Interim update from Vico Therapeutics on their CAG-targeting drug, VO659

Vico Therapeutics have shared interim data about their drug, VO659, which targets the CAG expansion that causes several genetic diseases, including #Huntingtonsdisease and #spinocerebellarataxia

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Vico Therapeutics recently presented at several conferences to share an interim update on their Phase 1/2a clinical trial testing their drug called VO659, which targets the repeating C-A-Gs in people with Huntington's disease (HD). These data suggest that VO659 may be able to reduce levels of the toxic HD protein in the small group of participants tested so far and gives insights into safety. But how does VO659 work and how is Vico's approach different to that of other companies? Let's get into it.

Too many C-A-G repeats are the cause of HD

In everyone's genetic code, there are 2 copies of a gene called Huntingtin, often shortened to HTT. Near the start of the HTT gene code, there are repeating C-A-G DNA letters. In folks who don't have HD, both gene copies will have less than 35 C-A-G's repeating in a row.

Basket trials can help more quickly assess the safety of a drug as well as how well it works in more people.

However, people with HD will have more than 35 C-A-G repeats, typically in just one of the copies of their HTT gene. This expansion of the C-A-G's in the DNA is the genetic cause of HD.

Our DNA is like a recipe book for the molecules that make up the cells of our bodies. Our cell's machinery carefully copies down each recipe into a message molecule which can then be used as a template to make the protein molecule it encodes.

The HTT gene is the DNA recipe that encodes the HTT protein molecule. So if the DNA encodes a C-A-G expansion, we will also see this expansion in the copy of the message molecule and in the protein.

VO659 - a drug to target repeats

VO659 is a type of drug called an antisense oligonucleotide or ASO, developed by the Dutch company, Vico Therapeutics. VO659 is delivered by spinal injection so that it can spread through the nervous system and into the brain.

ASO's are designed to specifically bind onto certain types of genetic message molecules, which results in them being sent to the cell's trash can. Without the message molecule, the protein molecule they encode cannot be made, so the level of this protein will decrease.

VO659 is designed to target long strings of repeating C-A-Gs in genetic message molecules, like the one found in the expanded HTT message in people with HD. This means that treatment with VO659 should specifically decrease the levels of the expanded HTT in the cell.

Expanding C-A-G repeats cause disease beyond HD

HD is not the only disease caused by expansion of C-A-Gs, there are in fact a total of 10 diseases which have similar genetics. In addition to HD, these include other rare diseases such spinocerebellar ataxias 1 and 3, often called SCA1 and SCA3.

Like HD, SCA1 and SCA3 are also caused by genetic mutations which increase the number of C-A-Gs over a specific threshold and result in neurological disease. These C-A-G increases occur in genes called Ataxin-1 and Ataxin-3 for SCA1 and SCA3 respectively. The expanded proteins encoded by C-A-G expanded Ataxin-1 and Ataxin-3 are thought to be toxic and a key driver of SCA1 and SCA3 disease.

As VO659 is designed to target long C-A-Gs, this means that it could be a useful drug to help reduce the toxic proteins made by any C-A-G expansion disease, including HD, SCA1, and SCA3.

Preferential lowering of the toxic copy

Runs of repeating C-A-Gs are found in many different genetic message molecules. Indeed, the regular healthy HTT gene typically has ~18 C-A-Gs. So how does VO659 work to target disease message molecules?

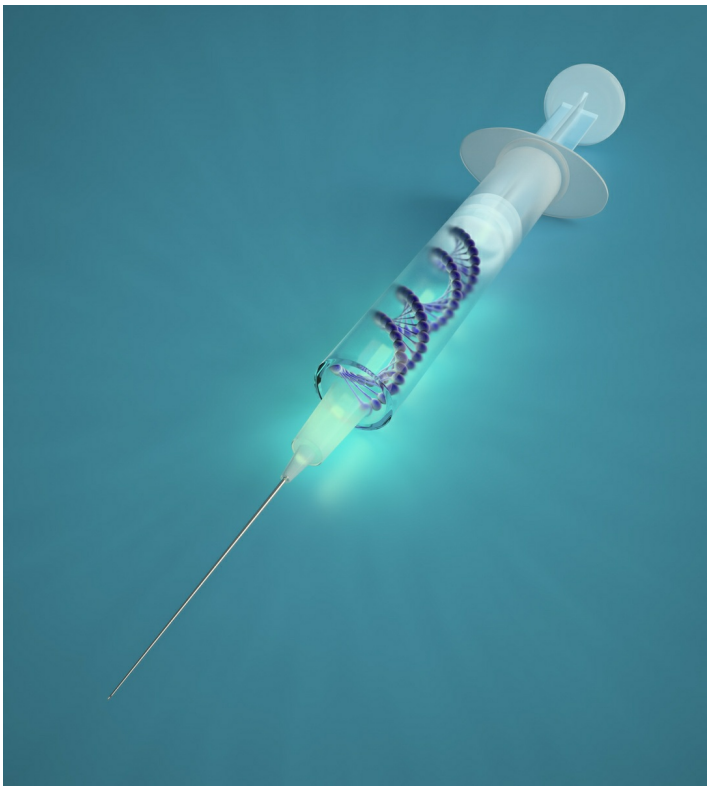
Data previously presented by Vico at the 2023 CHDI Therapeutics Meeting, reported on by HDBuzz, showed that the drug prefers very long C-A-G's so it mainly seems to target disease message molecules, like the expanded HTT message. This is a preference though, as the regular HTT message is still targeted by VO659, just to a lesser extent.

This is a completely different approach from other ASOs being tested in the clinic to treat HD. Some target total HTT (unexpanded and C-A-G expanded) such as tominersen developed by Roche, while others target only the disease-form of HTT, such as WVE-003 from Wave Therapeutics. Unlike Vico who are targeting the C-A-Gs that are present on both the expanded and unexpanded copies of HTT, [Wave's approach uses a unique genetic signature] (https://en.hdbuzz.net/371 that's only present on the expanded copy.

Basket trials can help us find new drugs for rare diseases more quickly

Given the promise that VO659 has for HD and other C-A-G repeat diseases like SCA1 and SCA3, the scientists at Vico Therapeutics designed a "basket trial" to test it out. A basket trial is where people with different diseases which have a similar kind of molecular alteration are grouped together into one trial.

The basket trial approach can help to more quickly assess the safety of a drug, as well as how well it works, in more people. HD is considered a rare disease with ~1 in 4000 people affected. SCA1 and SCA3 are even more uncommon, both with ~1 in 100,000 people affected.



VO659 is an antisense oligonucleotide, or ASO, delivered by spinal injection so that it can spread through the nervous system and into the brain.

With so few people, it can be very challenging to recruit enough participants for a trial exclusively for just one of these diseases. By grouping people with different types of C-A-G repeat diseases, it can help scientists more quickly and efficiently test a drug in the clinic which might work for all of them.

In this case, Vico enrolled people with SCA1, SCA3, or HD, all of whom have an increased C-A-G repeat in their Ataxin-1, Ataxin-3, or HTT genes, respectively, into their Phase 1/2a clinical trial.

Designing a trial to test VO659 in people with C-A-G repeat diseases

To be enrolled in the trial, participants must be 25-60 years old and have a genetic diagnosis of SCA1, SCA3, or HD. These tests report back a C-A-G number and to qualify for the trial, people with SCA1 need 41+, SCA3 need 61+, and HD need 36+.

Participants of the trial also need to be in the early stages of SCA1, SCA3, or HD. For people with SCA1 and SCA3, this was defined as mild to moderate disease with a Scale for Assessment Rating of Ataxia (SARA) score of 3-18. For people with HD this is defined as Stage I disease with a Total Functional Capacity (TFC) Score of 11-13 and a Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Level (DCL) of 4. All of these acronyms stand for different clinical metrics which can help doctors measure how far along in disease someone is.

The data presented so far are from a total of 23 people enrolled into the trial; 6 with HD, 3 with SCA1, and 14 with SCA3. The trial seeks to test 3 different doses of VO659 (10, 20, and 40 mg) to work out which dose is safe and also effective at targeting the disease-causing message molecules. All of the people with HD in the trial are receiving the top 40 mg dose of the drug.

Everyone in the trial is receiving four doses of the drug given once every 4 weeks. However the trial is continuing for 23 weeks after dosing has ended, allowing measurements to be made of folks who have taken the drug, to see how well it may be working and how safe it is after dosing has stopped.

Interim update results - what do we know about VO659 so far?

This interim update was shared via a press release and also through presentations at the recent EHDN and ENROLL-HD 2024 meeting in Strasbourg in September, and at the International Congress of Ataxia Research (ICAR) in London in November. Let's get into the new data...

Safety

In a Phase 1/2a trial, one of the most important things to be determined about a new drug is how safe it is in people. The recent press release from Vico-announces-positive-interim-phase-1-2a-clinical-data-of-vo659-in-treatment-of-huntingtons-disease/) states that the drug is generally safe and tolerated which seems like good news. However, when data from the interim update were presented at the recent EHDN and ICAR meetings, we learned that this wasn't the full picture.

Of the 6 people with HD who were given the drug, 1 person experienced radiculitis, a condition characterized by inflammation of certain nerve cells that can lead to painful sensory changes or motor weakness in the lower body and legs. 2 people in the SCA1 group and 1 person in the SCA3 group also experience radiculitis.

This is a side effect observed in studies investigating other ASO therapies. Vico plan to mitigate this issue moving forward by lowering the amount of drug given to people in the trial. Fortunately, 3 of the 4 people experiencing this side effect are showing signs of recovering.

All other side effects were minor, including headaches, dizziness, and nausea, and were in line with what was expected for this type of clinical trial.

NfL

Neurofilament light, also called NfL, is a biomarker of brain health. Measured in the spinal fluid, if NfL levels go up, it is generally an indicator that brain health is declining. (So, for NfL levels, up is bad and down is good.)

The data presented at ICAR and EHDN suggest that NfL might go up a bit after dosing in some people, which could be reasonably expected after a lumbar puncture. Looking at all the data collected so far for folks who have reached their 4th dose, the good news is that in nearly everyone who received the drug so far, the levels didn't go up significantly in the long run.

In more recent data from the ICAR presentation, it actually looks like there might be a 2.5% decrease in 5 people with HD who received the 40 mg dose after 120 days, 5 weeks after their last dose. This is encouraging, but we should be cautious with data from such a small number of people.

VO659 prefers to target longer C-A-Gs, like that found in the expanded HD gene

HTT lowering

Vico looked at how the levels of the expanded HTT protein changed in people with HD who received the drug. As this expanded form of HTT is only made in people with HD, they had samples from just 6 people to look at. Two people in this group of the trial have very early HD so the levels of expanded HTT in their spinal fluid were actually too low to measure with confidence.

In the press release and presentation at EHDN, a 28% reduction in expanded HTT levels was seen for folks with HD receiving 40mg of the drug after their 4th dose. This shows that the drug is working as expected and lowering HTT levels.

In more recent data presented at ICAR, HTT levels were shown to be reduced by 38% in 3 people. This data was collected at 120 days, 5 weeks after these folks received their last dose. This seems to suggest that the effect of the drug is long lasting, and expanded HTT levels remain low even after dosing with the drug has stopped.

What about people with SCAs?

Data have been shared for folks in the trial with SCA3, to see how their expanded Ataxin-3 levels changed in both spinal fluid and blood samples. No change was seen in spinal fluid but it does look like the levels seem to go down in blood samples in some people.

There doesn't seem to be a dose-dependent effect in these changes i.e., more lowering in people who got more drug. However, it's very early days with very few people, so we might need to wait for more data from more people to know for sure.

What's next for VO659?

More data

This Phase 1/2a study is ongoing and there is a lot more data to be collected. Until we have those final and complete datasets, we won't quite know the outlook of this therapeutic approach for the different diseases being investigated.

Dosing strategy

Something we knew from the preclinical data (aka data gathered in the lab from cells in a dish or animals that model HD) shared by Vico is that this drug really seems to hang around and keep working for a long time after it is administered. The fancy science term for this is that the drug has a long half life. This can have potential issues if too much drug accumulates in specific tissues in the body over time, but can also have the benefit of meaning that you don't need to dose people quite so often.

The radiculitis in 4 folks who received the highest dose of the drug could well be linked to the fact that the drug sticks around for a long time but we don't yet know the exact cause. Moving forward, Vico have stated that they are planning to dose people with VO659 much less frequently, between 1-3 times a year, in future studies of this drug.

Another trial?

Vico believes that VO659 appears to be a promising treatment for people with SCA3 and HD. They are already in discussions with regulators on a plan for a phase 2 trial of this drug in people with HD.

At the end of the day, these early stage clinical trials are designed to test safety and tolerability of new drugs, which is exactly what Vico are working out with this trial. While there do seem to be a few potential safety issues with the highest dose of VO659 being tested, Vico are following up on those and evolving their strategy to address the issues they've seen. We'll be sure to keep you updated as VO659 advances.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

Total Functional Capacity A standardized rating scale for function in HD, used to assess

capacity to work, handle finances, perform domestic chores and self-care tasks

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

NfL biomarker of brain health

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

inflammation Activation of the immune system, thought to be involved in the HD disease process

therapeutics treatments

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

UHDRS A standardized neurological examination that aims to provide a uniform assessment of the clinical features of HD

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15
