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Therapy focus – Antisense projects raise Huntington's hopes

Madeleine Armstrong

Breathless coverage this week of Ionis's antisense Huntington's disease candidate IONIS-HTTrx might have made it appear that a cure for the neurological disorder is imminent.

But the project – now licensed to Roche – still has plenty of hurdles to clear. Still, there is renewed optimism around the antisense approach more broadly and two contenders from Wave Life Sciences are also in early-stage development for the degenerative condition. With little else in the Huntington's pipeline, any setbacks with this approach will be a massive blow for the field (see table below).

It is hoped that antisense technology could slow the progression of disease, rather than just managing symptoms like current drugs such as Lundbeck's Xenazine and Teva's Austedo, which was approved in April.

Ionis has not released any data from the phase I/II dose-escalation study of IONIS-HTTrx, saying only that the trial found dose-dependent reductions of mutant huntingtin protein that "exceeded expectations". Full details have been saved for an unnamed medical conference in the first half of 2018 – possibly the CHDI Foundation meeting in February or the American Academy of Neurology congress in April.

In Huntington's, an aberrant gene codes for a mutant huntingtin protein that gradually destroys neurons; it is hoped that reducing production of the protein could stall the disorder. However, a definitive link between a reduction in mutant huntingtin and symptoms has yet to be proven.

While the pathophysiology of Huntington's disease is well understood, lending support to the antisense mechanism, one challenge could be getting enough of the drug into the brain regions where huntingtin is produced. Both Ionis's and Wave's candidates are given intrathecally, via injection into the spinal canal.

The responsibility for later-stage trials, which will need to measure disease progression and safety over a much longer period than previous studies, now rests with Roche. The IONIS-HTTrx data were enough to tempt the Swiss company to exercise its option to license the project, adding $45m to the $52m that it has already paid to Ionis in connection with the candidate.

New Wave?

It is not clear yet what IONIS-HTTrx will need to show in order to be approvable; interestingly, the phase I/II trial of IONIS-HTTrx and the ongoing studies of Wave's candidates are placebo-controlled and include clinical outcome endpoints and various potential surrogate measures, though they are primarily designed to assess safety.

When asked if the current trials could form a basis for approval, Wave's chief executive Paul Bolno told *EP Vantage*: "Registration endpoints are up to regulators. We can't decide. The initial study is still relatively short – what we want to see early on is knockdown of the protein and preservation of the nerve."

Wave is around a year and a half behind with its two wholly-owned candidates, WVE-120101 and WVE-120102. The projects target different single nucleotide polymorphisms (SNPs) on the mutant huntingtin gene: rs362307 (SNP1) and rs362331 (SNP2) respectively. Around 70% of Huntington's patients carry SNP1, SNP2 or both, according to Wave.

The company's approach might be safer and more effective than Ionis's due to its specificity, stemming from Wave's use of one stereoisomer that selectively targets the mutant huntingtin allele. "We can create a molecule that can just take the mutant protein down, not healthy protein," said Mr Bolno.

Meanwhile, Ionis's antisense oligonucleotide is stereorandom, meaning it targets both wild-type and mutant huntingtin alleles. As healthy huntingtin protein is thought to have an important role in neuronal function, knocking this out could have safety consequences.

That means Wave might be able to use a higher dose and achieve greater reduction in mutant protein, Mr Bolno added. "We can bring a baseball bat on the toxic protein, and be very ginger on the healthy protein –

unlike the Roche programme."

However, top-line data with the Wave projects are not expected until the first half of 2019.

Elsewhere

The remaining Huntington's pipeline looks stale, with various projects having fallen by the wayside since *EP Vantage* last carried out this analysis (*Therapy focus – One step forward but two steps back in Huntington's, August 3, 2016*).

Selected projects in the Huntington's disease pipeline				
Product	**Company**	**Pharma class**	**Trial(s)**	**Primary completion**
Phase II				
Triheptanoin Oil	Ultragenyx/Baylor/INSERM	Metabolic disease agent	Trihep3 (NCT02453061)	Jun 2017
Laquinimod	Teva	Immunomodulator	Legato-HD (NCT02215616)	Jun 2018
VX15/2503	Teva/Vaccinex	Anti-semaphorin 4D/CD100 MAb	Signal (NCT02481674)	May 2020
Phase I/II				
IONIS-HTTRx	Roche/Ionis	Huntington's disease antisense	NCT02519036	Reported
SRX246	Azevan Pharmaceuticals	Vasopressin 1a receptor antagonist	NCT02507284	Jun 2018
WVE-120101	Wave Life Sciences	Huntingtin SNP1 antisense	Precision-HD1 (NCT03225833)	Sep 2019
WVE-120102	Wave Life Sciences	Huntingtin SNP2 antisense	Precision-HD2 (NCT03225846)	Sep 2019
Source: EvaluatePharma, Clinicaltrials.gov.				

At that time, Raptor's Procysbi had failed to meet its primary endpoint in the phase II/III Cyst-HD trial, but the company had said it was pressing on into a pivotal trial. Since then, Raptor has been acquired by Horizon, and no such study has been listed on Clinicaltrials.gov.

Meanwhile Teva's pridopidine, which had its own problems in its previous life as Huntexil, did not show a benefit on the primary endpoint of the phase II Pride-HD trial last year. At the time Teva said it had gained insights into what it needed to do in phase III, but no details have emerged here yet either.

Teva's laquinimod has not been without its problems either. The highest dose in the Legato-HD trial had to be dropped after cardiovascular events were seen in two separate multiple sclerosis studies. The primary completion date for Legato-HD also appears to have been pushed back from August 2017 to June 2018.

The fate of another phase II candidate, Som Biotech's SOM3355, is also unclear. The project is still listed on Som's website, but a proof of concept study that was due to start in the third quarter of 2016 does not appear to have begun. The phase II trial of Omeros's OMS824 has been suspended.

With the pipeline thinning down, the Huntington's field needed a boost. But it will be a while before investors – and patients – discover whether the antisense approach can live up to expectations.

To contact the writer of this story email Madeleine Armstrong in London at madeleinea@epvantage.com or follow @ByMadeleineA on Twitter

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754