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Ionis Phase I Huntington's disease trial at halfway mark: 'No surprises so far' means good news

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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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WEDNESDAY, OCTOBER 19, 2016

Ionis Phase I Huntington’s disease trial at halfway mark: ‘No surprises so far’ means good news

At its halfway mark, Ionis Pharmaceuticals' historic Huntington’s disease Phase 1 gene-silencing clinical trial is on track to finish as scheduled in late 2017, company officials said in an interview on September 26.

“What we can say is that the trial is going well,” said Frank Bennett, Ph.D., Ionis senior vice president of research and the franchise leader for the company’s neurology programs.

Dr. Bennett added that no “issues” have arisen so far in the Phase 1 safety and tolerability study of its drug IONIS-HTT_{Rx} in patients with early HD. IONIS-HTT_{Rx} aims to reduce the production of huntingtin protein in brain cells. This approach, if it advances to Phases 2 and 3, may have the potential to slow, halt or perhaps even reverse the progression of HD symptoms. The trial began in September 2015, with participants in England, Germany, and Canada.

The Ionis HD team explained that the Phase 1 trial is not assessing the drug’s efficacy. Each patient in the trial receives the drug for just three months – not long enough to gauge any impact on symptoms.

Furthermore, the trial is “double-blinded”: trial participants, trial administrators, and Ionis scientists do not know who is getting the drug or a placebo. This insures that bias and other external factors don’t affect the trial results.

Nevertheless, the absence of problems is good news.

No surprises have occurred to date, commented Anne Smith, Ph.D., the Ionis director of clinical development and the individual responsible for the day-to-day management of the trial.

“It’s blissfully quiet,” Dr. Smith said. “You don’t want surprises in clinical trials. Most surprises in safety trials are bad surprises. This one is surprise-free to date.”

Also, trial participants had no difficulties with the delivery of the drug via injections into the spine (so-called intrathecal injections), added Roger Lane, M.D., the Ionis vice president for neurology clinical development and one of the designers of the trial.

Watch my reaction after the interview at Ionis headquarters on September 27 in the video below.

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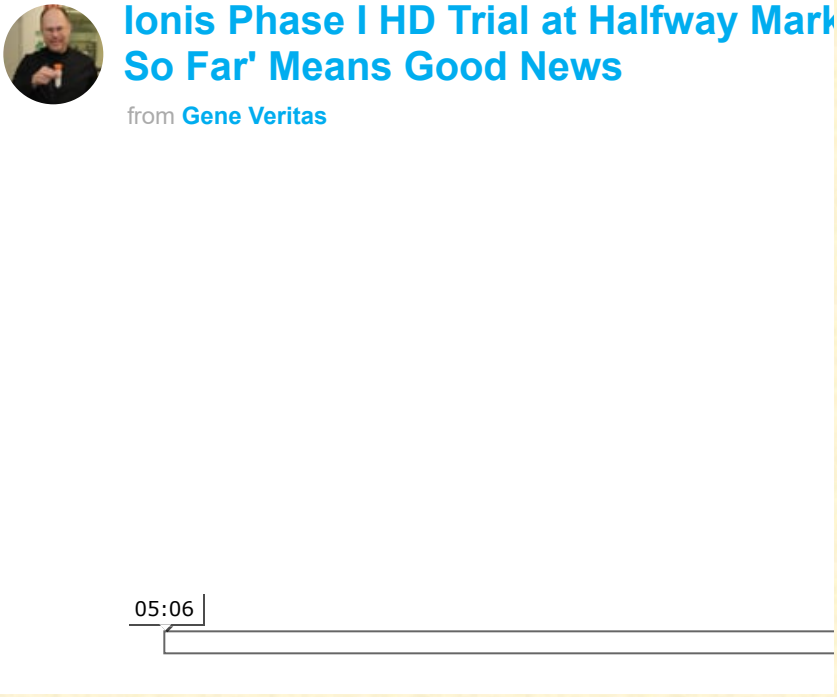

Ionis Phase I HD Trial at Halfway Mark: 'No Surprises So Far' Means Good News from Gene Veritas on Vimeo.

Phase 2 could start in 2018

"We're continuing to enroll patients in the study," Dr. Bennett said. A total of 36 patients divided into four cohorts – each subsequent cohort taking a higher dose of IONIS-HTT_{Rx} – will participate in the trial.

Ed Wild, M.D., Ph.D., one of the administrators of the trial at University College London, announced in June at the annual convention of the Huntington's Disease Society of America in Baltimore that the third cohort had received permission to receive the drug. (Click here to watch a video of Dr. Wild's presentation.)

"This is a new therapy, and we want to make sure that we're doing no harm," Dr. Bennett emphasized. "Everything is geared towards the safety of the drug at this stage."

If Phase 1 confirms safety and tolerability, a year-long Phase 2 trial to measure efficacy in a larger number of patients likely would start in 2018, Dr. Bennett said.

Infants on an Ionis SMA drug living longer

The update provided by the Ionis HD team came in the wake of further validation of the company's scientific approach.

Ionis makes antisense oligonucleotides (ASOs, artificial strands of DNA) that alter the expression of genes and can therefore potentially serve as treatments for genetic diseases. On August 1, Ionis and its partner Biogen actually halted a Phase 3 trial of an Ionis ASO (nusinersen) in infants with spinal muscular atrophy (SMA) because the drug, which increases the level of a key protein, was working so well.

On September 27, Biogen announced that it had completed its application for priority review of nusinersen by the U.S. Food and Drug Administration (FDA).

Like HD, SMA is a genetic neurodegenerative disorder. It primarily affects children, who "end up becoming paralyzed over time," Dr. Bennett explained, and become vulnerable to respiratory infections or other diseases. Children diagnosed with the most severe form of SMA generally live less than a year, he said. In a less severe form of SMA, children lose the ability to walk over time as they grow up, Dr. Bennett added.

"I think the surprising thing that we found – and this was evidence early in the program – was that we didn't just stop the decline in these patients, but we actually reversed it," Dr. Bennett said. "That was really unexpected. I should say that they're not cured of the disease, but they're doing much better now than expected. They are surviving longer based on the natural history of the disease."

These results demonstrated the body's capacity to mend once the cause of a disorder is removed, he observed.

"We're hopeful that will also occur in Huntington's," Dr. Bennett affirmed. "We have to demonstrate it, but I think there's a precedent now in these neurodegenerative diseases. If you remove the insult or the toxicity, you can recover function."

Dr. Frank Bennett of Ionis makes a point during discussion of the company's Phase 1 clinical trial for a Huntington's disease treatment (photo by Kristina Bowyer, Ionis)

Preparing for the HD clinical study

In the Phase 1 IONIS-HTT_{Rx} trial, clinical trial investigators are collecting some information about the drug's effect on biomarkers (indicators of a disease mechanism or drug impact) that may help the team design a potential Phase 2.

According to Dr. Lane, before a patient receives each of the four planned doses, the trial administrators collect samples of cerebrospinal fluid (CSF) that will be used to measure levels of huntingtin protein and a variety of other protein markers of neuronal injury and inflammation. Patients also

undergo brain scans to look at the volumes of, and the connectivity between, different parts of the brain that are known to be affected in HD.

Another biomarker is neurofilament, described by Dr. Bennett as a protein involved in the cytoskeleton or internal "scaffold" of neurons. "It's something very specific to neurons," said Holly Kordasiewicz, Ph.D., the Ionis director of neuroscience drug discovery, who participated in selecting the ASO, researched it in animals, and is developing biomarker tests for the Phase 1 study. "When the neurons are damaged, neurofilament is released. In a number of neurodegenerative diseases, neurons are dying and neurofilament levels go up."

In HD, brain cells die. In a clinical study, a decrease in neurofilament would suggest that the drug is protecting neurons, Dr. Kordasiewicz added.

Ionis Huntington's disease clinical trial planners Dr. Anne Smith (left), Dr. Roger Lane, and Dr. Holly Kordasiewicz meet with Gene Veritas (in green shirt) on September 26, 2016, to provide an update on the company's Phase 1 HD trial (photo by Kristina Bowyer of Ionis)

Getting the design of Phase 2 right

The participants in the IONIS-HTT_{Rx} study undergo a battery of tests that assess memory, thinking, movement, behavior problems, and abilities to perform every-day activities. This is in preparation for use of such measures in a potential Phase 2.

"We're trying to get the information to design the best efficacy study that we can," said Dr. Kordasiewicz. "A really sad outcome would be failure of an efficacy study due to the wrong design, not because the drug's not working. You have to be sure you're picking the right dose and the right endpoints for the efficacy study. That's why all the extra stuff goes into these Phase 1 trials, so that you can get the design right and have the best shot at giving the drug the best chance at working."

The large burden of work on patients and trial administrators in Phase 1will ultimately allow Ionis (and its partner Roche) to "simplify" potential Phase 2 and 3 trials, making them quicker and making it easier for patients to participate, Dr. Bennett added.

Seeking answers to key questions

This is the first time that an HD gene-silencing drug is going into the human brain. In animals such as mice and non-human primates, the drug gets into both the cortex (the outer, main part of the brain, linked to

consciousness) and the striatum (a part of the brain deep under the surface that is involved in movement). Both areas are affected by HD.

A key question for researchers: must IONIS-HTT_{Rx} reach the striatum to help alleviate HD?

According to Dr. Kordasiewicz, the latest research in HD mice (conducted by William Yang, M.D., Ph.D., of the University of California, Los Angeles) demonstrates that silencing the huntingtin gene in the cortex was more effective than silencing the gene in the striatum, but that silencing in both cortex and striatum was the most effective approach.

Another concern of scientists and HD patients and their families involves the abilities of the ASO, or gene-silencing drug. Should the ASO be designed to reduce only the so-called "bad,"mutant huntingtin? Or is it okay to reduce both the bad and the normal version, which is inherited from the unaffected parent? The IONIS ASO is expected to do the latter.

According to the Ionis HD team, the controversy over this question is diminishing. Studies in animals support the safety of approaches that reduce both mutant and normal huntingtin. Additionally, Dr. Guohao Wang's work in mice showed that eliminating huntingtin completely in later life did not have any adverse consequences.

"That was good evidence to support our approach," said Dr. Lane.

Involving the U.S., thanking patients and families

Many in the HD community have asked: why didn't Ionis conduct Phase 1 in the United States? And would a potential Phase 2 include Americans?

"I'd be surprised if the U.S. wasn't involved in a Phase 2 study, as well as additional countries, but I don't think we are in a position to say specifically which countries are going to be involved," Dr. Bennett commented. "There were strategic decisions that caused us to go to Europe and Canada first. It's not that we want to ignore the U.S." He explained that it was faster to start a trial in Canada and Europe.

The Ionis HD team thanked the Phase 1 participants and their families for their involvement in the Phase 1 study.

"It's been a very good community and very supportive of our efforts," said Dr. Bennett. "We also want to thank them for their patience."

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

(Click on the links below for past coverage of the Ionis HD project.)

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Posted by Gene Veritas at 8:34 AM

Labels: Anne Smith , ASO , clinical trial , CSF , Frank Bennett , gene-silencing , genetic , Holly Kordasiewicz , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , neurodegenerative , Phase 1 , Roger Lane , treatment

4 comments:

Anonymous said...
Outstanding work. Thank you for sharing.
1:44 PM, October 19, 2016

Anonymous said...
Hopeful, indeed. Thank you!!!
6:18 PM, October 22, 2016

Maureen Morehead said...
Hopeful for those of us waiting! Thank you, scientists, and thank you, Gene.
6:21 PM, October 22, 2016

Unknown said...
Amazing. Could be the answer to so many prayers!
8:59 PM, April 13, 2017

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