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Roche confirms tominersen as ineffective, while Triplet provides key details for trial of drug to slow major driver of Huntington's disease

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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 confirms tominersen as ineffective, while Triplet provides key details for trial of drug to slow major driver of Huntington's disease

Following up on news that it had halted dosing, Roche has confirmed that its historic GENERATION HD1 clinical trial, aimed at the genetic causes of Huntington's disease, failed to improve symptoms in study participants.

The disappointing trial outcome for the drug candidate tominersen was revealed on April 27 by Scott Schobel, M.D., M.Sc., Roche's medical leader of GENERATION HD1, at the virtual 16th Annual HD Therapeutics Conference, sponsored by CHDI Foundation, Inc., the nonprofit virtual biotech focused solely on developing HD treatments and a collaborator in the effort.

More than 1,000 people registered for this greatly anticipated meeting.

"Nobody wanted this result," Dr. Schobel said in his online talk, the first scientific presentation describing why an independent review committee had recommended, and Roche accepted, that GENERATION HD1 be halted. "This is a setback, and it's a setback which is emotional. It's a setback which we all feel, because, after being able to lower the huntingtin protein for the first time, there's a lot of hope in that."

An opportunity to learn

Dr. Schobel displayed a series of slides demonstrating tominersen's lack of effect on trial volunteers, who showed "progressive decline," reflected in key measures of cognition and

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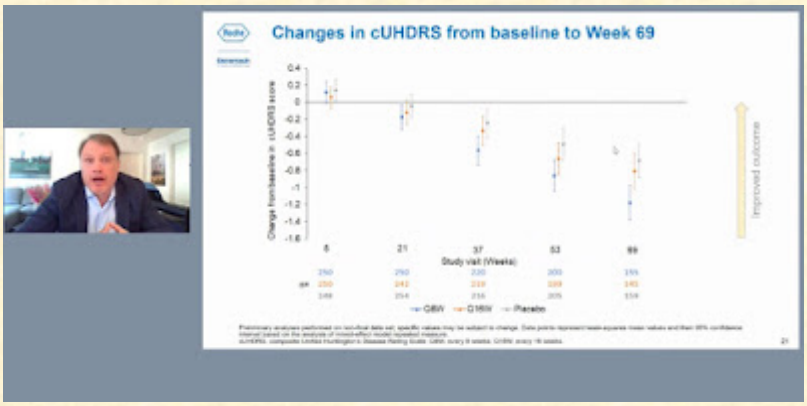
control of bodily movements. Observations by physicians also showed "increasing severity" of disease in the participants, Dr. Schobel said.

Still, he said the researchers established a "new setpoint for the field": reducing the level of the mutant protein in the early-stage tominersen clinical trial.

That achievement was a historic first, and many HD scientists still believe that this strategy can lead to an improvement in symptoms. However, it now remains for potential future trials to demonstrate that huntingtin-lowering can actually help patients.

Roche is "compelled" to use the trial results "as an opportunity to learn," Dr. Schobel said. The company still has a "wealth of data" to analyze regarding tominersen and its implications for the huntingtin-lowering approach. The firm will share results with the HD community.

The Huntington's Disease Society of America will hold a webinar at noon Eastern time on April 29 with an update for the community on the Roche results. (Click here to register.)



Dr. Scott Schobel of Roche displays slide demonstrating decline in volunteers' condition in the GENERATION HD1 clinical trial at the 16th Annual HD Therapeutics Conference (screenshot by Gene Veritas, aka Kenneth P. Serbin)

Drug candidate's target chosen

On this first day of the three-day conference, Irina Antonijevic, M.D., Ph.D., the chief medical officer at Triplet Therapeutics, Inc., revealed key details of the firm's drug program to develop a genetic strategy that contrasts sharply with the idea of lowering the huntingtin protein. The firm also issued a press release.

Dr. Antonijevic focused on Triplet's efforts to slow or stop a key driver of HD, somatic expansion, the mutant huntingtin gene's tendency for continued expansion with age.

Triplet's research exploits continuing breakthroughs in HD genetics, also the topic of this year's Therapeutics Conference. Those advances have revealed that so-called modifier genes linked to the speeding or slowing of somatic expansion can hasten or delay the age of HD onset by just a few years or by as many as 40.

Triplet scientists and others believe that the longer that expansion, the more toxic the gene and its product, the huntingtin protein, become.

Building on these developments, in 2020 Triplet announced its drug candidate TTX-3360, aimed at slowing or stopping somatic expansion.

In her conference presentation, Dr. Antonijevic announced that the specific biochemical target of TTX-3360 is the modifier gene MSH3, involved in the maintenance and repair of DNA.

In studies of mice, Triplet has demonstrated safe and effective lowering of MSH3 using TTX-3360. Additional safety studies were done in nonhuman primates.

Injection directly into the brain

Like the Roche drug, TTX-3360 is an antisense oligonucleotide (ASO), a synthetic modified single strand of DNA. Both the early-stage trial of tominersen and GENERATION HD1 delivered ASOs via spinal tap.

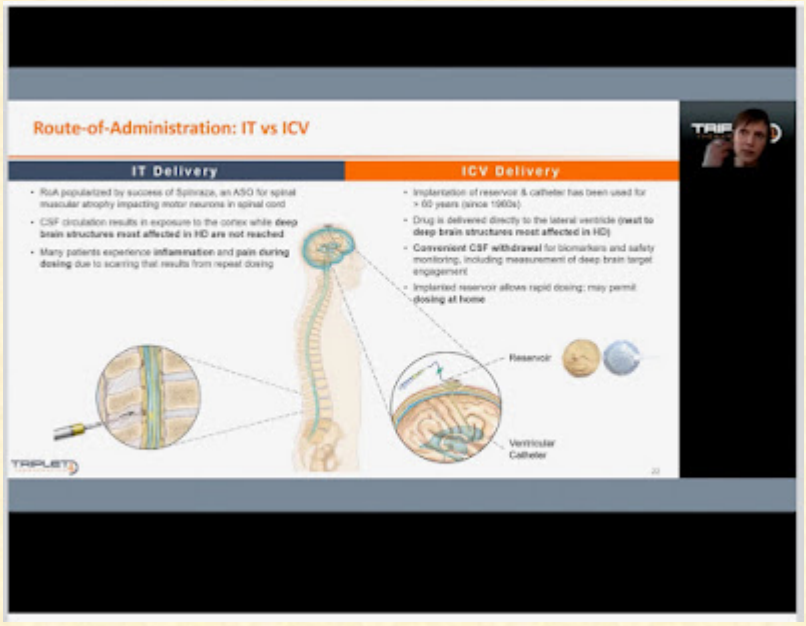
However, Dr. Antonijevic announced that TTX-3360 will be introduced into the brain using an intracerebroventricular (ICV) injection. The ICV device is a small reservoir implanted at the top of the head with a catheter going into the brain. ICVs have been used in medical treatments since the 1960s, including injection of anti-cancer drugs.

Dr. Antonijevic explained that, in contrast with the spinal tap – whereby an ASO had to travel along the spine before entering the brain – the ICV will permit Triplet to get its drug deeper into the brain, including areas severely affected by HD.

With spinal taps, patients can experience pain and inflammation during dosing because of scarring that results from repeated dosing, Dr. Antonijevic asserted. The ICV permits easy withdrawal of cerebrospinal fluid (which bathes the brain) for monitoring of drug safety and efficacy, she added.

The ICV also allows for rapid dosing – perhaps even at home – whereas the spinal tap requires a visit to a doctor's office, Dr. Antonijevic pointed out.

(According to one scientific article, an ICV can remain in place for life. However, long-term usage is not well understood. The device should be monitored for leakage or failure. If necessary, the device can be removed or replaced.)



At the HD Therapeutics Conference, Dr. Irina Antonijevic of Triplet Therapeutics discusses a slide comparing two methods of drug delivery: spinal taps (intrathecal injections) and intracerebroventricular injection (screenshot by Gene Veritas)

Triplet aims to file an investigational new drug application with the U.S. Food and Drug administration (and/or a clinical trial application in Europe or Canada) by year's end for a Phase 1/2a study of TTX-3360, which will address primarily the safety and tolerability of the compound. Triplet will recruit presymptomatic and early symptomatic individuals for the trial.

Triplet also announced a pledge of one percent of its equity to a "patient support fund," to be managed independently, to support patients suffering from HD and other, similar disorders, known as repeat expansion disorders. The fund will help patients and families secure access to care and therapies.

(For background on the Triplet clinical trial program, click here. Stay tuned to this blog here for further coverage of the conference.)

(For additional coverage of the conference, click here).

Posted by Gene Veritas at 10:49 AM

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