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Abstract Title: Discovery and Early Clinical Development of ISIS-HTTRx, the First HTT-Lowering Drug to be Tested in Patients with Huntington’s Disease

Press Release Title: Potential Treatment for Huntington’s Disease Is Safe, Effective in Mice, Monkeys

Objective: To design an antisense oligonucleotide (ASO) that specifically, potently and safely reduces HTT mRNA in patients with Huntington’s disease (HD).

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Background: HD is an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in the HTT gene. To date, no treatments have been shown to modify HD progression in patients. In pharmacology studies in transgenic rodent models of HD, CNS delivery of ASOs targeting HTT mRNA delays disease progression and results in sustained reversal of the disease phenotype (Kordasiewicz et al. 2012; Stanek et al. 2013). Therefore, ASO-mediated suppression of huntingtin production may be an effective treatment of HD.

Design/Methods: ASOs were designed and tested in HD fibroblasts and in transgenic mice to identify the optimal drug candidate. Toxicology studies were performed in rodents and non-human primates to determine the candidate’s safety, pharmacokinetic and pharmacodynamic profiles. The results from the toxicology studies informed the design of the early clinical program.

Results: ISIS-HTTRx, a second generation 2'-O-methoxyethyl chimeric ASO with mixed backbone, was tested in IND-enabling toxicology studies in rodents and non-human primates (NHPs). ISIS-HTTRx was administered intrathecally to NHPs at doses up to 20mg without dose-limiting side effects. These findings guided design of clinical study ISIS-443139-CS1 - a multi-center, randomized, double-blind, placebo-controlled study assessing ascending doses of intrathecally administered ISIS-HTTRx in patients with early manifest HD. The study endpoints, which include neuroimaging, electrophysiological, clinical and biochemical outcomes, serve both as safety measures and as exploratory measures of potential pharmacodynamic effects.

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Conclusion: ISIS-HTTRx is the result of a comprehensive drug discovery effort to design a well-tolerated, potent ASO with high specificity for human HTT mRNA. ISIS-HTTRx-mediated reduction of HTT mRNA and huntingtin protein is a promising therapeutic strategy for the treatment of HD and is under active investigation in clinical study ISIS-443139-CS1 (NCT02519036).

Study Supported by: Ionis Pharmaceuticals and is part of Ionis’ collaboration with Roche to develop antisense drugs to treat Huntington’s disease.