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ESC: Arrowhead Aims For Best-In-Class In FCS

by Elizabeth Cairns

But Ionis might be first to reach this small but potentially lucrative market.

Arrowhead Pharmaceuticals, Inc. trails *Ionis Pharmaceuticals, Inc.* in the race to bring an RNAi therapeutic to market for the rare disease familial chylomicronemia syndrome (FCS), but it looks like it might have the more effective product. That is according to the full results of the Phase III PALISADE study of plozasiran, which were presented at the European Society of Cardiology meeting in London, UK, on 2 September.

FCS is a serious hereditary disease that prevents the body from breaking down chylomicrons, lipoprotein particles that are 90% triglycerides. Patients are at high risk of acute pancreatitis and other chronic health issues like fatigue and severe abdominal pain. No therapies are approved in the US specifically for FCS, and triglyceride lowering drugs are generally ineffective. All patients can do to manage their condition is eat an extremely low-fat diet.

That PALISADE had hit on triglyceride reduction, its primary endpoint, was

Key Takeaways

- Data from the Phase III PALISADE trial suggest that Arrowhead's RNAi therapeutic plozasiran could be more effective than Ionis's rival product in familial chylomicronemia syndrome.
- A significant benefit on acute pancreatitis could be a particular differentiating factor.
- But Ionis's olezarsen could gain US

revealed in June. (Also see "*First Phase III Success Opens Up Cardiovascular Pathway For Arrowhead*" - Scrip, 4 Jun, 2024.) But the crucial point is that plozasiran seems to have had a more powerful effect than Ionis's rival oligonucleotide, olezarsen, managed in its pivotal trial, BALANCE, a year ago – even when correcting for the different treatment periods.

> approval six months or more ahead of plozasiran.

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It should be noted that this is imperfect even as cross-trial comparisons go: the values for the PALISADE trial are medians, whereas those in the BALANCE trial are means. Another point of distinction was that both doses of plozasiran hit significance versus placebo on triglyceride levels, whereas the lower dose of olezarsen missed significance on this. (Also see "*Ionis Closer To First Wholly-Owned Drug Launch With Olezarsen Phase III Success*" - Scrip, 26 Sep, 2023.)

Plozasiran was also more effective than olezarsen in a secondary endpoint of cutting patients' levels of apolipoprotein C-III (APOC3), a protein that acts to increase blood triglycerides. This can be seen in the second tab in the graph above.

Pancreatitis

Another key point of comparison between these two products was their effect on acute pancreatitis, one of the life-threatening sequelae of FCS. Here, too, Arrowhead's agent looks like the better bet.

In PALISADE, two positively adjudicated acute pancreatitis events occurred in the pooled plozasiran groups, versus five among placebo patients. This gave an odds ratio of 0.17 and was a significant difference, with a p value of 0.03.

"This is a statistically significant reduction in the severity of acute pancreatitis with an 83% relative risk reduction," said Gerald Watts of the University of Western Australia, presenting the data at the ESC meeting. "That's an impressive result, and that's the sort of results that I want to take back to patients in my clinic and start therapy."

In the BALANCE trial, 11 episodes of acute pancreatitis had occurred in the placebo group, and one in each of the olezarsen groups, giving a rate ratio of 0.12. But this was after 12 months' treatment, and the study investigators could not claim statistical significance here, since the lower dose of Ionis's drug missed significance on BALANCE's primary endpoint.

Arrowhead intends to submit for approval in the US by year-end and in other territories thereafter. The company parked its other RNAi product for FCS, zodasiran, in order to focus on plozasiran just after it reported the topline PALISADE data. (Also see "*Arrowhead's Focus On Plozasiran Intensifies Competition With Ionis*" - Scrip, 26 Jun, 2024.) But Ionis might get there first – the group will receive a US approval decision for olezarsen on 19 December, and even though the lower dose failed, the product could still gain approval thanks to the unmet need for FCS therapies.