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Tough news for Huntington's, other neurological disease patients: Roche halts dosing in historic clinical trials on signs of inefficacy

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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.

Blog Archive

- ▼ 2021 (12)
  - ► November (1)
  - ► September (1)
  - ► July (1)
  - ► May (2)
  - ► April (3)
  - ▼ March (2)
    - Tough news for Huntington's, other neurological di...
    - Blog article No. 300: who exactly is Gene Veritas?
  - ► February (2)
- ► 2020 (16)
- ► 2019 (19)
- ► 2018 (16)
- ► 2017 (14)
- ► 2016 (13)
- ► 2015 (24)
- ► 2014 (24)
- ► 2013 (30)
- ► 2012 (26)
- ► 2011 (33)
- ► 2010 (26)
- ► 2009 (21)
- ► 2008 (7)
- ► 2007 (7)
- ► 2006 (4)
- ► 2005 (17)

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TUESDAY, MARCH 23, 2021

Tough news for Huntington's, other neurological disease patients: Roche halts dosing in historic clinical trial on signs of inefficacy

Calling it "tough news to share" and "even more difficult to receive," pharmaceutical giant Roche announced on March 22 that it has halted dosing in the firm's historic Phase 3 Huntington's disease clinical trial of its gene silencing drug tominersen, GENERATION HD1, because of unfavorable efficacy data, as seen by an independent review committee.

"The committee recently met for a pre-planned review of the latest safety and efficacy data from GENERATION HD1 and made a recommendation about the investigational therapy's potential benefit/risk profile," wrote David West, Roche's senior director, for Global Patient Partnership, in a letter addressed to the international HD community. "Based on the committee's recommendation, we will permanently stop dosing with tominersen and placebo in the GENERATION HD1 study."

GENERATION HD1 began in early 2019, paused for several months to recalibrate dosing, and became fully enrolled in April 2020. Volunteers were to receive the drug over 25 months, and Roche had expected to finish the trial and report results in 2022. Tominersen developer Ionis Pharmaceuticals, Inc., Roche's partner, had completed a Phase 1/2a trial of the drug (testing for mainly safety and tolerability) in 2017. That trial was so successful that Roche skipped a full-blown Phase 2 and went directly to Phase 3, GENERATION HD1.

West noted that the review committee's recommendations resulted not from "any new emergent safety concern, but on a broad

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assessment of the benefit/risk" for those receiving the drug as compared to those getting the placebo.

This means that the drug demonstrated an "unfavorable efficacy trend," an official of U.S. Roche's subsidiary Genentech wrote me in an e-mail. If successful, the trial would have demonstrated that tominersen could slow, halt, or even reverse HD symptoms.

"This is brutal and I am absolutely devastated for our patients and families," Jody Corey-Bloom, M.D., Ph.D., the director of the Huntington's Disease Society of America (HDSA) Center of Excellence at the University of California, San Diego, wrote me.

Trial participants in Dr. Corey-Bloom's clinic were among those taking part in GENERATION HD1. "I am glad that Roche will continue following patients for safety and clinical outcomes," she added.

Veteran HD physician LaVonne Goodman expressed a similar sentiment. "Hope has been so very high for this drug; our community will feel not just disappointment, but real grief," Dr. Goodman wrote me. "However, we're accustomed to grief, and are resilient. I think part of the community message should be that supporting each other is vitally important now."

HDSA Chief Scientific Officer George Yohrling, Ph.D., called the news "devastating." "HD families around the world had their hopes held high that this experimental drug could one day soon become an effective therapy for HD," Dr. Yohrling stated. "While this is clearly not the news we wanted to hear, I am confident that in the coming weeks the Generation HD1 data will help the scientific community understand why tominersen did not meet its desired outcome."

Robert Pacifici, Ph.D., the chief scientific officer for CHDI Foundation, Inc., the nonprofit virtual biotech dedicated to discovering HD therapies and a collaborator of Roche and Ionis, also commented on the development.

"Roche's decision to discontinue dosing in most of its Huntington's disease studies based on a recommendation from the unblinded [with access to data] Independent Data Monitoring Committee that periodically reviews study data is a very disappointing outcome," Dr. Pacifici wrote. "However, knowing our colleagues at Roche we are confident that this decision has been made in good faith with the best interests of study participants uppermost in mind."

No new safety concern caused the halt

The stop to the Roche trial underscores the fact that an effective treatment still eludes not only HD scientists, but also researchers of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and other neurological conditions.

The reviewers who recommended the halt to GENERATION HD1 work separately from Roche. The committee has not yet shared its specific reasoning or data with Roche.

"It is important to note that the recommendation is not based on any new emergent safety concern," West's letter stated.

Roche has notified the clinical trial sites in the 18 participating countries of the halt. The sites are contacting the 791 symptomatic volunteers who had enrolled in the program.

The participants were receiving intrathecal (spinal) injections of tominersen or a placebo. Participants in GEN-EXTEND (an

extension study for participants coming from any Roche HD study) will also no longer receive doses.

"It is our intention to provide as much information as we can to the community, which at this time is limited until we have accessed and analyzed full data," West's letter explained.

West acknowledged "the tremendous contribution of the families who are participating in these studies, as well as the broader Huntington's community for their collaboration."

Next steps depend on the data

Although Roche has stopped giving tominersen to the volunteers, the trial has not yet ended.

"The studies will remain ongoing (without further dosing in GENERATION HD1 and GEN-EXTEND) and it is intended that study participants will be followed by their physicians for safety and clinical outcomes," West stated. Roche has not provided a timeline for the remainder of the work to be completed.

A Q&A appended to West's letter states that "Roche remains committed to the HD space and our studies are continuing," and data from GENERATION HD1 "will advance our understanding of tominersen and inform research for other disease modifying treatments." It adds: "In addition to tominersen, the Roche family of companies is investigating gene therapy approaches to treating Huntington's disease."

The conclusions about GENERATION HD1 – and possible next steps by Roche and Ionis – will depend on the analysis of the independent reviewers' explanations and all of the massive data from the Phase 3 trial.

As Dr. Pacifici noted, only when data from the independent review committee has been "shared with the wider HD community" will it become possible to "form a scientific opinion" about the halting of the trial.

A perplexing result

Ionis held a public conference call on March 22 to answer questions about the Roche announcement.

"This is the largest Huntington's trial ever conducted," stated Ionis CEO Brett Monia, Ph.D. "It was conducted on a wealth of information."

Monia stated that, "while we are saddened by today's outcome, we are committed to the HD community and focused on delivering treatments for this and other devastating neurological diseases."

Monia added, "Although this is a disappointing setback for Ionis and the HD community, we are confident in the potential of our technology platform to address many neurological diseases."

Various questioners on the call asked Dr. Monia and Ionis scientists to speculate about the reasons for the halt and future potential approaches using the company's technology (antisense oligonucleotides, or ASOs), but the Ionis officials emphasized that answers are premature without access to the data.

"We are still strong believers in the ASO approach," Dr. Monia asserted.

However, Ionis Chief Scientific Officer Frank Bennett, Ph.D., the long-time coordinator of the firm's HD program, added that the news of the potential ineffectiveness of using an ASO to reduce the amount of huntingtin protein in patients was "perplexing and disappointing to us," leaving many unanswered questions.

Eric Swayze, Ph.D., Ionis's executive vice president for research and one of the developers of the ASO, reminded the participants on the call of a fundamental reality of HD: "It's a complex disease."

Dr. Monia added that "one silver lining" in the halt to GENERATION HD1 was that it did not, as noted above, result from a concern about safety.

Diversification necessary

Although the pioneering Roche-Ionis program had electrified the HD world with the hope of the first effective treatment, the HD research community has also deliberately diversified the approaches to treating HD.

Thus, companies like Triplet Therapeutics, Inc. have leveraged publicly available knowledge gained from the Roche/Ionis program and others to plan their own, unique drug development strategies.

Triplet aims to start a clinical trial in the second half of this year for a potential drug targeted at stopping the mutant huntingtin gene's tendency for continued expansion with age. That expansion compromises brain cells and triggers disease. In this respect, HD is known as a repeat expansion disorder (RED), with the triplets of the genetic code CAG recurring too many times and thus causing disease.

As a Triplet scientist explained last year, the Roche/Ionis approach is like "putting a brake" on the disease, whereas Triplet's ASO will target the expansion of the gene and therefore seek to "remove the foot on the gas." (Click here to read more).

Using the same mechanism, in addition to HD, Triplet hopes to develop transformative treatments for many of the more than 50 other REDs. For REDs of the central nervous system, it would use the same drug as for Huntington's.

Although unavailable for comment on the Roche announcement, Triplet executives offered encouragement in an e-mail to me: "Triplet's thoughts are with the HD community, and our clinical development plans in HD and other repeat expansion disorders remain on track and unchanged."

As one scientist wrote me (and as I also felt), the Roche announcement was like a punch to the gut. However, I am also heartened by the potential of other clinical trials like Triplet's. (I

will further explore the implications of the Roche trial halt in upcoming articles.)

To echo Dr. Goodman's words, our community and its scientists are indeed resilient.

(For more on the Roche announcement, see the article in HDBuzz).

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

Posted by Gene Veritas at 4:34 PM

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