An Investigational RNAi Therapeutic Targeting Factor XII (ALN-F12) for the Treatment of Hereditary Angioedema

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Abstract

Hereditary angioedema (HAE) is a genetic disorder caused by a defect in the C1-inhibitor that results in poor control of contact pathway activation and bradykinin generation. Excessive bradykinin generation increases vascular permeability and is ultimately responsible for the episodes of swelling characteristic of HAE. We hypothesized that the use of RNA interference (RNAi) to knockdown Factor XII, which lies atop the contact pathway signaling cascade, would reduce contact pathway activation and prevent excessive bradykinin generation. To this end, a subcutaneously administered investigational RNAi therapeutic targeting F12 mRNA (ALN-F12) was developed and evaluated in mice and non-human primates. Administration of ALN-F12 resulted in dose-dependent reduction of vascular permeability in two different mouse models of bradykinin-driven vascular permeability, demonstrating that Factor XII knockdown can mitigate excessive bradykinin stimulation. In cynomolgus monkeys, single dose administration of ALN-F12 at 3 mg/kg resulted in >85% reduction of Factor XII. Further, Factor XII knockdown was durable with greater than 70% and 50% reduction at 2 and 3 months post-dose, respectively. Together, these data suggest that RNA-mediated knockdown of Factor XII is a potentially promising approach for the prophylactic treatment of HAE.

Figure 1. ALN-F12 for HAE Prophylactic Therapeutic Hypothesis

Figure 2. ALN-F12 Decreased Plasma FXII Protein Levels in Mice

Figure 3. ALN-F12 Rescued ACE Inhibitor-Induced Vascular Permeability

Figure 4. ALN-F12 Normalized Mustard Oil-Induced Vascular Permeability in a C1-INH Deficient Mouse Model

Figure 5. ALN-F12 Dose-Dependent Durable Knockdown of Circulating FXII in Cynomolgus Monkeys

Summary

- ALN-F12 is a subcutaneously administered investigational RNAi therapeutic targeting hepatic F12 gene expression.
- Single dose administration of ALN-F12 resulted in robust, durable reduction of F12 mRNA and plasma FXII in mice and non-human primates. Knockdown of plasma F12 normalized vascular permeability in two different rodent models of bradykinin-induced vascular leakage. ACE inhibitor-induced and Mustard Oil-induced.
- Non-human primates - single dose administration of ALN-F12 resulted in robust and durable reduction of plasma FXII at 3 mg/kg, the top dose evaluated in this study, led to >85% and >75% reduction of plasma FXII at 1 and 2 months post-administration, respectively.
- Together, the data suggest RNA-mediated knockdown of FXII is a potentially promising approach for the prophylactic treatment of hereditary angioedema.