Therapeutic for the Treatment of Familial Amyloidotic Cardiomyopathy (FAC)

Abstract

Familial amyloidotic cardiomyopathy (FAC) is a rare, hereditary disease caused by the deposition of misfolded, prion-like amyloid fibrils composed of the transthyretin (TTR) protein. The deposition of amyloid fibrils in the heart leads to congestive heart failure, an arrhythmia, or sudden death. Current therapies include medical management of heart failure symptoms, as well as heart transplantation in a small number of patients young enough to undergo this procedure. ALN-TTRsc, which is being developed to treat FAC, is an RNA interference (RNAi) therapeutic. It is comprised of a small interfering RNA (siRNA) that binds and transports serum retinol binding protein (RBP)/Vitamin A and minor fraction of serum thyroxine (T4) to the liver. ALN-TTRsc is a tetrameric siRNA designed to knockdown the expression of wild-type and all mutant forms of TTR. Multiple doses of ALN-TTRsc generally safe and well tolerated in small number of patients young enough (<70 yrs) to undergo FAC. Nadir TTR knockdown achieved ~10 days after single dose. Statistically significant (p<0.01), dose-dependent knockdown of serum TTR at doses of ≥2.5 mg/kg. Consistent level of TTR knockdown with weekly dosing; durable effects lasting weeks after last dose. Evaluation of every-other-week dosing and evaluation of 7.5 mg/kg multi-dose schedule. Evaluation of single-dose and multiple-dose ALN-TTRsc treatment in non-human primates, rodents, and human volunteers. Excellent correlation of human to non-human primate TTR knockdown on mg/kg basis. Phase III study planned for 2014. Plan to initiate in 2014.