Evaluate Vantage

May 15, 2017

Investors scent blood after death in Ionis trial

Jonathan Gardner

As Ionis goes, so goes Alnylam in the opposite direction. News of a patient death and cases of thrombocytopenia in inotersen sodium's pivotal trial had investors placing bets this morning that Alnylam's rival patisiran will be the treatment of choice in familial amyloid polyneuropathy.

Ionis was quick to point out that enhanced patient monitoring had satisfied regulators and the study's data safety monitoring board, not to mention helped manage adverse events. Nevertheless, Ionis shares fell 7% as investors saw increased risk of regulatory rejection or partner Glaxosmithkline vacating the collaboration.

Alnylam shares rose 12% on the possible new opening for patisiran, which in any case is the favourite of the sellside. Despite having yet to report its own phase III data, patisiran has a consensus sales forecast of $747m in 2022 for Alnylam and partner Sanofi, according to *EvaluatePharma*; inotersen, known also as Ionis-TTRRx and GSK2998728, is forecast at $4m.

Over to the regulators

News of three cases of thrombocytopenia, with one patient dying from intracranial haemorrhage, overshadowed what would otherwise have been a positive data readout.

The Neuro-TTR trial found statistically significant improvements in a clinical endpoint called the modified neuropathy impairment score +7 (mNIS+7) and the patient centred Norfolk quality of life-diabetic neuropathy measure at eight and 15 months for patients taking inotersen, compared with those taking placebo. P values were <0.0001 and 0.0006 respectively.

A combined five serious adverse events – thrombocytopenia and renal side effects – stimulated an enhanced patient monitoring protocol agreed by the DSMB and regulators, executives said. No new serious adverse events were recorded after the new monitoring guidelines; Ionis executives said the trial had not been put on clinical hold.

They also pointed to patirisiran's own side-effect profile. Because of injection site reactions from its intravenous administration once every three weeks, patients must be pretreated with high-dose steroids, which have effects that can among other things induce osteoporosis.

With data now in hand, Ionis executives said they planned along with Glaxo to submit applications to US and European regulators this year. Glaxo still needs to decide whether to opt into a full licensing deal, which would entail a $45m milestone to Ionis.

Next catalyst

Attention will now turn to readout of patisiran's pivotal Apollo trial, expected mid-year. This is using the same mNIS+7 clinical endpoint, but unlike inotersen's trial a quality of life measure is not being used as a co-primary endpoint.

Leerink analyst Paul Matteis wrote that the inotersen results were a positive for Alnylam because both used the same mechanism – modulation of RNA that produces the misfolded TTR protein – and, in addition, because Alnylam's project is in a larger trial.

Meanwhile, he pointed out that the need for frequent patient monitoring for inotersen offset its advantage as a self-administered subcutaneous injection – platelet monitoring will likely require once-a-week clinic visits.

Once Apollo reads out regulators and payers will have much to consider. The timing of the two trial readouts should allow for some near-term decisions that should declare a winner.

Product	Trial	ID
Ionis-TTRRx	Neuro-TTR	NCT01737398
Patisiran	Apollo	NCT01960348

To contact the writer of this story email Jonathan Gardner in Virginia at jonathang-us@epvantage.com or follow @ByJonGardner on Twitter