Unpacking Wave's PRECISION-HD2 huntingtin-lowering trial announcement

Wave Life Sciences announces that its antisense drug WVE-120102 has lowered mutant huntingtin protein in cerebrospinal fluid, but investors seem disappointed. Rather confusing – what do we know for sure?

By Dr Jeff Carroll | January 03, 2020 | Edited by Professor Ed Wild

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DNA-based drugs called antisense oligonucleotides, or ASOs, are now in multiple clinical trials in Huntington's disease, aiming to lower production of the harmful mutant huntingtin protein in the brain. Wave Life Sciences has been running parallel trials of two new ASO drugs, administered by injection into the spine. Just before the new year, Wave announced that the drug in the PRECISION-HD2 trial had successfully lowered the concentration of mutant huntingtin in the spinal fluid. The reduction was quite modest, at 12%, so the company will be adding a higher-dose cohort to both its trials. While the investment community seems disappointed that another trial arm is needed, and we need to see the results in full, to us it's good news that there are now multiple huntingtin-lowering drugs in the world.

Lowering huntingtin

The genetic mutation that causes Huntington's disease does damage to the brain by telling cells to make a harmful protein, mutant huntingtin. Reducing production of this protein - or **Huntingtin Lowering** - is the biggest focus of drug development in HD.

A drug called HTTRx made a big splash a couple of years ago when it was reported that it had successfully lowered the production of mutant huntingtin in the spinal fluid of HD patients. That drug has been renamed RG6042 and is now being tested by Roche/Genentech in the GENERATION-HD1 trial which will hopefully tell us whether lowering huntingtin production slows the progression of the disease.

RG6042 is a drug made from DNA that interrupts the protein production chain. DNA drugs like that are called antisense oligonucleotides or **ASOs**.

Wave Life Sciences was the second company to start testing ASO drugs for Huntington's disease. Wave wants to achieve the same aim – lowering mutant huntingtin – but with a twist.

Every person has two copies of the huntingtin gene - one inherited from mom, and one from dad. One abnormal copy is enough to cause HD by causing cells to make the mutant protein. But those cells also produce the normal or healthy version of the protein. Scientists call this healthy version of a gene or protein “wild-type” because it’s the one most commonly seen “in the wild”.

Roche’s RG6042 has equal effects on the mutant and healthy version of huntingtin - it cannot distinguish between the two production lines and is expected to lower mutant and wild-type huntingtin equally.

Wave’s ASO drugs aim to target just the mutant version of the huntingtin protein, leaving wild-type production relatively unaltered.

This is much harder to do, which is why Wave had to design two different drugs, each targeting a little single-letter genetic spelling differences that are sometimes passed down along with the mutation that causes HD. These spelling differences don’t do anything in themselves, but they can be used to steer the drug to the mutant side of the protein production line, in people who have the right genetic markers in the right place. Wave estimates that about two-thirds of the HD population will have one or other of the necessary genetic markers to make them suitable for treatment with one of their two drugs.

Wave’s two trials launched in 2017. They were called PRECISION-HD1 and PRECISION-HD2, testing drugs called WVE-120101 and WVE-120102 respectively. Within each trial, patients were allocated randomly to treatment with the drug or placebo (injection without any drug). Four different doses of the drug were tried as the trial proceeded, which is important to remember as we look at the results of this study. The trials were short - about five months’ treatment per patient.

The headlines

Wave’s latest press release sets out the first results from the PRECISION-HD2 trial. The release announces that WVE-120102 **successfully lowered mutant huntingtin** in the spinal fluid, when all of the active treatment arms were looked at together and compared against the placebo-treated group. Wave’s announcement gives a figure of about **12%** for the degree of mutant huntingtin lowering.

If a drug is working, we expect higher doses to produce a bigger effect. This is called a **dose-dependent response**, and if you can show it in a clinical trial, it strengthens the case that your drug is doing what you intended. Without giving much detail, Wave’s announcement states that the huntingtin-lowering did show a dose-dependent response at the highest doses tested when looking across all of the treatment groups together.

To be clear - Wave has not yet released enough information for us to understand exactly how the amount of mutant Huntingtin in the spinal fluid is related to the dose of the drug given in the PRECISION-HD2 study. We expect that, as commonly happens with these small

early trials, more data will become available soon and we'll be able to evaluate this relationship.

Important but easily glossed-over is the primary reason behind the trial: safety. From the information given, the short-term safety looks good. 'Adverse events' were no more common in drug-treated patients than in those receiving the placebo. In itself, that is a very solid result from this first-in-human trial.

Apples and oranges?

The first person to climb a mountain has a tough job, but gets lots of cheers. The second person to the summit may have an easier time, thanks to the first person mapping out a route - but is likely to be asked questions like "how did your time compare?" when they get there.

It's similar with drugs. Roche's RG6042 was the first ASO drug to lower huntingtin, and two years down the line, we have much more detail about how they did it and the full results of the trial have been published. It's inevitable that Wave's results will be scrutinised to see how they compare. Such comparisons may not be terribly helpful, because of the important differences between Wave's drugs and Roche's – but let's do it anyway and see what we can learn.

How does Wave's 12% reduction in mutant huntingtin compare? Well, RG6042 reduced mutant huntingtin by roughly 40 to 60% in patients on higher doses. 12% is less than 40%, so that means the Wave drug is less good, right? Not so fast...

Fundamentally, no drug has yet been shown to slow progression of HD, so**we don't know how much mutant huntingtin reduction is ideal**. Furthermore, we don't yet know whether reducing only mutant Huntingtin, as Wave is trying to do, is going to be more beneficial and safer than RG6042, which targets both forms of Huntingtin. That's why we do these studies - so we can figure out what approach is safest and has the biggest impact on HD symptoms.

Another important wrinkle to keep in mind is that the doses of drug used in the two trials were very different - the highest dose in the RG6042 study was 120 milligrams and the highest dose tested in the PRECISION-HD2 study was 16 milligrams - that's a big difference!

Based on these results showing their drug was safe at lower doses, Wave has already announced it will now add an extra dosing arm to the PRECISION-HD2 trial, to test higher doses – 32 milligrams per injection. That's twice the amount tested at the highest dose in this trial. So the 12% mutant huntingtin reduction they're reporting may well be a stepping stone to a bigger reduction from a higher dose.

Adding extra dosing arms like this is a fairly common strategy in drug development, where it can be very difficult to predict what dose will be ideal, even if very detailed work is done in animals before going into humans. Sometimes it is necessary to keep increasing the dose,

guided by some measure of success, until some hint of a problem is seen, then step back to the previous dose and test that in a bigger trial.

Testing a higher dose will help Wave find whether greater reductions in mutant huntingtin can be achieved, and whether doing so is safe. It may be necessary to go even higher, depending on what the results of the new 32 milligram dose show.

Wave has also added a 32 milligram dose to its other trial, PRECISION-HD1. Because of this, **the final results of both trials will now arrive later than initially planned, in late 2020** .

Mutant, wild-type and total

There's another complication to understanding these results: remember that the Wave drug is trying to lower the mutant form of the protein without reducing the wild-type form, whereas the Roche drug is expected to lower them both equally.

So even if both drugs achieved the same degree of mutant huntingtin reduction, there is more happening behind the scenes that the headline 'mutant huntingtin' percentage doesn't tell us. We don't yet have any clear idea whether lowering wild-type huntingtin alongside the mutant form makes any difference, and until Roche's big trial completes, we are unlikely to find out.

To us, this is another reason to be cautiously pleased that a reduction in mutant huntingtin has been reported, and wait as patiently as we can for more information.

Talking of wild-type huntingtin – what can we say about whether Wave's drug succeeded in leaving it unaltered while lowering the mutant version? So far, not a lot!

For reasons to do with how awkward the protein is, we can measure the level of mutant huntingtin quite accurately, but there is no direct way of measuring how much wild-type huntingtin the spinal fluid contains. We **can** measure the **total** amount of huntingtin in spinal fluid – that's the combined pool of mutant and wild-type. When Wave did that, they found that the drug hadn't altered it.

That might seem weird - if they reduced mutant huntingtin by 12%, and didn't change the level of wild-type huntingtin, then surely the total level of protein should fall by 6%? Possibly - but every measurement has error in it, and simple assumptions like that might be built on shaky foundations.

What's certainly true is that with a small reduction in mutant huntingtin, it is very hard to say anything for sure about the drug's effects on wild-type protein. At this point, we don't think any conclusions can be drawn on that front. We need more information, from more people, before we can start to understand the relationship between changes in mutant and total Huntingtin in the spinal fluid of HD patients in these studies.

Life's complicated

One thing we've noticed in the wake of this announcement is a fair amount of speculation on social media and in the news. There seems to be a 'received wisdom' among investment folks that these results should disappointing for Wave.

We don't really agree with that position, which seems to have come from an over-simplistic comparison of the headline percentages in mutant huntingtin reduction, and the potentially expensive addition of a new higher dose arm.

In fact, RG6042 went through exactly the same process when it was first tested in patients by Ionis Pharmaceuticals. Initially, four dosing levels were planned, but then a fifth, higher dose was added when the trial was already well underway. The main difference here is that Wave has announced their initial results at the same time as the decision to add another dosing arm.

Our advice here is – as ever – to take speculation in the news and especially on social media with a large pinch of salt. Try to get your information from many sources, and if things are confusing, it may well be because nobody knows the full answer.

As scientists driven by progress towards effective treatments for HD, we are interested above all in facts and data. Assuming Wave's announcement is an accurate reflection of the trial data, it represents an important milestone: for the first time, there are multiple drugs in the world that can lower mutant huntingtin in the spinal fluid of patients. Critically, we have drugs that target total Huntingtin, and others that target only mutant Huntingtin, allowing us to compare the risks and benefits of both approaches, in the only place that matters, which is HD patients.

Many questions remain unanswered, and for now we have to be OK with that. What's the best dose of Wave's drugs? Will Wave's drugs slow progression of Huntington's disease? How will they compare with other huntingtin-lowering drugs? These questions will take much longer to answer, and we must be patient and determined to get the trials done and hope that clear answers will emerge. For now, we're cautiously pleased that 2020 has begun with a little ray of light.

Dr. Carroll has conducted sponsored pre-clincial research with Wave Life Sciences, but has no personal financial interest in the company. Dr. Wild served as an advisor to Wave Life Sciences before the launch of the PRECISION-1 and -2 studies, but he has played no role in the studies since their launch and has not financial interest in Wave Life Sciences. For more information about our disclosure policy see our FAQ...

GLOSSARY

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

huntingtin protein The protein produced by the HD gene.

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

wild-type the opposite of 'mutant'. Wild-type huntingtin, for example, is the 'normal', 'healthy' protein.

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they’re taking a pill that doesn’t work.

cohort a group of participants in a clinical research study
