IONIS™ InBrief
27 Feb 2020

CHDI Foundation's 15th Annual Huntington's Disease Therapeutics Conference

Ionis and partner highlight tominersen (formerly known as IONIS-HTT$_{Rx}$ and RG6042) data at annual Huntington's disease drug discovery conference

Ionis, along with its industry and academic partners, provided research updates on IONIS-HTT$_{Rx}$ (RG6042), now with the generic name of tominersen, at the 15th Annual Huntington's Disease Therapeutics Conference in Palm Springs, Calif., Feb. 24-27. Roche is pursuing a broad development program for tominersen, an antisense drug designed to reduce the production of huntingtin, the protein that causes Huntington's disease (HD). The program includes a global Phase 3 study, a natural history study, a long-term open label extension (OLE) study and a pharmacokinetic study.

> *I am pleased by the progress that Ionis, Roche and the HD research community continue to make in pursuit of a potentially effective treatment for this progressive, incurable and ultimately fatal disease that affects thousands of people worldwide. While much work remains to be done, tremendous strides have been made and I am heartened by the courage of all the HD patients and families who are participating in the studies."*
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> **Sarah Tabrizi, Ph.D.,** professor of clinical neurology at University College London, director of the UCL Huntington's Disease Center and an investigator for tominersen clinical trials.

KEY TAKEAWAY

Taken as a whole, the latest tominersen data provide further insights into huntingtin lowering and support this approach as the optimal strategy for treatment of Huntington's disease.

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- **Preliminary results from a 15-month open-label extension (OLE) study investigating RG6042 huntingtin protein (HTT) antisense oligonucleotide (ASO) in adults with manifest Huntington's disease (HD).**
  Preliminary fluid biomarker data from Roche's 15-month open label extension study reinforces the conclusion that an infrequent dosing schedule (in this case every two months) achieves or exceeds the level of mutant huntingtin (mHTT) protein lowering in CNS tissues predicted to provide benefit based on preclinical models. In addition, infrequent dosing is well tolerated and is more convenient for patients and caregivers. (S. Schobel, M.D., Roche)
- **Changes in brain activity with antisense oligonucleotide (ASO) RG6042 treatment in early manifest Huntington's disease.**
  An analysis describing electroencephalography (EEG) data from a tominersen Phase 1/2 study compared to EEG data in healthy controls showed that EEG brain activity is abnormally low in HD patients, and treatment with tominersen (but not placebo) reverses the deficit in brain activity. (D. Hawellek, Ph.D., Roche)
- **Development of non-clinical pharmacokinetic/pharmacodynamic model to predict CSF reductions in huntingtin protein in individuals with Huntington's disease.**
  A description of the pharmacokinetic/pharmacodynamic model developed to predict changes in CSF mHTT, CNS tissue mHTT protein and mRNA and drug exposures which has been used to guide dosing decisions for the program. (D. Norris, Ph.D., Ionis)
- **Reliability and validity of passively collected step frequency variability as a measure of real-life walking impairment in Huntington's patients.**
  An update on the use of remote patient monitoring as a reliable and valid approach to capturing frequent, detailed data on walking impairment in Huntington's disease patients. (C. Simillion, Ph.D., Roche)
- **A mechanistic framework for understanding the relationship between huntingtin (HTT) lowering and neurofilament light chain protein (NfL).**
  An overview of studies initiated by Roche to investigate potential mechanisms responsible for the transient increase in neurofilament light chain (NfL) observed in the tominersen clinical trials, including following up on data from publications demonstrating that expression of mHTT protein suppresses thevexpression of neurofilament protein in CNS tissues. (M. Benekareddy, Ph.D., Roche)
- **Huntingtin protein acts in trans to regulate somatic instability of long CAG tracts.**
  Data demonstrating that the inhibition of huntingtin protein decreased genome instability of huntingtin and ataxin 2, a gene associated with related CAG repeat diseases, suggesting that huntingtin lowering could benefit several repeat disorders. (J. Carroll, Ph.D., Western Washington University)

Ionis InBriefs provide updates on the company's pipeline, programs and events.