12-16-2017

Ionis scientists provide initial assessment of successful Phase 1/2a Huntington's disease trial and discuss next steps

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.

About Me

GENE VERITAS

View my complete profile

HD Links

Huntington's Disease Society of America
International Huntington Association

SATURDAY, DECEMBER 16, 2017

Ionis scientists provide initial assessment of successful Phase 1/2a Huntington's disease trial and discuss next steps

After announcing December 11 that Ionis Pharmaceuticals' gene-silencing drug for Huntington's disease safely reduced the production of the toxic HD protein, company officials analyzed the firm's successful Phase 1/2a clinical trial and discussed the next step: larger trials that are designed to test IONIS-HTT_{Rx}'s efficacy in alleviating symptoms by modifying the course of the disease.

I met with two lead scientists from Ionis' HD team at company headquarters in Carlsbad, CA: Frank Bennett, Ph.D., Ionis senior vice president of research and the franchise leader for the company's neurology programs, and Anne Smith, Ph.D., the Ionis director of clinical development and the individual responsible for the day-to-day management of the trial.

Drs. Bennett and Smith stressed that, because the two-year trial ended just last month, they could provide only an initial assessment of the results. The company plans to present detailed clinical trial findings at medical conferences in early 2018 and then publish the results in scientific journals.

Ionis will transfer administration of the next clinical trial phases to Roche, a key partner in the project since 2013. Roche now holds the license to IONIS-HTT_{Rx}, will lead further development, and handle all potential sales. Phase 1/2a took place in Canada, England, and Germany, but the next phase will have sites in the U.S. and other countries, to be determined next year by Roche. Ionis will continue to play an advisory role in the project.

"We are very appreciative of the community, and the patience that the community has exhibited," Dr. Bennett said. "We understand how important this is for the HD community. We're very pleased it's going forward. The community has been very respectful towards the company and has allowed us to conduct this study in a way that was very robust."

Drs. Bennett and Smith focused on how the trial revealed a reduction in the mutant huntingtin protein that "substantially exceeded our expectations," according to the December 11 press release. The key, initial piece of trial data came from the measurement of the protein in the HD patients' cerebrospinal fluid (CSF). Other trial data such as brain scans and blood samples will become available later.

IONIS-HTT_{Rx} and other Ionis drugs are antisense oligonucleotides (ASOs, artificial strands of DNA), which alter the expression of genes. In August 2016, Ionis and its partner Biogen actually halted a Phase 3 trial of an Ionis ASO in infants with spinal muscular atrophy (a motor neuron

Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
Thomas Cellini Huntington's Foundation
HDSA Orange County (CA) Affiliate
HD Free with PGD!
Stanford HOPES
Earth Source CoQ10, Inc.

HD Blogs and Individuals

Chris Furbee: Huntingtons Dance
Angela F.: Surviving Huntington's?
Heather's Huntington's Disease Page

disease) because the drug was extending their lives. The FDA (Food and Drug Administration) approved the drug, with the commercial name SPINRAZA, in December 2016.

In October, Ionis and Biogen won a biotechnology prize for SPINRAZA (click here to read more). Ionis is also collaborating with Biogen to develop a drug for amyotrophic lateral sclerosis (Lou Gehrig's disease).

Dr. Frank Bennett (left) with Gene Veritas (aka Kenneth P. Serbin) and Dr. Anne Smith (photo by Kristina Bowyer, Ionis)

Following are key excerpts from the interview.

Compelling changes in mutant huntingtin levels

GV: How did patients react to the intrathecal administration of the drug, that is, via a spinal tap?

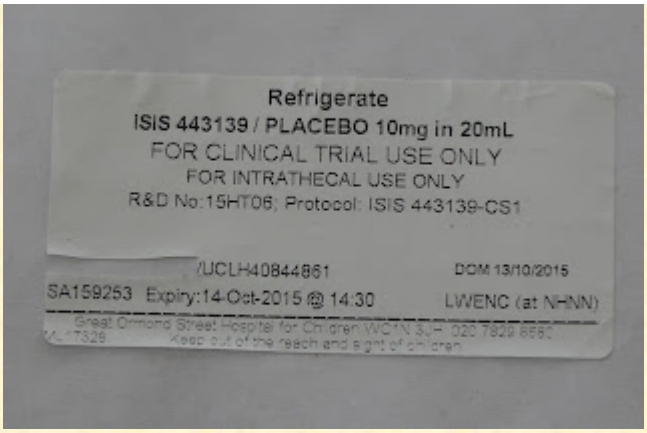
AS: We didn't hear from any of the physicians that there were any difficulties. There was probably some nervousness, but there were few side effects, and that ones they had were manageable. I think it's telling that all 46 patients completed the trial.

GV: What was observed in the HD patients in this trial?

AS: We're still in the process of getting these next waves of data in. That will come out over months. It's important to recognize that the trial just ended in November. But at this stage we did see a promising safety profile, meaning that we didn't have any clinical concerns with the drug.

We saw clear, compelling changes in mutant huntingtin levels in the CSF. It was sort of gravy in this study. It's designed as a safety study. We didn't know when we entered the study whether we'd be able to even measure mutant huntingtin in CSF. But it is the best evidence of target engagement that we have – meaning that it is evidence that the drug is doing what it ought to do.

We were pleased that the assay [lab test] was developed to the point that we could use it to measure mutant huntingtin. The test is relatively new and fortunately came online at about the right time that we needed it.



The label from the first vial of the Phase 1/2a clinical trial, administered in London, September 2015 (photo by Gene Veritas)

GV: *The reductions of mutant huntingtin "substantially exceeded" your expectations. To what extent?*

FB: When we began the program with Roche, we picked a target level of reduction of mutant huntingtin in CSF, and, based upon that, we would decide to go forward with the program [into the next phase].

We put the mutant huntingtin data at the top of the list, because it was the data that was going to drive a business decision from Roche, but also, importantly, it was the data that would help them design the next study. So we prioritized that as being the first thing we would look at. It's the basis for telling us what are the doses that we should be using for the next study.

GV: So can you specify the amount of mutant huntingtin reduction?

FB: We're going to save that for a medical meeting.

Phase 1/2a too early for improving symptoms

GV: You project from your pre-clinical animal studies that the level of reduction in the brain itself should be greater than what is seen in the CSF, correct?

FB: Yes. An important nuance for the community is that the level of reduction that we're seeing in CSF is not a one-to-one correlation with the level in [brain] tissue, which is where you want the drug to be working. We haven't proven it in patients, but we're very confident that it will translate [into higher levels of reduction in the brain].

AS: We've tested this drug in several species and are able to understand that relationship between what you see in CSF versus what you see in [brain] tissue, which is why it was really important this assay [CSF measurement] was online. It really is a window into the brain.

To understand that relationship in animals, the animals have to be sacrificed, to measure the level in the [brain] tissue. So we won't ever 'prove' it in humans, so to speak, but we have a good understanding of it through the animals. And that it's consistent from species to species is comforting. We can draw a conclusion about what's likely happening in the human.

GV: Many in the HD community want to know: in this trial, did you see any signs of disease modification? Were there any hints at all from the doctors or from the data?

AS: We get anecdotal reports from physicians, but this is a population with a high placebo effect. These are motivated and excited physicians and

patients as well. So I wouldn't read anything into that. It'll be several months before we have an understanding, though I would really caution any expectations along those fronts, because this is a short-term study.

We're not expecting to see any sort of disease modification, just because of the way the study was designed. We dosed for three months, but it wasn't even full drug effect for three months, because you build up the effect. This is the precursor to what would be long-term dosing.

GV: Have you observed whether there was also a reduction in the wild type (normal) huntingtin protein that all HD patients also have?

FB: There isn't a good assay [lab test] for measuring wild type at this point. We have the samples, and once the assay is robust enough, we'll look at it. The team is working on it, as well as others.

GV: Were there any surprises in the data that you've seen so far?

FB: It's only surprising that it's worked as we predicted it would [laughter]. Oftentimes when you go from pre-clinical to clinical, things don't quite work out as well. But the drug is doing what it should be doing, which is lowering mutant huntingtin in cerebrospinal fluid. I think it's all very positive from that perspective.

Phase 2 versus Phase 3

GV: What have you learned that will be helpful in planning phase 2?

FB: We asked a lot of the sites and the patients – because we collected a tremendous amount of data from them – for data that will be useful in designing a Phase 3 trial. We wanted to figure out which of the clinical outcome measures, which of the imaging measures, is actually reproducible, robust, and sensitive, to make sure it's not "noisy" data.

AS: Another important learning will be whether there are differences from site to site. In a multi-site, multi-country trial, if a particular test just doesn't translate well to German, for example, then we'll have learned that. We can spare Roche from collecting data that are difficult to interpret, because they're difficult to operationalize across sites and countries.

GV: You said "Phase 3" and not Phase 2. Why?

FB: Yes. At this point, Roche has not made a final decision on the next step. One of the options being considered is going right to a Phase 3 study. There's a trade-off. You can do a smaller Phase 2 study – get more data that make it more probable that you'll be successful for the Phase 3 – or you can go directly to a Phase 3 study. Those are the decisions that Roche is looking at right now very carefully.

The plus side is: if they go right to Phase 3, it would accelerate getting the drug to market. When we've reviewed with them the size of the study and the time of the study, there's not a big difference between doing a Phase 3 and doing a more traditional Phase 2 first. It's more expensive to go right to Phase 3, but it would save a lot of time.

GV: For an entity such as the FDA, is it okay to go from a Phase 1/2a to a Phase 3?

FB: The FDA will pay a lot of attention to the safety of the drug which – so far, knock on wood – looks very good. And then they leave it to the sponsor whether they want to risk the program. They may advise – because they ultimately want the drug to be successful, too – that this isn't the best thing to do, but ultimately that's the drug company's decision. Roche will engage with the FDA.

GV: What is leading Roche to think it could maybe go directly to a Phase 3?

FB: It's safety and tolerability [shown in Phase 1/2a], and the fact that we now know what dose of the drug produces this level of huntingtin lowering. Without that, they wouldn't be able to go to Phase 3, but with that data, you could say that "this dose" should then produce "this level" of huntingtin lowering.

GV: Going straight to Phase 3, how much shorter would the whole program be?

AS: It's definitely in the years.

FB: Yes, because if they were to do a Phase 2 study first, it would probably take three years to enroll and run. Roche wants to get this drug to patients as quickly as possible, assuming it works. They understand the disease. They understand the need for the patients.

GV: Whether Phase 2 or 3, when would the next study begin?

FB: I would anticipate towards the end of next year.

An important milestone

GV: What is the historical significance of the Ionis breakthrough?

FB: It's an important milestone for the Huntington's community. The mutation in the huntingtin gene was described in 1993. This is the first drug to go into clinical trials that is directly on target. It addresses the cause of the disease. We're extremely excited that we're actually seeing this basic science and all the work that NIH and other agencies have funded over the last 25 years now being translated into something that could actually have an impact for Huntington's patients.

This bodes well for other neurological diseases. It has potential to markedly change how we treat those diseases. Perhaps this technology platform [the Ionis gene-silencing approach] would be beneficial for them as well. For patients out there overall, this is extremely important.

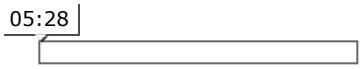
(For additional information about next steps in the IONIS-HTT$_{Rx}$ program, click here for a Q & A with Dr. Ed Wild, an advisor and investigator of the program. You can also read a FAQS from the Huntington's Disease Society of America by clicking here.)

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

(In the video below, watch my report on the December 11 Ionis announcement.)

News from Ionis: drug reduces toxic Huntington's protein, trial may jump straight to Phase 3!

from **Gene Veritas**



News from Ionis: drug reduces toxic Huntington's protein, trial may jump straight to Phase 3! from Gene Veritas on Vimeo.

Posted by Gene Veritas at 6:56 AM

Labels: Anne Smith , antisense oligonucleotide , clinical trials , CSF , drug , Frank Bennett , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , mutant huntingtin , mutation , Roche , spinal tap , symptoms , treatments

1 comment:

Bev said...

Thanks so much for your excellent questions. I am tempering my excitement with a dose of realism, but it is wonderful to have something like HTTRx to look forward to.

5:53 PM, December 18, 2017

Post a Comment

Newer Post Home Older Post

Subscribe to: Post Comments (Atom)