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JOURNAL CLUB

**Article Summary by: Mohammad Dalabih, MBBS, MHA**

## ARTICLE

Sotatercept for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2021 Apr 1;384(13):1204-1215. doi: 10.1056/NEJMoa2024277.

## CLINICAL QUESTION

What is the effect of sotatercept on pulmonary vascular resistance (PVR) in patients with pulmonary arterial hypertension on background therapy?

## SUMMARY

**Background:** Bone morphologic protein receptor type 2 (BMPR2) is a member of the transforming growth factor β (TGF-β) family. Loss-of-function mutations in BMPR2 and/or decreased BMPR2 signaling are found in many patients with familial PAH, as well as in patients with idiopathic disease. Reduced activity of the BMPR2 pathway is associated with endothelial and smooth muscle cell dysfunction and cellular proliferation. Sotatercept is a fusion protein that binds to ligands in the TGF-β family and restores balance between growth-promoting and impaired BMPR-II growth-inhibiting pathways in pulmonary artery endothelial cells and smooth muscle cells.

**Methods:** PULSAR was a multicenter, randomized, double blind, phase 2 trial. The trial had a 24-week placebo-controlled treatment period that is reported in this article. An 18-month active-drug extension period is ongoing. The study was sponsored by Acceleron Pharma.

**Population:** Patients had group 1 PH (PAH), with a WHO functional class (FC) II or III. Patients with portopulmonary disease, schistosomiasis, and HIV were excluded. Patients had to be stable on background PAH therapy for 90 days prior to enrollment. Patients could be on single, double, or triple combination therapy with any of the currently available PAH-specific agents.

**Procedure:** Patients were stratified according to the baseline WHO FC and initially randomly assigned in a 3:3:4 ratio to placebo (saline), sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg, given as a subcutaneous injection every 21 days.

**End Points:** The primary end point was the change in pulmonary vascular resistance (PVR) from baseline to week 24. Secondary end points included change from baseline in 6-minute walk distance, NT-proBNP levels, TAPSE (a measure of right ventricle function), WHO FC, clinical worsening, and quality of life as measured by CAMPHOR and SF-36 questionnaires.

**Statistical Analysis:** Efficacy and safety analysis were performed in the intention-to-treat population. The analysis of the primary end point was done using the analysis of covariance method (ANCOVA).

**Results:** From June 2018 through July 2019, a total of 163 patients were screened, with 106 undergoing randomization. The placebo and the 0.3 mg/kg sotatercept arm included 32 patients each and the 0.7 mg/kg group included 42 patients. The three groups were similar in demographic and baseline clinical characteristics. 59 patients (56%) were on triple combination background therapy and 39 (37%) were receiving parenteral prostacyclin therapy.

**Primary end point:** At 24 weeks, the least-squares mean change from baseline in PVR was a reduction of 162.2 dyn.sec.cm$^{-5}$ (2 WU) in the sotatercept 0.3-mg group and 255.9 dyn.sec.cm$^{-5}$ (3.2 WU) in the 0.7-mg group. The placebo group had a 16.4 dyn.sec.cm$^{-5}$ decrease in PVR. The least-squares mean difference between the 0.3-mg sotatercept and placebo group was -145.8 dyn.sec.cm$^{-5}$ (-1.82 WU) (95% CI -241.0 to -50.6; p=0.003) and between the 0.7-mg and placebo groups it was -239.5 dyn.sec.cm$^{-5}$ (3.0 WU) (95% CI, -329.3 to -149.7; P<0.001). This effect was consistent across groups including those on combination therapy and parenteral prostacyclin. There was a significant reduction in the mean pulmonary artery pressure (mPAP) in the sotatercept groups with little change in the cardiac output and pulmonary artery wedge pressure.

**Secondary end points:** No p values were reported for the secondary end points. The least-squares mean change in the 6-minute walk distance (6MWD) was an increase of 58.1 m in the sotatercept 0.3-mg group and an increase of 50.1 m in the sotatercept 0.7 mg and of 28.7 m in the placebo group. The least-squares mean difference compared to the placebo group was 29.4 m (95% CI 3.8 to 55.0) in the 0.3-mg sotatercept group and 21.4 m (95% CI, -2.8 to 45.7) in the 0.7-mg treatment group. In addition, there was a reduction in NT-proBNP in the treatment arms and an increase in the placebo arm and no significant difference in the TAPSE between the three groups. Quality of life as measured by CAMPHOR and SF-36 questionnaires was stable in the three groups.

**Safety:** Thrombocytopenia occurred in 2 patients (6%) in the sotatercept 0.3-mg group and in 5 patients (12%) in the sotatercept 0.7-mg group. Hemoglobin increase was reported in 1 patient (3%) in the sotatercept 0.3-mg group and in 7 patients (17%) in the 0.7 mg group. 3 patients (1 in the 0.3-mg group and 2 in the 0.7-mg group) were withdrawn from the trial due to an increase in the hemoglobin levels to above 18 g/dL. Thrombocytopenia resulted in the withdrawal of 2 patients from the study (1 per protocol and 1 withdrew consent), both from the 0.7-mg group. One patient died of cardiac arrest in the 0.7-mg group during the trial.

**Discussion:** 24-weeks treatment with sotatercept resulted in a significant reduction in PVR compared to placebo. 6MWD and NT-proBNP also improved with therapy. The most common hematologic abnormalities were thrombocytopenia and an increase in hemoglobin. The decrease in the PVR was noted regardless of background therapy strategy. Despite the observed thrombocytopenia, there were no clinically significant bleeding events associated with treatment.

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## GROUP OPINION

This study assessed the effect of sotatercept on PVR in patients with PAH. This is a first-in-class fusion protein that targets the activin-growth differentiation factor and the BMPR2 pathway. It is the first drug to target a novel pathway in this therapeutic area in decades. Importantly, BMPR2 signaling is not just decreased in patients with BMPR2 mutations, but is also downregulated in many PAH patients in absence of such mutations and therefore a clinically highly significant target. The effect on PVR in a population that is already on background therapy, including combination and parenteral therapy, is notable. The study population had indicators of severe disease, with roughly half the patients starting at WHO functional class III on therapy, and more than half of the patients being on triple combination background therapy. The study was sufficiently powered to show a significant improvement on sotatercept in the primary end point of PVR but was likely underpowered for the secondary outcomes. Also notable was the one incident of cardiac arrest in a patient in the 0.7-mg group which needs further exploration. This agent is attractive if eventually proven to be effective in the treatment of PAH due to its ease of administration but will require close monitoring of relevant lab values and side effects. Several larger phase 3 studies of sotatercept in PAH are currently underway.

**References:**

Humbert, Marc, et al. "Sotatercept for the treatment of pulmonary arterial hypertension." *New England Journal of Medicine* 384.13 (2021): 1204-1215.

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