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Sotatercept: A Novel Entity with Promising Potential for Treating PAH

Announcer:
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Dr. Preston:
Hello, I'm Dr. Ioana Preston, the Director of the Pulmonary Hypertension Center at Tufts Medical Center in Boston. Welcome today, and thank you for joining me to discuss sotatercept, a novel entity for combination therapy in PAH.

Sotatercept is activin signaling inhibitor and it is proposed to act as a reverse remodeling agent through rebalancing the anti-proliferative and pro-proliferative signaling pathways depicted in this cartoon between activin and BMP.

As a background, we know that PAH patients have mutations in the bone morphogenetic protein receptor 2, or BMPR2, to which is a member of the TGF-beta superfamily. And these mutations are a major cause of heritable PAH. They are seen in a large proportion of patients with idiopathic PAH. And those patients who do not have a mutation, may have a defective BMP pathway functioning. So sotatercept is a novel first-in-class fusion protein of human activin receptor type IIa, which is fused to the Fc domain of human IgG1.

Sotatercept was studied in a phase 2 clinical trial called PULSAR, that enrolled patients with PAH. And the main results showed that there was a reduction in pulmonary vascular resistance in the sotatercept arms that was driven by the reduction in mean PA pressure, with no significant effects on the cardiac output or the wedge. Similar findings were obtained when stratified by number of agents of background therapy and by the presence of prostacyclin infusion in the background therapy. The graph shows the magnitude of improvement in pulmonary vascular resistance.

So the key points from PULSAR finding are that there were no changes in cardiac output or TAPSE, which suggests the direct effect on pulmonary circulation leading to treatment effect. Sotatercept reduced PVR, improved 6-minute walk distance, and reduced NT-proBNP even in patients on background triple therapy. Adverse events were largely manageable, and they included thrombocytopenia and increased hemoglobin. No bleeding events recorded in the trial. Continued sotatercept treatment for PAH suggests clinical efficacy is maintained up to 48 weeks. The placebo assignment did not affect the ability to respond after 24 weeks.

As a consequence, sotatercept has been further evaluated in several phase 3 programs. Today we will talk about STELLAR. STELLAR is a phase 3 randomized, double-blind, placebo-controlled, multicenter, parallel-group study that evaluated sotatercept on top of background therapy in adults with PAH in functional class II or III. The efficacy and safety data through treatment week 24, which was the endpoint, and the cumulative safety and time to death or clinical worsening, were reported as of August 26, 2022.

This slide summarizes the study design. The patients who were included in the study were functional class II or III, they are part of Group 1 PAH, and they were randomized 1:1 to either placebo or sotatercept 0.3 mg/kg starting dose that was increased to 0.7 mg/kg dose every 3 weeks in an injection. The primary endpoint was 6-minute walk distance at 24 weeks. And there were several secondary endpoints that were tested hierarchically, and they are listed in the box on the right-hand side.

So let's look at patient characteristics. Patients enrolled in this trial had an average time from diagnosis of over 8 years. So these are

long-standing patients with PAH. A large proportion had heritable PAH as the etiology of their disease, which is slightly larger proportion compared to other clinical trials in PAH. And also they were on multiple background therapy. The large majority were already on triple therapy, and 40% of patients were on infusion prostacyclins.

The primary endpoint the change from baseline in 6-minute walk distance at week 24, improved by an average of 40 meters compared to placebo. And this was calculated by several statistical analyses to ensure the accuracy of data. The improvement was based on the improvement in the treatment arm and not by a decrease or worsening in the placebo arm.

Also, importantly, the secondary endpoints that are listed here show a statistically significant improvement in 8 out of 9 secondary endpoints. And these are clinically important multicomponent improvement, pulmonary vascular resistance, NT-proBNP, and so on. So, all but one were improved in the treatment arm, including two of the three categories of quality of life questionnaires. The between-group reduction from baseline in least-squares mean pulmonary artery pressure, which was an exploratory endpoint at week 24, was also 13.9 mmHg, an important decrease in the – a direct decrease in mean PA pressure.

And also importantly, time to first occurrence of death or non-fatal clinical worsening events were favorable for the sotatercept arm. After a median follow-up of over 32 weeks across the treatment groups, the hazard ratio in the sotatercept arm was 0.6, so it was a decrease by 84% in the first occurrence of death or non-fatal clinical worsening event.

Talking about safety data, there were certain adverse events of interest and included bleeding events, telangiectasia, increased hemoglobin, decrease in thrombocytes, and increase in blood pressure. And those with an incidence of at least 10% included epistaxis, telangiectasia, and dizziness.

In summary, STELLAR is the first phase 3 trial of sotatercept, an activin signaling inhibitor in adults with PAH and functional class II and III. Sotatercept improved 6-minute walk distance at an average of over 40 meters, and delivered broad clinical benefit across multiple domains, including hemodynamics, functional class, disease biomarkers, risk scores, and patient-reported outcomes. Sotatercept reduced the risk of death and non-fatal clinical worsening events by 84% versus placebo. Sotatercept was generally well tolerated. Adverse events more frequent with sotatercept versus placebo included minor bleeding events, telangiectasia, dizziness, increased hemoglobin levels, thrombocytopenia, and increased blood pressure. These results established the clinical utility of sotatercept administered in combination with approved PAH therapies as a potentially new treatment for PAH. Thank you for joining me.

Announcer:
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