**Title: ACC 23: Efficacy and Safety of MK-0616 In Hypercholesterolemia Patients**

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**Dr Christie Ballantyne**

What is the importance of this trial?

"-Why would we want an oral PCSK9 inhibitor? So as you know, the drugs have been highly effective. Lowering LDL cholesterol, reducing events. We haven't seen very good uptake. And some of this may be due to access, some may be due to injections, but the hope would be is to develop... We see that most people are taking for asymptomatic conditions pills. And if you have another medication, which is equally effective but easier to access, the hope is that this could help more people get their LDL to target.

What are the key findings?

Yeah, so this is a phase II study, dose finding. And there were five groups. There were four different dosages, 6, 12, 18, 30 milligrammes and a placebo group. And it turns out that even at their first dose of six milligrammes, 41% reduction, once you got to 12 milligrammes, you were really in that 50s and at the top dose of 30 milligrammes, it was a 61% reduction. So that is very consistent with what you get with an injectable monoclonal antibody hitting that 60% target. This was a short-term study basically looking at tolerability in terms of discontinuations. They were low. There was no evidence of any dose-dependent discontinuations of the therapy. Side effect profile looked very good. It was a short-term study, but basically, this is the kind of information that looks to be very helpful for moving to the next part of a phase three programme. What's really interesting to me as an investigator is that I was told a decade ago, it would be impossible to make a small molecule to inhibit PCSK9. It's a very difficult target and this is kind of the marriage of biotechnology screening macrocyclic peptides, library of 10 to the 14th, hooked to a messenger RNA. They find a molecule that work well and then it has remarkable medicinal chemistry to improve that. So it's really a tour de force I think of kind of a marriage of biotechnology with medicinal chemistry to come up with what it's thought to be an undruggable oral pill.

What are the clinical implications of these findings?

I found it very interesting 'cause we have in another area, there's GLP-1 agonism. The oral formulation is not as effective as the injections with it. It has efficacy. But it was just, to me, this improvement in terms of the technology to be able to screen macrocyclic peptides and be able to get, if you get them potent enough, even though you don't need that much to be absorbed because they're so potent. So I find it fascinating. We've seen the application. You find a new target, fully human monoclonals, siRNAs, now macrocyclic peptides. So it's really exciting to see what's happening in the field of drug development. So one important aspect of the study was it was looking at a broad range of patients. So about 49% were women. And it turns out, if you look at the group, you had 65% white, 40% Hispanic, 16% Asian and it was a mixture of people with cardiovascular disease, 38% high risk, a little over half and some who are lower risk with high LDLs. So the thought was, let's get a look at this at how it works in a broad group of people, some on statins, some not on statins in terms of its efficacy.

What are the next steps?

Based upon these very promising results, a phase three programme is being designed.”