

SCIENTIFIC ABSTRACT

Familial hypercholesterolemia (FH) is a Mendelian genetic disease caused by mutations in the gene encoding the LDL receptor (LDLR). Patients homozygous for defective LDLR genes (hoFH) have severe elevations of serum LDL and develop premature and lethal coronary artery disease. There is no effective treatment for hoFH except for orthotopic liver transplantation. We describe the rationale for treating hoFH with gene therapy and present a proposed phase I study to evaluate the safety of infusing a vector based on adeno-associated virus serotype 8 (AAV8) to transduce hepatocytes with a normal LDLR gene. The clinical candidate vector expresses normal LDLR driven from a liver-specific promoter in the context of a capsid-derived from AAV serotype 8, which is the capsid used in a recent hemophilia B gene therapy trial. Intravenous injection of the clinical candidate vector in a mouse model of hoFH demonstrated a stable (> 52 weeks) reduction of LDL and regression of pre-existing atherosclerosis. Dose response studies failed to show any dose-limiting toxicities in the mouse model. Studies in nonhuman primates confirmed the studies in mice in terms of the safety of the vector. The proposed phase I study will evaluate the safety of the clinical candidate vector administered IV into adults with hoFH. The study will include three cohorts (N=3-6 subjects/cohort), with each cohort receiving a different vector escalated $\frac{1}{2}$ log between cohorts. The primary endpoints are based on safety although subjects will also be evaluated for metabolic efficacy by following their serum LDL and performing LDL turnover studies before and after gene therapy.