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Roche: less frequent dosing for Phase 3 Huntington's clinical trial, easing burden 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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FRIDAY, MARCH 22, 2019

Roche: less frequent dosing for Phase 3 Huntington's clinical trial, easing burden on patients

With preliminary data in hand, the pharmaceutical firm Roche has announced that it will reduce the frequency of dosing in its historic Phase 3 Huntington's disease gene-silencing clinical trial, thus easing the burden on the participants, their families, and clinics.

In the recently initiated trial, GENERATION HD1, volunteers will now undergo a bi-monthly instead of a monthly spinal tap (lumbar puncture), Roche announced in a letter to the HD community on March 21, 2019. Lumbar punctures are routine and generally safe procedures, although they can cause side effects such as headaches and bleeding. In GENERATION HD1 it will be a 20-minute outpatient procedure.

Roche based the change on new data taken from 46 volunteers after nine months into the 15-month, so-called open-label extension trial (OLE) that it started for its drug RG6042. Those individuals previously participated in the successful Phase 1/2a clinical trial of RG6042, originally developed by Ionis Pharmaceuticals, Inc. The drug substantially lowered the amount of mutant huntingtin protein, the purported cause of the disease, in the patients' cerebrospinal fluid. All OLE participants received the drug (as opposed to 25 percent getting the placebo in the 1/2a trial).

"The 15-month open-label extension of the Phase1/2a study is evaluating RG6042 treatment in doses every month (every four weeks) and every two months (every eight weeks)," the Roche announcement stated. "Review of nine-month data showed effects on lowering mutant huntingtin protein levels in the cerebral spinal fluid that support the exploration of less frequent dosing. Based on the totality of the data, including safety and tolerability, there appears to be no overall advantage to treatment monthly versus every two months."

GENERATION HD1 has three cohorts of clinical trial volunteers, known as "arms." The planned 660 participants at 80-90 sites around the world are randomly assigned to one of the arms. The study is double-blinded: neither the volunteers nor the trial physicians and their staff know which arm the volunteers are assigned to.

As a result of the update to the trial, all participants will undergo bi-monthly punctures over 25 months. In "arm 1" of the study, the dosing schedule will switch from a monthly puncture and administering the drug bi-monthly (with a placebo in between) to a bi-monthly puncture with no placebo at all. Arm 3 will go from getting a monthly puncture with placebo to a bi-monthly puncture with placebo.

To test the possibility of reducing potential future drug dosing even further, arm 2 will go from a monthly puncture with the drug to a bi-monthly puncture but with

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the drug given only every four months (with a placebo in between).

"I am delighted by today's news that the Generation HD1 protocol will be amended to be less burdensome to trial participants, families and HD clinics around the globe," George Yohrling, Ph.D., the senior director of mission and scientific affairs for the Huntington's Disease Society of America, commented in an e-mail. "We are all indebted to the 46 trailblazing research heroes participating in the Phase 1/2a and open-label extension studies that showed us we could not only lower huntingtin in humans, but could do so *without* monthly infusions of RG6042. Their contributions have forever changed the landscape of HD drug development."

"The amended trial is good news for the HD community," LaVonne Goodman, M.D., the founder of Huntington's Disease Drug Works and a physician to many HD patents, wrote in an e-mail. "For the shorter term, it will make for fewer visits and spinal taps for all involved in the trial. And for the longer term, if the trial at completion is successful by clinical measures, it may further establish whether quarterly dosing is adequate and effective. If so, that would make it easier on the larger number of patients who would need to receive this drug life-long."

Simplifying the study

Dr. Goodman added: "It was fortunate that the Roche analysis and amendment came at the very beginning of the GENERATION HD1 trial, so that changes could be made without a major time disruption."

A statement on the Ionis website observed that the new trial design "will greatly simplify the operation of the study."

Although amending the trial will cause a "slight delay" as Roche seeks regulatory approvals, "we don't expect this delay will change the timing of study completion, and may even accelerate time to study completion," the Ionis statement concluded.

"Our team is working to rapidly activate the updated study protocol around the world," the Roche statement said.

Individuals who had already started GENERATION HD1, which began in January, will be eligible to switch to GEN-EXTEND, an OLE study in which everybody receives RG6042 (no placebo). Participants will receive drug every two or four months.

Great news for the HD community

As the Roche statement noted, the data from the Phase 1/2a OLE do not address the efficacy and long-term safety of the RG6042. That is the purpose of

GENERATION HD1.

The update from Roche came in the wake of remarks by GENERATION HD1 scientific coordinator Scott Schobel, M.D., that the company is "actively thinking" about when and how to expand research to target groups beyond the current criterion of early- to mid-stage HD patients aged 25-65. That includes asymptomatic gene carriers like me and sufferers of juvenile HD (click here to read more).

The scientist-written site HDBuzz described the amended trial design as a "surprise" but also a "good thing."

"Clearly Roche and their partners didn't predict that we'd be able to deliver [the drug] only every four months when they started the GENERATION HD1 study," its article on the Roche statement observed. "The fact that they've seen data convincing them that we can get away with it is great news for the future of this program, and for future HD community members receiving treatment."

HDBuzz further noted that other companies using the Ionis-Roche approach (antisense oligonucleotides) can now "consider using longer intervals between treatments."

As an HD gene carrier and also a sufferer of chronic back pain, I was relieved to learn that the number of lumbar punctures for a potential drug could be as few as three per year.

The Roche announcement coincided with the news that the U.S.-based biotech firm Biogen and its Japanese partner Eisai had announced that they were halting two phase 3 clinical trials for an Alzheimer's disease drug because an interim analysis concluded that the compound was unlikely to benefit patients. The drug was given through intravenous infusions.

The results of that trial once again underscored the extreme difficulty of treating neurological disorders and the need to the need to have realistic expectations about RG6042 (click here to read more). Not just Alzheimer's and Huntington's, but also Parkinson's, Lou Gehrig's, and other neurological disorders lack effective treatments.

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

Posted by Gene Veritas at 12:10 PM

Labels: Alzheimer's , cerebral spinal fluid , clinical trials , dosing , GEN-EXTEND , GENERATION HD1 , George Yohrling , Huntington's disease , Ionis , lumbar puncture , mutant huntingtin , open-label extension , Roche , treatments

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