Abstract Title: Effects of IONIS-HTTRx (RG6042) in Patients with Early Huntington's Disease, Results of the First HTT-Lowering Drug Trial

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Background: HD is an autosomal dominant neurodegenerative disease caused by CAG repeat expansion in the HTT gene resulting in polyglutamine expansion in the mutant huntingtin protein (mHTT) with a toxic gain-of-function disease mechanism. No disease-modifying treatments are currently available. In transgenic rodent models of HD, suppressing HTT production delays disease progression and reverses disease phenotype. A drug discovery effort, including extensive preclinical testing, was undertaken to design a well-tolerated ASO with high specificity to human HTT mRNA that potently suppresses HTT production.

Design/Methods: In this first-in-human, multi-center, double-blind clinical trial (NCT02519036), 46 patients were randomized (3:1) to receive four doses of IONIS-HTTRx or placebo by monthly bolus intrathecal (IT) injection followed by a 4-month untreated period. Five ascending-dose cohorts were enrolled with independent DSMB review of safety, PK and target engagement prior to dose escalation.

Results: IONIS-HTTRx was well-tolerated at all doses tested. Adverse events were mostly mild and unrelated to study drug. There were no adverse trends in laboratory parameters. No patients prematurely discontinued from treatment. ASO was measurable in CSF and plasma. Significant, dose-dependent reductions in CSF mutant HTT (mHTT) were observed.

Conclusions: ASO technology has the potential to provide disease-modifying benefits to patients with neurodegenerative diseases. In this Phase 1/2a trial in early stage HD patients, IONIS-HTTRx delivered via IT injection was well tolerated with no study drug-related adverse safety signals during the treatment or follow-up periods. Significant dose-dependent reductions in CSF mHTT were observed, suggesting that IONIS-HTTRx is a promising therapeutic for the treatment of HD.
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