SCIENTIFIC ABSTRACT

X-linked Chronic Granulomatous Disease (**XCGD**) results from mutations in the *CYBB* gene encoding the gp91phox protein, a component of the anti-microbial oxidase activity in phagocytic leukocytes. Allogeneic hematopoietic stem cell transplantation (**HSCT**) can be clinically beneficial for XGCD, by allowing production of normal leukocytes from the donor hematopoietic stem cells (**HSC**) which may provide anti-microbial immunity. Graft versus host disease risks and lack of well-matched donors may limit the availability of HSCT for some XCGD patients. Transplantation of autologous HSC that are genetically corrected may provide similar benefits as allogeneic HSCT, although prior clinical trials for CGD had severe complications from the gene transfer vector causing leukoproliferation, myelodysplasia and leukemia. A new gene transfer vector has been developed for XGCD that may have reduced potential to cause this complication, although this has only been shown using murine cells in culture and transplants. 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 XCGD. Transplantation will be performed using autologous G-CSF mobilized CD34-selected peripheral blood stem cells (**PBSC**) transduced *ex vivo* by the G1XCGD lentiviral vector, carrying a codon-optimized human *CYBB* cDNA under transcriptional control of a chimeric promoter derived from cellular genes expressed in myeloid cells. It is packaged by transient transfection in a VSV-G pseudotype, concentrated by down-stream processing, and certified to meet release criteria for potency, identify, sterility and absence of replication competent lentivirus. Subjects will be 10 males with XCGD and refractory infections or inflammatory complications lacking an HLA-identical sibling or unrelated donor, meeting defined eligibility criteria. Subjects will undergo mobilization of PBSC with G-SCF for up to 5 days followed by leukopheresis. A portion of the leukopheresis product will be cryopreserved without processing to serve as a “back-up”. CD34+ PBSC cells will be isolated from the remainder of the leukopheresis product and transduced by *ex vivo* culture with the G1XCGD lentiviral vector in the presence of recombinant hematopoietic growth factors. During this time, the subjects will receive non-myeloablative conditioning using busulfan (with dose adjustment based on measurement of busulfan pharmacokinetics) over three days. Final cell products (G1XGCD-transduced autologous CD34+ PBSC) that meet release criteria will be transplanted by intravenous infusion. 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 post-transplantation visits at regular intervals, for monitoring safety 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 safety and efficacy, in terms of reconstitution of biochemical and functional leukocyte oxidase activity, improvement of immunity to bacterial and fungal infections, as well as evaluation of post-transplant HSC engraftment kinetics and stability.