3-28-2018

Roche gears up for pivotal Phase 3 Huntington's disease gene-slicing clinical trial

Kenneth P. Serbin
University of San Diego

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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WEDNESDAY, MARCH 28, 2018

Roche gears up for pivotal Phase 3 Huntington's disease gene-silencing clinical trial

Pharmaceutical giant Roche – currently without a timeline, but mindful of the urgency – is gearing up for the pivotal Phase 3 clinical trial of IONIS-HTT_{Rx}, the gene-silencing drug shown to dramatically reduce the amount of the toxic protein implicated in Huntington's disease in Phase 1/2a trial results announced March 1.

The earlier study was aimed only to assess safety and tolerability, but also provided signals regarding the drug's potential efficacy. IONIS-HTT_{Rx} lowered the mutant huntingtin protein an average of 40 percent, with a maximum reduction of 60 percent, in the cerebrospinal fluid (CSF) of participants in the Ionis Pharmaceuticals Phase 1/2a trial, completed in December 2017. Based on animal studies, that corresponds to reductions in the cerebral cortex of 55-85 percent. (Click here to read more.)

If Phase 3 is successful, that reduction in the cerebral cortex could mean alleviation or even reversal of HD symptoms. The source of thought and language, the cortex is the most developed area of the brain, and the most severely hampered by HD.

IONIS-HTT_{Rx} clinical trial leaders presented the results at the 13th Annual Huntington's Disease Therapeutics Conference, sponsored by CHDI Foundation, Inc., and held at the Parker Palm Springs hotel in Palm Springs, CA. A nonprofit virtual biotech, CHDI has invested hundreds of millions of dollars in the quest for treatments, including a $10 million payment to Ionis, later repaid to the foundation. It has helped draw attention to HD in the pharmaceutical industry.

Roche officials confirmed that the company would take the unusual step of skipping a Phase 2 trial (testing efficacy for the first time) and going directly to a Phase 3 (confirming efficacy in hundreds of participants).

The impressive Phase 1/2a results were the best news for the HD community since the discovery of the huntingtin gene in 1993. Forty-six early-stage HD patients took part at sites in England, Germany, and Canada.

A partner in the Ionis HD program since 2013, Roche now holds the license to IONIS-HTT_{Rx}. It is already conducting an open-label extension of the Phase 1/2a study, whereby all patients – including those who got placebo – will receive the drug. The extension allows researchers to gather critical additional data for planning Phase 3.

Roche now calls the drug RG6042. "R" is for Roche, and "G" for Genentech, a major U.S.-based biotech firm acquired by Roche in 2009. The number 6042 is a standard drug number assigned by the company. All U.S-based Roche personnel and products still use the name Genentech.

International Huntington Association
Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
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With a 120-year history and about 94,000 employees worldwide, Roche will bring considerable resources to bear in the Phase 3 trial. Hundreds will become involved in the project. It had a major presence at the CHDI meeting: twelve researchers and other personnel attended, including Scott Schobel, M.D., M.S., clinical science leader of product development.

"We're all in," Dr. Schobel told me, referring to the company's commitment to the program.

To learn more about the plans for Phase 3, I interviewed three key members of the HD team, all based at Roche headquarters in Basel, Switzerland.

Lauren Boak, Ph.D., in her twelfth year at Roche, is the global development team leader, responsible for helping design, set up, and analyze clinical trials. Also in his twelfth year, Erik Lundgren, a Harvard University MBA, is the lifecycle leader of the HD team, involved in the manufacture and supply of the potential medicine, plus related matters such as regulatory approvals and educating the community about the drug. In her fifth year, Mai-Lise Nguyen is the patient partnership director for the HD program.

Members of the Roche HD clinical trial team watch the presentation of the IONIS-HTT_{Rx} Phase 1/2a data, March 1, 2018. From left to right, Scott Schobel, M.D., M.S., Lauren Boak, Ph.D., Erik Lundgren, and Mai-Lise Nguyen (photo by Gene Veritas).

Phase 3 'appropriate and reasonable'

The three representatives were excited about working with the HD community and passionate about their work on the Roche HD project.

GV: From Roche's standpoint, what was observed in the HD patients in the Ionis-HTT_{Rx} Phase 1/2a trial?

LB: We're very pleased to see that over a number of increasing doses, over four doses, the drug was safe and tolerable in HD patients and, also, that there was lowering of huntingtin, in a dose-dependent manner. As you increase the doses, the protein reduction was also increased. So, fantastic results from that study.

EL: It's a step towards validating this hypothesis that we can target and reduce the causal protein, the root of this disease. It's extraordinarily important to be able to demonstrate that that's possible therapeutically. But it's also important to remind everyone that this is an early, Phase 1 study. It's 46 patients, and we certainly all owe a debt of thanks to those 46 people for being a part of early research. This

trial also only studied four doses. So while we are very encouraged about these early results, there are still extremely important questions that we need to address as we go forward.

GV: Will you go straight to Phase 3?

EL: Yes. We do think it's appropriate and reasonable to go from here into larger studies that would support registration and filings for drug approval, so what would typically be referred to as Phase 3. In a rare disease, it's not necessarily important to think about Phase 1, Phase 2, Phase 3. What we're really focused on is: what are the requirements of regulators to ultimately look at the supporting evidence for this experimental medicine and make a determination that it's acceptable for approval and, ultimately, to make accessible to the HD community? That is a registrational study, or a pivotal study.

However, an important caveat is: ultimately, we need to engage with – and we're doing this work – FDA and global health authorities to understand what those requirements are, and to make sure that we're building a clinical study program that addresses their questions.

Gene Veritas (right, aka Kenneth P. Serbin) interviews Lauren Boak, Ph.D., and Erik Lundgren (photo by Mai-Lise Nguyen, Roche).

Confidence in moving forward

GV: Was it the strong data from Phase 1/2a that led you to this conclusion? Ionis officials said that huntingtin was lowered "beyond expectations" in the CSF.

LB: Actually, it's more related to the disease itself, and how much we know about the underlying cause of Huntington's disease. It's a monogenetic disease, and we know that it's caused by a mutation in the gene that leads to the formation of a toxic protein, mutant huntingtin. Because of that knowledge, we have elevated confidence – versus, say, other neurodegenerative disorders – that if we target that mutant huntingtin and reduce it, it will lead to clinical benefit. That gives us confidence that we would be able to have a shorter path to demonstrate efficacy and therefore get to an approved medicine.

EL: But it's not only about the monogenetic nature of the disease; it's about the incredible commitment and selflessness of this community that's dedicated to building a knowledge base that we can hopefully use to really accelerate from this point forward. The evidence that has been generated for Huntington's disease and by the HD community is what gives us that scientific confidence. It's the work of groups like CHDI and the rest of the HD community over years – of being a part

of registry studies, of really being committed to and dedicated to research. We say "thank you" to the community for doing that.

MN: We've had relationships with the community. Now we're at the point where we can build them further, by having discussions with the patient groups, with HD-Cope. We're speaking with members of the community to make sure that we're designing this next phase together.

CHDI's role

GV: It's evident that the investment CHDI has made in Huntington's research is part of what you're talking about.

EL: Yes.

GV: Have you consulted with CHDI as you move ahead?

LB: One of the great achievements that CHDI has spearheaded is the development of the Enroll-HD platform. Obviously, this built upon Registry and other efforts in the field. What the Enroll-HD platform gives – with over 16,000 patients worldwide enrolled – is a wealth of data available characterizing the natural history of patients (people living with HD over a period of time). We can learn a lot from this data.

The way CHDI has funded this, it's an open source available for all researchers and industry. It's just an incredible resource that is actually unique to Huntington's. It's such a rich resource, because of the number of years since the gene's been discovered, and the countless efforts that have gone into it. From the standpoint of working together with CHDI, we'll certainly be leveraging this along with a number of other groups such as HSG [Huntington Study Group], EHDN [European Huntington's Disease Network], and just the broader community.

GV: In the pharmaceutical industry, how common is it to go from a Phase 1 directly to a Phase 3?

EL: It's not particularly common. You need confidence in the science. You need a medicine that shows promise. And there needs to be some urgency: the

devastation of this disease, and the urgent needs of this community. So, while it is not common, there is a well established regulatory pathway for us to follow.

LB: This is very well recognized by regulatory agencies. That's why there is, as much as possible, flexibility within the pathways available for diseases such as this, with this type of potential medicine. Other areas that have this sort of Phase-1-to-Phase-3, seamless approach include oncology, where you have the obvious devastation of cancer and life-threatening nature of the disease.

EL: The ability to target is the other place where this overlaps with oncology – the ability to identify biologically a target and to develop a molecule that can effectively engage with that target and act on it.

Ionis' comprehensive preparation

GV: Is the extreme care, amount of time, and extensive collaboration that Ionis used in developing its antisense oligonucleotide drug (ASO, an artificial strand of DNA blocking the production of the HD protein) one of the reasons for the jump to Phase 3?

LB: Ionis has developed a very comprehensive package for this medicine, and their expertise in ASOs is unparalleled. They have done a lot of work to develop a preclinical package – the preclinical animal data – to support the move into the clinic. That strength in the preclinical package gives us confidence in what we see in the clinic. We've got evidence that the drug is getting into the brain and is lowering mutant huntingtin.

Our confidence in whether this amount of mutant huntingtin would be enough to potentially lead to clinical benefit in humans is based on this solid animal, preclinical package. If we lower mutant huntingtin to a certain extent, based on the broad phenotypic [observable] changes and improvements in animals, in HD transgenic models, that will lead to a similar, broad effects in humans. Obviously, we need to do the next clinical study to prove that the lowering of the huntingtin protein leads to improved symptoms in patients with HD.

In addition, the Phase 1/2a study was designed and executed seamlessly. They chose very experienced scientific and collaborative investigators. It was a very solid and dedicated team, as is, we're learning, the HD community in general.

Adding the U.S., other countries

GV: What are the key elements of the work you need to do as you head into Phase 3?

LB: We're starting to think about what the next clinical trial will look like, and how it will be designed. We're working with different stakeholders that will help guide this, such as patients, patient organizations and the regulators, to understand what the needs are to move this drug forward to approval. That's a big effort and well underway. The medicine is moving into a global study. The Phase 1/2a was in Germany, the United Kingdom, and Canada. This next study will be across

more countries, including the U.S. So we're at the stage of exploring what additional countries the study will be conducted in and then identifying sites.

EL: The other group that's really important here are payers, so insurers or national payers in European or other non-U.S. markets. The goal is to make this medicine available to people, and that means you have to address regulatory questions first, then you have to provide compelling data so that insurers will allow people to have access to the medicine.

GV: Do you know much you'll have to spend to get this into Phase 3?

EL: No. And it's not something that's the driving force. Honestly, at this point, it's about getting the answers right. We've made significant investments, and we'll continue to do what needs to be done to answer the questions in front of us.

GV: How many participants are you estimating will take part in the next phase?

LB: We don't know at this point. It's dependent on the final design of the study, how many dose arms [dosages] we have, the particular endpoints [outcome measures], as examples. But likely in the hundreds.

A 'small army' at work

GV: How many people at Roche are working on the project?

EL: It's a small army [laughter]. Obviously, the number is increasing as we've opted into move the program forward. It's a team that is mostly based in Basel, but is global in scope. It's an incredibly passionate group of people.

GV: Are we talking dozens of people on the HD team? Hundreds?

EL: It will be hundreds, for sure. It takes an unbelievable amount of effort to go from here to where we and the HD community need to be. The global aspect is extremely important. If you're living with HD – whether you have the gene yourself or are symptomatic or are a caregiver or just an interested party – it's a very individual issue. So we have to find a way to serve the individual nature of this problem, but also have an eye to the global nature of what we need to do to be able to serve every appropriate person that could potentially benefit, and that's not only people that reside within the United States, for instance. It increases the complexity of the work that we have to do quite significantly.

We'll be communicating on sites and timing and all those sorts of issues later. I can confirm that U.S. clinical trial sites will definitely be included in for the next phase. The trial will be important, but the trial is not the vehicle for people to have access to the drug. Ultimately, approval by health authorities [in specific countries] is the path for people to have access.

Timeline pending

GV: When will the next phase will start?

EL: We can't commit at this point to when the next phase will start. There's just a lot of unknown factors. We understand that that's a pressing question that everyone wants an answer to. What's most important for us is doing the work to make sure that the pivotal study is going to address and answer all of the questions that need to be addressed. We cannot afford to cut corners.

GV: Do you have an estimate of how many years it will take?

EL: It depends on a lot of things. When do we get it started? How long do people need to be in a study for us to have confidence that, if there's a benefit to be observed, we give ourselves the best chance to see it in that study? So is it a one-

year, 18-month, two-year, three-year, or four-year study? We're very data-driven in how we make those determinations.

Another huge factor is: how many patients will we need in the study? It's going to go faster if it's fewer patients. It's going to take longer if it's more patients. The other piece that's really important is: how long does it take to recruit that number of patients for the study? We'll be able to give you a better answer to these questions later in the year.

An HD patient (photo by Mike Nowak)

Roche's interest in HD

GV: How and why did Roche get involved in this project? What is it about HD that has attracted the company?

LB: This project was of real high interest to [former Roche executive] Luca Santarelli and the neuroscience group at the time because of the incredible groundbreaking science that Ionis had done and the promise of this particular medicine and, clearly, what potential it had to transform the lives of those with Huntington's disease.

EL: Our organization has two principal pillars. First and foremost, Roche and Genentech are science-based organizations. The first thing we look for is: is the science compelling? Is it innovative? Is there a hypothesis we have confidence in? Right next to that is the need of the community. We've got a really excellent track record of transforming diseases that needed transformation, and hard problems: oncology, multiple sclerosis, ophthalmology, immunology. From that perspective, Huntington's disease is an area where the science is rich and the needs of the community very well-established.

We're being flooded with people within Roche that want to be a part of the HD program, because it speaks so powerfully to those two central parts of really who we are as an organization.

Roche is known in the broader scope for the innovation and transformation we brought to oncology. A really great example of that would be in HER2-positive breast cancer. HER2-positive is the most aggressive form of breast cancer. It had significantly higher rates of mortality. But it's now become what people would like to have because effective treatments are available.

It's also a really good example of not resting on laurels. We brought a product called trastuzumab, or Herceptin, to that community in 1998. And then, within the

past five or six years, we've brought two more therapies that have improved upon trastuzumab and led to even more radical improvements for those patients.

MN: That is probably our most famous medicine. Roche has 30 medicines on the World Health Organization's essential medicines list. Roche's legacy has continued to grow, including with the integration with Genentech, which was the first biotech company in the world.

A new era for neurodegenerative treatments?

GV: What other neurodegenerative diseases are you focusing on?

LB: In our late-stage portfolio, we have two monoclonal antibodies in development for Alzheimer's disease, as well as a number of others in earlier stage development for Alzheimer's, Parkinson's and ALS. In neuroscience generally, we have Ocrevus, which was recently approved for multiple sclerosis. We also have a number of programs in development for neuromuscular disorders and autism.

GV: What would treating HD effectively with RG-6042 mean for the field of neurodegenerative diseases?

LB: It would be a historic moment obviously for Huntington's disease patients, but for the neurodegenerative field in general. One of the achievements would be to get a targeted therapy to the brain. We've seen evidence of that already with this medicine. The next step is to show that reducing a causative protein leads to clinical benefit. If we can do this, the hope is that this will herald a new era for neurodegenerative diseases because of what we can learn from Huntington's disease and then apply to Alzheimer's disease, to Parkinson's disease, to ALS.

GV: It seemed that the pharmaceutical industry was moving away from neurodegenerative diseases. The companies were frustrated because they couldn't develop treatments. The scientists were frustrated because they nobody wanted to invest anymore. You have jumped into what appears to have been a difficult situation. Can you comment on this?

EL: Neurodegenerative diseases are hard, because the science is opaque in many cases. Getting medicines to the brain has been an incredibly difficult challenge. The endpoints – the way in which clinical trials measure a treatment effect – are complex. It's hard to see and measure and be able to prove with statistics that you're having an effect in neurodegenerative diseases. In some of these diseases, it can take a really long time for the disease course to run. It makes it hard to run these trials.

We're not discouraged. We're quite *en*couraged, because in this case we think we do understand the science. We have been able to demonstrate that RG6042 gets into the brain and that we're able to affect this protein.

Rare-disease status not a problem

GV: How does the fact that HD is a "rare disease" factor into your plans for Phase 3 and the rest of the project?

LB: The fact that it's rare from a clinical trial perspective is important. There aren't as many patients to participate in a clinical trial as in other diseases. However, because of our confidence in our understanding the disease and the mechanism of the medicine, the actual clinical trial size doesn't necessarily need to be that big.

Also, it's a rare disease, but not *very* rare disease. It's actually a high-prevalence rare disease. In the case of HD, we are blessed with clinical trial networks that already exist that we can leverage such as HSG and EHDN.

EL: I don't like the term "rare disease." It makes it feel small, something off to the side. What all of us are personally struck by is: if you're an HD family or a gene carrier or affected with symptoms, it doesn't feel small. We think of HD as a really big problem to address.

Spinal injections to continue

GV: In the Phase 1/2a trial, patients received the drug via an intrathecal (spinal) injection, with the medicine carried to the brain via the natural flow of the CSF. In 2013, Luca Santarelli spoke of a possible alternative: using "brain shuttle" technology to introduce the Ionis drug into the brain in the form of a pill. What is the status of this research? Will it be used in Phase 3?

EL: The brain shuttle is exciting. We continue to invest in understanding that technology better. For us, the most important thing right now is to demonstrate the safety and effectiveness of RG6042 in people living with HD. There is enough complexity with just that question that we need to be laser-focused on first addressing that one before we add in the additional uncertainty that would be introduced by the unproven brain shuttle. Longer-term, we understand the attractiveness of something like a brain shuttle in HD.

GV: So will Phase 3 use the spinal injection?

LB: Yes.

EL: An intrathecal injection is a way to get around the blood-brain barrier, one of the central problems of neurodegenerative diseases. It's an effective and reasonably well-tolerated approach, especially in a disease like HD.

Participants to use special smartwatch

GV: What other new technologies, techniques, and approaches might be used in Phase 3?

LB: One thing that we are developing – building on recent experience in multiple sclerosis and Parkinson's disease – is a Roche HD Digital Monitoring Platform. It's a smartphone and watch for use in the clinical study. We've tailored it for Huntington's disease to measure appropriate symptoms and activity in the disease. Instead of just irregular clinic visits – single-day data points on patients' symptoms and how they're feeling – we'll have potentially daily, continuous monitoring of this.

This has potential to increase sensitivity to detect treatment effects. There are 365 days of the year, and imagine if there's only twelve visits in that period. There's a lot that happens over the course of a day, let alone a month. There's an inherent problem also with being able to remember, for anybody, how you were feeling a day ago, let alone a week ago, etc. It's your recall bias. We're really excited about this. We've already started deploying it in the open-label extension study. We're going to learn and perhaps adapt this for inclusion in the pivotal study, Phase 3.

GV: Will the participants wear electrodes?

LB: No, there is a smartwatch and smartphone and everything that's already built in, like a gyrometer and accelerometer. These are sensors that will detect movement.

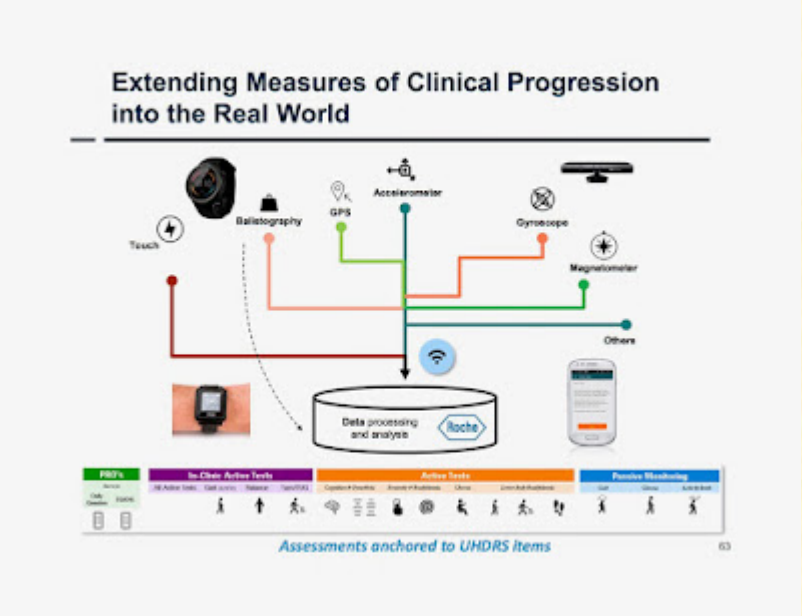
EL: We don't want to miss any signals – good ones or bad ones – that our trial participants have. It gives us more confidence that we'll be able to see something happening, measure it, quantify it, and, ultimately, prove it. This is obvious to the HD community, but it's important for how we design our study. HD affects so

many different domains. It's not just walking speed and spasticity and motor symptoms; it's cognition, too.

There are two aspects of this digital platform: active monitoring and passive monitoring. The active monitoring will have different tests for the individual to do on a given day, such as a walking or cognitive test. With the passive monitoring they can have the smartphone in their pocket or on a belt and be monitored on how much they move in the course of a day.

GV: Will it measure pulse or be connected to the blood in any way?

EL: No. It's a smartphone like you buy off the shelf. The software is what's special, and the analytics engine behind it. A tremendous amount of data comes in. The algorithms and how you make sense of that is what our team has been working hard on developing.



A graphic illustrating the Roche-HD Digital Monitoring Platform (source: Roche)

Earning the community's trust

GV: For many people, including in the HD community, "big pharma" is just out for profits. I understand that these are business enterprises, and we don't live in a socialist system. But then you have things like the opioid crisis, which is driven by a lot of bad actors in the business. There's also the idea that some companies just want to go for blockbuster drugs while ignoring smaller disease communities. Would you like to comment on this?

EL: We're all quite passionate about this issue.

MN: We can only speak to Roche. I personally think Roche is a very unique company. We've had the same name over the door for over 120 years. We are still a majority family-owned company. The Hoffman-Roche family's descendants are still involved in the company. Our vice chairman, André Hoffmann, said a phrase when he was speaking with some students this past summer. He and the whole leadership team believe that Roche needs to be a "net-positive contributor" to society.

We are lucky already that our core business is about health care. We're already a contribution to society. But how do you be that net-positive? It's about serving healthcare solutions, but we do so many other things with the communities that we operate in and beyond, whether it's with social programs and philanthropy.

EL: We owe it to the HD community to earn trust. So we're here to listen and engage, and we hope to hear back from the HD community if we fail in that test. This is not transactional for us. This is about partnering to make a difference. We've all chosen to do this because we're moved by it. On our life cycle team, we talk about what we care about. One of our core pillars is keeping people with HD in the center of every decision we make. At the end of every meeting, we go around the room and score ourselves on that. It is not lip service.

(For the slides from a March 2, 2018 conference call and webcast regarding the Ionis-Roche clinical trial program, click here.)

(For updates on the RG6042 program, stay tuned to this blog and also visit www.HDSA.org and HDSA's HD Trial Finder)

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

Posted by Gene Veritas at 11:40 AM

Labels: CHDI Foundation , clinical trials , Erik Lundgren , gene silencing , huntingtin lowering , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , Lauren Boak , Mai-Lise Nguyen , Phase 3 , RG6042 , Roche , treatments

7 comments:

ROB PATTINSON for Dummies said...
THANK YOU SO VERY MUCH...

4:46 PM, March 28, 2018

Bev said...
GV's great questions led to excellent answers that give me a sense of Roche's corporate values. Of course I want the trial to start soon and include many people, but I understand the need to design the trial carefully. This is the first time I heard about monitoring patients via a smartphone-like device. That's a really good idea. Let's all keep hope alive!

5:56 PM, March 28, 2018

Elissa Clarke said...
As a HD Caregiver and Wife.. I feel Hopeful. Thank you. ♥

6:26 AM, March 29, 2018

Unknown said...
My father and brother both have Huntington Chorea Disease. I have not been tested nor am I symptomatic. My question is, upon my death, can I do full body donation?

8:39 AM, March 29, 2018

Anonymous said...
I hope that the final result of the study is successful, and the community around the world can have access to the drug.
Move forward without hesitation
Sincerely

Rodrigo Osorio P.

Chairman
Agrupación Chilena de Huntington

1:53 PM, March 29, 2018

ThereseHDAdvocate said...

The question/answer was very informative. Thank you GV for sharing.

1:09 PM, March 31, 2018

Unknown said...

Feeling very uplifted and positive- great reading and can only move forward now with the brilliance of those scientific minds. Great times ahead! X

12:59 AM, April 28, 2018

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