**Title: ACC 23: The STELLAR Phase III Trial: Sotatercept in Patients With Pulmonary Arterial Hypertension**

**Participants: Dr Marius Hoeper**

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**Dr Marius Hoeper**

"- Hi, my name is Marius Hoeper. I'm a respiratory physician from Hannover Medical School in Hannover, Germany. I've been taking care of patients with pulmonary hypertension for more than 30 years now, and I'm very excited to have a chance now to present for the first time the data from the STELLAR Study with sotatercept.

What is the background of this study?

The background of this STELLAR study is quite complicated, but what we've learned over the past couple of years is that pulmonary arterial hypertension is a disease caused by remodelling of the small pulmonary arteries. And this remodelling is due to a disbalance between anti-proliferative and pro-proliferative signalling pathways. And among the proliferative signalling pathways activin signalling plays an important role. Sotatercept is the first in class activin signalling inhibitor. It's a fusion protein composed by the FC domain of human immunoglobulin G, which is bound to the extracellular domain of human Activin Receptor IIA receptor. It acts as a ligandtrap for activins and other ligands of the transforming growth factor beta super family, and is believed to restore the balance between the antiproliferative and pro-proliferative signalling. And the concept behind this is that it probably does not only delay disease progression, but by really bringing cells that occlude the lumen of the pulmonary vessels, endothelial cells, muscle cells into apoptosis. It seems to have the possibility of reopening these vessels, at least to some extent, so to achieve reverse remodelling.

What was the patient-population and study design?

So STELLAR was a double-blind, randomised, placebo-controlled study that enrolled patients with pulmonary arterial hypertension who were in functional class two or three, despite receiving background therapy with approved PAH medications. So the patients were randomised one-to-one to receive either placebo or sotatercept administered subcutaneously every three weeks. The primary endpoint of the STELLAR study was change from baseline at week 24 and six minute walk distance. In addition to that, the study had nine secondary endpoints tested hierarchically also at week 24, except from the time to death or clinical worsening, which was assessed at the cutoff date, which was when the last patient completed the week 24 visit.

What are the key findings?

The key findings of this study were, first of all, that the primary endpoint was met, so the change in six minute walk distance, the difference here between placebo and sotatercept was about 40 metres. And of course, this was highly statistically significant. In addition to that, the study met eight of out of the nine pre-specified secondary endpoints, including multi-component improvement, which was a composite endpoint of predefined improvements in functional class, 6-min walk distance, NT-proBNP. In addition to that, there were improvements in hemodynamics especially the pulmonary vascular resistance, but also the mean PA pressure in BNP in risk scores, and importantly in the PAH-SYMPACT tool, which is a disease specific quality of life score. We have seen adverse events and side effects in the study, as in all studies. And the overall number of adverse events was the same in in both groups. Adverse events related to treatment were more common with sotatercept, whereas serious or severe adverse events, or adverse events leading to drug discontinuation were more common in the placebo group. What we saw as adverse events related to sotatercept were mostly bleeding episodes, especially minor or mild epistaxis and gum bleeds. We also saw telangiectasia, which are small vasodilations on the skin, which we saw in about 14% of the patients at the cut-off date. In addition to that, there were slight increases in haemoglobin, which were expected, mild thrombocytopenia, some dizziness and some hypertension.

What is the implication of these findings on both clinical practice and future research?

I think the study and the findings are going to have substantial clinical implications on how we treat patient with pulmonary hypertension in the future. I think that the currently available treatments are not going to go away, and I believe that especially combination of oral drugs and the receptor antagonist and PDE5 inhibitors will continue to be the backbone of PAH treatment. But after that, I assume that most physicians will start sotatercept early on in the course of the disease to just achieve what we have seen in the STELLAR study, and also believe that patients will ask for that.

What further study is needed?

The findings of STELLAR open the door to further research, which is really necessary. I mean, it's of course other compounds that will be explored, but also here with sotatercept, I think, the long-term efficacy is quite important. We have two ongoing phase three studies. One is called Thinness, which enrols patients who have very advanced disease. The other is called HYPERION, which enrols patients who have newly diagnosed disease. Now, especially this one is to me of utmost importance because the results that we saw in STELLAR were achieved in patients in whom the interval between the time of initial PAH diagnosis and enrollment in study had been about nine years. So, I mean, it's at least possible that if we give this compound very early during the course of the disease, that you may even achieve more than what we've seen in STELLAR. And to me, this is one of the key questions for the years to come.”