PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0601

Unrelated Donor Reduced Intensity Bone Marrow Transplant for Children with Severe Sickle Cell Disease

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Primary Objective: The primary objective is to determine event-free survival (EFS) at 1 year after unrelated donor (URD) hematopoietic stem cell transplantation (HCT) using bone marrow (BM) in patients with sickle cell disease (SCD). Death, disease recurrence or graft rejection by 1 year will be considered events for this endpoint.

Secondary Objectives: Secondary objectives include determining the effect of HCT on clinical and laboratory manifestations of severe sickle cell disease including stroke and determining the incidence of other transplant-related outcomes. The latter include: overall survival; neutrophil, and platelet recovery; grades II-IV and grade III-IV acute graft-versus-host disease (GVHD); chronic GVHD; hepatic veno-occlusive disease (VOD); idiopathic pneumonia syndrome (IPS); central nervous system (CNS) toxicity (reversible posterior leukoencephalopathy syndrome [RPLS], hemorrhage, and seizures); neurocognitive dysfunction; cytomegalovirus (CMV) infection; adenovirus infection; Epstein Barr virus infection; invasive fungal infection; immune reconstitution; and health-related quality of life (QOL).

Study Design: The study is a Phase II, single arm, multi-center trial. It is designed to estimate the efficacy and toxicity of unrelated donor HCT using a reduced-intensity conditioning regimen in patients with SCD and high risk features who are between 3.0 and 19.75 years of age.

Accrual Objective: The target sample size is 30 BM recipients.

Accrual Period: The estimated accrual period is 4 years.

Eligibility Criteria: Patients 3.0-19.75 years old with symptomatic SCD AND one or more of the following complications: (a)-(i) a clinically significant neurologic event (stroke) or any neurologic defect lasting > 24 hours and accompanied by an infarct on cerebral magnetic resonance imaging (MRI); OR, (a)-(ii) patients who have a TCD velocity that exceeds 200 cm/sec by the non-imaging technique (or TCD measurement of >185 cm/sec by the imaging technique) measured at a minimum of 2 separate occasions one month or more apart; OR, (b) Minimum of two episodes of acute chest syndrome within the preceding 2-year period defined as new pulmonary alveolar consolidation involving at least one complete lung segment (associated with acute symptoms including fever, chest pain,

tachypnea, wheezing, rales, or cough that is not attributed to asthma or bronchiolitis) despite adequate supportive care measures; OR, (c) History of 3 or more severe pain events (defined as new onset of pain that lasts for at least 2 hours for which there is no other explanation) per year in the 2 years prior to enrollment despite adequate supportive care measures (if patients are receiving hydroxyurea and compliant with therapy, being symptomatic is an indication for transplantation; however, if patients decline hydroxyurea or non-compliant with this therapy, they would still remain eligible for study if pain criteria as described above are met). Lansky/Karnofsky performance score must be ≥ 40. Hb S must be ≤ 45%. Patients must have an unrelated adult bone marrow donor who is HLA-matched at 8 of 8 HLA-A, -B, -C and -DRB1 at high resolution using DNA-based typing. Patients with bridging fibrosis or cirrhosis of the liver, with uncontrolled bacterial, viral, or fungal infection in the past month, or seropositivity for HIV are excluded. Patients with HLA-matched family donors, or who have received prior HCT, and females who are pregnant or breast feeding are excluded.

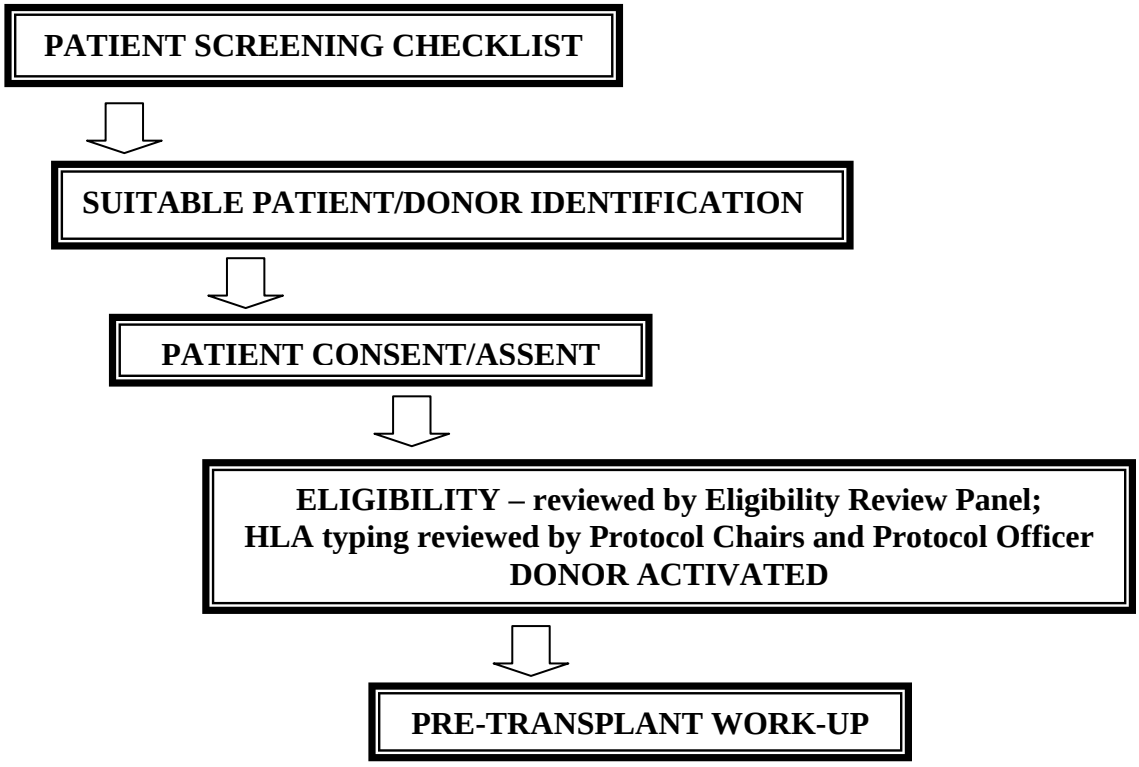
Treatment Description: The HCT preparative regimen will consist of the following:

- Alemtuzumab: Children weighing 10 kg or more will receive 10 mg, 15 mg, 20 mg intravenously (IV) on Days -21, -20, and -19, respectively
- Fludarabine: 30 mg/m^2/day IV on Days –8 through –4
- Melphalan: 140 mg/m^2 IV on Day –3
- Rest on Day -2, -1
- Day 0 is the day of transplant
- GVHD prophylaxis: Tacrolimus or cyclosporine beginning Day –3, methotrexate (7.5 mg/m^2/day) Day 1, 3, and 6 and methylprednisolone/ predisone on Day +7 to +28 followed by a taper if there is no GVHD

Study Duration: Patients will be followed for two years post-transplant for evaluation.

TREATMENT SCHEMA

(see Section 4.0 for enrollment procedures)



Day	Treatment[1]
24 hours prior to 1st dose of Alemtuzumab	Alemtuzumab test dose 3 mg IV once
-22 -21 -20 -19 -18	 Alemtuzumab 10 mg IV[1] Alemtuzumab 15 mg IV[1] Alemtuzumab 20 mg IV[1]
-8	Fludarabine 30mg/m^2 IV
-7	Fludarabine 30mg/m^2 IV
-6	Fludarabine 30mg/m^2 IV
-5	Fludarabine 30mg/m^2 IV
-4	Fludarabine 30mg/m^2 IV
-3	Melphalan 140 mg/m^2 IV
-2	Rest
-1	Rest
0	Stem cell infusion
+7	G-CSF 5 μg/kg/day continue until neutrophil engraftment

[1] *Alemtuzumab doses may be administered between Days -22 and -18 but are required to be on 3 consecutive days.*

TREATMENT SCHEMA (cont'd)

GVHD Prophylaxis Regimens

Day	Regimen
-3	Tacrolimus or cyclosporine dosed to maintain appropriate levels. Given though Day 100 then taper to Day 180
0	Stem cell infusion
+1	Methotrexate 7.5 mg/m^2 IV
+3	Methotrexate 7.5 mg/m^2 IV
+6	Methotrexate 7.5 mg/m^2 IV
+7	Methylprednisolone 1.0 mg/kg/day IV or Prednisone 1.2 mg/kg/day PO in divided doses Continued through Day +28, then taper

TWO-YEAR FOLLOW-UP