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Novel oral LDL-c lowering therapies on the horizon: CETP inhibition

Dr. Laufs:
Hello. My name is Ulrich Laufs from Leipzig University in Germany, and we are going to discuss today new oral LDL cholesterol-lowering therapies on the horizon, with a specific focus on CETP inhibitors.

These are my conflicts of interest.

And I would like to introduce 3 new LDL-lowering drugs that are currently in advanced phases of clinical development. Two are oral – one PCSK9 inhibitor, MK-0616, and the CETP inhibitor of obicetrapib – and one subcutaneous novel PCSK9 inhibitor, which is called lerodalcibep.

I would like to introduce 3 new LDL-lowering drugs, 2 orals, 1 subcutaneous: 2 PCSK9 inhibitors and 1 novel CETP inhibitor. Now MK-0616, is a macrocyclic oral PCSK9 inhibitor that prevents the binding of PCSK9 to the LDL receptor, leading to approximately 50% to 60% LDL reduction in the phase 2 studies and is now going into a large phase 3 study program called CORAL. The difference to the existing PCSK9 inhibitors is the oral application of this component.

A second PCSK9 inhibitor in clinical development is the lerodalcibep. This is an adnectin. It works basically like an antibody, and this is coupled to human albumin, which results in 2 important features. One is it can reduce the volume of injection to 1.2 mL and has a longer half-life; 4 weeks is the application period. So it's 1.2 mL subcutaneous injection every 4 weeks. And similar to other PCSK9 inhibitors, the phase 2 and 3 studies show approximately 50% to 60% LDL reduction.

Now, the third novel component that I would like to spend a little more time on is the CETP inhibitor, obicetrapib. It's an oral drug, and just one slide to remind on the pathophysiology of CETP, which is basically forming a tunnel between HDL and LDL particles. Now, our lipoproteins are not stable; they are currently changing their composition and their cholesterol content. And CETP basically transfers cholesteryl esters from HDL to LDL. So CETP inhibition results in reduction of hepatic cholesterol levels, and this leads, via the mechanisms that you are familiar with, to an upregulation of the LDL receptor, similar to the effect in the end of drugs, such as PCSK9 inhibitors, statins, or ezetimibe, that all lead to an upregulation of the LDL receptor, but then increases clearance of LDL particles from the blood and results in the reduction of plasma cholesterol levels.

Now, we have good genetic data for CETP. Individuals that carry variants associated with reduced CETP activity have reduced risk of cardiovascular disease. Now, this made CETP an attractive target for pharmaceutical strategies. However, there is a very complex history of trials that address CETP inhibition. I tried to provide an ultra-short summary on one slide. There was one study testing a component torcetrapib, the ILLUMINATE study, that was negative due to off-target effects, especially related to aldosterone-mediated increased blood pressure. The dalcetrapib, which was tested in the Dal-OUTCOME study, the study was neutral because this component, most likely the explanation is that dalcetrapib increased HDL but had no effect on LDL, so there was no LDL lowering. The 2 other studies with evacetrapib and anacetrapib showed nonsignificant trends, so there was a trend towards reduction of major cardiac events that did not meet the line of statistical significance. The ACCELERATE study was underpowered and too short, and in the REVEAL study, the LDL lowering was not very large; it was only approximately 11 mg/dL.

Now, the fifth component in this class, obicetrapib, differs substantially from the others here, compared to anacetrapib and evacetrapib, because the drug is less lipophilic and therefore more potent with regard to LDL lowering. You can see on the bottom of this slide, a 45% reduction in this comparative table, much more significant LDL reduction compared to the other 4 components, also increase of HDL as expected from the class.

Now in the phase 2 study program, you can see here the dose escalation effect with a 45% LDL reduction of this oral drug in the 5- and 10-mg dose. The ROSE study tested obicetrapib on top of high-intensity statin. The following slides are going to show you the 5-mg and the 10-mg dose on top of statin, leading to a 38 to 44 reduction of LDL cholesterol, irrespective of the method of measuring, accompanied by ApoB reduction, reduction of non-HDL cholesterol, and an increase of HDL cholesterol between 122% and 157%. So significant increase of HDL in the ROSE study.

Now, a special feature that is repeated and confirmed throughout the available study program is a quite remarkable reduction of lipoprotein(a), around 40% to 50% with the obicetrapib 10-mg dose. So this is a much more potent lipoprotein(a) reduction compared to any other oral drug that we have seen in the past.

Upregulation of the LDL receptor as a mechanism obviously suggests that there could be a synergy with inhibition of entero cholesterol absorption by ezetimibe. So this analysis shows you obicetrapib in combination with ezetimibe on top of high intensity-statins, leading to an additional – this is the green bar compared to the blue bar – up to 60% LDL reduction, combination of obicetrapib with ezetimibe on top of statin.

Now, safety is key for any new development in lipid-lowering therapies. Therefore, special focus needs to be, as always, on adverse events. And there was no disbalance on any of these categories in the ROSE study. And similarly, there was no disbalance with regard to any treatment-emergent adverse events in the ROSE 2 study. And because torcetrapib, one of these early studies, increased blood pressure, this is a special focus within this class, and therefore, blood pressure is a specific point to look at across the study program. And I'm showing you here the pooled analysis of the studies that are listed on the top of this slide, and there was no signal with regard to systolic or diastolic pressure with the different doses.

The phase 3 BROOKLYN study with obicetrapib in patients with heterozygous FH has released a press release. Important feature about this study is that obicetrapib is tested in well-treated patients with all different combinations of the existing lipid-lowering therapies, including PCSK9 inhibitors. And the top-line results show, after 1 year, a 40% reduction in this phase 2/3 study on top of an extensive lipid-lowering therapy. And importantly, again, there was no disbalance with regard to adverse events, and there was no disbalance with regard to patients stopping their medication.

The cardiovascular outcome study is called PREVAIL. It's fully recruited and expected to report in 2026. This year, you are likely to see the results of the phase 3 BROADWAY study and the phase 3 TANDEM study that is testing a fixed-dose combination of obicetrapib with ezetimibe.

Thank you very much for your attention.