Evaluate Vantage

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Alnylam touts givosiran win despite toxicity fears

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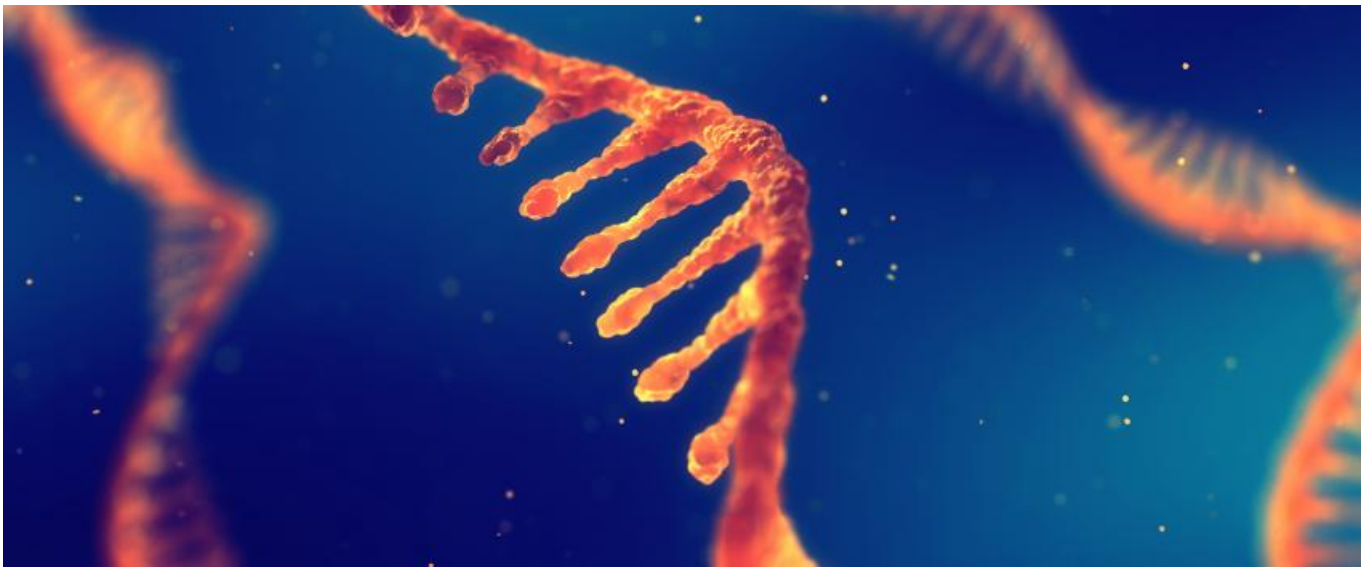

Alnylam looks likely to get approval for its second RNAi candidate, givosiran. But toxicity issues have tainted the Envision trial win.

On the face of it Alnylam now has another approvable drug in the form of its acute hepatic porphyria candidate givosiran. But an efficacy result in the phase III Envision trial came with caveats, namely toxicity worries.

In a conference call today Alnylam blamed the underlying disease for an increase in kidney problems and liver enzyme elevations with givosiran; this might seem strange given the lower incidence of these events in the placebo arm. Investors were evidently not convinced, with Alnylam's stock opening down 3% this morning.

Envision hits…

Envision did hit its primary endpoint, showing a reduction in the annualised rate of porphyria attacks at 12 months in subjects with acute intermittent porphyria, who accounted for 89 of the 94 patients in the trial.

Though Alnylam trumpeted a p value of less than 0.00000001 it declined to reveal the absolute benefit, which is what ultimately will determine givosiran's clinical relevance. The company said it would present full data from Envision on April 13 at the Easl meeting in Vienna. But the group's president of R&D, Akshay Vaishnaw, described the numbers as "quite robust".

Envision also met several secondary endpoints, including reductions in levels of the biomarkers delta-aminolevulinic acid and porphobilinogen, substances that build up in acute hepatic porphyria (AHP).

However, several secondary outcomes were not hit, including pain, fatigue and nausea – important for patients who deal with these symptoms in between the more dramatic porphyria attacks, life-threatening episodes involving severe abdominal pain, vomiting and sweating.

Alnylam execs pointed to nominal significance on the final secondary endpoint, the physical component summary of the SF-12 health survey in AIP patients. However, this was analysed last in the statistical hierarchy so cannot be counted as a win.

Some analysts on today's call raised the question of whether failure on these secondary endpoints might prevent givosiran's approval – something dismissed by Alnylam's chief executive, John Maraganore, who stressed that the primary endpoint win would be the most important factor for regulators.

Alnylam plans to complete its rolling submission for givosiran by mid-2019, and hopes to launch the project in early 2020.

…but raises safety questions

Whatever the chances of approval, givosiran's commercial prospects look dimmer after toxicity concerns reared their heads again.

An earlier update from Envision had already revealed that a patient had discontinued givosiran after experiencing liver enzyme elevations eight times the upper limit of normal (*Markets punish Alnylam for givosiran win, September 27, 2018*).

And a liver signal was apparent again today. Including the previous discontinuation, seven patients in the givosiran cohort showed liver enzyme increases three times the upper limit of normal, versus one in the placebo group. Alnylam was keen to note that the other six givosiran-treated subjects with this issue either continued dosing or had a short break before resuming therapy.

Meanwhile, five givosiran-treated patients reported chronic kidney disease, versus none in the placebo arm.

The company put these adverse events down to AHP itself, with Mr Vaishnaw saying it was common to see liver and kidney impairment in the disease. Over 70% of patients in the trial had some degree of renal impairment at baseline, he added.

However, this does not explain the imbalance in the givosiran and placebo arms, unless there was a similar asymmetry between the groups at baseline.

Alnylam's chief medical officer, Pushkal Garg, suggested that this was the case, at least for the liver issue, saying that, on entry, 20% of givosiran recipients had had elevated alanine aminotransferase levels, versus 4% with placebo.

The Alnylam execs stressed that safety issues had not stopped patients from continuing into an open-label extension of givosiran, pointing out several times that 99% of them had done so.

The company also quashed suggestions that there might be problems with its GalNAc-conjugate platform, used by givosiran and Alnylam's other pipeline projects. Mr Maraganore pointed to a large dataset with another GalNac candidate, inclisiran, which is being developed by The Medicines Company for cardiovascular indications.

Overall, Mr Vaishnaw described givosiran's safety profile as encouraging, particularly given the high unmet need in AHP. This might be enough for regulators, but today's data were far from the home run Alnylam had been hoping for.