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Combatting the pandemic, Roche also forges ahead with critical Phase 3 Huntington's disease clinical trial

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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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THURSDAY, APRIL 23, 2020

Combatting the pandemic, Roche also forges ahead with critical Phase 3 Huntington's disease clinical trial

Using its expertise to combat a coronavirus pandemic that has left more than 180,000 people dead worldwide and a third of the earth's people on lockdown, pharmaceutical giant Roche is also forging ahead with its Phase 3 clinical trial for the Huntington's disease gene silencing drug RG6042, now known by the generic name tominersen.

The final step in a clinical trial program, Phase 3 tests the efficacy of a drug. A successful Phase 3 allows a pharmaceutical company to apply to regulatory agencies for permission to market the drug. In a time of "social distancing" and a shutdown of normal life, Roche and HD clinical trial administrators are seeking to mitigate the risks associated with the spread of COVID-19, the disease caused by the coronavirus.

In an April 20 letter to the global HD community, Roche announced that it had completed recruitment for the trial, GENERATION HD1. A total of 791 symptomatic volunteers across 18 countries have been enrolled, just ten fewer people than Roche projected after the trial got under way last year – almost 99 percent of the target.

"This achievement is a result of the HD community's commitment from the beginning, and we are very grateful to all trial participants, their families, the clinical trial sites and staff, and the broader HD community who have supported the design, initiation and recruitment phases of the study," Roche global patient partnership directors David West and Mai-Lise Nguyen stated in the letter.

West and Nguyen reassured the community that "tominersen studies are ongoing at clinical trial sites around the world," and, in collaboration with local health authorities, "ensuring patient safety and data integrity throughout the studies given the ongoing impact of COVID-19."

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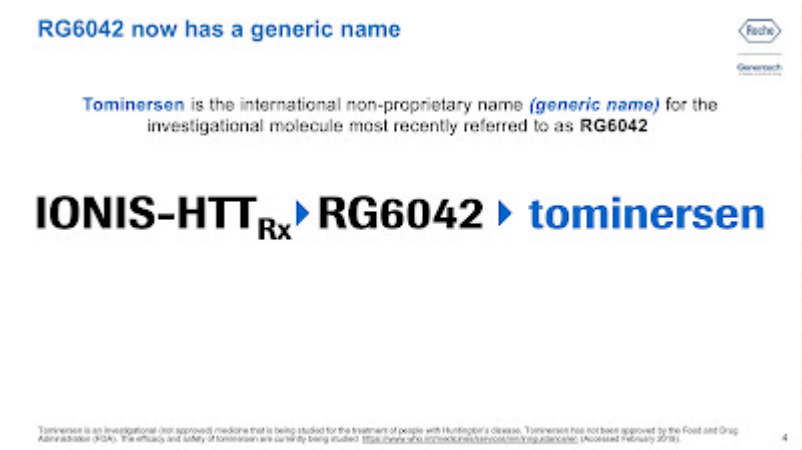

On February 27, Roche announced the generic name for its HD gene-silencing drug candidate RG6042, formerly known as IONIS-HTT$_{Rx}$, developed by Ionis Pharmaceuticals, Inc. With assistance from Roche, Ionis ran the successful Phase 1/2a trial for the compound, shown to be safe and tolerable in trial participants. It also lowered the amount of mutant huntingtin protein, a major suspect in the disease, in volunteers' cerebrospinal fluid. (Slide courtesy of Roche.)

Aiming to analyze data in 2022

"Given the dynamic situation with COVID-19, we decided to close recruitment at 791 participants globally in order to avoid additional pressure on clinical trial sites who were screening potential participants," they added, noting that the number of participants is "sufficient" to assess tominersen's efficacy.

Roche is "working closely with the research teams, trial sites and local authorities to reduce any new risks posed by COVID-19 and ensure the trial can continue as long as it is safe to do so," the letter stated. Roche advises participants to "discuss individual circumstances with their respective study sites."

"Where patients and families can no longer go into [the] hospital to receive treatment or assessments, research teams will be in close contact over the phone to monitor their health and discuss any potential adverse events or any other issues," the letter added.

Roche expects to complete the trial and start analyzing data by 2022, after each of the volunteers has completed the 25-month program involving intrathecal (spinal) injections of tominersen or a placebo, tests, medical evaluations, and digital monitoring, West and Nguyen stated.

If tominersen demonstrates efficacy and safety, Roche will submit applications to national health authorities to obtain approval as a treatment.

"During these exceptional times, we continue to consider how we can best support the community and welcome any suggestions," the letter concluded.

In an April 21 e-mail to me, West noted that GENERATION HD1 recruitment was "completed within expected timelines," unaffected by the COVID-19 crisis. In line with plans announced last October, Roche will also extend the study to China "as soon as possible," West added.

Combatting COVID-19

The April 20 statement on GENERATION HD1 followed a general statement by Roche on March 19 discussing the March 11 announcement of the pandemic by the World Health Organization and the company's efforts to combat it.

"We recognise that the public and private sectors across the globe need to work together to help effectively manage this developing situation," said the statement, noting that Roche was engaged in developing a COVID-19 "diagnostics test which was granted Emergency Use Authorization by the U.S. Food and Drug Administration."

Scientists, physicians, and public officials have stated repeatedly that vastly increased testing for the virus is needed in the battle against the pandemic.

Roche also confirmed initiation of COVACTA, a global Phase 3 clinical trial to evaluate the safety and efficacy of its rheumatoid arthritis drug Actemra/RoActemra in treating patients with severe COVID-19 pneumonia. The study started to enroll patients on April 3, with a target of 330 globally, including the U.S., Canada, and Europe.

Roche is also examining other drugs in its portfolio for potential testing to treat COVID-19.

(Click here to read more on Roche's efforts against the coronavirus.)

A key supplementary trial

The February 27 announcement of the generic name tominersen took place at the 15th Annual Huntington's Disease Therapeutics Conference, sponsored by CHDI Foundation, Inc., in Palm Springs, CA. (For an overview of the conference, click here.)

Scott Schobel, M.D., M.Sc., Roche's associate group medical director and medical leader of the GENERATION HD1 effort, introduced the name when presenting the preliminary results of the so-called open label extension study (OLE) study of the compound. For 15 months, Roche continued to give the drug to all of the 46 participants of the successful Ionis trial, completed in December 2017. That same day, Roche posted the slides of Dr. Schobel's presentation on its website.

The OLE reinforced the findings of the Phase 1/2a trial, which showed tominersen to be safe and tolerable in trial participants. Tominersen also lowered the amount of mutant huntingtin protein, a major suspect in the disease, in volunteers' cerebrospinal fluid.

Also, when still in progress in early 2019, the OLE led Roche to temporarily halt GENERATION HD1 to redesign it in line with the OLE's promising early data.

In the original GENERATION HD1 design, participants would undergo monthly spinal tap (lumbar puncture) procedures over 25 months. One-third of participants would receive tominersen each month and one-third every other month. Another third would get a placebo.

In the updated trial, which resumed in June 2019, Roche decreased lumbar punctures to once every other month over the same period of time. In this revised design, one-third of participants are receiving tominersen every other month and one-third every four months. Another third will receive a placebo every other month. (Click here to read more.)

Less frequent dosing eases the burden on participants, their families, and clinical trial administrators.

The OLE also investigated potential biomarkers (signs of the disease and drug efficacy) for use in GENERATION HD1.

The OLE formed part of Roche's strategy for skipping the usual Phase 2 trial to test efficacy and entering directly into Phase 3 to confirm efficacy in a larger population (click here to read more).

Scott Schobel, M.D., M.Sc., presenting open label extension study data for tominersen at the 15th Annual HD Therapeutics Conference (photo by Gene Veritas)

The 'ultimate' question: efficacy

After his presentation, Dr. Schobel met briefly with HD advocates to discuss his presentation and GENERATION HD1.

For the HD community, the takeaway message was the OLE's confirmation of a less frequent dosage, and its helpful data for GENERATION HD1. Except for one person who decided to drop out to take a trip around the world, all of the OLE participants had continued taking the drug, putting them now at 20 months of follow-up, he explained.

Roche has great "confidence" in the sufficiency of the less frequent dosing in GENERATION HD1, Dr. Schobel emphasized.

With the OLE, Roche has "been able to learn" and apply it directly to GENERATION HD1 "in a way that we couldn't have done if did a more traditional drug development path, which we feel great about," he said.

What remains is the "ultimate" question: will tominersen be an effective treatment?

"We're well-positioned with GENERATION HD1 to answer that question," Dr. Schobel concluded.

If the trial is successful, tominersen will become the first treatment to slow, halt, and perhaps even reverse the symptoms of Huntington's disease.

(I hope to report soon on other ways in which COVID-19 has impacted the HD community and research.)

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

Posted by Gene Veritas at 10:48 PM

Labels: CHDI Foundation , clinical trials , coronavirus , COVID-19 , dosage , GENERATION HD1 , Huntington's disease , mutant huntingtin , open-label extension , Roche , safety , Scott Schobel , tominersen , treatments , volunteers

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