Investigational IONIS-HTTRx Lowers Mutant Huntingtin Protein in Early-stage Patients, Phase 1/2 Data Show

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IONIS-HTTRx, a potential therapy for Huntington's disease, was able to reduce the levels of mutant huntingtin (mHTT) protein in early-stage patients, according to results from a Phase 1/2 clinical trial.

Trial results were published in the study, "Targeting Huntingtin Expression in Patients with Huntington's Disease," in *The New England Journal of Medicine.*

Huntington's is caused by a mutation in the *huntingtin* (*HTT*) gene. Because genes are transcribed into messenger RNA molecules that serve as genetic blueprints for making proteins, this means that the mutation in the *HTT* gene leads to the production of abnormal RNA molecules and, ultimately, an abnormal HTT protein.

IONIS-HTTRx is an antisense oligonucleotide (ASO), or antisense therapy, which is designed to stick to a faulty *HTT* messenger RNA, targeting the mRNA for degradation. This reduces the amount of abnormal huntingtin protein that is produced by the cell.

This strategy was show to effectively delay disease progression and even reverse disease symptoms in mouse models of Huntington's disease.

IONIS-HTTRx, developed by Ionis Pharmaceuticals, is designed to target and destroy all forms of mutated huntingtin protein, which means it has the potential to treat all Huntington's patients, regardless of their individual *HTT* mutation.

The Phase 1/2 trial (NCT02519036) evaluated the safety and tolerability of IONIS-HTTRx in patients with early-stage Huntington's disease. Additional objectives included the therapy's pharmacokinetics — essentially how the body affects a medicine — in the cerebrospinal fluid (CSF), which surrounds the brain and spinal cord.

A total of 46 participants were randomized to receive either one of five doses of IONIS-HTTRx (34 individuals) — 10 mg, 30 mg, 60 mg, 90 mg, or 120 mg — or a placebo (12 individuals) administered once a month by an injection in the spinal canal, known as an intrathecal (IT) administration, followed by four months without treatment.

Nearly all the patients (98%) reported adverse effects; however, they were mild (83%) or moderate (17%) in severity. The most commonly reported side effects in those treated with IONIS-HTTRx were procedural pain and a headache after the lumbar puncture. No patient stopped treatment early.

Researchers observed that IONIS-HTTRx reduced the levels of mutant HTT protein in the CSF in a dose-dependent manner, while the levels of the mutant HTT protein in the placebo-treated patients continued to increase.

Compared with the start of the study, the median decrease in mutant HTT protein levels among patients given IONIS-HTTRX was 20% in the 10 mg dose group; 25% in the 30 mg group; 28% in the 60 mg group; 42% in the 90 mg group; and 38% in the 120 mg group.

Researchers saw no differences in other functional, cognitive, psychiatric, and neurological clinical outcomes between placebo- and IONIS-HTTRx-treated patients, regardless of the dose.

"Intrathecal administration of HTTRx to patients with early Huntington's disease was not accompanied by serious adverse events. We observed dose-dependent reductions in concentrations of mutant huntingtin," they concluded.

Patients who completed this Phase 1/2a trial are now participating in an extension trial (NCT03342053) to further examine the treatment's safety, patients' ability to tolerate it, and its pharmacokinetics and pharmacodynamics — the interactions between the body and a compound.