Evaluate Vantage

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Eplontersen hits – but how hard?

Elizabeth Cairns

Astrazeneca and Ionis are to file eplontersen for hereditary transthyretin-mediated amyloid polyneuropathy after a planned interim analysis in the phase 3 Neuro-TTRansform trial came out positive. The antisense oligonucleotide achieved a statistically significant and clinically meaningful change from baseline in serum transthyretin concentration versus what Astra called "an external placebo group" – historical control. It also hit the trial's other co-primary endpoint, change from baseline on mNIS+7 score, a measure of neuropathic disease progression, versus external placebo. The partners have not disclosed the extent of eplontersen's success, but a look at the three approved therapies for this subtype of transthyretin amyloidosis shows the sort of thing doctors will be looking for. It should be noted that unlike Neuro-TTRansform, the pivotal trials of these drugs did contained placebo arms. The control in Neuro-TTRansform was in fact Ionis's own approved Tegsedi; so far no data on this arm has been released. Stifel analysts write that the extent of the improvement on mNIS+7 is crucial, and safety, described by Astra as "favourable", with no specific concerns, will also be important given that Tegsedi's label has a black box warning for thrombocytopenia and glomerulonephritis.

Cross-trial comparison of therapies for hereditary transthyretin amyloid polyneuropathy

Company	Drug	Description	Trial	Time point	Pbo-adj chg on mNIS+7	Pbo-adj chg on Norfolk QoL-DN
Alnylam	Onpattro	IV TTR RNAi therapeutic, given every 3wk	Apollo	18mth	-34.0	-21.1
Alnylam	Amvuttra	SC TTR RNAi therapeutic, given every 3mth	Helios-A	9mth	-17.0	-16.2
Ionis	Tegsedi	SC TTR antisense, given once weekly	Unnamed	66wk (15.2mth)	-19.7	-11.7
Astrazeneca and Ionis	Eplontersen	SC TTR antisense, given once monthly	Neuro-TTRansform	35wk (8mth)*	Hit	Hit

*mNIS+7 = modified neuropathy impairment score +7. Norfolk QoL-DN = Norfolk quality of life questionnaire-diabetic neuropathy. *Interim data; final readout at 66wk. Source: drug labels, company releases.*