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Isis Pharmaceuticals launches historic clinical trial to silence Huntington's disease gene

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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)
- ► 2020 (16)
- ► 2019 (19)
- ► 2018 (16)
- ► 2017 (14)
- ► 2016 (13)
- ▼ 2015 (24)
  - ► December (3)
  - ► November (2)
  - ► October (2)
  - ► September (3)
  - ► August (1)
  - ▼ July (1)
    - Isis Pharmaceuticals launches historic clinical tr...
  - ► June (1)
  - ► May (3)
  - ► April (2)
  - ► March (1)
  - ► February (3)
  - ► January (2)
- ► 2014 (24)
- ► 2013 (30)
- ► 2012 (26)
- ► 2011 (33)
- ► 2010 (26)
- ► 2009 (21)
- ► 2008 (7)
- ► 2007 (7)
- ► 2006 (4)
- ► 2005 (17)

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FRIDAY, JULY 24, 2015

Isis Pharmaceuticals launches historic clinical trial to silence Huntington's disease gene

Isis Pharmaceuticals, Inc., based in Carlsbad, CA, has launched its long-awaited clinical trial to test a drug designed to attack Huntington's disease at its genetic roots.

In a July 21 press release, Isis said it had initiated a Phase I human clinical study of ISIS-HTT_{Rx}, its compound aimed at diminishing the symptoms of HD. HTT_{Rx} signifies a medication for HD. The disease is caused by a defect in both the huntingtin gene and protein, which are symbolized by the letters htt.

"ISIS- HTT_{RX} is the first therapy to enter clinical development that is designed to directly target the cause of the disease by reducing the production of the protein responsible for HD," the release stated.

In partnership with Roche, the Switzerland-based pharmaceutical giant sharing costs of the typically expensive clinical trial, Isis thus becomes the first entity to use a gene-silencing technique in the attempt to stop HD.

"Although the toxic protein produced from the huntingtin (HTT) gene in HD patients has been a target of interest for many years, no therapies have advanced to clinical trials to treat the underlying cause of the disease," Frank Bennett, Ph.D., Isis's senior vice president of research, stated . "Our antisense technology has enabled us to discover and develop ISIS-HTT_{Rx}, the first therapeutic approach designed to treat the genetic cause of HD."

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Frank Bennett, Ph.D., of Isis Pharmaceuticals (photo by Dr. Ed Wild)

A 'significant milestone'

HTT_{Rx} is an antisense oligonucleotide, an artificial strand of DNA created by Isis to block the action of the RNA molecules that translate the huntingtin genetic code to make the huntingtin protein.

Involving about 36 early-stage HD patients at about six sites in Europe and Canada, the Phase I trial focuses on the safety and tolerability of HTT_{Rx}. According to an Isis spokesperson, the sites will start recruiting participants as early as in a few weeks.

Depending on the pace of recruitment, Phase I most likely will end in 2017. If Phase I is successful, a larger Phase II trial to test efficacy likely would take place in 2018. A successful Phase II trial would be followed by a Phase III trial. Together all three phases of a clinical trial program typically take at least five years.

Last August, scientists from Isis and CHDI Foundation, Inc., the nonprofit virtual biotech firm that funded the early stages of the Isis research starting in 2007, provided extensive details about the plans for the trial. (Click here to read more.).

"The initial development of this antisense drug for Huntington's disease came out of a longstanding productive partnership between Isis and CHDI, and its advancement now to clinical trial is testament to Isis' perseverance and scientific expertise," CHDI president Robi Blumenstein stated in the press release. "It's exciting that therapeutic candidates grounded in the biology of Huntington's disease are finally making their way to clinical trial."

"The initiation of the ISIS-HTTRx study is a significant milestone in the history of Huntington's disease research as this marks the first time a drug designed specifically for Huntington's patients has transitioned into the clinic," George Yohrling, Ph.D., senior director for mission and scientific affairs for the Huntington's Disease Society of America (HDSA), wrote in

an e-mail. "My hope is that this study not only shows that the drug is safe, but serves as an informative beacon for all future huntingtin-lowering trials."

Martha Nance, M.D., the director of the HDSA Center of Excellence at Hennepin County Medical Center in Minneapolis and a member of the executive committee of the Huntington Study Group, said that "it would be impossible to overstate the importance of this trial."

"I am old enough to have grown up in the 1960s, swept up as a young child with the excitement of space exploration, and I remember, almost as clearly and importantly as the Apollo 11 mission that actually LANDED on the moon, the Apollo 8 mission over Christmas 1968, during which William Anders took the iconic picture of the earthrise over the moon," Dr. Nance wrote in an e-mail. "There were several more steps, several more Apollo missions, before Neil Armstrong could jump off the ladder onto the moon. The ISIS study is the HD equivalent of the Apollo 8 mission."

LaVonne Goodman, M.D., the founder of Huntington's Disease Drug Works, said that there are "high hopes and expectations" about the trial. "We celebrate those individuals with HD, heroes who are selflessly participating in this trial and all others, 'taking one for the team,'" she wrote in an e-mail.

"We're very enthusiastic about the drug," Dr. Bennett said in a 2014 interview.

As he put it previously, Isis technology is like a "laser-guided missile" that targets a specific, disease-causing messenger RNA and destroys it or takes it out of the body "so that you don't produce that messenger RNA."

The Isis-Roche partnership

According to the press release, with the initiation of the clinical trial, Isis – a small company – earned a $22 million milestone payment from Roche. To date, Isis has earned $52 million in upfront and milestone payments from the partnership. It can earn more as the project progresses, as well as royalties on potential sales.

Roche can exercise the option to license ISIS- HTT_{Rx} from Isis through the completion of the Phase 1 trial. If so, Roche will assume responsibility for global development, the acquisition of regulatory approvals, and marketing the drug.

The partnership is critical. Isis cannot alone afford to carry out a clinical trial. Drugs usually cost hundreds of millions of dollars to develop.

According to the press release, Isis's drug projects include 38 drugs aimed at treating a wide range of diseases, among them cardiovascular disease, metabolic disorders, cancer, and severe and rare diseases, including neurological disorders such as HD.

A huge dose of hope

The announcement of the historic trial's launch provides a huge dose of hope for the HD community.

Since the discovery of the huntingtin gene in 1993, scientists have published thousands of research papers on HD and identified hundreds of potential "targets" for treatments.

In recent years, scientists and drug companies have initiated an increasing number of clinical trials in the quest for effective treatments. However, to date none has proven successful in halting the disease.

A necessary leap

As seen in animal studies, the infusion of HTT_{Rx} into the brain has led to the disappearance of the HD-like symptoms.

Scientists warn that it's a still a huge leap from animals to humans when it comes to testing drugs. Also, only about one in ten clinical trials results in a drug reaching the market.

Earlier this year prominent HD specialist Bernhard Landwehrmeyer, M.D., Ph.D., cautioned that it could still take decades for the gene-silencing approach to play an effective part in managing the disease.

"We should all be extremely excited and hopeful, but remember that there is a lot of work ahead for researchers, doctors, patients, and families before we will get to our moon, and no guarantee of success," wrote Dr. Nance.

Nevertheless, the Isis-Roche trial is a major step. At a minimum, it will help answer key questions about the gene-silencing approach.

If it is successful in ameliorating symptoms, it could mean the beginning of the end of Huntington's disease as a threat to the tens of thousands of families affected worldwide.

* * *

Below see links to previous reports on Isis.

"Moving toward a potential treatment: Isis, CHDI researchers outline upcoming Huntington's disease gene-silencing clinical trial"

"A key new ally in the search for Huntington's disease treatments"

"Quickening the pace towards a Huntington's disease gene-silencing clinical trial: pharma giant Roche, Isis enter partnership"

"Designing the best drug possible to defeat Huntington's disease"

"Building a 'laser-guided missile' to attack Huntington's disease"

"Observing the cure in progress"

Also see coverage at HDBuzz by clicking here.

(Disclaimer: I hold a symbolic number of Isis shares.)

Posted by Gene Veritas at 8:15 AM

Labels: antisense oligonucleotide , CHDI , clinical trial , DNA , drug development , Frank Bennett , genetic , hope , huntingtin , Huntington's disease , Isis Pharmaceuticals , ISIS-HTTRx , protein , RNA , Roche , symptoms , treatments

5 comments:

Anonymous said...
Awesome!

7:17 PM, July 26, 2015

Anonymous said...
Is it expensive treatment? I mean ISIS-HTTRx itself and delivering into the spinal? I consider such type of cerement will be refunded by the government.

4:09 AM, July 27, 2015

Anonymous said...

Have you heard anything about using Vitamin B3 (Niacin) for Huntington's Disease?

I came across an old article by the late Dr. Abram Hoffer (he was a biochemist & psychiatrist I believe) from the 1970s mentioning someone with HD who came to him. The patient took Niacin and his neuro symptoms disappeared, something like that??

I haven't seen anything else on that so I'm checking out various blog posts etc

10:17 PM, September 02, 2015

Unknown said...

I am happy for this progress but sad to have to read about the royalties to the compamny. In the end it makes it clear this is still about corporate business, will HD families be able to afford it?

2:31 PM, September 05, 2015

Jason said...

Why is it sad for them to earn royalties on the treatment? The hard-working scientists that are developing this drug deserve to be paid for their dedication. This is their job, they have families to feed, mortgages and student loans to pay.

Sure, the drug will probably be expensive -- in large part because the *trials* are so expensive to conduct, not simply because people are greedy -- but that's why we have health insurance. No individual or family can reasonably be expected to pay for this kind of treatment from out-of-pocket, and no treatment like this could realistically be developed inexpensively enough for people to do so. That's why medical insurance (or nationalized health care) exists.

11:22 PM, September 10, 2015

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