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Unpacking GENERATION HD1, the Roche 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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Pharmaceutical giant Roche's September 16 announcement of the 2019 start of its Phase 3 Huntington's disease clinical trial has raised great expectations about whether this drug could be the first effective treatment for this devastating disorder.

The short answer: it's still too soon to tell.

During a September 26 Huntington's Disease Society of America (HDSA) hour-long webinar on the trial, Roche representatives received hundreds of questions via chat from HD community members. They had time to answer only a few, with HDSA pledging to compile and post answers to unanswered questions on its website soon. (Click here to watch the webinar.)

Likewise, in response to my September 16 posting about the Roche announcement, many people in Facebook HD discussion groups have sought further information about the trial.

Roche plans to test the efficacy of RG6042, a gene-silencing drug aimed at slowing, halting, and perhaps even reversing HD symptoms, in 660 volunteers over 25 months. The test will take place at 80 to 90 sites in approximately 15 countries. Each month, participants will receive the drug or placebo through a lumbar puncture. Roche will announce the sites gradually in the coming months.

Roche has named the study GENERATION HD1 (short for Global EvaluatioN of Efficacy and safety of Roche/genentech AnTIsense OligoNucleotide for Huntington's Disease).

Let me try to address some of the key questions about the trial from the HD community, as well as my own relationship to it as a presymptomatic HD gene carrier.

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Scott Schobel, M.D., M.S. (left), Roche clinical science leader of product development, announces GENERATION HD1 at the European Huntington's Disease Network Meeting in Vienna, Austria, on September 16, 2018 (photo courtesy of HDBuzz.net).

'How do I sign up?'

A frequent question from the community: "How do I sign up for the trial?"

During the webinar, Roche officials stressed that patients should consult with their HD doctors and families about eligibility for the trial, the pros and cons of participation, and logistics such as transportation or relocation to a trial site.

J. P. Sacksteder, of Genentech Advocacy Relations, said that Roche will announce the sites as each becomes ready to enroll patients. (Genentech, a major U.S.-based biotech firm, was acquired by the Swiss-based Roche in 2009. All U.S-based Roche personnel and products still use the name Genentech.)

"We ask for your patience and understanding as we share these trial sites," Sacksteder said, noting that many factors influence site selection, including experience in conducting HD studies. "We understand that each of your situations is unique, so please continue to discuss your situation with your HD specialist."

Erik Lundgren, lifecycle leader of the Roche HD program, recognized the great "desire" of HD-affected individuals to take part, but also pointed out the substantial "commitment" required in a rigorous, 25-month clinical research project.

Clinicaltrials.gov and HDTrialfinder.org will provide the latest information on GENERATION HD1.

Roche officials further noted that participants could continue taking most HD-related medications, including anti-depressants as well as drugs to control involuntary movements such as Austedo and Xenazine. Excluded drugs are memantine and riluzole. Participants must start any new regimen of medicines at least three months prior to the trial's start. Individuals cannot participate in a concurrent trial, but are not barred if they had participated in past HD trials.

For those aged 25-65

Roche will recruit volunteers who are between the ages of 25 and 65 at the start of the trial, explained Scott Schobel, M.D., M.S., Roche clinical science leader of product development.

Based on statistical studies of the HD population, people in the 25-65 age group have a more predictable progression of symptoms than younger or older groups, Dr. Schobel explained. Focusing on that cohort, he said, will furnish trial researchers with the best, most efficient way to measure whether RG6042 alleviates symptoms.

The later a person's motor onset, the standard diagnosis of HD, the "potentially less of a progression of symptoms over time," he added. Motor symptoms involve involuntary movements and imbalance.

Thus, including people over 65 in GENERATION HD1 would be less helpful to researchers trying to gauge the drug's impact.

Dr. Schobel's assertion about later motor onset reassured me a bit regarding my own potential disease progression as an HD gene carrier. At my latest HD checkup earlier this year, I had not shown such symptoms. My HD-stricken mother's onset occurred probably in her late 40s, and by age 58 (my current age) she had full-blown HD. She died at 68.

I hope that the lack of motor symptoms at this stage means that, after my inevitable onset, I, too, will have a lesser progression of symptoms.

Healthy gene carriers excluded

However, I can't participate in GENERATION HD1, because, at this time, presymptomatic gene carriers are ineligible. My question during the webinar requesting further details about this wasn't answered.

In general, presymptomatic gene carriers haven't been invited to participate in most HD clinical trials because it's hard to measure a drug effect on an apparently healthy person.

There are also safety and ethical concerns in involving healthy individuals in a complex clinical trial like GENERATION HD1 – for example, exposing a healthy person to the potential side effects of the trial.

Regarding presymptomatic individuals and also the excluded juvenile HD population, Roche stated in its September 16 announcement: "We recognize the critical medical need for a treatment for HD, especially for people living with severe forms like juvenile onset HD. In consultation with HD community experts, our team will explore the potential use of

RG6042 in populations beyond manifest [symptomatic] HD once there is sufficient scientific and safety rationale."

At the September 16 announcement of GENERATION HD1, Dr. Schobel pointed out that the drug might act differently in the still developing brains of children and young people.

The ultimate goal of researchers is to develop a preventive treatment.

Concerns about frequent spinal taps

Even if eligible, I would have to seriously consider the risks of undergoing the lumbar punctures. The punctures, also known as spinal taps, introduce the drug into an individual's cerebral spinal fluid (CSF) and allow researchers to withdraw some CSF for analysis.

Lumbar punctures are routine and generally safe procedures, although they can cause side effects such as headaches and bleeding. The 46 subjects in the Phase 1/2a trial of RG6042, completed in December 2017, had few side effects. Ed Wild, M.D., Ph.D., who conducts research on the CSF in HD, underwent the procedure as a demonstration for the HD community

Still, I'm personally concerned about the lumbar puncture, which, if a medicine is approved, would likely be the initial pathway for it to be administered.

In 1977, at age 17, I suffered two herniated disks in my lower spine while shoveling heavy snow in my hometown of Mentor, Ohio. Ever since, I have struggled with low back pain.

An MRI (magnetic resonance imaging) scan ten years ago revealed that the disks mainly healed, but I suffer daily with muscular pain, or myofascial pain syndrome. Occasionally, severe flareups prevent me from walking and performing some daily activities.

Since that MRI, I've consulted regularly with pain management specialists. I've also worked with physical therapists to incorporate other exercises into my morning stretching routine to strengthen my core and back.

Along with daily aerobic exercises, I want to stay strong and flexible to help forestall my inevitable HD onset and, later, to help ameliorate symptoms.

Alternative drug delivery methods?

In 2013, as a participant in the PREDICT-HD (Neurobiological Predictors of Huntington's Disease) research project at the University of Iowa, I considered a request to provide a sample of my CSF.

After reviewing my lower spinal MRI, a doctor at Iowa concluded that a lumbar puncture was too risky.

Also, had I suffered any complications after the procedure, I would have had to obtain medical care not in Iowa, but only after returning to my current hometown of San Diego, where I have health coverage.

I wanted to assist with the research, but ultimately believed that the potential risks outweighed the benefits.

Given these concerns, during the webinar I posed two questions regarding the spinal taps. First, what will Roche due to minimize the impact of the 25 monthly procedures? Secondly, how will Roche address the fact that many people in the U.S. suffer from lower back problems?

I look forward to hearing Roche's ideas, including the latest research on alternatives to spinal taps such as Roche's "brain shuttle" technology and/or devices for delivering the drug.

If back pain is part the price for an effective HD treatment, I am willing to endure it.

Timeline and cost

Another major concern of the community: if GENERATION HD1 is successful, when might drug approval come?

"I can't ultimately commit to what that timeline looks like," Lundgren said. "We are doing everything we can to speed it up."

First, Roche must enroll all 660 volunteers. "That's a big variable," he said. "We can't complete the study until 25 months after the last patients receive their first dose."

Then researchers must organize and analyze the data. If the latter appear promising, then Roche must seek regulatory approval from the U.S. Food and Drug Administration and similar agencies around the world.

According to a September 17 article on the scientist-produced site HDBuzz, "Not every patient enrolls on the first day of the trial, so a trial in which each participant is involved for 25 months will take around twice that long to run, and possibly longer."

It's also too early to project the cost of the potential drug, Lundgren said. He added that Roche is committed to providing access to those with inadequate insurance.

Working towards the best treatments

Dr. Schobel addressed concerns about the fact that RG6042, developed by Ionis Pharmaceuticals, Inc., is designed to reduce both the harmful mutant huntingtin protein involved in HD and normal huntingtin, essential in cell function.

According to Dr. Schobel, the drug's effect "fundamentally is partial and can reverse and is titratable [adjustable], versus those kinds of experiments that are in the scientific literature, which shut off the gene 100 percent. That is not what we're doing, for either the mutant protein or the so-called normal or total levels of protein. We have the ability to find a sweet spot potentially where there's benefit and less risk, or even pause dosing."

The Roche-Ionis approach differs from the two current Phase 1b/2a clinical trials by Wave Life Sciences, whose drugs target only the harmful protein by using genetic markers present in most but not all people with HD. (Click here to watch a presentation on the trials by Wave's Michael Panzara, M.D., MPH.)

These and other clinical trials seek to find the best approach. Scientists have said that a combination of approaches, or an "HD cocktail," may be needed to treat this complex disease.

(I hold a symbolic amount of Ionis shares.)

This article is dedicated to the many donors and walkers who supported the Serbin Family Team in the 2018 HDSA-San Diego Team Hope Walk, held today. See photos below. Thanks to you, we raised over $4,000 towards the care and cure of HD! You can still donate by clicking here.

The Serbin Family Team of the 2018 Hope Walk: above, from left to right, Lance Ramsey, Adi Drapkin, Alexandra Drapkin, Regina Serbin, Gene Veritas (aka Kenneth P. Serbin), Maria Ramos, Peter Kim, Yuka Kim, and Lily Kim (in stroller). Below, from left to right, Tom Johnson, Yuka Kim, Peter Kim, Lily Kim (in stroller), Judy Melville, Gene Veritas, Patrick Melville, Sean Naficy, and Sam Melville (personal photos).

Posted by Gene Veritas at 6:12 PM

Labels: brain shuttle , clinical trials , gene-silencing , GENERATION HD1 , HDSA , Huntington's disease , Ionis , lumbar puncture , motor onset , presymptomatic gene carrier , RG6042 , Roche , Scott Schobel , symptoms , treatments

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