Evaluate Vantage

March 23, 2021

The Huntington’s pipeline takes a blow

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The failure of Roche and Ionis’s late-stage candidate tominersen casts doubt on Wave’s approach, too.

Huntington’s disease patients hoping that a therapy might finally be on the horizon were dealt a blow yesterday with the discontinuation of a pivotal trial of Roche and Ionis’s antisense project tominersen.

There were few details on why the pivotal Generation HD1 study was halted, but the possibility that the antisense approach simply might not work also hurt the groups’ rival Wave Life Sciences. With few other potentially disease-modifying therapies in the pipeline, the future in Huntington’s looks bleak.

Tominersen has not formally been discontinued, but such an outcome seems likely. Ionis and Wave both opened down 17% this morning.

Biodistribution at fault?

Roche and Ionis only said that the decision to stop dosing came after a pre-planned analysis of Generation HD1 by an independent data-monitoring committee, and was based on tominersen’s risk/benefit profile.

The companies added that no new safety signals had been seen.

With little to go on, analysts speculated about what might have tripped up tominersen. Stifel and Evercore ISI both questioned whether the project, which is administered intrathecally, sufficiently penetrated the deep brain tissues involved in Huntington’s.

If true, this would be bad news for Wave, whose WVE-120101 and WVE-120102 are also intrathecally delivered antisense oligonucleotides. However, Wave has long argued that its assets, by knocking down mutant but not wild-type HTT, could have benefits over less selective candidates like tominersen. If the failure of the Roche/Ionis project is related to knockdown of wild-type HTT this would be positive for Wave.

Notably, tominersen has been linked with increases in neurofilament light chain, a marker of axonal damage, which spurred Roche to space out the dosing repeatedly as Generation HD1 continued.

With the cause of tominersen’s failure unclear, other companies with projects designed to decrease HTT protein also saw their stock fall today, including Uniqure, down 6%, and PTC Therapeutics, which fell 8%.

Uniqure has a mid-stage gene therapy candidate, AMT-130, which consists of an AAV5 vector carrying a microRNA designed to silence the huntingtin gene and thereby inhibit production of mutant HTT protein. That

project is administered via a catheter inserted into the relevant brain areas, so should not have a problem with biodistribution, Stifel believes.

PTC's phase I asset PTC518, meanwhile, is a small-molecule splicing modulator designed to decrease HTT protein levels. Healthy volunteer data are due in the first half of 2021.

Pipeline

As for the rest of the Huntington's pipeline, there is little else in late-stage development. One phase III candidate, Neurocrine's tardive dyskinesia drug Ingrezza is only being trialled for the chorea associated with the disease, and would not represent a disease-modifying therapy.

At least one other mid-stage project is on shaky ground: Vaccinex's pepinemab failed its phase II study, Signal. The company is continuing development, and is looking for a partner for a pivotal trial.

Of the rest of the phase II crop, Wave has a big readout soon, with results from a high-dose cohort of WVE-120102 due this quarter (*Wave gets another shot at Huntington's, March 19, 2021*). Still, that update will only concern knockdown data and will not likely shed further light on the debate about clinical endpoints, Leerink noted.

The mid/late-stage Huntington's pipeline				
Project	**Company**	**Description**	**Status/trial details**	**Note**
Phase III				
Ingrezza (valbenazine)	Neurocrine Biosciences	VMAT2 inhibitor	Ph3 Kinect-HD for Huntington's chorea	Topline data due Q4 2021
Pridopidine	Prilenia Therapeutics	Sigma 1-receptor agonist	Ph3 Proof-HD	Completes Mar 2023
Phase II				
SOM3355	Som Biotech	VMAT2 inhibitor	Ph2a completed for Huntington's chorea	Ph2b to start 2021
SRX246	Azevan Pharmaceuticals	Vasopressin 1a receptor antagonist	Ph2 completed in Huntington's irritability	Concluded safe & tolerable and can move forward
Pepinemab (VX15)	Vaccinex	Semaphorin 4D antibody	Ph2 Signal study failed in Sep 2020	Development continues
WVE-120101	Wave Life Sciences*	Stereopure huntingtin SNP1 antisense oligonucleotide	Ph1/2 Precision-HD1	Data due Q1 2021
WVE-120102	Wave Life Sciences*	Stereopure huntingtin SNP2 antisense oligonucleotide	Ph1/2 Precision-HD2	Data due Q1 2021
AMT-130	Uniqure	MicroRNA targeting huntingtin gene	Ph1/2	Initial data due YE 2021
ANX005	Annexon Bioscience	Complement factor C1q antibody	Ph2	Completes May 2022
**Takeda has option to co-develop and co-commercialise. Source: Evaluate Pharma & company releases.*				

This story has been updated to include pridopidine.

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