Transcript Details
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Phase 3 study results of plozasiran in patients with FCS

Dr. Watts:
I should like to present the results of the PALISADE study, a randomized, placebo-controlled, phase 3 study of the SRNA plozasiran in patients with familial chylomicronemia syndrome.

By way of background, what is persistent chylomicronemia? Persistent chylomicronemia refers to an extremely high plasma triglyceride level in excess of 10 mmol/L or 880 mg/dL in which the fact that you eat and then it's absorbed as particles called chylomicrons cannot be cleared from the circulation. It is due to ultrarare biallelic recessive variants, so-called familial chylomicronemia syndrome, FCS, or more common genetic variants, a multifactorial polygenic chylomicronemia syndrome, both of which impair the lipolytic enzyme lipoprotein lipase that clears large chylomicron particles and large VLDL [very low-density lipoproteins] particles.

Chylomicronemia causes multiple symptoms: physical, cognitive, emotional, and social, the most severe being acute pancreatitis and its life-threatening sequalae. Current therapeutic agents – fibrates, omega 3 fatty acids, statins, niacins – are unproven as therapy and are generally ineffective; hence, persistent chylomicronemia constitutes a major unmet medical need.

How can we address this? Well, we may address this by focusing on a target called ApoC3, apolipoprotein C3, which is manufactured in the liver and, when elevated, delays the clearance of chylomicron particles and VLDL particles by inhibiting LPL- dependent pathways as well as LPL-independent pathways. So effectively you don't want ApoC3 in the system if you got hypotriglyceridemia. So we can abrogate or now antagonize ApoC3 with gene-silencing therapy, in which the silencing RNA, such as plozasiran, a first in class, may be used to, as it were, shoot the messenger for ApoC3 in the cytoplasm, therefore enhancing triglyceride lipolysis, triglyceride remnant clearance by hepatic receptors, and reducing plasma triglycerides attributable to chylomicrons, VLDL, and remnants.

PALISADE was then a randomized, placebo-controlled, phase 3 study in which 75 adult patients were randomized to receive placebo, plozasiran at 25 mg, or 50 mg dose every 3 months, and the study lasted 12 months. It recruited patients from several countries and several centers to increase generalizability. We report now on the primary endpoint, the placebo-adjusted mean percentage change in triglycerides, as well as a number of secondary endpoints, in particular, the incidence of acute pancreatitis.

So these are the characteristics of the patients who entered the trial, and I'd like to summarize those by pointing out the fact that they were generally middle-aged. There was a equal proportion of men and women. BMI was within an acceptable range. Plasma triglycerides were sky-high, in excess of 20 mmol/L or in excess of 2,000 mg/dL; 70% were receiving treatment for hypertriglyceridemia conventional treatment, 40% of them had diabetes, roughly 60% of them had genetically confirmed FCS, and importantly, almost 90% of them had previous episodes of recurrent pancreatitis.

So from here now, I'd like to present the results, and this is the main result, the primary endpoint on the left. This is the triglyceride median percentage change from baseline. And you can see quite clearly that there was roughly an 80% reduction in the median triglycerides at 10 months and at 10 to 12 months with both doses of the plozasiran. No surprises, but ApoC3 fell by more than 90%, really, and that was the effective mechanism that achieved those reductions in triglycerides, as described earlier.

This is another important slide. And this is a time-dependent analysis, showing that the amount reduction in triglyceride at 80% occurs within the first month after dosing, and it's sustained throughout the study.

The other way to look at the data important for clinical practice is the proportion of people who achieve the treatment goals for triglycerides to prevent pancreatitis. And on the left-hand side, you can see the median reduction in the plasma triglycerides with plozasiran 25 and 50 mg. It may be easier to interpret this using a waterfall plot here, and these are individual data points, and the first

thing that you can see is that 80% the active treatment groups achieved a 50% reduction in triglyceride, which is, as it were, a recommended treatment target. And more importantly, that to prevent pancreatitis, your triglycerides have to fall below 10 mmol/L, and you can see 880 mg/dL at 75% of the 25-mg dose achieved this. And also, at a lower level of triglyceride, with less than 5.5 or 500 mg/dL, at 50% of the 25-mg dose achieved this.

So it's no surprise actually that there was a significant reduction in the incidence of acute pancreatitis with the plozasiran. This is a survival analysis, or Kaplan-Meier plot analyzing the time to first pancreatic events. And the analysis was statistically significant for adjudicated definite episodes of acute pancreatitis with an 83% relative risk reduction *P* value less than 0.05. And this was a prespecified secondary endpoint

This table summarizes the adverse events, and in the box is a summary of that data. A greater proportion of placebo-treated patients experienced serious adverse events. This is not surprising because they had recurrent abdominal pain and acute pancreatitis. Hence there were fewer premature discontinuation rates with plozasiran. There were no reductions in platelet counts, and hyperglycemia with plozasiran was confined to patients with prediabetes and diabetes, and they were readily corrected by adjustment in anti-glycemic therapy. There were no deaths in the study.

So the conclusion. The PALISADE trial met all trial endpoints that were alpha controls, so all the endpoints were significant. Plozasiran quarterly dosed, every 3 months, significantly reduced triglyceride in patients with persistent chylomicronemia at 10 months. Over half the patients achieved the triglyceride treatment goals. That's important.

And hence, the reductions in triglycerides and ApoC3 were apparent at 1 month and were sustained thereafter, with comfortable efficacy in genetically defined and clinically defined patients. Plozasiran significantly reduced acute pancreatitis at 12 months. It had a favorable safety and tolerability profile similar to placebo and, hence, plozasiran is a novel therapeutic candidate for reducing plasm triglycerides and, hence, chylomicron particle and associated risk of acute pancreatitis and recurrent abdominal pain and potentially improvement in quality of life in patients with persistent chylomicronemia.

Thank you.