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Valid until: 04/30/2025
Time needed to complete: 34m

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ACC 2024: SHASTA-2 Final Study Results

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Dr. Gaudet:
Hello, I'm Daniel Gaudet, professor of medicine at the University of Montreal, and today I will present the final study results of SHASTA-2.

SHASTA-2 is a clinical trial that has been conducted in patients with severe hypertriglyceridemia and assessing the safety and efficacy plozasiran, a small interfering RNA against APOC3, a key target for lipoprotein management. Plozasiran is a small interfering RNA. It's a double-stranded oligonucleotide, which penetrates the hepatic cell and interferes with the expression of the APOC3 gene, the translation of this gene, and thus preventing the production of APOC3 protein. This is why and how the plozasiran decreases TG [triglyceride] levels. Plozasiran, being an APOC3 inhibitor, accelerates the triglyceride-rich lipoproteins' catabolism and clearance through LPL-mediated and LPL-independent mechanism simultaneously.

SHASTA-2 was a double-blind, phase 2B, placebo-controlled, dose-ranging study assessing plozasiran in subjects with TG levels between 500 mg/dL and 4,000 mg/dL. Those patients with complete LPL deficiency or chylomicronemia syndrome were excluded. The study objective was to evaluate at 24 weeks the primary endpoint, which was the level of TG levels compared to baseline, and the key lipoprotein parameters, which have also been assessed were APOC3, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, and remnant cholesterol. Data analysis evaluated the efficacy at Week 24, but a safety follow-up has been added until Week 48. Patients were injected with plozasiran either 10, 25, or 50 mg versus placebo at baseline and at Week 12.

Participants to the study were mainly white male, mid-age males, with very, very high TG levels. In each cohort, the mean TG levels were above 850 mg/dL, whereas the median of TG levels was above 600 mg/dL.

After 24 weeks, both APOC3 and triglyceride levels decreased by approximately 70% in each cohort, whereas the effect was still observable at Week 48, despite the fact that patients were not injected after Week 12, so the effect was thus sustained. Remnant cholesterol, non-HDL cholesterol decreased as well, and HDL cholesterol increased.

Thus, the conclusion of the study was that plozasiran was effective to decrease APOC3, triglyceride, remnant cholesterol, while increasing HDL cholesterol at Week 24, and this effect was persistent until Week 48. Over 90% of subjects treated with plozasiran achieved TG levels below 500 mg/dL at Week 24 and 25, and 500 mg/dL is the threshold at which chylomicrons, the largest lipoproteins, those transporting fat after your meal, are dominating, and these chylomicrons, when they are too numerous, constitute the risk of acute pancreatitis, thus decreasing below 500 mg/dL means that the risk of pancreatitis was low after treatment. Half of subjects reached values below 150 mg/dL of triglyceride, which is huge, and plozasiran had a favorable safety profile at Week 48.

So these data taken together support further development of plozasiran in planned phase 3 programs for the treatment of chylomicronemia or severe hypertriglyceridemia, and the dose of 25 mg has been selected for the phase 3 program.

Based on these results, this also suggests that RNA-mediated silencing of hepatic APOC3 expression via plozasiran is a promising potential treatment for subjects with severe hypertriglyceridemia, which is still, at this point, an unmet medical need in hepatology.

Thank you for your attention.

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