Phase 1/2 Clinical Trial of Autologous Hematopoietic Stem and Progenitor Cell Gene Therapy for Cystinosis

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Cystinosis is a lysosomal disorder characterized by cystine accumulation within the lysosomes of all organs caused by mutations in the *CTNS* gene encoding the transmembrane lysosomal cystine transporter, cystinosin. Major complications of cystinosis include early renal Fanconi syndrome, chronic kidney disease, renal failure, and ocular pathology that can lead to blindness. Cystinosis also affects the heart, thyroid, skeletal muscle, pancreas, and CNS, eventually causing premature death in early adulthood. Cysteamine delays, but does not stop, disease progression.

Here we report results from the phase 1/2 open-label clinical trial (NCT03897361) evaluating safety and efficacy of CTNS-RD-04 in adult patients with cystinosis. CTNS-RD-04 consists of autologous $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) transduced with a lentiviral vector (LV) carrying the *CTNS* cDNA encoding for cystinosin (CCL-EFS-CTNS-WPRE). Peripheral blood $CD34^+$ HSPCs are collected via apheresis after mobilization with G-CSF and Plerixafor and transduced with CCL-EFS-CTNS-WPRE LV. Myeloablative-busulfan conditioning at a targeted AUC of 90 mg×h/L is followed by CTNS-RD-04 infusion. Oral and topical cysteamine are withdrawn prior to infusion.

The trial is fully enrolled, and six participants (ages 20 to 46 years) have been treated with CTNS-RD-04 with follow-up ranging from 1 to 36 months. CTNS-RD-04 cell doses ranged from 3.63×10^6 to 9.59×10^6 $CD34^+$ cells/kg with VCNs ranging from 0.6 to 2.9 copies/dg. In all five infused patients with 42+ days of post-CTNS-RD-04 infusion follow-up, polyclonal hematopoietic reconstitution occurred. Peripheral blood VCN at 12 months post-gene therapy ranged between 0.43 to 1.99. In the five first treated patients, white blood cell cystine and tissue cystine crystals in skin and rectal mucosa decreased compared to Baseline. All subjects are no longer taking oral cysteamine. Patient 2 restarted eyedrop cysteamine one-year post-infusion. No adverse events related to drug product and no serious adverse events have been reported to date. Updated data will be presented.