PROTOCOL SYNOPSIS – BMT CTN 1503
v5.0
A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults with Severe Sickle Cell Disease

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Study Design: This study is designed as a phase II, multi-center trial of hematopoietic cell transplantation (HCT) versus standard of care in adolescents and young adults with severe sickle cell disease (SCD). Eligible participants are biologically assigned to HCT or standard of care based on the availability of HLA-matched related or unrelated donor after confirmation of clinical eligibility. Insurance coverage and donor availability are not known at referral or consultation.

Primary Objective: The primary objective is to compare the overall survival (OS) at 2 years after biological assignment between those assigned to the donor arm and to the no donor arm. Those assigned to the donor arm are expected to undergo HCT and those on the no donor arm, to receive standard of care supportive therapy.

Secondary Objectives: Secondary objectives will compare changes in SCD related events (pulmonary hypertension, cerebrovascular events, renal function, avascular necrosis, leg ulcer) and functional outcomes [6-minute walk distance (6MWD), health-related quality of life (HRQoL), cardiac function, pulmonary function, and mean pain intensity as assessed by a multidimensional electronic pain diary from baseline to 2-years after assignment to treatment arms. Additionally, some outcomes will also be measured at 1 year. Baseline, 1- and 2-year assessments will be done at the same sites to minimize variability. Secondary objectives for the donor arm include neutrophil recovery, platelet recovery, graft failure, chimerism, acute and chronic graft-versus-host disease, idiopathic pneumonia syndrome, veno-occlusive disease, and central nervous system toxicity.

Eligibility Criteria: Eligible patients are ≥ 15 and < 41years of age with severe sickle cell disease [any clinically significant sickle genotype, for example, Hemoglobin SS (Hb SS), Hemoglobin SC (Hb SC), Hemoglobin S Beta thalassemia (Hb Sβ), or Hemoglobin S-OArab genotype] with at least one of the following manifestations:

a. Clinically significant neurologic event (stroke) or neurological deficit lasting > 24 hours;
b. History of two or more episodes of acute chest syndrome (ACS) in the 2-year period preceding enrollment or referral despite adequate supportive care measures (i.e. asthma therapy);
c. An average of three or more pain crises per year in the 2-year period preceding enrollment or referral (required intravenous pain management in the outpatient or inpatient hospital setting);
d. Administration of regular red blood cell (RBC) transfusion therapy, defined as 8 or more transfusion events per year (in the 12 months before enrollment) to prevent vaso-occlusive clinical complications (i.e. pain, stroke, or acute chest syndrome);
e. An echocardiographic finding of tricuspid valve regurgitant jet (TRJ) velocity ≥ 2.7 m/sec.
f. Ongoing high impact[1] chronic pain on a majority of days per month for ≥ 6 months as defined as ONE or more of the following: Chronic pain without contributory SCD complications[2], OR Mixed pain type in which chronic pain is occurring at site(s) (arms, back, chest, or abdominal pain) unrelated to any sites associated with Contributory SCD complications[2] (e.g. leg ulcers and/or avascular necrosis).

Adequate physical function as defined by all of the following**:**

a. Karnofsky/Lansky performance score ≥ to 60;
b. Cardiac function: Left ventricular ejection fraction (LVEF) > 40%; or LV shortening fraction > 26% by cardiac echocardiogram or by MUGA scan;
c. Pulmonary function: Pulse oximetry with a baseline O2 saturation of ≥ 85% **and** DLCO > 40% (corrected for hemoglobin);
d. Renal function: Serum creatinine ≤ 1.5x the upper limit of normal for age as per local laboratory **and** one of the following: creatinine clearance > 70 mL/min calculated using the CockcroftGault calculator, creatinine clearance >

[1]High impact chronic pain is identified as those reporting "severe interference" with life activities OR "usually or always" experiencing a limitation of their life or work activities including household chores. (See guidelines for identifying HICP in the BMT CTN 1503 Manual of Procedures)
[2]Contributory SCD complications are defined as clinical signs (e.g. presence of leg ulcers) or clinical assessments (e.g. imaging confirmation of splenic infarct or avascular necrosis). Chronic pain attributed solely to contributory SCD complications is excluded.

70 mL/min by 24 hour urine (preferred), **or** GFR > 70 mL/min/1.73 m2 by radionuclide GFR;

e. Hepatic function: ALT and AST < 5 times upper limit of normal as per local laboratory; serum conjugated (direct) bilirubin ≤ 2x upper limit of normal for age as per local laboratory Participants are not excluded if the serum conjugated (direct) bilirubin is >2x the upper limit of normal for age as per local laboratory **and**: There is evidence of a hyperhemolytic reaction after a recent RBC transfusion, **OR** there is evidence of moderate direct hyperbilirubinemia defined as direct serum bilirubin < 5 times ULN and not caused by underlying hepatic disease.

Additional inclusion required for donor arm participants to proceed with transplant:

a. Liver MRI (≤ 90 days prior to initiation of transplant conditioning) to document hepatic iron content is required for participants who are currently receiving ≥8 packed red blood cell transfusions for ≥1 year or have received ≥20 packed red blood cell transfusions (cumulative). Participants who have hepatic iron content ≥7 mg Fe/ g liver dry weight by liver MRI must have a liver biopsy and histological examination/documentation of the absence of cirrhosis, bridging fibrosis[1], and active hepatitis (≤ 90 days prior to initiation of transplant conditioning).

b. Lack of clinical or radiologic evidence of a recent neurologic event (such as stroke or transient ischemic attack) by Cerebral MRI/MRA within 30 days prior to initiating transplant conditioning. Subjects with clinical or radiologic evidence of a recent neurologic event will be deferred for ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation

c. Documentation of participant's willingness to use approved contraception method until discontinuation of all immunosuppressive medications is to be documented in the medical record corresponding with the consent conference.

Exclusion Criteria:

1. HLA typing with donor search prior to referral (consultation with HCT physician).

[1]The absence of bridging fibrosis will be determined using the histological grading and staging scale as described by Ishak and colleagues as described in the Manual of Operating Procedures.

a. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time, and also did not have an unrelated donor search, the patient will be considered eligible.
b. If a subject has had HLA typing and a related donor search that did not identify a suitably matched relative (i.e., sibling) at any time and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
c. If a subject has had HLA typing with no related donor search and had an unrelated donor search that did not identify a suitably matched unrelated donor ≥ 1 year prior to enrollment, the patient will be considered eligible.
d. Subjects with a known HLA-identical sibling or HLA-matched unrelated donor are excluded

2. Uncontrolled bacterial, viral or fungal infection;
3. Seropositivity for HIV;
4. Previous HCT or solid organ transplant;
5. Participation in a clinical trial in which the patient receives an investigational drug or device must be discontinued prior to date of enrollment;
6. A history of substance abuse as defined by version IV of the Diagnostic & Statistical Manual of Mental Disorders (DSM IV);[1]
7. Demonstrated lack of compliance with prior medical care as determined by referring physician;
8. Pregnant or breast feeding females;
9. Inability to receive HCT due to alloimmunization, defined as the inability to receive packed red blood cell (pRBC) transfusion therapy;

Treatment Description: **Donor arm:** All donor arm patients receiving an unrelated donor HCT will receive busulfan, fludarabine, and r-ATG as their preparative regimen using a bone marrow graft. For donor arm

[1]American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. (4th ed.). Washington, DC American Psychiatric Association.

patients receiving a related donor HCT, there are 3 acceptable preparative regimens for this study:

a. Regimen A: Busulfan/Fludarabine/r-ATG using a bone marrow graft (preferred regimen)
b. Regimen B: Alemtuzumab/TBI 300 cGy using a peripheral blood graft
c. Regimen C: Alemtuzumab/Fludarabine/Melphalan using a bone marrow graft

The preparative regimen to be used for HLA-identical sibling transplants must be declared to the DCC by the site and used for all HLA-identical sibling transplants at that site.

GVHD prophylaxis

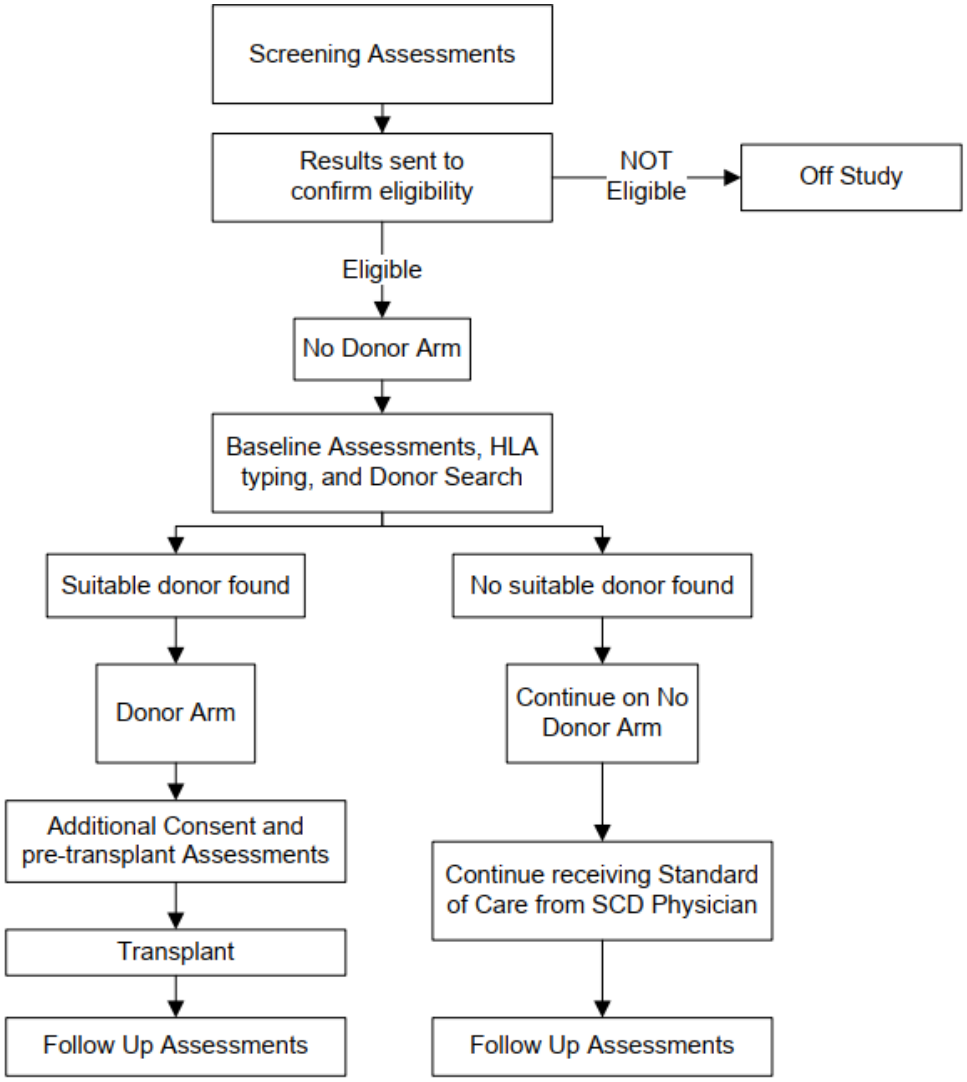
a. GVHD prophylaxis for patients receiving an unrelated donor transplant or Conditioning Regimen A: Tacrolimus commences on day -3 and extends through day +180 after transplantation, with methotrexate (MTX) administered intravenously on days +1 (15mg/m^2), +3 (10mg/m^2), +6 (10mg/m^2) and +11 (10mg/m^2). Patients unable to tolerate tacrolimus may receive cyclosporine.
b. GVHD prophylaxis for Conditioning Regimen B: Sirolimus commences on day -1 and extends through day +180 after transplantation or until donor CD3+ chimerism >50%, whichever is later
c. GVHD prophylaxis for Conditioning Regimen C: Tacrolimus commences on day -3 and extends through day +180 after transplantation, with methotrexate (MTX) 7.5 mg/m^2 administered intravenously on days +1, +3, and +6. Patients unable to tolerate tacrolimus may receive cyclosporine.

No-donor arm: Will continue with standard of care per their SCD physician.

Primary Endpoint: The primary endpoint is a comparison of the difference in the observed proportion of patients surviving at 2 years post biological assignment between the two treatment arms. Biologic assignment will occur ≤ 180 days after eligibility is confirmed by enrollment or the eligibility review committee (ERC). Participants will remain in their assigned treatment arm for analysis of all endpoints (intent-to-treat [ITT] principle).

Secondary Endpoints:	Comparison of SCD-related events and functional assessments by administering the 6MWD test, HRQoL and a 28-day e-pain diary to capture mean pain intensity. The secondary endpoints will examine changes between baseline, 1- year, and 2-years between participants on the donor and no donor arms. All baseline, 1-, and 2-year tests will be conducted at the same institution (to minimize variability).
Accrual Objective:	The sample size for the donor arm is fixed at 60 participants. Based on donor availability for ~30% of participants the sample size for the no donor arm is anticipated to be 140.
Accrual Period:	3 years.
Study Duration:	Participants will be followed for 2 years from time of biological assignment. Overall survival outcomes will continue to be measured between years 3 and 10.
Interim Analysis:	There will be no interim analyses for efficacy.
Stopping Guidelines:	Patients on the donor arm will be monitored for mortality at day 100 and 1-year post transplant and graft rejection at day 100 post transplant. The stopping rules for unacceptable day 100 mortality considers all patients together and for 1-year mortality, separately for HLA-matched related and unrelated donor transplants. For day 100 graft rejection, patients will be considered separately for HLA-matched related and unrelated donor transplants.

Study Design



Treatment Schema – Donor Arm

Unrelated Donor Transplant Conditioning Regimen,
and HLA-identical Sibling Transplant Conditioning Regimen A

Days	Treatment
-8	IV busulfan 3.2 mg/kg
-7	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2
-6	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, r-ATG 0.5 mg/kg
-5	IV busulfan 3.2 mg/kg, fludarabine 35 mg/m^2, r-ATG 1.0 mg/kg
-4	IV fludarabine 35 mg/m^2, r-ATG 1.5 mg/kg
-3	IV fludarabine 35 mg/m^2, r-ATG 1.5 mg/kg
-2	r ATG 1.5 mg/kg
-1	Rest day
0	Infusion of bone marrow

GVHD Prophylaxis for the Unrelated Donor Transplant Conditioning Regimen
and HLA-identical Sibling Transplant Conditioning Regimen A

Days	Prophylactic Agent
-3 through +180	Tacrolimus, begin taper +180 per institutional guidelines
0	Infusion of bone marrow
+1	IV methotrexate 15 mg/m^2
+3	IV methotrexate 10 mg/m^2
+6	IV methotrexate 10 mg/m^2
+11	IV methotrexate 10mg/m^2

HLA-identical Sibling Transplant Conditioning Regimen B

Days	Treatment
-7	IV Alemtuzumab: 0.03 mg/kg
-6	IV Alemtuzumab: 0.1 mg/kg
-5	IV Alemtuzumab: 0.3 mg/kg
-4	IV Alemtuzumab: 0.3 mg/kg
-3	IV Alemtuzumab: 0.3 mg/kg
-2	TBI 300 cGy with testicular shielding
-1	Rest day

0	Infusion of mobilized PBSC

GVHD Prophylaxis for Conditioning Regimen B

Days	Prophylactic Agent
-1 through +180	Sirolimus, begin taper +180 per institutional guidelines if donor CD3+ >50%

HLA-identical Sibling Transplant Conditioning Regimen C

Days	Treatment
-22	IV Alemtuzumab: 3 mg test dose
-21	IV Alemtuzumab: 10 mg
-20	IV Alemtuzumab: 15 mg
-19	IV Alemtuzumab: 20 mg
-8	IV Fludarabine 30 mg/m^2
-7	IV Fludarabine 30 mg/m^2
-6	IV Fludarabine 30 mg/m^2
-5	IV Fludarabine 30 mg/m^2
-4	IV Fludarabine 30 mg/m^2
-3	IV Melphalan 140 mg/m^2
-2	Rest Day
-1	Rest day
0	Infusion of bone marrow

GVHD Prophylaxis for Conditioning Regimen C

Days	Prophylactic Agent
-3 through +180	Tacrolimus, begin taper +180 per institutional guidelines
0	Infusion of bone marrow
+1	IV methotrexate 7.5 mg/m^2
+3	IV methotrexate 7.5 mg/m^2
+6	IV methotrexate 7.5 mg/m^2