

Cystinosis Clinical Trial – Stem Cell Gene Therapy Treatment

Inclusion:

The following criteria must be met by all subjects considered for study participation.

1. Cohorts 1 and 2: Male or female subject is ≥ 18 years of age.
2. Cohort 3: Male or female subject is ≥ 14 years of age.
3. Subject is diagnosed with cystinosis, i.e., early onset of Fanconi syndrome, and history of elevated white blood cell cystine level and/or history of or presence of cystine crystals in the eye.
4. Subject has a Karnofsky Performance Status or age-dependent Lansky Performance of ≥ 60 .
5. If subject has had a kidney transplant, he or she must be at least one-year post kidney transplant status.
6. Subject has adequate hematologic function:
 - a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L
 - b. Platelet count $\geq 100 \times 10^9$ /L
 - c. Hemoglobin ≥ 9.0 g/dL
7. Subject has adequate hepatic function:
 - a. Bilirubin ≤ 2.0 mg/ dL
 - b. ALT ≤ 3 x institution's upper limit of normal (ULN)
8. Subject has adequate renal function:
 - a. Serum creatinine < 2 x ULN
 - b. Creatinine clearance ≥ 50 mL/min/1.73 m²
9. Subject has adequate coagulation:
 - a. PT/aPTT ≤ 1.2 x ULN
 - b. INR ≤ 2
10. Subject has adequate thyroid function (with or without thyroid replacement therapy):
 - a. TSH 0.27-4.2 uIU/mL
 - b. Total T4 ≤ 2 x ULN
11. If female: female of childbearing potential (i.e., not surgically sterile [tubal ligation, hysterectomy, or bilateral oophorectomy] or not at least 2 years naturally postmenopausal) agrees to remain sexually abstinent or utilize the same acceptable form of highly effective contraception from screening through two years post-transplant.
 - The acceptable forms of contraception for this study include hormonal contraceptives (oral, implant, transdermal patch, or injection) associated with inhibition of ovulation at a stable dose for at least 3 months prior to screening, barrier (condom with spermicide, diaphragm with spermicide), intrauterine device, or a partner who has been vasectomized for at least 6 months and has documented medical assessment of surgical success of a vasectomy.

Note: males with cystinosis are sterile.
12. If male: males must agree to remain sexually abstinent or utilize an acceptable form of highly effective contraception from screening through two years post-transplant.
13. Subject is willing and able to comply with the study restrictions and requirements.
14. Subject is willing to provide written informed consent/permission/assent prior to participation in the study.
15. Subject must be willing to refrain from donating sperm after receiving the conditioning regimen. For subjects planning on (or for whom there is a possibility of) fathering children in the future, sperm banking prior to administration of conditioning regimen will be recommended.

16. Subject must be willing to refrain from donating blood, organs, tissues, or cells for transplantation from 30 days prior to screening through any time after CTNS-RD-04 treatment.
17. Subject must be willing and must be able (in the judgment of the investigator) to discontinue his or her cysteamine therapy (oral and/or eye drop).

Exclusion:

Subjects presenting with any of the following will be excluded from the study.

1. Subject has an active, uncontrolled, acute bacterial, viral, or fungal infection during screening or within 30 days prior to starting the conditioning regimen.
2. Subject has positive serology at screening for any of the following:
 - a. HIV1-2
 - b. HTLV 1-2
 - c. Hepatitis B core and surface antibody and surface antigen
 - d. HCV
 - e. Cytomegalovirus (CMV)-IgG
 - f. CMV
 - g. Rapid plasma reagin (RPR)
 - h. Chagas Disease
 - i. QuantiferonTB
3. Subject has a known clinically significant immunodeficiency disorder.
4. Subject is a female of childbearing potential that is nursing, planning a pregnancy, or has a positive serum pregnancy test.
5. Subject has received a prior marrow or stem cell transplantation or is planning to receive one within 90 days of study initiation.
6. Subject has had an active bleeding disorder within 90 days prior to screening OR requires anticoagulation therapy prior to treatment with ex vivo gene therapy.
7. Subject has an active malignancy or history of malignancy including lymphoma (except primary, cutaneous basal cell or squamous cell cancer appropriately treated prior to transplantation).
8. Subject has end-stage renal disease (defined as GFR <15 mL/min) and is already on a transplantation list or who may be planning to register for kidney transplant within 90 days of study initiation.
9. Subject has impaired pulmonary function (based on FVC or FEV1 of <80% predicted, or an FEV1/FVC ratio less than age- and gender-specific normal threshold value).
10. Subject has impaired cardiac function within 90 days prior to screening including any of the following:
 - a. Myocardial infarction
 - b. Clinically significant abnormal electrocardiogram (ECG)
 - c. Uncontrolled arrhythmia
 - d. Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension).
11. Subject has a severe or uncontrolled medical disorder (e.g., pancreatitis, severe liver disease, unstable diabetes mellitus) that would, in the investigators' opinion, impair their ability to receive study treatment and follow the study procedures.
12. Subject has history of allergic reactions attributed to compounds of similar chemical or biologic composition to Busulfan or allergy or contraindication to use of other agents used in study, including iohexol, acid-citrate-dextrose Formula A (ACDA), G-CSF or plerixafor.

Exclusion cont.

13. Subject has a known history of drug or alcohol addiction.
14. Subject has undergone a major surgery within 90 days (or longer if not fully recovered) prior to screening.
15. Subject is receiving cytotoxic or immunosuppressive agents within 60 days prior to screening or requires treatment with such agents prior to treatment with ex vivo gene therapy.
16. Subject has previously received gene therapy at any time.
17. Subject is currently receiving or anticipates receiving another investigational agent, device, or procedure from 30 days prior to screening through study completion.
18. Subject has any condition, in the opinion of the investigator, that compromises compliance with study requirements