Evaluate Vantage

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Wave waves goodbye to its first generation

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The group discontinues its first-generation antisense Huntington's projects on disappointing efficacy, leaving its next-gen asset with much to prove.

Wave Life Sciences had hoped that increasing the dose of its Huntington's projects WVE-120101 and WVE-120102 would lead to improvements over disappointing results seen just over a year ago. No such luck: the latest data are even worse, and Wave is discontinuing the candidates, it said after market close yesterday.

The group does have a back-up plan in the form of WVE-003, which uses Wave's next-generation chemistry. The group believes the asset to have better potency and durability than its first-gen compounds. But, after the failure of Roche and Ionis's tominersen last week, there are now doubts about the entire antisense approach in Huntington's.

It will be a while before it becomes apparent whether Wave is on to something with WVE-003: the asset is only just about to go into clinical trials. The company's stock fell 28% this morning, and now sits at an all-time low.

Unimpressive knockdown

All of Wave's so-called stereopure Huntington's projects aim to reduce mutant huntingtin (HTT) protein but preserve levels of wild-type HTT. As wild-type HTT is important for neuronal function, the theory is that this approach could have clinical and safety benefits over projects that knock down mutant and wild-type HTT alike; the now-failed tominersen is an example of the latter.

The problem so far for Wave has been knocking down mutant HTT.

The latest results come from the Precision-HD1 and Precision-HD2 phase 1/2 trials of WVE-120101 and WVE-120102 respectively. Precision-HD2 is so far the only one of these to yield data from the highest-dose group, 32mg. This was added after an interim analysis of the study, which evaluated doses of 2-16mg, found a 12% reduction in mutant HTT – technically a hit, but an underwhelming number.

However, increasing the dose has not helped. Wave said yesterday that there was no statistically significant reduction in mutant HTT after single or multiple doses of WVE-120102 versus placebo, and no evidence of a dose response.

Homing in on the 32mg dose, the results were unimpressive: mutant HTT decreased by a median of 10%, well below the 20-30% bar that Wave had set itself (*Wave gets another shot at Huntington's, March 19, 2021*).

There was also an increased in serious adverse events with the 32mg dose, and six of 13 patients in this cohort

discontinued owing to an adverse event.

Precision-HD1, for which results with up to 16mg of WVE-120101 are currently available, painted a similar lacklustre picture on mutant HTT knockdown. Wave has yet to report data from the 32mg cohort of this study, but it has seen enough to pull the plug on both projects.

The silver lining, if there is one, is that wild-type HTT did not appear to be affected, suggesting that the projects might indeed be selective for mutant HTT, as hoped. Also on the bright side, levels of neurofilament light chain, a marker of axonal damage, did not increase.

Next generation

Wave is therefore pressing on with its stereopure approach with WVE-003, which uses the group's new molecular backbone chemistry and targets the SNP3 mutation, seen in around 40% of Huntington's patients.

As with WVE-120101 and WVE-120102, Takeda has an option to co-develop WVE-003.

Wave believes that preclinical data bode well for its new project, and plans to start a phase 1/2 trial of WVE-003 in up to 40 patients this year. The company is not giving any details on dose, for now, but its medical officer, Michael Panzara, said during a conference call yesterday that this would start at a range that should lead to target engagement, but with "plenty of room to move".

It is not clear when data will be available, but Wave has enough cash to take it into 2023, so there is no immediate pressure to generate results.

Still, there are reasons to question WVE-003's chances of success.

One potential explanation for the failure of Roche/Ionis's rival antisense asset tominersen was that it might not sufficiently penetrate the deep brain tissues involved in Huntington's (*The Huntington's pipeline takes a blow, March 23, 2021*). Tominersen and Wave's projects are all administered intrathecally so, if this is the problem, it could also hit WVE-003.

When asked about this, Wave's chief executive, Paul Bolno, pointed to mouse studies showing distribution of WVE-003 to multiple regions of the brain, including the striatum and cortex. However, Stifel analysts noted: "The translatability of this deep brain biodistribution profile into larger human brains is very much unclear."

Another possible explanation for the lack of progress in Huntington's is that mutant HTT is not the right target. If this turns out to be the case it would be another huge disappointment, not only to Wave but also the broader Huntington's field.