Title: OCEAN(a)DOSE Extension: Olpasiran in Patients with Atherosclerotic CVD and Elevated LP(a)
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Dr Michelle O'Donoghue

"Hi, I'm Michelle O'Donoghue. I'm a cardiologist at Brigham Women's Hospital and a senior investigator with the TIMI Study Group.

The Role of LP(a) and Available Treatments for Addressing LP(a) Concentrations

So we have a growing body of evidence that LP(a), or Lipoprotein little A, plays a causal role in the development of many different atherosclerotic disease states. But to date, we've actually not had an effective therapy for lowering it. In fact, a lot of the traditional therapies we reach for risk factor mitigation, such as statin therapy, may, if anything, raise LP(a). PCSK9 inhibitors can lower LP(a) but perhaps not sufficiently for it to have a meaningful clinical impact.

Questions This Extension Study Aimed To Address

Well, in this phase two study, we evaluated different doses of olpasiran, which is an RNA interference medication that reduces LP(a) concentration. In the primary results that we previously presented, back in November 2022, we saw that the higher doses of olpasiran reduced LP(a) by more than 95%. These are now the extension phase results. So from that same study, we then had an off-treatment period. And what we found was that those patients who had been treated with the higher doses of olpasiran up to about a year after their last dose, they still had, on average, about a 40% to 50% placebo-adjusted reduction in LP(a) concentration. So really a prolonged duration of effect.

Study Design and Eligibility Criteria

So the Ocean(a) Dose study enrolled patients who had an LP(a) concentration of at least 115 animals per litre and who had established atherosclerotic disease. Everyone

was eligible to participate in the extension period because this was actually part of the primary protocol. During that prolonged period, we also collected safety events and importantly, we didn't see any new evidence of a safety signal during that more prolonged duration of follow-up.

Key Findings

So what we found was that those patients who had been treated with the higher doses of olpasiran, they had still maintained a 40% to 50% placebo adjusted percent reduction in LP(a) more than a year or up to a year after that last dose was administered. So suggesting that it has a very prolonged duration of effect. The other thing that we looked at during the on-treatment period was the effect of olpasiran on oxidized phospholipids, on ApoB. These are believed to be important proinflammatory mediators that may be part of the causal pathway for LP(a) in atherosclerotic disease. And what we found was that olpasiran also markedly reduced oxidized phospholipid concentration during the on-treatment period.

Take-Home Messages

So I think that the key areas to emphasize after the results of this study is that we now have very exciting, novel therapeutics in development that have a very pronounced effect on lowering LP(a). And in the case of olpasiran, these effects are really quite sustained through longer-term follow after administration is stopped. So this is, I think, very encouraging for a lot of people out there who have high LP(a) values and yet have not been able to turn to any therapies to date to effectively lower it. So we now have the phase three study ongoing, and that will give us the definitive answer about the efficacy and safety of olpasiran."