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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The STELLAR Phase 3 Trial: A Study of Sotatercept in Combination with Background Therapy fo the Treatment of Pulmonary Arterial Hypertension

Announcer:
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Dr. Hoeper:
Hello, my name is Marius Hoeper. I'm a respiratory physician here at Hanover Medical School in Hannover, Germany. I've been taking care of patients with pulmonary hypertension for the past 30 years. And I had the honor and the pleasure to be the Global Principal Investigator of the phase 3 STELLAR study with sotatercept for pulmonary arterial hypertension, the results of which I will summarize within the next couple of minutes.

As you know, these data were recently presented at the annual conference of the American College of Cardiology and were published simultaneously in *The New England Journal of Medicine*. The background is rather intriguing. What we've learned over the past couple of years is that pulmonary arterial hypertension is the disease not caused by pulmonary vasoconstriction, but by pulmonary vascular remodeling, which is at least in part due to an imbalance between anti-proliferative i.e., BMPR-II-mediated, and pro-proliferative, i.e., ActRIIA-mediated signaling pathways which lead to hyperproliferation of vessel wall cells, especially endothelial cells, vascular smooth muscle cells, that obliterate the lumen.

And sotatercept is the first member of new class of drugs called activin signaling inhibitors. It is a fusion protein. It is composed by the Fc domain of human immunoglobulin G, which is bound to the extracellular domain of ActRIIA receptors, which act as ligand trap on activins and other growth factors coming from the TGF-beta superfamily. And by binding those ligands, the drug is proposed to restore the balance between pro-proliferative and anti-proliferative signaling, and ideally, not only slow disease progression but cause at least some partial reverse remodeling of the pulmonary vascular modeling, as we've seen in animal models. And we had a positive phase 2 study already with sotatercept called the PULSAR study which showed improved pulmonary vascular resistance and 6-minute walk distance in patients with pulmonary arterial hypertension.

So STELLAR was a phase 3 randomized, double-blind, placebo-controlled multicenter study that enrolled patients with pulmonary arterial hypertension who were in functional class II or III with PVR more than 400 dynes, and a 6-minute walk distance between 150 and 500 meter, despite being on PAH background therapy. The patients were randomized 1:1 to receive, on top of the background therapy, either placebo or sotatercept, which was administered subcutaneously every 3 weeks at a target dose of 4.7 milligrams per kilogram.

The primary endpoint of the study was to change a 6-minute walk distance at week 24. In addition, the study had 9 secondary endpoints that were tested hierarchically, which were all assessed at week 24, except for time to death or clinical worsening, which was assessed

at the cutoff date, which was the date at which the last patient had completed the week 24 visit. And the study met its primary endpoint and most of the secondary endpoints. So the primary endpoint again being changed a 6-minute walk distance, we saw an improvement a 6-minute walk distance in patients on sotatercept of about 40 meter at week 24. This was not only highly statistically significant, this is of course also clinically relevant, and as the minimum important difference for this measure is about 30 meters.

In addition, we saw improvements in multicomponent improvement endpoint which was a composite of predefined improvements in functional class, 6-minute walk distance, NT-pro BNP. We saw improvements in the pulmonary vascular resistance by about 230 dyne, NT-proBNP improved substantially, as did WHO functional class. We had improvements in clinical worsening, and I will come to this in a second, in differential risk score, and in 2 out of 3 domains of the PAH-SYMPACT tool, which is a disease-specific quality-of-life score. In addition to that, we saw a decline in the mean pulmonary artery pressure by about 14 millimeters of mercury, which is something that we've never seen in PAH trials when drugs were added on top of existing medications. This all translated into a substantial impact on time to clinical worsening, which was a composite endpoint including all-cause deaths and prespecified clinical worsening events. And this was also at the end of the day in favor of sotatercept with a hazard ratio of 0.16 which is an 84% risk reduction.

Safety and tolerability is also an important issue of course in this study and is in most studies. The majority of patients had adverse events during the study. Adverse events related to study medications were more common in patients who received sotatercept; however, serious and severe adverse events, as well as adverse events leading to study drug discontinuations were more common in the placebo arm. The adverse events that we saw more frequently with sotatercept were bleeding events, which were mostly mild epistaxis and gum bleeds, and the development of telangiectasia, which occurred in 14% of the patients at the cutoff date. As expected, there was some increase in hemoglobin levels by a mean of 1.3 grams per deciliter, so mostly mild thrombocytopenia, none of that led to study discontinuation. In addition, there was some increased blood pressure and some dizziness, but in general, the medication was quite well tolerated by the majority of the patients.

So overall, STELLAR was the first phase 3 study of sotatercept, an activin signaling inhibitor in adults and patients who suffer from PAH, WHO functional class II or III despite receiving background therapy. In fact, most of the patients' background therapy was two or three approved medications. And in these patients, sotatercept improve the 6-minute walk distance by about 40 meter. And it delivered a broad clinical benefit across multiple domains, which included hemodynamics, PAH disease severity, which is functional class, biomarkers, risk score, and patient-reported outcomes.

In addition, we saw a substantial reduction in fatal or non-fatal clinical worsening events by 84%. And the drug was generally well tolerated with a unique adverse event profile, which included minor bleeding events, as I mentioned, mostly epistaxis and gum bleeds, telangiectasia, and some dizziness, increased hemoglobin levels, thrombocytopenia, and increased blood pressure.

And overall, we believe that these results establish the clinical utility of sotatercept, administered in combination with approved PAH medications as a new treatment for pulmonary arterial hypertension.

Thank you very much for listening.

Announcer:
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