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Prilenia hopes to buck the Huntington's trend

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Prilenia's pridopidine is the last big late-stage hope in the disorder, but it already failed phase 2, and phase 3 under the name Huntexil.

After the recent failures of several high-profile projects in Huntington's disease the industry pipeline is decidedly bare. The only novel late-stage asset now in development is Prilenia Therapeutics' pridopidine, which started phase 3 late last year.

But the oral project, once known as Huntexil, has already flunked two late-stage studies in the hands of the now defunct Danish group Neurosearch and its licensee Teva. This does not bode well for its future. Still, Prilenia's chief executive, Michael Hayden, tells *Evaluate Vantage* that the group has learnt from the experience and designed a new pivotal study to maximise the chance of a win.

It will be a while before it becomes clear whether he is right: the phase 3 trial, Proof-HD, is to finish enrolling in November, he says, with topline results due in late 2022 or early 2023.

Not dopamine

Mr Hayden reckons that a big reason for the previous failures was a lack of understanding about pridopidine's mechanism of action. Teva had thought the project to be a dopamine modulator, so had evaluated it as a potential therapy for the motor symptoms of Huntington's. The primary endpoint of the phase 2 study, Pride-HD, was change in unified Huntington's disease rating scale-total motor score at week 26.

"However, during that study we recognised that we had the wrong biology and that the mechanism of action was sigma 1 activation," says Mr Hayden, who at the time was Teva's chief scientific officer.

Teva became more interested in pridopidine's impact on a prespecified secondary endpoint, total functional capacity (TFC). "We extended the study to 52 weeks, and we did that in an effort to assess TFC – because this is the earliest you can measure TFC."

While Pride-HD showed no benefit on the UHDRS motor score over placebo, there was a nominally significant improvement in TFC. Furthermore, a post-hoc analysis found that the latter was driven by early stage Huntington's patients.

Given these results Teva had hoped to continue development of pridopidine, Mr Hayden claims, but then undertook a dramatic cost-cutting drive. When he left the company in 2017 he took pridopidine with him, and formed the Netherlands/Israel-based Prilenia, which is privately held.

Before that pridopidine/Huntexil was first said to succeed in the MermaiHD phase 3 trial in Huntington's, but its then-owner, Neurosearch, bizarrely then admitted that this result was a flop (*Neurosearch data blunder dents confidence, April 28, 2010*). Neurosearch stock crashed, and the company was wound up and its assets sold off.

Significant is meaningful

Prilenia, however, insists that it has now defined the right endpoint, patient population, trial duration and dose for another phase 3 trial of pridopidine.

The primary endpoint of Proof-HD is TFC over 65 weeks, and Prilenia is focusing on early patients: those with a baseline TFC score of seven or greater. The dose is 45mg twice daily; Teva had tested higher and lower doses, and had found a bell-shaped dose-response curve, Mr Hayden says.

TFC comprises five parameters – occupation, finances, domestic chores, activities of daily living and care level – and gives a value of 0-13, with a lower score representing greater impairment.

“The bigger the effect, the better,” Mr Hayden says. “But any significant change in TFC would be regarded as meaningful. There’s never been a drug that has had any impact on TFC.”

This includes the two approved Huntington’s drugs, Teva’s Austedo and Lundbeck’s Xenazine, both VMAT2 inhibitors that are only indicated for chorea – the jerky movements associated with the disorder.

The only other late-stage Huntington’s project, Neurocrine’s Ingrezza, is also a VMAT2 inhibitor, so even if this succeeds it will not represent much of an advance over existing therapies (*The Huntington’s pipeline takes a blow, March 23, 2021*).

Other uses?

Meanwhile, Mr Hayden claims that pridopidine could have neuroprotective effects. This might also give it utility in other neurodegenerative disorders; the project is being evaluated in amyotrophic lateral sclerosis as part of the Healey ALS platform trial, an academic effort testing several potential therapies. Data are expected in the third quarter of 2022.

Prilenia also hopes to start a study soon in pre-symptomatic Huntington’s.

Acording to Teva's regulatory filings, pridopidine's patent expired last year; however, Prilenia says it has composition of matter patents for pridopidine analogues expiring in 2035.

The Huntington's pipeline was hit last month by the failure of three antisense projects designed to decrease levels of mutant huntingtin protein: first Roche and Ionis's late-stage candidate tominersen, then Wave Life Sciences' two mid-stage projects WVE-120101 and WVE-120102.

As for Prilenia, Mr Hayden concludes: “I feel we have a shot, but there’s no guarantee.”

This story has been updated to clarify Prilenia's location, and pridopidine's patent situation.