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Roche announces first sites for key Huntington's disease observational study

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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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Roche announces first sites for key Huntington's disease observational study

Pharmaceutical firm Roche has identified nine sites in the U.S. and Canada for an observational study that will seek to answer key questions for the company's upcoming Phase 3 trial of a gene-silencing drug to treat Huntington's disease.

In a November 7 e-mail to the Huntington's Disease Society of America (HDSA) and other HD groups, the Swiss-based Roche announced that it plans to carry out its HD Natural History Study, beginning by the end of this year.

The HD Natural History Study is part of Roche's global development program for the gene-silencing drug, RG6042. The Natural History Study will provide context for GENERATION HD1, the company's Phase 3 clinical trial of RG6042, which will start enrolling volunteers in early 2019.

The HD Natural History Study will seek to deepen understanding of the natural progression of HD, the role of the mutant huntingtin protein in the disorder, and the assessment of biomarkers (signs of the disease measured in patients) and their efficacy in predicting the effects of the drug.

Initial sites

Roche announced the sites listed below.

Canada

Centre for Movement Disorders, Toronto, ON
University of British Columbia, Vancouver, BC

U.S.

Columbia University, New York, NY
Georgetown University, Washington, D.C.
Hereditary Neurological Disease Center, Wichita, KA
Johns Hopkins University, Baltimore, MD
Rocky Mountain Movement Disorders Center, Englewood, CO
University of California Davis, Sacramento, CA
University of Texas, Houston, TX

"These sites are not fully activated nor recruiting yet, but we hope to complete the final steps as quickly as possible," wrote Mai-Lise Nguyen, the patient partnership director for the Roche HD team, in the e-mail.

Roche will announce a total of eight additional sites in Germany and the United Kingdom. It hopes to enroll 100 volunteers with early symptomatic (Stage I and II) HD for the 15-month study (preceded by one month of

Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
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screening). Participants must be between 25 and 65 at the start of the study.

"I am pleased to share that setup has progressed well in all four countries in which the HD Natural History Study is planned," Nguyen added.

The pivotal Phase 3 trial

In March, researchers announced the impressive results of the Phase 1/2a trial for RG6042, completed in December 2017 with 46 participants in Canada, Germany, and the United Kingdom. That trial tested primarily safety and tolerability (click here to read more). Those results led Roche to skip the usual Phase 2 trial and go directly to a pivotal Phase 3, named GENERATION HD1.

RG6042 was developed by Ionis Pharmaceuticals, Inc., which partnered with Roche in 2013. Roche now holds the license to the drug.

The GENERATION HD1 trial, to take place at 80 to 90 sites in 15 countries, will test whether RG6042 can slow, halt, and perhaps even reverse HD symptoms in 660 volunteers over 25 months.

Each month, GENERATION HD1 participants will receive the drug or placebo through a lumbar puncture. Physicians will also withdraw samples of participants' cerebrospinal fluid (CSF) to measure the level of mutant huntingtin and other biomarkers.

Roche will announce GENERATION HD1 sites gradually in the coming months.

Why a natural history study?

Roche officials said that the HD Natural History Study will start by the end of 2018.

Participants in this observational trial will receive no drug. They will undergo four lumbar punctures, with withdrawals of CSF for analysis. They will also undergo MRI scans, blood tests, neurological examinations, and two phone checkups. Like the volunteers in GENERATION HD1, they will use digital monitoring devices.

Researchers have studied both the normal and mutant forms of the huntingtin protein since the late 1990s. However, for GENERATION HD1, Roche needs a deeper understanding of mutant huntingtin's role in the progression of the disease. Only in recent years have researchers started examining the CSF of HD-affected individuals, so a critical question is how mutant huntingtin levels change over time naturally.

That data will provide context for researchers to interpret the GENERATION HD1 data.

Furthermore, the RG6042 program involves just one Phase 3 trial, but regulatory agencies frequently want a second. Thus, the HD Natural History Study can help with the proper interpretation of Phase 3. Roche is collecting additional data from an "open-label extension" study involving all participants in the Phase 1/2a study. Each is receiving the drug.

"We're really trying to understand better the natural history of the disease and the predictive power of the biomarkers at baseline to predict clinical outcome," commented Scott Schobel, M.D., M.S., Roche clinical science leader of product development, in a September 26 HDSA webinar on the RG6042 program.

Dr. Scott Schobel announces GENERATION HD1 at the European Huntington's Disease Network Meeting in Vienna, Austria, on September 16, 2018 (photo courtesy of HDBuzz.net).

Supporting GENERATION HD1

According to Frank Bennett, Ph.D., Ionis senior vice president of research and franchise leader for neurological programs, the Natural History Study aims to further understand the correlation between mutant huntingtin in the CSF and other clinical measures of HD.

"Several studies have previously described the natural history of the disease," Dr. Bennett stated in an interview posted on the Ionis site on September 17. "Many, however, have focused on specific clinical outcome measures or changes in brain volume using imaging."

The HD Natural History Study, he noted, will examine participants from various angles: "This study will provide high-quality, longitudinal data to help inform patients and clinicians about the course of HD, including well-validated clinical measures of HD, novel clinical outcomes, measurement of mutant huntingtin in CSF and the use of wearable devices to measure disease burden. Results from the HD Natural History study will provide valuable information in support of our Phase 3 Generation HD1 study."

(With another scientist, Dr. Bennett recently received the $3 million Breakthrough Prize in Life Sciences. He also received the 2018 Hereditary Disease Foundation Leslie Gehry Brenner Prize for Innovation in Science.)

The Natural History Study participants could later have an opportunity to take the drug.

"For all patients who complete the HD Natural History study, an open-label extension study with the option of receiving RG6042 (no placebo control) is planned, pending approval by authorities and ethics committees/institutional review boards and if data support the continued development of RG6042," Nguyen stated.

An HDSA FAQ

As with GENERATION HD1, Roche will not require participants to live within a certain distance of the study sites. However, a seven-page FAQ on the Roche program posted by HDSA on October 17 states that "the travel burden will likely be considered during the screening" of volunteers.

"A major move or a long-distance commitment could create additional stress on a participant and his/her loved ones," the document continues. "Excessive travel may also make it more likely for someone to drop out of a trial, which could hamper the success of GENERATION-HD1 or the HD Natural History Study. Clinical studies are subject to international, national and local laws and regulations.

"Additionally, factors such as institutional site policies and health insurance may impact your ability to relocate and be accepted into one of the study sites. Eligibility and enrollment are ultimately decided by the study investigator at each site, who takes into account all these factors and may also wish to speak to you or your local HD specialist for more information."

The FAQ addresses many of the hundreds of questions posed by the HD community before, during, and after the September 26 webinar (click here to read more). Topics include study eligibility requirements, the potential risks of RG6042, and the procedures, examinations, and other activities of the clinical appointments for both GENERATION HD1 and the Natural History Study.

'Difficult to predict the outcome'

The imminence of the Natural History Study indicates that Roche is on track to carry out its plan to gradually announce GENERATION HD1 sites in the coming months and enroll the first patients in early 2019.

People can track the progress of the Natural History Study at ClinicalTrials.gov. That site and HDSA's HDTrialFinder will also provide information on GENERATION HD1.

Regarding the duration of GENERATION HD1 and next steps if the drug works, the HDSA FAQ points out that "it's very difficult to predict the outcome and timing of a large international drug study.[...] If the results are promising, approvals would need to move through regulatory health authorities."

For now, the watchwords for the HD community are commitment, patience, and hope.

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

Posted by Gene Veritas at 4:35 PM

Labels: biomarkers , clinical trials , CSF , gene-silencing , GENERATION HD1 , HD Natural History Study , Huntington's disease , Ionis , lumbar puncture , mutant huntingtin , observational study , RG6042 , Roche , symptoms , treatments

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