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Exploring the role of a novel CETP inhibitor in lipid management

Dr. Mehrna:
Hello. My name is Roxana Mehran from Mount Sinai Hospital in New York. Today we're going to discuss exploring the role of novel CETP inhibitors in lipid management. These are my important disclosures.

Despite treatment with high-intensity statins, which should be something we do for all of our patients, two-thirds of patients don't reach the goals that we would like them to get to. There's a really important need for new therapies to produce that effective reduction that we are looking for for LDL cholesterols, especially in combination with high-intensity statin. Early studies of CETP inhibitors, especially obicetrapib, demonstrated reductions of LDL cholesterol by 45%. I'm going to take you through some of these studies.

Before that, I want to tell you that CETP inhibitors decrease hepatic cholesterol resulting in upregulation of that LDL receptor, which then improves LDL and ApoB clearance through the liver. It's the same mechanism of action as existing LDL cholesterol drugs. There's some synergy here that we've now observed and know about, especially with CETP inhibitors, on top of high-intensity statins. It's also important to note that a CETP score with risk of major adverse events is very, very important dependent on the ApoB-containing lipoproteins. You can see that this Mendelian randomization analysis that the impact of inhibiting CETP on the risk of cardiovascular events is very much dependent on alterations of the ApoB-containing lipoproteins rather than HDL because we do see an elevation of HDL. These are really very much consistent What data do we have available on obicetrapib?

This ROSE study is a placebo-controlled, double-blind, randomized trial, phase 2, it's a dose-finding study to evaluate the effect of nobicetrapib 5 and 10 milligrams, two doses, as an adjunct, not instead of, but as an adjunct to high-intensity statin therapy. You can see the randomization in the study design it was to evaluate these two doses on top of high-intensity statins and looking at LDL cholesterol levels. Patients who are included are those stable patients who are also on stable dosing of high-intensity statins, and the fasting LDL cholesterol of greater than 1.8 millimoles per liter. Patients were randomized to placebo versus obicetrapib at 5 or 10 milligrams and followed for the PK assessments over the next ensuing follow-up periods. What was found that there was a magnificent and significant change of LDL cholesterol from baseline by different measurement approaches. Whether it was the preparative ultracentrifugation, or by the Friedewald approaches there was a consistent benefit in reducing LDL cholesterol 42% and 51%. ApoB as well as non-HDL percent change was also significantly reduced and there is a dose-response that you can see here between 5 and 10 milligrams as well. Conversely, ApoA1 and HDL percent change raised from baseline. Lp(a) interestingly, was also reduced by significant numbers as was triglycerides. ROSE was a successful study of a phase 2 trial evaluating the efficacy and the safety of 5 and 10 milligram of obicetrapib on top of high-intensity statins, which were very well tolerated. It reduced median LDL cholesterolby 42% to 51% from baseline, and of course, it was very, very importantly evaluated to be a valuable addition for these high-risk ASCVD patients who do not achieve the target we would like them to get to despite the use of high-intensity statins.

ROSE2 actually is the follow-up study led by Christie Ballentyne, and this was a combination of obicetrapib and ezetimibemto evaluate the lowering, and whether or not there was another synergy in terms of really going not only just to high-intensity statins but the addition of ezetimibe. The primary evaluation was to evaluate this and most importantly the tolerability and then pulling these data to look at some of the safety events. ROSE2 enrolled 119 patients randomized to obicetrapib 10 milligrams or the 10 milligrams dose plus ezetimibe or placebo. Everyone was on high-intensity statins, high-dose statins. Of course, they had stable dosing of those high-intensity statins eight weeks before randomization and screening. The primary efficacy endpoint was the percent change from the baseline in

LDL cholesterol compared to placebo, but everything else was also measured. As expected, there was a significant reduction, but even more so with ezetimibe on top of the 10 milligrams obicetrapib. You could see that very, very nicely shown here. Furthermore, the non-HDL cholesterol was also changed from baseline all the way to almost 56% with obicetrapib 10 milligrams and 10 milligrams of ezetimibe.

How did we do to the targets? 87% of those patients included reached the targets that we were looking for of less than 55 milligrams per deciliter when obicetrapib and ezetimibe was added to high-intensity statins. I think that is a very, very important message here of seeing how well we're reaching the target of less than 55 milligrams per deciliter. If you look at the total LDL particles, you see that significant reduction, the small LDL particles, and of course you see the percent change from baseline of the LDL particle size is significant. Importantly, Lp(a) was also changed from baseline almost by 40% to 47%. In fact, a very, very important conclusion was that the median LDL cholesterols were significantly reduced by 43% and 63% respectively on top of high-intensity statins when you added obicetrapib 10 milligrams, or in combination of obicetrapib 10 milligrams and ezetimibe. The combination of obicetrapib and ezetimibe was observed to reduce total cholesterol particles and small LDL particles by large numbers, 72% and 95%. 87% of the patients who are on this combination therapy on top of high-intensity statins achieved the goal that we would like them to achieve to get below 55 milligrams per deciliter. This combination was also extremely well tolerated, and the data support to continue to develop a fixed-dose combination of obicetrapib plus ezetimibe.

What clinical programs do we have now since we have these two fantastic phase two studies that really set the stage for a large outcomes program? Well, let's take a look at the projected clinical programs over the next multiple years, and you can see that there is the monotherapy and then of course, where there is a combination therapy with ezetimibe that has been well-planned, and I'll go through these one by one for you.

The BROOKLYN study is one that will evaluate in 300 patients the effects of obicetrapib in patients with heterozygous familial hypocholesterolemia. The protocol is based on all of the feedback we have from the FDA, and you can see these are familial hypercholesterolemic patients who have been diagnosed and confirmed by genetic testing and fit the WHO criteria, 70% of them are on high-intensity statin. Then of course, 10% are intolerant to statin. We also have been able to bring in very important therapies to get them to where we need to go. Of course, we're excluding those with cardiovascular disease less than three months, and of course, uncontrolled hypertension with a primary efficacy endpoint to look at the LDL cholesterol lowering.

The next one is the BROADWAY, which is obicetrapib. Here we have 2,400 patients to evaluate this with the familial hypercholesterolemic patients and or ASCVD patients. These patients are going to be randomized, 1600 at a two-to-one randomization to obicetrapib 10 milligrams versus placebo, and of course, the safety will be very, very important to look at this in the larger patient populations.

Last but not least, the large program of PREVAIL, where obicetrapib cardiovascular outcome trial that has now been designed to show the reduction of cardiovascular morbidity mortality in patients with established cardiovascular disease. These are 9,000 patients with established disease who will have their visit and then of course get into the study and randomized in a double-blind placebo-controlled fashion on top of high-intensity statins to obicetrapib 10 milligrams versus placebo. Then followed at 1, 3, 6, and 12 months and the following years, every six months, very important. 4-point MACE endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, and non-elective, or urgent coronary revascularization. Then with important secondary endpoints of LDL cholesterol and new-onset diabetes. We're very excited to show that these are patients who are on maximally tolerated lipid-lowering therapy, including high-intensity statins who are unable to get into their guideline goals. These are truly the unmet need and we look forward to these data.

In conclusion, ladies and gentlemen, CETP inhibitors really are giving us a positive feedback loop of beneficial effects of cholesterol balance and block of CETP transport from HDL cholesterol to LDL cholesterol, significantly increasing HDL and reducing LDL. CETP inhibitors decreases the hepatic cholesterol resulting in that upregulation of the LDL receptor levels and improving LDL and ApoB clearance through the liver. We showed this with the phase 2 trial, both at 5 and 10 milligrams of obicetrapib as an adjunct to a high-intensity statin therapy to be well tolerated, lowering cholesterol, and it could absolutely be a valuable addition to high-intensity statin therapies. In combination of obicetrapib at 10 milligrams with ezetimibe was shown in ROSE2 to be very well tolerated. It reduced the median LDL significantly and achieved goals on most patients in that phase 2 trial. Of course, now, we're set the stage for large-scale clinical program that have now been planned that will evaluate the safety and efficacy of obicetrapib in addition to high-intensity statins in patients who are at risk for cardiovascular events. I want to thank you for your attention.