required, CMV viremia (by PCR) or antigenemia (by ELISA) should be documented weekly beginning once the WBC>1000 and until discharge. Monitoring of CMV viremia or antigenemia is recommended to continue on a weekly basis until at least day 60, and preferably weekly until patients are off immunosuppressive therapy. Patients who are viremic or antigenemic will be treated preemptively per institutional guidelines.

5.8 Transfusion support
Platelet and packed red cell transfusions will be given per current institutional recommendations.
5.9 Anti-ovulatory treatment
Menstruating females should be started on an anti-ovulatory agent (recommended agent is Lupron) prior to the initiation of the preparative regimen.

5.10 Post-BMT evaluation
Patients will be followed during (i) the initial post-BMT period (ii) IPOP care and (iii) after discharge to the referring physician as per standard practice.

6.0 DATA MONITORING AND MANAGEMENT
This is a Level II study under the SKCCC CRO Data and Safety Monitoring Program. External data monitoring of this protocol by the SKCCC CRO QA Department will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Additionally, the protocol will be monitored internally by Dr. Brodsky, Dr Petri and Dr. DeZern on a routine basis. Trial monitoring and reporting will be done through the Data and Safety Monitoring Committee (DSMC).

6.1 Monitoring review plan
The protocol will be monitored internally by the co- principal investigators. The investigators (Dr. Petri, Dr. Brodsky and Dr. Bolaños Meade) will review data to assure the validity of data, as well as, the safety of the

subjects. They will also monitor the progress of the trial. The investigators will be responsible for maintaining the clinical protocol. The research nurses 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.

6.2 Adverse Event Reporting

Adverse events that will be reported should include: any mortality within the first 100 days after BMT, any graft failures (defined as <5% donor chimerism) associated with failure of neutrophil recovery to >500/mm^3 by day ~60 after transplantation, and all unexpected events as deemed significant by the PIs.

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 one of the PIs 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 4.0 at regular intervals as defined in the patient monitoring section (section 7.0).

Sponsor SAE Reporting to the FDA (for Sponsor/Sponsor-Investigator INDs) - All SAEs are reported to the FDA by the trial's IND Sponsor/Sponsor-Investigator via the IND annual report per 21 CFR 312.33. All SAEs deemed unexpected and related to the investigational product qualify for expedited reporting and must be submitted to the FDA by the IND Sponsor/Sponsor-Investigator per 21 CFR 312.32

Clinical Research Review and Monitoring Committee
550 North Broadway, Suite 1121
Baltimore, MD 21205
Phone: 410-955-8866
Fax: 410-614-1328

6.3 Toxicity Monitoring

6.3.1 GVHD

A major toxicity of allogeneic BMT is GVHD. Acute graft-versus-host disease (GVHD) shall be graded clinically according to the Keystone criteria. 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. In patients who develop GVHD, the GVHD Questionnaire must be completed at the time of onset, weekly until GVHD resolves, and 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 <u>acute GVHD</u>:

- 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 GVHD (Appendix 4).

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.

6.4 Transplant-related mortality (TRM)
Causes of TRM, i.e., death in the absence of relapse, 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 (<100 d post-BMT) or later times post-BMT.

6.5 Data Management
Enrollment data will be maintained in CRMS, and study data will be maintained on paper case report forms and appropriate Graft Engineering Laboratory spreadsheets. The research team will make assessments of GVHD. GVHD assessment will be evaluated and scored by the GVHD team, the Research Nurse, the attending BMT physician and PI. 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.

The study team will also compile and maintain a master adverse event log as well as a master protocol deviation log in Excel in compliance with the requirements of the JHU SKCCC Safety Monitoring Committee.

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)

	Initial	Allowable Time from consent	Day <60	Day 30	Day 60	Suspected

		date		+/-7	+/-7	GVHD
History and Physical	X	Within 30 days			X	
Performance status	X	Within 30 days				
CBC with Diff	X	Within 7 days	Weekly	X	X	
Comprehensive Metabolic Panel	X	Within 7 days	Weekly	X	X	
Bone marrow biopsy	X	Within 60 days			X	
CXR	X	Within 30 days			X	
Pregnancy test in women of child bearing age	X	Within 30 days				
Chimerism analysis	X			X	X	
PT/PTT	X	Within 30 days				
ECG	X	Within 30 days				
MUGA or ECHO	X	Within 30 days				
HepB Ag, HBC Ab, HCV Ab, HSV IgG, CMV IgG, RPR, HIV, VZV IgG (if possible)	X	Within 30 days Within 30 days				
Toxicity assessment	X			X	X	
HLA typing	X	Must be done at JHH				
PFTs (Spirometry and DLCO)	X	Within 30 days				
GVHD questionnaire	X	Within 30 days		X	X	
Sinus CT	X	Within 30 days				
Lymphocyte subsets	X				X	

Medical history

All patients will require documentation of a detailed history and physical examination.

I. Baseline investigations including:

a) Completion of all activity indices (physician's global asssessment, SELENA SLEDAI, PGA) and responder indices (BILAG, RIFLE – see Appendix); SLICC Damage Index, and SF-36 (health status)
b) SLE serologies
    i. C3, C4
    ii. ANA, anti-dsDNA, antiphospholipid antibodies (anticardiolipin, aCL, and lupus anticoagulant, LA)
    iii.
c) Hematologic
    i. CBC with platelets, differential.
    ii. PT, PTT
    iii. ABO and Rh typing
    iv. ESR
d) Hepatic
    i. Serum SGOT/AST, SGPT/ALT, Alkaline phosphatase, total and direct bilirubin,

7.1 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.

7.1.1 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) Episodes of CNS/extramedullary involvement
e) Allergies
f) Current medications
g) Assessment of performance status
h) Assessment of clinical activity of SLE, to be used in completion of the clinical indices (SELENA SLEDAI and SLAM) and responder indices (BILAG and RIFLE).

7.1.2 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.

7.1.3 Baseline investigations including:

a) Completion of all activity indices (physician's global assessment, SELENA SLEDAI, PGA see Appendix) and responder indices (BILAG, RIFLE – see Appendix); SLICC Damage Index, and SF-36 (health status)
b) SLE serologies

    i. C3, C4, ~~CH50~~
    ii. ANA, dsDNA (Crithidia), antiphospholipid antibodies (anticardiolipin, aCL, and lupus anticoagulant, LA)

c) Hematologic
   i. CBC with platelets, differential, reticulocyte count
   ii. PT, PTT
   iii. ABO and Rh typing
   iv. Bone marrow aspirate and biopsy
d) Chemistries
   i. Comprehensive chemistry panel
e) Renal
   i. M6, M12
   ii. Routine microscopic urinalysis with C &S
   iii. Serum creatinine
   iv. 24-hour urine for creatinine clearance and total protein, or spot protein/creatinine ratio
f) Cardiac
   i. EKG
   ii. Echocardiogram or MUGA scan with Left Ventricular Ejection Fraction (LVEF)
g) 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)
h) 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
i) RFLP studies will be drawn as a baseline for subsequent engraftment studies when the donor and patient are the same gender.
j) Additional tests (if applicable)
   i FSH (females)
   ii Testosterone (males)
   iii Beta HCG

7.2 Post-transplant Evaluation

7.2.1 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 daily with a WBC differential once the total WBC is greater than 100 until ANC > 500 for three days or two consecutive measurements over a three day period. Then, CBC weekly with differential.
b) Comprehensive metabolic panel once a week.
c) Patients will have evaluations for infectious complications as clinically indicated. Surveillance cultures according to JHOC BMT program standards are recommended.
d) Evaluations by history and physical examination for GVHD will be performed as per BMT unit standards. For study purposes, weekly GVHD summaries will be taken from these standard examinations from Day 14 through Day 60.

7.2.2 Evaluations on Day ~ 30 (+7 days)

a) History and physical examination.
b) T cell and unsorted chimaerism or XY FISH for donor chimerism on peripheral blood.
c) CBC and differential, comprehensive panel.
d) GVHD questionnaire.

7.2.3 Evaluations on day ~60 (+7 days)

a) History and physical examination.
b) T cell and unsorted chimaerism Studies for donor cell chimerism on peripheral blood and bone marrow.
c) CBC and white blood cell differential, reticulocyte count, comprehensive panel, lymphocyte subsets.
d) GVHD questionnaire.

8.0 RISKS AND TOXICITIES

8.1 Cyclophosphamide after graft infusion

The major risk of participating in this research protocol is that shifting part of the standard BMT dose of cyclophosphamide after the graft infusion may damage the graft. The consequences of damaging the graft may include delayed hematologic recovery, graft failure, or treatment-related malignancy in donor cells. The risk of delayed hematologic recovery does not appear to be severe, because patients who have engrafted with donor cells in the setting of a nonmyeloablative preparative regimen incorporating the same post-BMT dose of cyclophosphamide experienced only approximately two weeks of neutropenia. However, the risks of delayed hematologic recovery in this study cannot be directly extrapolated from referenced studies due to more intense pre-transplant chemotherapy with busulfan and cyclophosphamide in this protocol. 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 given the use of a myeloablative preparative regimen and haploidentical donors. 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 4.0for the first 60 days post BMT.
Since this trial is an out-patient trial, the definition of an adverse event 'interfering with daily function' and 'clinically significant' will be events that require hospitalization. For example, if a patient has a neutropenic fever that requires hospitalization, then 'neutropenic fever' will be captured and graded as an adverse event. An example of a non-captured event is if a patient has hypotension that is corrected by fluid administration in the outpatient setting. This will not be captured as an adverse event unless the patient requires a hospital admission for further treatment of the hypotension.
Once the patient becomes hospitalized, the above definition of 'requiring hospitalization' cannot be used to capture adverse events. For these already hospitalized patients, events will only be recorded once the event is greater than a grade 3 or 4 as stated below.
The following is a list of categories that will not be recorded unless the event becomes a grade 4 or meets the criteria of a 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 Cyclophosphamide (Cytoxan)
Cyclophosphamide Toxicities:

a) Hematologic: Leukopenia, anemia
b) Dermatologic: Alopecia
c) Gastrointestinal: Nausea, vomiting, increased AST, ALT, mucositis, diarrhea
d) Neurologic: Headache, dizziness
e) Cardiovascular: Cardiac necrosis rarely with high dose cyclophosphamide
f) Renal: Hemorrhagic cystitis, SIADH
g) Other: teratogenic, may cause secondary neoplasms, anaphylaxis (rare)
h) Fluid retention. Cy has anti-diuretic effect usually counteracted by furosemide administration. Careful physical examination should be made and accurate weights should be determined to detect fluid overload early.
i) Cardiomyopathy. At doses greater than 200mg/kg, Cy can cause fatal myocardial necrosis with clinical heart failure. Non-specific ST changes on EKG are not unusual but a decrease in voltage is significant.
j) 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.

8.5 Mesna (sodium -2-mercapto ethane sulphonate)
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.

8.6 Tacrolimus/FK-506
Adverse reactions include tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction.

8.7 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. The drug has been associated with fetal malformations.

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

8.9 Aplasia
Pancytopenia is an expected side effect of allogeneic BMT with the use of myeloablative preparative regimens. Given the previous experience with post-transplant cyclophosphamide 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.

9.0 STUDY PARAMETERS

9.1 Donor chimerism
Donor chimerism will be measured in the peripheral blood around day 30 and again in the peripheral blood and bone marrow around day 60. Patients with any amount of donor chimerism around day 60 will be considered as having 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 >0%, but <95%.
Complete donor chimerism will be defined as >95%. Patients who have relapsed or died prior to day 60 will not be evaluable for full donor chimerism, as these are competing risk factors.

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 relapse or progression, will be characterized at 100 days and 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 Antibodies developed after HLA mismatched bone marrow transplantation
Pre- and Post-Transplant Antibody Samples:
Ideally, in addition to a pre-transplant baseline (the pre-transplant sample is a routine clinical test that is performed on all patients being evaluated for HSCT), all participants will have multiple post-transplant samples tested for donor-specific antibodies. Recognizing that this requirement may limit participation, data will be accepted on any subject provided there is at least one post-transplant sample analyzed, preferably one tested between 2 weeks to 1 month post –transplant.

The following are the time points recommended, considering the transplant date as Day 0:
Pre-Transplant - 30 to -7 days (30 days to 1 week pre-transplant)
Post-Transplant 1 +7 to +14 days (1 week to 2 weeks post-transplant)

Post-Transplant 2 +14 to +30 days (2 weeks to 1 month post-transplant)
Post-Transplant 3 +2 to +3 months (2 to 3 months post-transplant)
Post-Transplant 4 +4 to 6 months (4 to 6 months post-transplant)

Antibody analysis will be performed by solid phase assays using soluble HLA molecules bound to microbeads as targets. To ensure comparable results, the antibody assays will be performed using flow cytometric or luminex platforms. Sera can be screened using multiantigen assays, but specificity should be confirmed with single phenotype and/or single antigen assays.

One red top should be drawn and sent with an immunogenetics requisition that is marked "Post-Transplant Antibody Assay". The contact person is:

Suraya Berger
saberger@jhmi.edu
410-955-3600
JHU Immunogenetics Laboratory
2041 E. Monument Street.
Baltimore, MD 21205

10.0 Statistical Methods

Overall Study Design

This study is a single-arm feasibility study of a busulfan/cyclophosphamide conditioning regimen and post transplantation cyclophosphamide with matched, partially matched, haplo-identical or unrelated donors in patients with refractory SLE. With this trial we seek to expand the donor pool as well as reduce the occurrence of graft versus host disease.

10.1 Accrual

We plan to enroll a total of 25 patients. It is estimated that one year of accrual will be necessary to enroll the targeted sample size. Patients will be followed on the study for a minimum of one year after accrual ends.

10.2 Primary Objective

The primary endpoint of this study will be the feasibility of this conditioning regimen and post transplantation cyclophosphamide in refractory SLE patients with donors having various degrees of matching.

10.3 Secondary Objectives

10.3.1 To estimate the improvement in the RIFLE (Responder index in Lupus Erythematosus) score with the goal as target organ complete response with no worsening in any other organ at 12 months.

10.3.2 Estimate the proportion of patients that have an improvement of 4 points on the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index).

10.3.3 Estimate the proportion of patients with an improvement in PGA (Physician's Global Assessment) to 0.5 or less.

10.3.4 To estimate the overall survival (OS) and event-free survival (EFS) at 1 year.

10.3.5 To estimate the cumulative incidence of full donor chimerism by day 60

10.3.6 To estimate the cumulative incidence of non–relapse-related mortality following transplant.

10.3.7 To estimate the incidences of primary and secondary graft failure following transplant.

10.3.8 To estimate the cumulative incidences of grade II-IV and grade III-IV graft versus-host disease (GVHD).

10.3.9 To estimate the cumulative incidence of chronic graft versus-host disease (GVHD).

10.3.10 Summarize all hematologic and non-hematologic toxicities.

10.4 Analysis of Primary Endpoint

The analysis of the primary endpoint will be descriptive, reporting the overall percentage of patients with full donor chimerism by day 60, no treatment related mortality, no primary or secondary graft failures, no relapse and no acute or chronic graft versus host disease. With 25 patients, the width of the exact binomial confidence interval for this proportion will be approximately ±0.26. Similar analyses will be done for each of the histocompatability categories: matched, partially matched, haplo-identical or unrelated. If the stopping rule for safety is not triggered and we see reproducible results across categories with varying degrees of matching, we would be interested in pursuing this treatment strategy for refractory SLE.

10.5 Analysis of Secondary Endpoints

10.5.1 For each patient's target organ, the 12 month response will be assessed as: complete, partial, the same, or worse. Response category proportions will be reported with exact binomial 95% confidence intervals.

10.5.2 SLEDA index scores will be assessed pre and post study. The changes in score will be summarized with a mean and 95% confidence interval. For patients with an initial SLEDAI of ≥4, the proportion of patients with an improvement of 4 points will be reported with a 95% confidence interval.

10.5.3 PGA scores will be evaluated pre and post study. Changes will be summarized descriptively and the proportion of patients with an improvement to 0.5 on this scale will be reported.

10.5.4 Overall survival: Standard life table methods will be used to analyze OS. We will report the one-year OS with a 95% confidence interval.

10.5.5 We will estimate the cumulative incidence function for achieving full donor chimerism, where relapse or death prior to full donor chimerism by day 60 will be considered as competing events. The period of time during which a transplant recipient is likely to achieve full donor chimerism will be calculated from the date of BMT to the date on which full donor chimerism is achieved. Graphs of cumulative incidence vs. time will be produced, and the cumulative incidence of full donor chimerism by day 60 will be estimated along with a 90% confidence interval.

10.5.6 NRM: To estimate the cumulative incidence of non–relapse-related mortality following transplant, a cumulative incidence curve will be produced. Incidence of NRM will be estimated at 60 days, 100 days, six months, and one year along with 90% confidence intervals. Disease progression or death related to disease progression will be considered as competing events.

10.5.7 Graft failure: To estimate the incidence of primary and secondary graft failure following transplant. Exact binomial 95% confidence intervals will be reported.

10.5.8 Acute GVHD: To estimate the cumulative incidence of grade II-IV and grade III-IV acute GVHD from day of transplant. The first day of acute GVHD onset for a given grade will be used to estimate the cumulative incidence curves. An overall cumulative incidence will be estimated along with a 90% confidence interval at 100 days post-transplant with graft failure, disease progression or death prior to occurrence of acute GVHD considered as competing events.

10.5.9 Chronic GVHD: To estimate the cumulative incidence and severity of extensive chronic GVHD from day of transplant, the first day of clinical onset of extensive chronic GVHD will be used to estimate a cumulative incidence curve. Incidences of chronic GVHD at one and two years post-transplant will be estimated along with

90% confidence intervals. Death, disease progression, or graft failure prior to occurrence of chronic GVHD will be considered as competing events.

10.5.10 Additional hematologic and non-hematologic toxicities: These will be recorded using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals as defined in the patient monitoring section (section 7.0). Toxicities will be tabulated by type and appropriate confidence intervals will be estimated.

10.6 Stopping Rule

A Bayesian monitoring rule for two adverse events, failure to engraft by Day 60 (A_1) and grade III-IV acute GVHD (A_2), will be used to monitor the trial for safety after every 5 patients. Use of this conditioning regimen would be reconsidered if the probability of engraftment failure by day 60 is > 25% or the probability of severe acute GVHD is > 25%. This design is based on the Bayesian posterior probability derived for the bivariate case [Etzioni et al. The likelihood assumes that occurrence of one adverse event precludes that of the other. In the absence of previous experience with this regimen, a bivariate uniform prior distribution is assumed. The posterior distribution is a product of piecewise beta densities and the calculation has been programmed using Mathematica [Mathematica].

Acceptable safety with this stopping rule is defined such that the posterior probability that the frequency of non-engraftment by day 60 is greater than 25% or severe acute GVHD is greater than 25% is < 0.80. In the course of this study, if the posterior probability exceeds 0.80, accrual to the trial will be temporarily halted and the DSMB will review the data and recommend either modification or termination of the trial.

Tables 2a-e show the stopping rule for the sample sizes of 5, 10, 15, 20, and 25 patients when the allowed probability of non-engraftment by day 60 is 25% and severe acute GVHD is 25%. The bolded/highlighted cells are combinations of non-engraftment and severe acute GVHD events that would temporarily halt the trial using a threshold for the Bayesian posterior probability of 80%. For example, if the current sample size of the study is 5 patients (Table 2a) and 3 patients fail to engraft by day 60 and 1 patient experiences severe acute GVHD, the posterior probability that this regimen is not acceptable would be 92% and the study would be halted for review.

Table 2a: Posterior probabilities of excessive engraftment failure (EF) and severe acute GVHD risk. Bolded/highlighted boundary corresponds to numbers of EF or GVHD where the posterior probabilities are high (80% or more) that these events' risks exceed the threshold of 25%. This table applies to the first five patients.

	Number of Grade III-IV aGVHD					
Number of EF	0	1	2	3	4	5
0	0.03	0.10	0.29	0.68	**0.95**	1
1	0.11	0.24	0.57	**0.90**	0.99	1
2	0.34	0.59	**0.88**	0.99	1	1
3	0.75	**0.92**	0.99	1	1	1
4	**0.97**	1	1	1	1	1
5	1	1	1	1	1	1

Table 2b: Posterior probabilities and stopping boundaries for the first 10 patients.

	Number of Grade III-IV aGVHD							
Number of EF	0	1	2	3	4	5	6	7
0	0.01	0.02	0.06	0.15	0.35	0.66	**0.90**	0.98
1	0.02	0.04	0.10	0.23	0.50	**0.81**	0.96	1
2	0.06	0.10	0.19	0.40	0.71	**0.92**	0.99	1
3	0.16	0.23	0.40	0.66	**0.89**	0.98	1	1
4	0.38	0.50	0.70	**0.89**	0.98	1	1	1
5	0.70	**0.80**	**0.92**	0.98	1	1	1	1

6	**0.92**	0.96	0.99	1	1	1	1	1
7	0.99	1	1	1	1	1	1	1

Table 2c: Posterior probabilities and stopping boundaries for the first 15 patients.

Number of EF	**Number of Grade III-IV aGVHD**									
	0	1	2	3	4	5	6	7	8	9
0	0	0.01	0.02	0.04	0.1	0.22	0.44	0.71	**0.9**	0.98
1	0.01	0.01	0.03	0.06	0.14	0.29	0.54	**0.8**	0.94	0.99
2	0.02	0.03	0.05	0.1	0.2	0.4	0.68	**0.89**	0.97	1
3	0.05	0.06	0.09	0.17	0.32	0.57	**0.82**	0.95	0.99	1
4	0.11	0.13	0.19	0.31	0.52	0.76	**0.93**	0.98	1	1
5	0.23	0.27	0.37	0.54	0.75	**0.91**	0.98	1	1	1
6	0.45	0.51	0.63	0.79	**0.91**	0.98	1	1	1	1
7	0.72	0.78	**0.86**	**0.94**	0.98	1	1	1	1	1
8	**0.91**	**0.93**	0.97	0.99	1	1	1	1	1	1
9	0.98	0.99	0.99	1	1	1	1	1	1	1

Table 2d: Posterior probabilities and stopping boundaries for the first 20 patients.

Number of EF	**Number of Grade III-IV aGVHD**												
	0	1	2	3	4	5	6	7	8	9	10	11	12
0	0	0	0.01	0.02	0.04	0.08	0.16	0.31	0.53	0.76	**0.91**	0.98	0.99
1	0	0	0.01	0.02	0.05	0.1	0.2	0.38	0.61	**0.83**	0.94	0.99	1
2	0.01	0.01	0.01	0.03	0.06	0.13	0.26	0.46	0.71	**0.89**	0.97	0.99	1
3	0.02	0.02	0.03	0.05	0.09	0.18	0.35	0.58	**0.81**	0.94	0.99	1	1
4	0.04	0.04	0.06	0.09	0.15	0.28	0.48	0.72	**0.89**	0.97	0.99	1	1
5	0.08	0.09	0.11	0.16	0.26	0.43	0.65	**0.85**	0.95	0.99	1	1	1
6	0.16	0.18	0.21	0.29	0.43	0.63	**0.82**	0.94	0.98	1	1	1	1
7	0.31	0.34	0.39	0.5	0.66	**0.82**	0.93	0.98	1	1	1	1	1
8	0.53	0.56	0.63	0.74	**0.85**	0.94	0.98	1	1	1	1	1	1
9	0.77	0.79	**0.84**	**0.9**	0.95	0.98	1	1	1	1	1	1	1
10	**0.92**	**0.93**	0.95	0.97	0.99	1	1	1	1	1	1	1	1
11	0.98	0.98	0.99	0.99	1	1	1	1	1	1	1	1	1
12	0.99	1	1	1	1	1	1	1	1	1	1	1	1

Table 2e: Posterior probabilities and stopping boundaries for 25 patients.

Number of EF	**Number of Grade III-IV aGVHD**														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	0	0	0	0.01	0.01	0.03	0.07	0.13	0.23	0.4	0.62	**0.81**	0.93	0.98	0.99
1	0	0	0	0.01	0.02	0.04	0.08	0.15	0.28	0.47	0.69	**0.86**	0.95	0.99	1
2	0	0	0	0.01	0.02	0.05	0.1	0.18	0.33	0.54	0.76	**0.9**	0.97	0.99	1
3	0.01	0.01	0.01	0.02	0.03	0.07	0.12	0.23	0.41	0.63	**0.83**	0.94	0.98	1	1
4	0.01	0.02	0.02	0.03	0.05	0.09	0.17	0.31	0.51	0.73	**0.89**	0.97	0.99	1	1
5	0.03	0.03	0.04	0.05	0.08	0.14	0.25	0.41	0.63	**0.83**	0.94	0.98	1	1	1
6	0.07	0.07	0.08	0.1	0.14	0.23	0.37	0.56	0.77	**0.91**	0.97	0.99	1	1	1
7	0.13	0.13	0.15	0.18	0.25	0.36	0.53	0.73	**0.88**	0.96	0.99	1	1	1	1
8	0.23	0.24	0.27	0.32	0.41	0.55	0.72	**0.87**	0.95	0.99	1	1	1	1	1
9	0.4	0.41	0.45	0.52	0.62	0.75	**0.87**	0.95	0.98	1	1	1	1	1	1
10	0.62	0.63	0.67	0.73	**0.82**	**0.9**	0.95	0.98	1	1	1	1	1	1	1
11	**0.81**	**0.82**	**0.85**	**0.89**	0.93	0.97	0.99	1	1	1	1	1	1	1	1
12	0.93	0.93	0.95	0.96	0.98	0.99	1	1	1	1	1	1	1	1	1

13	0.98	0.98	0.98	0.99	1	1	1	1	1	1	1	1	1	1	1
14	0.99	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Operating characteristics of stopping rule:

The probability of stopping the study early under three different scenarios, three thresholds, and fixed looks after every 5 patients is shown in Table 3. The maximum allowed risk of engraftment failure (EF) by day 60 is 25% and of severe acute GVHD (aGVHD) is 25%. The following table shows the frequency of stopping under several scenarios corresponding to different actual risks of these events. The probability of stopping early was calculated from 5000 simulated trials for sample sizes of 25 with 3 different posterior probability thresholds: 0.60, 0.70 and 0.80. This trial is using 0.80 for the posterior threshold. The average sample size of the simulated studies is given in parentheses.

Table 3: Probability of stopping early under three scenarios with average sample size in parentheses.

			"True" Risks in the Simulations	
Posterior Threshold	Planned Sample size	EF risk = 25% & aGVHD risk = 25%	EF risk =35% & aGVHD risk =.40%	EF risk =.25 & aGVHD risk = 45%
0.60	25	**.42 (18.7)**	**.88 (10.1)**	**.83 (10.9)**
0.70	25	**.36 (19.9)**	**.81 (11.2)**	**.76 (12.2)**
0.80	25	**.27 (21.2)**	**.74 (12.3)**	**.71 (12.9)**

11.0 RISKS AND BENEFITS

11.1 Risks and toxicity

The major toxicity of using bone marrow from HLA-mismatched, related donors is GVHD. The incidence of severe aGVHD (Grades III-IV)) on the phase I nonmyeloablative haploidentical BMT trial utilizing 2 doses of post-transplantation Cy, 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 nonmyeloablative BMT using post-transplantation Cy to maximize engraftment and minimize GVHD. The potential benefit of this trial is a durable recovery from systemic lupus erythematosus.

12.0 INFORMED CONSENT

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 JCCI IRB.

12.1 On-study date

Date of consent signing.

12.2 Off-study date

Upon completion of "Day 360" evaluations, patients have completed their treatment except for Patient follow-up beyond day 360 will consist of collecting information regarding ongoing engraftment, disease status, late effects of this protocol, acute and chronic graft vs- host disease, immune reconstitution, additional therapies, and survival as per standard BMT long-term follow-up. Patients will go off study early in the event of:

1. Death
2. Patient decision (or decision by a parent or guardian on behalf of a minor)
3. Unacceptable toxicity associated with protocol therapy, as determined by the treating physicians in consultation with the investigators.

APPENDIX 1

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.

LANSKY PERFORMANCE STATUS SCALE

100	Fully active, normal
90	Minor restrictions in strenuous physical activity
80	Active, but tired more quickly
70	Greater restriction of play *and* less time spent in play activity
60	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50	Lying around much of the day, but gets dressed; no active playing participates in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bedbound; needing assistance even for quiet play
20	Sleeping often; play entirely limited to very passive activities
10	Doesn't play; does not get out of bed
0	Unresponsive

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 ofassistance 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
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 bronchiolits 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
Acute GVHD Evaluation Form
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: RIFLE

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

RESPONDER INDEX FOR SYSTEMIC LUPUS ERYTHEMATOSUS (RIFLE)

PREPARED SEPTEMBER 14, 1998 AT IDEC MEETING by:
Michelle Petri, Ken Kalunian, Joan Merrill, David Wofsy, Ellen Ginzler, John Davis, Jill Buyon

GUIDELINE FOR USE: At each physician encounter, score RIFLE as a comparison to the previous encounter except at the last visit compare to both the first (baseline) encounter and the final encounter. All must be attributable to SLE.

A. ORGAN SYSTEMS

1. Neurological DEFINITIONS

a) CNS

psychosis

☐	*not present*	
☐	*worsening*	new or progressive as per SLEDAI glossary
☐	*present, no change*	
☐	*partial response*	signs of improvement with no increase in anti-psychotic meds
☐	*resolution*	no psychosis but can be on stable medication

seizures (any type)

☐	*not present*	
☐	*worsening*	new or increase in frequency
☐	*present, no change*	
☐	*partial response*	a 50% decrease in frequency (over 1 month) without increase in seizure meds
☐	*resolution*	no seizures for 3 months but can be on stable medications

impairment of cognitive function

☐	*not present*	
☐	*worsening*	new or progressive as per SLEDAI glossary (worsening mini mental exam)
☐	*present, no change*	
☐	*partial response*	improvement in mini-mental exam but not return to normalcy
☐	*resolution*	normal mini-mental exam

TIA/stroke

☐	*not present*	
☐	*worsening*	new TIA or CVA due to lupus including secondary aPS
☐	*present, no change*	
☐	*partial response*	decreased frequency of TIAs over three months
☐	*resolution*	no TIAs over three months, can be on stable therapeutic anticoagulation

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

meningitis (requires LP)

☐ *not present*
☐ *worsening* new meningitis by LP (culture negative), for pre-existing meningitis new physical findings, new obtundation, new papilledema
☐ *present, no change*
☐ *partial response* reduction in headache and meningeal signs, improvement in level of consciousness
☐ *resolution* no meningeal signs, normal level of consciousness, no papilledema

pseudotumor cerebri (requires CT or MRI)

☐ *not present*
☐ *worsening* new pseudotumor cerebri by LP, CAT, or MRI, if present worsening headache and visual symptoms
☐ *present, no change*
☐ *partial response* improvement in signs (as in meningitis) without new treatment (i.e., remains on stable treatments)
☐ *resolution* asymptomatic and normal fundoscopic exam

scleritis and episcleritis

☐ *not present*
☐ *worsening* new scleritis or episcleritis
☐ *present, no change*
☐ *partial response* ≥50% improvement by ophthalmologic exam
☐ *resolution* normal ophthalmologic exam and on no medications

optic neuritis

☐ *not present*
☐ *worsening* new optic neuritis
☐ *present, no change*
☐ *partial response* ≥50% improvement by ophthalmologic exam and/or visual acuity
☐ *resolution* normal ophthalmologic exam and/or visual acuity on no medications

uveitis

☐ *not present*
☐ *worsening* new uveitis
☐ *present, no change*
☐ *partial response* ≥50% improvement by ophthalmologic exam
☐ *resolution* normal ophthalmologic exam

retinitis

☐ *not present*
☐ *worsening* new retinitis
☐ *present, no change*
☐ *partial response* ≥50% improvement by ophthalmologic exam
☐ *resolution* normal ophthalmologic exam

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

chorea
- ☐ *not present*
- ☐ *worsening* new or worsening chorea
- ☐ *present, no change*
- ☐ *partial response* ≥50% improvement
- ☐ *resolution* not present

ataxia
- ☐ *not present*
- ☐ *worsening* new or worsening ataxia
- ☐ *present, no change*
- ☐ *partial response* ≥50% improvement
- ☐ *resolution* not present

encephalopathy
- ☐ *not present*
- ☐ *worsening* new coma or deteriorating level of consciousness
- ☐ *present, no change*
- ☐ *partial response* ≥50% improvement
- ☐ *resolution* not present

cord (transverse myelitis)
- ☐ *not present*
- ☐ *worsening* new or worsening sensory and/or motor symptoms or signs
- ☐ *present, no change*
- ☐ *partial response* any improvement in sensory and/or motor symptoms
- ☐ *resolution* complete resolution, normal neurologic exam

b) Peripheral

cranial neuropathy
- ☐ *not present*
- ☐ *worsening* new one and/or worsening of an existing one
- ☐ *present, no change*
- ☐ *partial response* decrease in total number of cranial nerves involved if originally more than one and/or improvement in a single cranial nerve if only one is involved (e.g., ptosis less marked if III, improved sensation if V, improved motor strength if VII)
- ☐ *resolution* absence of any cranial neuropathy

mononeuritis multiplex
- ☐ *not present*
- ☐ *worsening* new mononeuropathy or progression of existing mononeuropathy
- ☐ *present, no change*
- ☐ *partial response* improvement in sensory, motor, or reflexes, but not to normal in 3 months
- ☐ *resolution* normal motor, sensory, and reflex exam

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

neuropathy (sensory or motor)

☐ *not present*
☐ *worsening* new sensory or motor neuropathy or progression of existing sensory neuropathy
☐ *present, no change*
☐ *partial response* improvement in sensory or motor symptoms but not to normal
☐ *resolution* normal sensory exam

2. Renal

proteinuria

☐ *not present*
☐ *worsening* *a)* if baseline proteinuria <500 mg/24 h then increase of 500 mg/24 h
b) if baseline proteinuria ≥500 mg/24 h then 100% increase
☐ *no change*
☐ *partial response* improvement by 50% but not to normal value <500 mg/24 hr, *do not count if reduction in proteinuria is considered due to reduction in GFR or the addition of ACE inhibitors*
☐ *resolution* <500 mg/24 h, *do not count if reduction in proteinuria is due to reduction in GFR or the addition of ACE inhibitors*

RBC

☐ *not present*
☐ *worsening* *a)* if baseline 5-10, increase to >20
b) if baseline >10, increase by 200%
☐ *present, no change*
☐ *partial response* 50% reduction from baseline
☐ *resolution* decrease to <5 RBC/hpf

RBC casts

☐ *not present*
☐ *worsening* any new cast, or
a) if baseline 1-10, increase to 20 or greater
b) if baseline >10, 100% increase
☐ *present, no change* ***if baseline 1-10, no change means remains at 1-19***
☐ *partial response* *a)* if baseline >10 must be 50% reduction
☐ *resolution* no RBC casts

abnormal creatinine

☐ *not present*
☐ *worsening* *a)* increase >0.3 if baseline ≤1.5
b) increase >0.5 if baseline >1.5
☐ *no change*
☐ *partial response* *a)* decrease of 0.5 if baseline ≤2.5
b) decrease of 1.0 if baseline >2.5
☐ *resolution* ≤1.0 mg/dl

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

abnormal Cr clearance
☐ *not present*
☐ *worsening* 30% worsening
☐ *present, no change*
☐ *partial response* 30% improvement
☐ *resolution* normal for body mass

3. Mucocutaneous

photosensitivity
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

malar rash
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

discoid/follicular plugging
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

bullous
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

vasculitis
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

Rifle cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

mucocutaneous ulcers
☐ *not present*
☐ *worsening* new or more frequent (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

alopecia
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

panniculitis
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

angioedema/urticaria
☐ *not present*
☐ *worsening* new lesions or worsening (number, frequency, or distribution)
☐ *present, no change*
☐ *partial response* decrease by ≥50% (number, frequency, or distribution)
☐ *resolution* no lesions in 3 months

4. <u>Musculoskeletal</u>

arthritis
☐ *not present*
☐ *worsening* any new tender or swollen joint (even if synovitis in previous joints had improved)
☐ *no change*
☐ *partial response* ≥50% reduction in tender and swollen joints
☐ *resolution* no tender or swollen joints

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

myositis

☐ *not present*
☐ *worsening* new myositis or increasing weakness in 2 muscle groups or increase of ≥50% in CPK and/or aldolase
☐ *no change*
☐ *partial response* ≥50% improvement in CPK and/or aldolase and muscle strength within 3 months
☐ *resolution* normal CPK and aldolase, normal strength

tendinitis

☐ *not present*
☐ *worsening* new tendinitis (even if previous tendinitis improved) or worsening of existing tendinitis. Must be distinguished from the tender points of fibromyalgia.
☐ *no change*
☐ *partial response* ≥50% improvement
☐ *resolution* no tendinitis

5. <u>Cardiac</u>

pericarditis

☐ *no change*
☐ *worsening* new pericarditis, worsening by echo of pre-existing pericarditis, or signs of cardiac tamponade (pulsus paradoxicus)
☐ *no change*
☐ *partial response* any improvement in symptoms
☐ *resolution* no evidence of pericardial disease

myocarditis

☐ *not present*
☐ *worsening* new or worsening by echo and/or clinical symptoms or signs
☐ *no change*
☐ *partial response* improved symptoms and/or improved echo but not normal
☐ *resolution* no symptoms, echo returns to baseline, enzymes normal

valvular abnormalities

☐ *not present*
☐ *worsening* new murmur confirmed by echo or worsening valvular function by echo
☐ *no change*
☐ *partial response* reduction in valvular vegetations or valvular dysfunction by echo
☐ *resolution* normal valvular function and integrity by echo

pulmonary hypertension

☐ *not present*
☐ *worsening* new onset, or increase of ≥20 mm Hg in PA pressure by either echo or arteriogram
☐ *no change*
☐ *partial response* decrease of ≥20 mm Hg in PA pressure by either echo or arteriogram
☐ *resolution* normalization to <25 mm Hg in PA pressure by either echo or arteriogram

Rifle Cont.

Visit Date: _____
Patient Study Code: _____
Patient History Number: _____
Patient Name: _____
MD Initials: _____

6. Pulmonary

pleuritis

☐ *not present*
☐ *worsening* new symptoms or any increase in frequency or severity of symptoms, or increase in pleural effusions
☐ *no change*
☐ *partial response* any improvement in symptoms and/or reduction in pleural effusions
☐ *resolution* no signs or symptoms and nl CXR

pneumonitis

☐ *not present*
☐ *worsening* any new pneumonitis or any worsening in any pulmonary function tests or CXR or CT
☐ *no change*
☐ *partial response* any improvement in symptoms, PFTS, or CXR/CT
☐ *resolution* no signs or symptoms and nl PFTs and CXR/CT

hemorrhage

☐ *not present*
☐ *worsening* any new hemorrhage or worsening of hemorrhage as assessed by symptoms or signs
☐ *no change*
☐ *partial response* improvement by symptoms or signs (e.g., CXR)
☐ *resolution* asymptomatic and CXR returns to baseline

7. Gastrointestinal

vasculitis

☐ *not present*
☐ *worsening* new or worsening
☐ *no change*
☐ *partial response* any improvement by colonoscopy
☐ *resolution* asymptomatic, guaiac neg, normal colonoscopy

colitis

☐ *not present*
☐ *worsening* any new or worsening symptoms
☐ *no change*
☐ *partial response* ≥50% improvement in bowel movements and or decreased abdominal pain or blood loss
☐ *resolution* asymptomatic, guaiac neg, normal colonoscopy

serositis (peritonitis)

☐ *not present*
☐ *worsening* any new symptoms; worsening of symptoms or increasing ascites by ultrasound
☐ *no change*
☐ *partial response* any improvement in symptoms, reduction of ascites by ultrasound
☐ *resolution* asymptomatic and no ascites by ultrasound

Rifle Cont.

pancreatitis
- ☐ *not present*
- ☐ *worsening* any new symptoms; worsening of symptoms or increase of amylase or lipase
- ☐ *no change*
- ☐ *partial response* any improvement in symptoms or amylase or lipase
- ☐ *resolution* asymptomatic and normal amylase and lipase

hepatitis
- ☐ *not present*
- ☐ *worsening* any new or worsening of liver transaminases
- ☐ *no change*
- ☐ *partial response* any improvement in symptoms or liver transaminases
- ☐ *resolution* asymptomatic and normal liver transaminases

protein losing enteropathy
- ☐ *not present*
- ☐ *worsening* any new or increasing symptoms or decreasing serum albumin (x2)
- ☐ *no change*
- ☐ *partial response* any improvement in serum albumin and decrease in frequency of bowel movements
- ☐ *resolution* asymptomatic and normal serum albumin

8. <u>Hematologic</u>

splenomegaly
- ☐ *not present*
- ☐ *worsening* any new or increase in size of spleen by physical exam or ultrasound
- ☐ *no change*
- ☐ *partial response* any reduction in size by physical exam or ultrasound
- ☐ *resolution* asymptomatic and normal size by exam or ultrasound

hemolytic anemia
- ☐ *not present*
- ☐ *worsening* new hemolysis or decrease in HCT by 20% and lab confirmation of hemolysis
- ☐ *no change*
- ☐ *partial response* any improvement in HCT and decrease in reticulocyte count
- ☐ *resolution* return to baseline HCT and nl retic count

TTP
- ☐ *not present*
- ☐ *worsening* any new or worsening features of TTP
- ☐ *no change*
- ☐ *partial response* improvement in smear, HCT, plt count, fever or neurologic status, improvement in renal status
- ☐ *resolution* normal HCT, normal plt, normal renal function, normal neurologic status, no fever

leukopenia
- ☐ *not present*
- ☐ *worsening* new to <3,000 or decrease of ≥25% from pre-existing leukopenic value
- ☐ *no change*
- ☐ *partial response* 50% improvement
- ☐ *resolution* >3,000

Rifle Cont.

lymphopenia

☐	*not present*	
☐	*worse*	new to <1,000 or 25% decrease from pre-existing lymphopenic value
☐	*no change*	
☐	*partial response*	50% improvement
☐	*resolution*	>1,000

neutropenia

☐	*not present*	
☐	*worse*	new to <1,800 or 25% decrease from pre-existing neutropenic value
☐	*no change*	
☐	*partial response*	50% improvement
☐	*resolution*	>1,800

thrombocytopenia

☐	*not present*	
☐	*worsening*	new to <100k or 25% decrease from pre-existing thrombocytopenia
☐	*no change*	
☐	*partial response*	≥50% improvement
☐	*resolution*	≥150k

9. <u>Constitutional</u>

fever

☐	*not present*	
☐	*worsening*	new temperature to ≥38°C
☐	*present, no change*	
☐	*partial improvement*	improvement with or without antipyretics for 1 wk
☐	*resolution*	<38°C on no antipyretics

weight loss

☐	*not present*	
☐	*worsening*	new involuntary loss of 5% in 1 month
☐	*present, no change*	
☐	*partial improvement*	weight gain but not to baseline or desired weight
☐	*resolution*	no involuntary weight loss and either return to baseline or desired weight

lymphadenopathy (palpable, >1 cm diameter)

☐	*not present*	
☐	*worsening*	any new or increase in size and distribution of pre-existing lymphadenopathy not due to infection
☐	*present, no change*	
☐	*partial improvement*	any decrease in size and distribution
☐	*resolution*	no lymphadenopathy

<u>B. IMMUNE SYSTEM</u>

1. <u>Autoantibodies</u>

anti-dsDNA

☐	*not present*	
☐	*worsening*	newly positive by any assay, or doubling of abnormal titer
☐	*present, no change*	
☐	*partial improvement*	50% reduction in titer
☐	*resolution*	absence of detectable anti-dsDNA abs by any assay

Rifle Cont.

aPL

☐ *not present*
☐ *worsening* newly positive by ELISA or new dRVVT (LAC), or doubling of previously abnormal ELISA value
☐ *present, no change*
☐ *partial improvement* 50% reduction in titer of any isotype without increase in any other isotype
☐ *resolution* dRVVT normal (no LAC), aCL IgG and IgM in normal range, anti-β2GP1 in normal range

2. <u>Abnormal complement</u>

☐ *not present*
☐ *worsening* *a)* reduction of 25% in C4 to an abnormal range
b) reduction of 25% in C3 to an abnormal range
☐ *present, no change*
☐ *partial improvement* 50% improvement in either C3 or C4
☐ *resolution* *a)* normal C4 (unless C4 deficient)
b) normal C3

<u>Guidelines for interpretation of RIFLE</u>

<u>In any given parameter</u>:

yes = partial response or complete response
no = no change or worsening

<u>Outcomes</u>:

A. By patient

Favorable: (winner)
1. partial or complete resolution in at least one organ
<u>and</u>
2. no worsening in any organ

Unfavorable: (loser)
1. worsening in any organ

B. By organ/category

Favorable: 1. partial or complete resolution

Unfavorable: 1. no change or worsening

<u>Additional data for outcome measure</u>:

Physician must rank organ systems he/she feels would be most important to respond favorably, *e.g.*:

1. primary
2. secondary
a)
b)

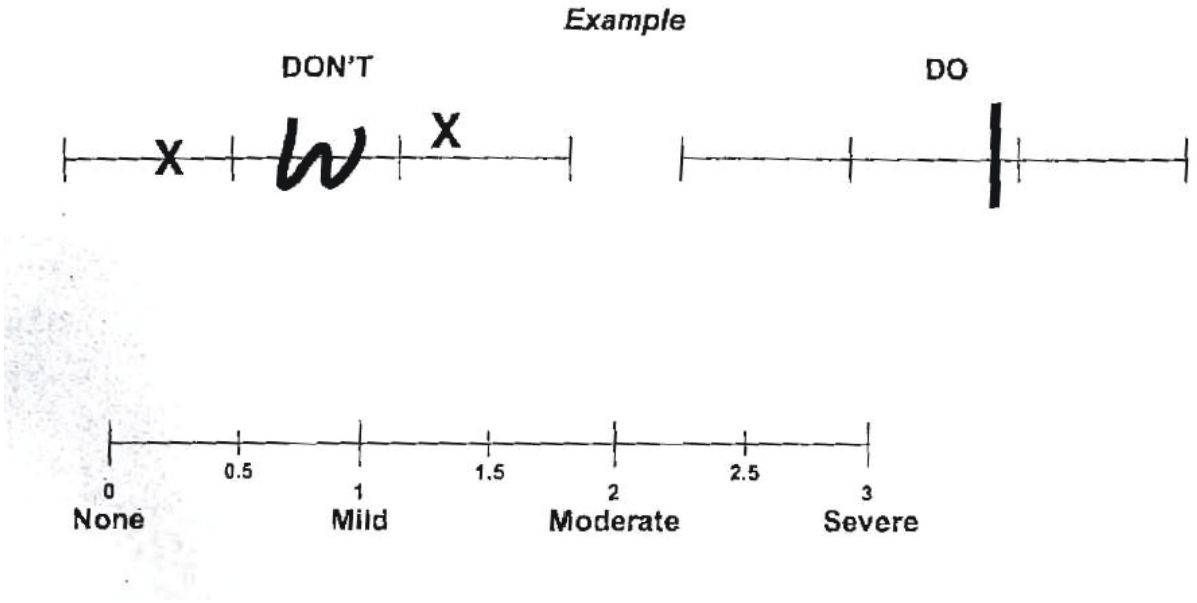
Appendix 6: SLEDAI

Wt	Present	Descriptor	Definition
8	☐	Seizure	Recent onset (10 days). Exclude metabolic, infection or drug cause, or seizure due to past irreversible CNS damage.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or Catatonic behavior.
8	☐	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual Disturbance	Retinal and eye changes of SLE include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroids, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐	Lupus Headache	Severe persistent headache: may be migrainious, but be non responsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i-e tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle itching/weakness, associated with elevated creatine Phosphokinase/aldose or electromyogram changes or a biopsy myositis.
4	☐	Urinary Casts	Heme-granules or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone infection and other causes.
4	☐	Proteinuria	New onset or recent increase of more than 0.5 gms/24 hrs.
4	☐	Pyuria	>5 WBC/high power field. Exclude infection.
2	☐	Rash	Ongoing inflammatory lupus rash.
2	☐	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to lupus.
2	☐	Mucosal ulcer	Ongoing oral or nasal ulceration due to active lupus.
2	☐	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or pleural thickening due to lupus.
2	☐	Pericarditis	Classic and severe pericardial pain or rub or effusion, or EKG confirmation.
2	☐	Low Complement	Decrease in CH50, or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	>25%binding by Farr assay or above normal range for testing laboratory.
1	☐	Fever	>38◦ C. Exclude infectious cause
1	☐	Thrombocytopenia	< 100,000 platelets/mm^3
1	☐	Leukopenia	<3000 WBC/mm^3. Exclude drug causes.

_____ TOTAL SCORE (Sum of weights next to descriptors marked present)

☐ **Mild or Moderate Flare**	☐ **Severe Flare**
☐ Change in SLEDAI of 3 points or more	☐ Change in SLEDAI to greater than 12
☐ New/worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE	☐ New/worse CNS-SLE Vasculitis Nephritis Myositis PLT<60,000 Heme anemia: Hb <7% or decrease in Hb >3% **Requiring**: double prednisone Prednisone>0.5 mg/kg/day Hospitalization
☐ Increase in Prednisone, but not to >0.5 mg/kg/day	☐ Prednisone>0.5 mg/kg/day
☐ Added NSAID or Plaquenil for disease activity	☐ New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)
☐ ≥ 1.0 increase in PGA, but not to more than 2.5	☐ Increase in PGA to >2.5

Appendix 7: PGA



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