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Ionis drug successfully reduces toxic Huntington's disease protein, paving way for Phase 2 trial of effect on patients

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At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

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Ionis drug successfully reduces toxic Huntington's disease protein, paving way for Phase 2 trial of effect on patients

In an initial clinical trial that marks a significant step toward finding an effective Huntington's disease treatment, the Ionis Pharmaceuticals gene-silencing drug safely reduced the production of the toxic mutant protein implicated in HD, the firm announced today.

Ionis has handed development of the expected Phase 2 trial to its partner in the project, the multinational pharmaceutical giant Roche, earning a $45 million license fee, today's Ionis press release stated. The drug is called IONIS-HTT_{Rx}: "HTT" stands for both the huntingtin gene and the protein it produces, and "Rx" signifies a remedy.

The trial was officially classified as Phase 1/2a. A Phase 1 trial measure's a drug's safety and tolerability in a small number of participants, while a Phase 2 trial examines efficacy in a larger group of patients. Though mainly Phase 1, this trial had elements of a Phase 2: actual HD patients took part, and it sought to determine whether the drug's basic mechanism worked.

"We are encouraged by the performance of IONIS-HTTRx in the Phase 1/2a clinical study," Frank Bennett, Ph.D., Ionis senior vice president of research, stated in the release.

The reductions of the mutant protein "observed in the study substantially exceeded our expectations," Dr. Bennett added. The study, which involved 46 participants with early HD symptoms, did not assess whether that reduction slowed disease progression.

Ionis stated that "dose-dependent reductions of mHTT were observed" in the trial: the higher the dosage, the greater the reduction in the amount of the mutant protein.

"We were equally encouraged by the safety profile of the drug," Dr. Bennett stated.

"The results of this trial are of ground-breaking importance for Huntington's disease patients and families," stated Dr. Sarah Tabrizi, professor of clinical neurology, director of the University College London's Huntington Centre, and the global lead investigator on the Phase 1/2a study. "For the first time, a drug has lowered the level of the toxic disease-causing protein in the nervous system, and the drug was safe and well tolerated. The key now is to move quickly to a larger trial to test whether IONIS-HTT_{Rx} slows disease progression."

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Frank Bennett, Ph.D. (above, photo by Kristina Bowyer, Ionis) and Dr. Sarah Tabrizi (below, photo by Gene Veritas)

Pharma giant Roche steps in

Ionis officials stated in June that a Phase 2 study could start as soon as 2018. Typically, all three phases of a clinical trial project take at least five years, although nobody can predict the actual course of a trial.

In 2013, Ionis, a mid-sized drug-discovery firm that does not produce or sell drugs or conduct clinical trials on its own, partnered with Roche, one of the world's largest and most successful pharmaceutical companies (click here and here to read more). Roche's expertise includes neurodegenerative brain diseases.

Roche will now take over the development of IONIS-HTT_{Rx}, including the Phase 2 and potential Phase 3 trials and bringing the drug to market. It will hold the license to the drug.

Roche also will administer the open-label extension of the Phase 1/2a study, announced in June, whereby all patients – including those who got a placebo – will continue to receive the drug. The extension allows researchers to gather more data, examine the drug's effects over a longer period of time, and better prepare for Phase 2. Patients also potentially benefit by receiving the drug longer.

Phase 2 to include United States

By attacking Huntington's disease near its genetic roots, IONIS-HTT_{Rx} could potentially reduce, partly reverse, and even prevent symptoms. Ionis drugs are antisense oligonucleotides, artificial strands of DNA. The drug aims to turn off the huntingtin gene messenger RNA that contains the instructions to make the huntingtin protein in brain cells.

Forty-six patients took part in the Phase 1/2a trial at sites in Canada, Germany, and England.

"Today is an exciting day for the Huntington's disease community," a joint Ionis-Roche letter to the HD community stated. "Future studies for the program will be conducted globally, including in the U.S. Roche will announce details about future studies, including eligibility criteria and planned start dates, as this information becomes available."

More than a decade of research

IONIS-HTT_{Rx} resulted from more than a decade of research involving Ionis, Roche, the lab of neurobiologist Donald Cleveland, Ph.D., at the University of California, San Diego, and CHDI Foundation, Inc., the nonprofit virtual biotech firm aimed solely at finding (and funding) HD treatments.

On December 3, Dr. Cleveland received the $3 million Breakthrough Prize, the world's richest science award, sponsored by Google, Facebook, and other entities. It is twice the value of the Nobel Prize. Dr. Cleveland received recognition for his career contributions to the life sciences, including work on a cause of Alzheimer's disease. (Click here to read more.)

Dr. Cleveland was honored at the 2012 gala of the San Diego Chapter of the Huntington's Disease Society of America. For a recent article explaining the Dr. Cleveland's role in the Ionis project, click here.

In interviews today, I hope to obtain further details about the progress regarding IONIS-HTT_{Rx}.

HDBuzz's take: a historic breakthrough

The HD research site HDBuzz, produced by scientists, stated that today's announcement is "likely to stand as one of the biggest breakthroughs in Huntington's disease since the discovery of the HD gene in 1993."

The site's article, written by Jeff Carroll, Ph.D. – an HD-gene carrier like me and a scientist dedicating his career to finding HD treatments – asserted that the "most exciting" part of today's news is that "dose-dependent reductions of mutant huntingtin were observed."

The clinical trial administrators know this because they examined samples of participants' cerebrospinal fluid, which runs along the spine and into

the brain. Participants received injections of the drug via a spinal tap.

"This means that patients treated with IONIS-HTTRx have reductions in the huntingtin protein in their cerebrospinal fluid," Dr. Carroll wrote. "Based on this result, it looks like the drug is doing what it's meant to do, and that huntingtin lowering has been achieved!"

Dr. Wild concluded: "This is a great day in the HD community, and it sets us on the path to even more exciting work in 2018. For the first time in history, HD patients are being treated with drugs known to reduce the amount of huntingtin protein in their brain. Until we conduct the next trial, we won't know if this reduces the impact of HD. And while we know the drug is safe in the short term, we will also have to watch carefully for any long-term adverse effects. But we're facing this problem with renewed excitement and hope. It's the best early Christmas present we could have hoped for."

Jeff Carroll, Ph.D., at the 2012 CHDI-sponsored HD therapeutics conference (photo by Gene Veritas)

(Disclosure: I hold a symbolic amount of Ionis shares.)

Posted by Gene Veritas at 7:28 AM

Labels: antisense oligonucleotide , clinical trials , DNA , Frank Bennett , huntingtin , huntingtin lowering , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , Jeff Carroll , RNA , Roche , Sarah Tabrizi , treatments

1 comment:

Anonymous said...

So hopeful. Thanks.

6:18 PM, December 13, 2017

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