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Roche Phase 3 clinical trial for Huntington's disease gene-slicing drug to enroll volunteers in early 2019

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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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SUNDAY, SEPTEMBER 16, 2018

Roche Phase 3 clinical trial for Huntington's disease gene-silencing drug to enroll volunteers in early 2019

The major drug company Roche expects to start enrolling subjects worldwide (including the U.S.) in early 2019 in its historic Phase 3 clinical trial of RG6042, a gene-silencing drug aimed at slowing, halting, and perhaps even reversing the symptoms of Huntington's disease.

Roche made the announcement today at the bi-annual plenary meeting of the European Huntington's Disease Network in Vienna, Austria, and issued a statement to the global HD community providing details (click here for the statement).

Designed by Roche partner Ionis Pharmaceuticals, Inc., and previously known as IONIS-HTT_{Rx}, RG6042 demonstrated impressive results in the Phase 1/2a trial completed by Ionis in December 2017.

On March 1, at CHDI Foundation's 13th Annual Huntington's Disease Therapeutics Conference, researchers revealed that RG6042 caused Phase 1/2a trial volunteers to experience a drop of 40 to 60 percent in the harmful mutant huntingtin protein in their cerebral spinal fluid (CSF). According to the researchers, projecting from tests in animals, that corresponds to as much as an 85 percent decrease in the cortex of the brain. However, this trial did not measure actual efficacy – only safety and tolerability. (Click here to read more.)

Scientists have identified mutant huntingtin protein, resulting from a defective huntingtin gene inherited by HD patients and carried by presymptomatic individuals like me, as a principal cause of HD.

Because of the solid Phase 1/2a results, Roche has taken the unusual step of skipping a Phase 2 trial (testing efficacy for the first time) and going directly to a robust Phase 3, where researchers hope to test efficacy in 660 volunteers over 25 months at 80 to 90 sites in approximately 15 countries, to be announced gradually in the coming months. Phase 1/2a involved only 46 individuals, who received the drug over just three months at nine sites in Canada, Germany, and the United Kingdom.

In a detailed interview at the CHDI meeting, Roche officials confirmed that U.S. sites would take part in Phase 3 (click here to read more).

GENERATION HD1: can it stop or slow HD?

"Following the completion of the Phase I/IIa first-in-human study of RG6042 in December, there are several important questions that still need to be answered before this investigational medicine can potentially be approved by Health Authorities in countries around the world," said today's Roche statement, signed by Mai-Lise Nguyen, the patient partnership director for the firm's HD program.

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Roche has named the study GENERATION HD1.

As outlined by Nguyen, GENERATION HD1 will gauge the effects of reducing mutant huntingtin and whether RG6042 can "slow or stop the progression of HD." It will also further examine the drug's safety in a larger group of people over more time.

Members of the Roche HD clinical trial team watch the presentation of the RG6042 Phase 1/2a results at the 13th Annual HD Therapeutics Conference in Palm Springs, CA, March 1, 2018. From left to right, Scott Schobel, M.D., M.S., clinical science leader of product development; Lauren Boak, Ph.D., global development team leader; Erik Lundgren, lifecycle leader of the HD program; and Mai-Lise Nguyen, patient partner director (photo by Gene Veritas).

The trial will also study whether less than a monthly dose, which was used in Phase 1/2a, can prove effective. One third of participants will receive monthly doses of 120 mg, one third a bi-monthly dose of 120 mg, and another third a placebo dose monthly. As in the Phase 1/2a trial, participants will receive the drug via a lumbar puncture (a so-called intrathecal injection).

To assure objectivity, the study will be "double-blinded" – neither the participants nor the researchers or site staff will know which dosage is administered. To reinforce objectivity, even the bi-monthly recipients (who won't know they're in this group) will take part monthly; they'll get the placebo every other month. Site information will be posted on the site www.HDTrialFinder.org.

Today's statement underscored the "urgency" felt by Roche to conduct GENERATION HD1 but pointed out that not all patients and research clinics will be able to participate. "Please understand the studies are designed to provide Authorities with the required data so that the benefit-risk of RG6042 can be determined as quickly as possible," it stated.

For now, because Roche needs to demonstrate the efficacy and safety of RG6042, the firm will offer access to the drug only through participation in clinical trials. This means patients cannot make early access (prior to regulatory approval), so-called compassionate use, or "right to try" requests.

At this time, presymptomatic gene carriers and juvenile HD patients are ineligible for GENERATION HD1.

Additional studies

In addition, Roche will conduct a second, 15-month observational study – without a drug – called The HD Natural History Study. Starting towards the end of this year, it will gauge the natural progression of the disease in up to 100 participants with early-stage HD at up to 17 sites in Canada, Germany, the United Kingdom, and the U.S.

By seeking to deepen understanding of the role of the mutant huntingtin protein in HD, the Natural History Study will provide context for GENERATION HD1. Participants will undergo four lumbar punctures, plus MRI scans, blood tests, and neurological examinations. Like the volunteers in GENERATION HD1, they will use digital monitoring devices.

Meanwhile, all 46 participants in the Phase I/IIa study continue to receive RG6042 as part of an "open-label extension" study run by Ionis to assess the safety and tolerability of longer use of the drug. Those who got placebo originally now get the medicine.

Fast-tracking drug evaluation

The EHDN update comes in the wake of an August 2 announcement by Ionis and Roche that RG6042 received "PRIME" (PRIority MEdicine) status from the European Medicines Agency (EMA), a regulatory body similar to the U.S. Food and Drug Administration (FDA).

"We are very pleased that the European Medicines Agency has granted PRIME designation for RG6042, as there is an urgent medical need to find treatment options for families affected by Huntington's disease," Sandra Horning, M.D., Roche's chief medical officer and head of global product development, stated in a press release.

According to the EMA, firms benefitting from PRIME "can expect to be eligible for accelerated assessment" in the drug approval process, reducing the standard timeframe of 210 days to 150 days.

A major step, but not the last

In March, after witnessing the revelation that RG6042 successfully lowered mutant huntingtin protein in the CSF, I wrote: "It's the best news the HD community has received since the publication of the research confirming the discovery of the gene 25 years ago this month. As scientists have observed, it's also a major step for disease and drug research in general."

The August 24 issue of the magazine *Science* published a balanced article about the Ionis-Roche clinical trials titled "Daring to Hope," including the struggles of Canadian woman and Phase 1/2a trial and open-label extension participant Michelle Dardengo. She describes some improvements in her symptoms – although doctors caution that her situation is merely anecdotal and not proof of actual drug effectiveness.

Michelle's 27-year-old son Joel has also tested positive for HD. He was more skeptical about her apparent improvement.

"I do wish for the best," Joel states in the article. "At the same time, I do prepare for the worst."

Like all of the HD community, Michelle, Joel, and I must wait for the completion of GENERATION HD1 early in the next decade to see if RG6042 can help save us from HD.

For discussion of the Roche announcement at the EHDN meeting, see the HDBuzz Twitter feed for September 16, 2018.

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

Posted by Gene Veritas at 7:58 PM

Labels: clinical trials , CSF , gene-silencing , GENERATION HD1 , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , Mai-Lise Nguyen , mutant huntingtin , presymptomatic , RG6042 , Roche , symptoms , treatments

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