SCIENTIFIC ABSTRACT

This is a prospective non-controlled, non-randomized Phase I/II clinical trial to assess the safety and efficacy of cellular gene therapy in patients with sickle cell disease (SCD), using transplantation of autologous bone marrow CD34+ cells transduced *ex vivo* by the Lenti β^{AS3}-FB lentiviral vector to express an anti-sickling (β^{AS3}-globin) gene. Adults (≥18 years old, n=3) who have SCD and meet specific eligibility criteria for disease severity, lack of therapeutic alternatives, and adequacy of organ function will be offered enrollment. Following the IRB-approved informed consent process, enrolled subjects will be screened to confirm full eligibility for participation. Eligible subjects will undergo two bone marrow harvests, have a portion of their bone marrow preserved as "back-up," with the remaining portion of marrow used to prepare the gene-modified Final Cell Product (autologous CD34+ hematopoietic stem cells (HSC) from the bone marrow of patients with SCD, modified by *ex vivo* transduction using the lenti/βAS3-FB lentiviral vector). If the cryopreserved Final Cell Product meets release criteria for viable CD34+ cell dosage, β^{AS3}-globin gene transduction, and microbiologic tests, subjects may proceed to transplant. They will receive marrow cytoreduction with dosage-targeted busulfan prior to intravenous infusion of the gene-modified cells. Standard in-patient clinical care for hematopoietic stem cell transplantation will be provided. The follow-up period will include an initial 2 years of out-patient follow-up, where the subjects will be seen at regular intervals for monitoring safety, feasibility and efficacy end-points, followed by offer of enrollment into a long-term follow-up study during years 3-15. The objectives of this study are to assess the safety of the procedure and the efficacy in terms of engraftment of gene modified HSC, production of erythrocytes expressing sufficient quantities of the β^{AS3}-globin protein to inhibit sickling of the red blood cells, and improvement of clinical and hematologic disease features. Autologous transplantation of β^{AS3}-modifed HSC may be safe and efficacious for SCD.