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https://reachmd.com/programs/cme/efficacy-and-safety-of-the-oral-pcsk9-inhibitor-mk-0616-a-macrocyclic-peptide-in-the-treatment-of-hypercholesterolemia-a-phase-2b-randomized-placebo-controlled-clinical-trial/15285/

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Efficacy and Safety of the Oral PCSK9 Inhibitor, MK-0616, a Macrocyclic Peptide

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Dr. Ballantyne:
Hi. I'm Christie Ballantine. I'm the Chief of the Section of Cardiovascular Research at Baylor College of Medicine, Houston, Texas. And I'm delighted to present the efficacy and safety of the oral PCSK9 inhibitor, MK-0616, a macrocyclic peptide in the treatment of hypercholesterolemia, a phase 2b randomized, placebo-controlled clinical trial. These are my disclosures.

Well, I think everyone's familiar that LDL is a primary causative factor in atherosclerotic cardiovascular disease. And despite effective treatments, we have a large proportion of patients who fail to achieve guideline and recommended levels of LDL cholesterol. Injectable treatments that target PCSK9 have demonstrated large reductions in LDL cholesterol, decreased ASCVD events, but access barriers and need for repeat injections have led to poor adoption. So an oral PCSK9 inhibitor may widen access and improve attainment of guideline recommended treatment goals.

So this is some background on this molecule, MK-0616. And this has been an interesting area. About 10 years ago, I was told it would be impossible to develop a small molecule because of the difficult nature to try to inhibit the interaction between PCSK9 and the LDL receptor. Now, this is kind of a marriage of biotechnology with medicinal chemistry. The biotechnology part is the macrocyclic peptidyl library, where you can display on messenger RNA, you can screen up to 10 of the 14 potential compounds. This was used to identify a molecule that inhibited the interactions. And then the next step was the aspect of improving that molecule.

So this is structure-based medicinal chemistry, in making changes in the structure to improve the structure activity relationship to PK and the stability. And that's a picture of the predecessor molecule that was further refined. The phase 1 data was presented at the AHA. And now this is the phase 2b dose-ranging study. Four dosages, 6, 12, 18, and 30 milligrams compared to the placebo. So 4 out of 5 chance that one got an active therapy, 3 week screening period, 8 weeks of treatment, 8 weeks of follow-up.

The goal was to have a fairly broad range. And although this was a fairly small study of 381 patients. What you can see is, it was quite diverse, 49% women. And if we take a look at race, 65% white, 16.5% Asian, there was 40% Hispano population. There was a range of ASCVD risk. So clinical ASCVD was about 39%, intermediate to high risk was the lower half, and 5% were borderline with – and each one of those had - to get to borderline, you had a higher LDL level. So it was a range of LDLs in this study. And also, there was a range of people who were on high-intensity statin therapy, moderate, or no statin therapy. The mean LDL was about 119 in the study.

Well, let's go straight to the primary endpoint. The reduction in LDL cholesterol. And even at the lowest dose of 6 milligrams, there was a

41.2% reduction compared to placebo. You can see by the second dose of 12 milligrams, that's over 50%. And at the highest dose, there was a 60.9% reduction in LDL. So you see nearly completed efficacy by 2 weeks. There was a persistent effect over the 8 weeks. And looking at the different populations in this study, we looked at prespecified subgroups, there was generally consistent results across all the subgroups.

Now in addition to LDL cholesterol, we're also very concerned about ApoB and non-HDL cholesterol. These are also important measures of atherogenic particles for ApoB or atherogenic cholesterol for non-HDL cholesterol. And also robust reductions at the lowest dose 32.8%, at the highest dose a 51.8% reduction in ApoB. Non-HDL cholesterol reduced 35.9% at the low dose of 6 milligrams, 55.8% at that 30-milligram dose. And as you might have expected, is that if you're seeing these kinds of reductions in terms of achieving, you know, the protocol-defined goals of treatment, it was very successful at the two highest dosages, about 91%.

So one of the things, this was a only an 8-week study, so you look at some of this tolerability and safety information, what you can see is in terms of discontinuations due to an adverse event, this was low. And we didn't see any dose-dependent discontinuations. If you looked at the different symptoms of AEs by organ category, there was nothing that was seen as a dose dependent over the different - from 6 to the 30 milligrams.

Well, let's summarize. So this is phase 2b randomized control trial in a diverse population of hypercholesterolemic patients. All the doses showed superior reductions compared to placebo, with up to 60.9% reduction in LDL cholesterol. There was improvement in ApoB and non-HDL in all of the groups with up to 51.8% reduction in ApoB, and a 55.8% reduction in non-HDL cholesterol. It was well tolerated. There were no overall trends in AEs across the treatment groups.

So these data were important in terms of the clinical trial process, you go phase 1, phase 2. So now there is the information which is available in terms of designing a phase 3 study, and their hopes are that this oral PCSK9 inhibitor may improve access to effective LDL cholesterol-lowering therapies and improve attainment of guideline-recommended LDL goals aimed at reducing cardiovascular risk. This was published online in *JCC*, at the same time as the presentation.

Thank you very much.

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