PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 1507

Reduced Intensity Conditioning for Haploidentical Bone Marrow Transplantation in Patients with Symptomatic Sickle Cell Disease

Co-Chairs: Robert Brodsky MD, Michael DeBaun, MD, Adetola Kassim, MD, and Mark Walters, MD

Study Design: This is a Phase II, single arm, multi-center trial, designed to estimate the efficacy and toxicity of haploidentical bone marrow transplantation (BMT) in patients with sickle cell disease (SCD). Patients are stratified into two groups: (1) children with SCD with strokes; and (2) adults with severe SCD. Based on their age and entry criteria, participants are enrolled in 2 strata as defined below. The primary endpoint of event-free survival (EFS) will be estimated in each age-specific stratum.

Primary Objective: The primary objective is to estimate EFS at 2 years after haploidentical BMT in patients with SCD enrolled in 2 strata – children 5.00 – 14.99 years of age at enrollment with SCD and adults 15.00 - 45.99 years of age at enrollment with severe SCD. Primary or secondary graft rejection, second transplant, or death will count as events for this endpoint. Stratum-specific estimates will be provided. If the protocol implements the planned treatment change in response to safety monitoring for graft failure, then the analysis will be based on the stratum participants under the active treatment plan at the close of the study and results for the other participants will be described.

Secondary Objectives: Secondary objectives include determining the effect of haploidentical BMT on clinical and laboratory manifestations of SCD by 2 years after transplantation and determining the incidence of other transplant-related outcomes. Secondary outcomes include: overall survival post-haplo BMT at 1 and 2 years post-enrollment; EFS at 1 year; graft rejection; disease progression; donor chimerism; grades II-IV and III-IV acute graft-versus-host disease (GVHD); chronic GVHD, severe chronic GVHD; neutrophil, and platelet recovery; hepatic veno-occlusive disease (VOD); idiopathic pneumonia syndrome (IPS); central nervous system (CNS) toxicity (reversible posterior leukoencephalopathy syndrome [RPLS], hemorrhage, and seizures); cytomegalovirus (CMV) infection; adenovirus infection; Epstein Barr virus post-transplant lymphoproliferative disease (EBV PTLD); invasive fungal infection; CNS outcomes; 28 day e-pain diary assessments; health-

related quality of life (HRQoL) in the adult stratum; lung function; TRJV; 6 minute walk distance; hematological outcomes; viral mold infections/bacterial or fungal sepsis; and proportion on immunosuppression. All objectives are within each stratum.

Eligibility: Eligibility criteria differ by age.

1. Children with SCD (Hb SS or Sß° Thalassemia) aged 5.00 – 14.99 years at Segment A enrollment who have a neurological event resulting in focal neurologic deficits that lasted ≥ 24 hours (classical clinical definition of stroke, not requiring imaging studies of the brain) **OR** a focal neurological event resulting in abnormalities on T2-weighted or FLAIR images using a MRI scan, indicative of an acute infarct, with no other reasonable medical explanation (definition of a stroke supported with MRI imaging scans of the brain), **OR** both.

   If there is 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 enrollment, participants will be deferred for ≥ 6 months with repeat cerebral MRI/MRA to ensure stabilization of the neurologic event prior to proceeding to transplantation.

2. Participants with SCD (Hb SS or Sß° Thalassemia) aged 15.00 – 45.99 years at Segment A enrollment who have one or more of the following:

   a. A neurological event resulting in focal neurologic deficits that lasted ≥ 24 hours (classical clinical definition of stroke, not requiring imaging studies of the brain) **OR** a focal neurological event resulting in abnormalities on T2-weighted or FLAIR images using a MRI scan, indicative of an acute infarct, with no other reasonable medical explanation (definition of a stroke supported with MRI imaging scans of the brain), **OR** both.

   b. History of two or more episodes of acute chest syndrome (ACS) in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e. asthma therapy and/or hydroxyurea);

   c. History of three or more severe vaso-occlusive pain crises per year in the 2-year period preceding enrollment despite the institution of supportive care measures (i.e. a pain management plan and/or treatment with hydroxyurea); painful episodes related to priapism, osteonecrosis or any sickle-related complication are acceptable;

d. Administration of regular RBC transfusion therapy, defined as receiving ≥8 packed red blood cell transfusions per year for ≥1 year in the 12 months before enrollment to prevent vaso-occlusive clinical complications (i.e. pain, stroke, and acute chest syndrome);

e. An echocardiographic finding of tricuspid valve regurgitant jet velocity (TRJV) ≥2.7 m/sec.

Participants in either age group must have adequate physical function as measured by all of the following:

1. Karnofsky or Lansky performance score ≥60.
2. Cardiac function: Left ventricular ejection fraction (LVEF) > 40%; **or** LV shortening fraction > 26% by cardiac echocardiogram or by MUGA scan.
3. Pulmonary function: Pulse oximetry with a baseline O_2 saturation of ≥85% **and** DLCO > 40% (corrected for hemoglobin).
4. Renal function: Serum creatinine ≤ 1.5 x upper limit of normal for age **and** estimated or measured creatinine clearance ≥ 70 mL/min/1.73 m^2.
5. Hepatic function:
   a. Serum conjugated (direct) bilirubin < 2x upper limit of normal for age as per local laboratory. Participants with hyperbilirubinemia as the result of hyperhemolysis, or a severe drop in hemoglobin post blood transfusion, are not excluded.
   b. ALT and AST < 5x upper limit of normal as per local laboratory.
6. Liver MRI using a validated methodology per institutional preference (T2* or R2* or by ferriscan [R2 MRI]) for estimation of hepatic iron content is required for participants who are currently receiving ≥8 packed red blood cell transfusions per year for ≥1 year or have received ≥20 packed red blood cell transfusions (lifetime cumulative). Participants who have hepatic iron content ≥ 10 mg Fe/g liver dry weight by liver MRI must have a Gastroenterology/hepatology consultation with liver biopsy and histological examination including

documentation of the absence of cirrhosis, bridging fibrosis[1], and active hepatitis.

7. Participants must be HLA typed at high resolution using DNA based typing at HLA-A, -B, -C, DRB1, and have available:

   An HLA haploidentical first degree relative donor (parents, siblings or half siblings, or children) with 2, 3, or 4 (out of 8) HLA-mismatches who is willing and able to donate bone marrow. A unidirectional mismatch in either the graft versus host or host versus graft direction is considered a mismatch. The donor and recipient must be HLA identical for at least one antigen (using high resolution DNA based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1. Fulfillment of this criterion shall be considered sufficient evidence that the donor and recipient share one HLA haplotype, and typing of additional family members is not required. Confirmatory donor HLA typing must be completed ≤ 100 days prior to Segment A enrollment

8. Umbilical cord blood or peripheral blood stem cell donors will not be accepted.

Exclusion criteria:

1. Participants who have an HLA-matched sibling who is able and willing to donate bone marrow.
2. Participants with uncontrolled bacterial, viral or fungal infection in the 6 weeks before enrollment (currently taking medication with evidence of progression of clinical symptoms or radiologic findings).
3. Participants with evidence of HIV infection or seropositivity for HIV.
4. Participants who have received a previous Hematopoietic Cell Transplant (HCT)
5. Participants who have received a prior solid organ transplant.
6. Participants who have participated in another clinical trial in which the participant received an investigational or off-label use of a drug or device within 3 months prior to enrollment.

[1]The absence of bridging fibrosis will be determined using the histological grading and staging scale as described by Ishak and colleagues (1995)[1,2,3].

7. Females who are pregnant or breast feeding.
8. Participants with clinically significant, uncontrolled autoimmune disease, requiring active medical management (immunosuppressive therapy or chemotherapy), which, in the judgment of the local Principal Investigator, indicates that the patient could not tolerate transplantation.
9. Females of child bearing potential (to include all female participants > 10 years of age, unless postmenopausal for a minimum of 1 year before the time of consent or surgically sterilized) who do not agree to practice two (2) effective methods of contraception at the same time, or who do not agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing of informed consent through 12 months post-transplant.
10. Males (even if surgically sterilized) who do not agree to practice effective barrier contraception, or who do not agree to practice true abstinence from the time of signing informed consent through 12 months post-transplant.
11. Presence of anti-donor specific HLA antibodies. HLA antibody presence and specificity will be determined by solid phase immunoassays. An anti-donor specific HLA antibody will be considered positive when the mean fluorescence intensity (MFI) is higher than the cut-off defined by each center. Recommended cut-off values are MFI >1000 for donor specific antibody to HLA-A, -B, and DRB1 and MFI >2000 for HLA-C, DQB1 and DPB1. This must be measured before the final donor selection, and $\leq$ 100 days before enrollment in Segment A (preferably $\leq$ 30 days before Segment A enrollment). If MFI >1000 for donor specific antibody to HLA-A, -B, DRB1 and/or MFI >2000 for HLA-C, DQB1 and DPB1, documentation must be submitted to the DCC coordinator for review and approval by a Protocol Chair and/or Protocol Officer prior to enrollment.

Treatment Description: The BMT preparative regimen will start on Day -70 with hydroxyurea 30mg/kg daily through Day -10. The conditioning regimen will also include Thymoglobulin (rATG) (0.5mg/kg on Day -9, 2mg/kg on Day -8, Day -7), Thiotepa 10mg/kg on Day -7, Fludarabine (30mg/m2 on Day -6 to Day -2), Cyclophosphamide 14.5mg/kg on Day -6 and Day -5, and TBI 200cGy on Day -1. Day 0 is the day of infusion with non T-cell depleted bone marrow. Cyclophosphamide 50 mg/kg and Mesna 40mg/kg is given on Days +3 and +4, and GVHD prophylaxis (sirolimus and mycophenolate mofetil) begin on Day +5.

If it is determined that the graft failure rate in a stratum has met the stopping rule within the first 12 evaluable participants in the stratum, and approval from the DSMB and Sponsor is provided, then the conditioning regimen with TBI 400cGy instead of TBI 200cGy will be used for future participants in the stratum, and an additional 40 participants will be accrued to that stratum.

Accrual Objective: The target sample size is 40 patients in each stratum; if the stopping rule for graft failure is triggered within the first 12 evaluable participants in either stratum using the 200cGy dose of TBI and the DSMB and sponsor approve the pre-defined switch in conditioning regimen, then accrual for that strata will restart under the modified conditioning regimen.

Accrual Period: The estimated accrual period is 4 years. If the safety monitoring for graft failure passes a stopping boundary within the first 12 evaluable participants, it is estimated that the accrual period will be extended up to an additional 15 months.

Study Duration: Participants will be followed for the 28-day pain diary (prior to 70-day conditioning period) and for 2 years from date of infusion (post-transplant).

Safety Monitoring: The rate of overall mortality by Day 180 post start of hydroxyurea therapy pre-transplant, acute grade III-IV GVHD at 100 days, and severe chronic GVHD at 18 months post-transplant will be monitored by using a sequential probability ratio test (SPRT) for censored exponential data for each of these. Graft failure at 100 days post-transplant will be monitored by using a sequential probability ratio test (SPRT) for binary data.

TREATMENT SCHEMA

Days –70 → –10	Hydroxyurea 30 mg/kg po daily
	Hgb S fraction < 35% prior to administration of Thymoglobulin. If Hbg S > 35%, automated exchange transfusion (RBC apheresis) is the preferred strategy to lower Hgb S with a goal of 20% and the maximum Hgb S fraction not to exceed 35%.
Day –9***	Thymoglobulin 0.5 mg/kg IV with pre-meds
Day –8***	Thymoglobulin 2 mg/kg IV qd with pre-meds
Day –7***	Thymoglobulin 2 mg/kg IV qd with pre-meds Thiotepa 5 mg/kg IV q 12 h (10 mg/kg total)
Days –6, –5	Fludarabine 30 mg/m2 IV over 30-60 minutes, then Cyclophosphamide (CY) 14.5 mg/kg IV over 1-2 hours*
Days –4 □–2	Fludarabine 30 mg/m2 IV over 30-60 minutes
Day –1	TBI 200 cGy with gonadal shielding**
Day 0	Non-T-cell depleted bone marrow
Days +3, +4	Cyclophosphamide 50 mg/kg IV Mesna 40 mg/kg IV*
Day +5	Begin sirolimus (section 2.4.5.1)**, mycophenolate mofetil (MMF) 15 mg/kg pot id with maximum daily dose 3 gm/d
Day +35	Discontinue MMF

*Uroprophylaxis may be altered per institutional preference (see below)
**See Section 2.4.2.10 and section 4.4.6 regarding planned protocol change in TBI dose if safety monitoring guideline for 100-day graft failure is passed in the first 12 evaluable participants per stratum.
***If using corticosteroids as premedication, discontinue before Day -1.