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Wave gets another shot at Huntington’s

Madeleine Armstrong

The group hopes for a better result with a higher dose of its antisense projects, but it also has a back-up plan.

Wave Life Sciences’ share price has been in the doldrums since late 2019, when its Duchenne muscular dystrophy project suvodirsen crashed, followed by disappointing data with one of its Huntington’s disease assets, WVE-120102.

In Huntington’s, at least, Wave will have another bite at the cherry soon, with more data from its phase I/II Precision-HD1 and Precision-HD2 trials of WVE-120101 and WVE-120102 respectively due in the first quarter. The group will hope that its decision to add a 32mg high-dose cohort to each of the studies pays off.

Still, only Precision-HD2 will initially yield results from its 32mg arm. Precision-HD1 will report data with doses of up to 16mg owing to Covid-19-related delays in the highest-dose group, Wave’s chief executive, Paul Bolno, explained. He declined to say when the 32mg data for this trial might be available.

Projects	WVE-120101 & WVE-120102
Company	Wave Life Sciences
NPV	$690m ('101) & $512m ('102)
% of market cap	256%
Event	Data from higher-dose cohorts of Precision-HD1 & Precision-HD2 trials
Date	Q1 2021

Wave added the 32mg cohort to both studies after reporting a 12% reduction in mutant huntingtin (HTT) protein in Precision-HD2 in December 2019 – technically a hit, but an underwhelming result compared with the 40% reduction that had previously been seen with Roche and Ionis’s rival antisense project tominersen in its phase I/II study.

With the higher dose, Wave hopes to see a 20-30% reduction in mutant HTT protein, as well as preservation of wild-type HTT protein, Mr Bolno told *Evaluate Vantage*.

The theory behind the company's stereopure antisense oligonucleotides is that, by selectively targeting mutant but not wild-type HTT, they could provide efficacy or safety benefits over other approaches that knock down all HTT protein. Wave has long argued that wild-type HTT is critical for neuronal function and that its suppression could lead to long-term adverse effects.

Obviously, the benefits of the wild-type-sparing approach would need to be proven in trials with harder clinical outcomes.

Plan A or B?

Wave's next steps depend on the data from Precision-HD1 and HD2, as well as those from two open-label studies also due to report this quarter. If the company gets the result it wants it will push WVE-120101 and WVE-120102 into phase III.

But if the data disappoint again it will not be the end for Wave in Huntington's. The company has a third project here, WVE-003, using its second-generation PN-backbone chemistry, which Wave believes will have improved potency and durability over the group's first-generation oligonucleotides.

As Mr Bolno put it: "The upcoming data will help us define if we push forward with first-generation chemistry and second-generation is additive, or if we transition to the next-generation chemistry."

WVE-003 is set to enter the clinic this year. Each of Wave's projects targets a different single nucleotide polymorphism (SNP) on the mutant huntingtin gene: WVE-120101 and WVE-120102 target SNP1 and SNP2 respectively, and WVE-003 hits SNP3. Takeda has an option to co-develop all three projects under a deal signed in 2018.

Wave also hopes to move into the pre-symptomatic Huntington's population with any of its three projects, Mr Bolno said.

If Wave ends up pivoting to its next-generation chemistry, though, Roche and Ionis will pull even further ahead with tominersen. That project is in a phase III trial, Generation HD1, which will read out in 2022.

However, in 2019 the companies modified this trial to move to less frequent dosing after seeing increases in neurofilament light chain, a marker of axonal damage, in clinical trials. This will be something to keep an eye on when the pivotal data with tominersen emerge; results are also due this year from a phase II open-label extension trial.