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New Ionis data show positive trends in clinical measures of Huntington's disease drug trial volunteers

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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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THURSDAY, APRIL 26, 2018

New Ionis data show positive trends in clinical measures of Huntington's disease drug trial volunteers

Exploratory analysis of new data showed positive trends in several clinical signs of Huntington's disease in the recently concluded Ionis Pharmaceuticals, Inc., gene-silencing Phase 1/2a clinical trial, the company announced April 24.

"Results from exploratory analyses of data from the study demonstrated correlations between reductions in mutant huntingtin (mHTT), the disease-causing protein, and improvements in clinical measures of Huntington's disease," an Ionis press release stated about its drug IONIS-HTT$_{Rx}$.

Initiated in September 2015 and completed in December 2017, the trial tested the drug in 46 symptomatic volunteers at nine sites in Canada, Germany, and the United Kingdom.

Because of the very limited size, duration, and scope of the Phase 1/2a trial, the newly studied clinical signals have only statistical importance. They do not demonstrate whether an individual patient got better, or by how much a person did better on a particular test.

However, they provide hope for the HD community because they showed an association between reducing, or lowering, mHTT, and the improved scores. The new data will help pave the way for the planned Phase 3 trial to test efficacy.

"These important clinical results further demonstrate that targeting the reduction of the toxic mutant huntingtin protein with IONIS-HTT$_{Rx}$ has the potential to be disease-modifying," Frank Bennett, Ph.D., Ionis senior vice president of research and franchise leader for neurological programs, stated in the release.

Sarah Tabrizi, FRCP, Ph.D., of University College London, the lead investigator of the Phase 1/2a trial, also presented the new information on April 24 at the annual meeting of the American Academy of Neurology (AAN) in Los Angeles. Out of more than 3,000 submissions, the talk was one of four selected for the top-featured session at the meeting, which drew more than 12,000 professionals.

Checking movements and cognitive loss

On March 1, at the 13th Annual HD Therapeutics Conference in Palm Springs, CA, Dr. Tabrizi revealed that the drop of 40-60 percent in mutant protein observed in the cerebral spinal fluid (CSF). Based on numerous animal studies done by Ionis, that corresponds to to a decrease of 55-85 percent in the cortex of the brain. The cortex is the most developed area of the brain and the source of thought and language, abilities severely hampered by HD. In the caudate – which helps control movement, another critical problem in HD – the corresponding decrease (based on animal data) ranged from 20-50 percent.

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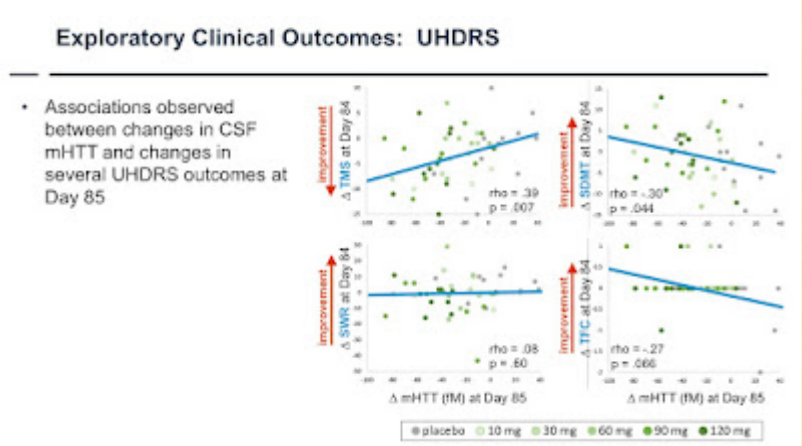
The new data demonstrate associations between reduction in mHTT (measured in CSF) and improvement on two clinical tests commonly used in HD clinical studies: the *total motor score* test (measuring impairments in movements) and the *symbol digit modalities* test (measuring cognitive loss).

The press release further noted a significant correlation between huntingtin reduction and an improved score on the Composite Unified Huntington's Disease Rating Scale (cUHDRS), which measures decline in patients.

Two tests showed neutral results: the *stroop word reading* (checking for cognitive loss) and the *total functional capacity* (assessing ability to perform daily tasks).



A slide from Dr. Tabrizi's talk at the AAN meeting illustrating improved scores in two clinical tests (top two graphs) and neutral scores in two others (bottom graphs) (slide courtesy of Ionis)

Larger, longer studies needed

At the AAN meeting, Dr. Tabrizi emphasized that the three-month Phase 1/2a trial was not designed to measure a true clinical benefit from IONIS-HTT_{Rx}. It sought primarily to gauge safety and tolerability of the drug.

The researchers used so-called "exploratory post-hoc analysis."

As explained by Ionis officials in an e-mail, post-hoc means that Ionis did not predefine the analyses in the clinical trial protocol. Such analyses cannot provide conclusive proof of a drug effect. These analyses are common in early-stage clinical trials, where drug companies look for interesting signals worthy of careful evaluation in later-stage trials.

The officials also pointed out that, in analyzing the data using the gold-standard technique for demonstrating effect - comparing clinical test results of drug-treated participants with those on placebo - no improvements were found. This was not a surprise, given the limited scope of a Phase 1/2a trial.

In fact, they added, the trial planners included the clinical tests primarily to monitor for unexpected worsening.

The Ionis officials described the relationship between mHTT-lowering and potential clinical benefit as "subtle."

They emphasized the need for larger and longer trials to demonstrate efficacy.

A 'hint of clinical benefits'

"The measurements were done during the trial, but these statistical analyses were not pre-specified, and so we say that they are post-hoc and exploratory," Jody Corey-Bloom, M.D., Ph.D., the director of the Huntington's Disease Society of America (HDSA) Center of Excellence for Family Services and Research (COE) in San Diego, explained in an e-mail.

Dr. Corey-Bloom described the correlations between the clinical measurements and the reduction in the huntingtin protein as "positive but weak. This is very welcome news and clearly in the right direction! We will obviously need larger and longer studies to really confirm a potential clinical benefit, though."

Swiss pharmaceutical giant Roche, which now holds the license to the Ionis drug, has confirmed that it will take the unusual step of skipping a Phase 2 trial and going directly to Phase 3. Phases 2 and 3 measure a drug's efficacy. Roche, which renamed the drug RG6042, does not yet have a timeline. (Click here to read more about Roche's plans.)

"Though press releases and post-hoc analysis can be problematic, the reported improvement in clinical measures in this early clinical trial, if borne out by subsequent study, is a 'wow' for the HD community," LaVonne Goodman, M.D., the founder of Huntington's Disease Drug Works, commented in an e-mail. "So I look forward to seeing the full data set in a peer-reviewed article. If results from this first trial are borne out in the larger Phase 3 trial, this drug is a game changer for HD. And also great, if results are similar to the present trial, it might take less than the earlier predicted three years to show it."

"It is quite exciting to see any hint of clinical benefits," Martha Nance, M.D., the director of the Minneapolis COE, wrote via e-mail. "It is important to know that these clinical results are not definitive, but this report adds to the growing list of favorable results from this groundbreaking trial of gene silencing in HD. The HD community has every right to be excited about these results!"

* * *

For additional coverage of the Ionis news, click here and here.

For HDSA's Q & A on the news, click here.

For background on the development of clinical tests for HD, click here.

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

(This article was updated on April 27, 2018, to include additional comments on the clinical trial analyses by Ionis officials.)

Posted by Gene Veritas at 2:51 PM

Labels: clinical measures , clinical trials , huntingtin lowering , Huntington's disease , Ionis Pharmaceuticals , IONIS-HTT-Rx , mutant huntingtin , Roche , Sarah Tabrizi , symbol digit modalities test , total motor score

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