Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

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Methods

- Phase 3, multicenter, double blind, randomized control trial
- Looking at safety and efficacy of Sotatercept in addition to background therapy for pulmonary arterial hypertension (PAH)
- 323 patients underwent randomization, 91 sites, 21 countries
- Randomly assigned 1:1 of subcutaneous sotatercept (target dose 0.7mg/kg) or placebo (given every 3 weeks), in combination with stable background therapy

Inclusion/Exclusion criteria

- Inclusion:
  - confirmed diagnosis of PAH (idiopathic, heritable, drug-induced, CTD, or after shunt correction), WHO FC II or III
  - Baseline (PVR) of ≥ 400 dynes/sec/cm5 (5 WU) and wedge <15 mmHg
  - Receiving background therapy mono, double, or triple therapy for 90 days before enrollment
- Exclusion criteria
  - subtypes associated with portopulmonary disease, schistosomiasis, HIV, or veno-occlusive disease
  - Uncontrolled hypotension or hypertension
  - Untreated OSA
  - LVEF <45%
  - Significant valvular disease

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Sotatercept (N=163)	Placebo (N=160)	Total (N=323)
Female sex — no. (%)	129 (79.1)	127 (79.4)	256 (79.3)
Age — yr	47.6±14.1	48.3±15.5	47.9±14.8
Geographic region — no. (%)			
North America	49 (30.1)	56 (35.0)	105 (32.5)
South America	13 (8.0)	15 (9.4)	28 (8.7)
Europe	91 (55.8)	77 (48.1)	168 (52.0)
Asia–Pacific	10 (6.1)	12 (7.5)	22 (6.8)
Race — no. (%)†			
White	147 (90.2)	141 (88.1)	288 (89.2)
Black	2 (1.2)	5 (3.1)	7 (2.2)
Asian	1 (0.6)	6 (3.8)	7 (2.2)
Other	7 (4.3)	6 (3.8)	13 (4.0)
Missing	6 (3.7)	2 (1.2)	8 (2.5)
Body-mass index‡	26.1±5.7	26.6±6.1	26.4±5.9
Body-mass index ≥30 — no. (%)‡	36 (22.1)	38 (23.8)	74 (22.9)
Time since diagnosis of pulmonary arterial hypertension — yr§	9.2±7.3	8.3±6.7	8.8±7.0
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	83 (50.9)	106 (66.2)	189 (58.5)
Heritable	35 (21.5)	24 (15.0)	59 (18.3)
Associated with connective-tissue disease	29 (17.8)	19 (11.9)	48 (14.9)
Drug-induced or toxin-induced	7 (4.3)	4 (2.5)	11 (3.4)
Associated with corrected congenital shunts	9 (5.5)	7 (4.4)	16 (5.0)
WHO functional class — no. (%)¶			
II	79 (48.5)	78 (48.8)	157 (48.6)
III	84 (51.5)	82 (51.2)	166 (51.4)
Background therapy for pulmonary arterial hypertension — no. (%)‖			
Prostacyclin infusion therapy**	65 (39.9)	64 (40.0)	129 (39.9)
Monotherapy	9 (5.5)	4 (2.5)	13 (4.0)
Double therapy	56 (34.4)	56 (35.0)	112 (34.7)
Triple therapy	98 (60.1)	100 (62.5)	198 (61.3)
Hemoglobin — g/dl	13.9±1.7	13.7±1.6	13.8±1.6
Estimated glomerular filtration rate — ml/min/1.73 m^2	91.2±34.6	88.3±35.8	89.8±35.2
6-Minute walk distance — m	397.6±84.3	404.7±80.6	401.1±82.4
NT-proBNP — pg/ml	1037.5±2498.6	1207.8±2694.4	1121.1±2593.8
Pulmonary vascular resistance — dyn·sec·cm^{-5}	781.3±398.5	745.8±313.5	763.7±358.8
Cardiac output — liters/min	4.9±1.3	4.8±1.2	4.8±1.2
Cardiac index — liters/min/m^2	2.7±0.6	2.7±0.6	2.7±0.6
Mean pulmonary artery pressure — mm Hg	53.0±14.6	52.2±13.0	52.6±13.8
Right atrial pressure — mm Hg	8.0±4.3	8.5±4.5	8.2±4.4
Pulmonary arterial wedge pressure — mm Hg	9.7±3.2	9.8±3.1	9.8±3.1

Primary endpoint

- Median change from baseline in 6MWD at 24 weeks:
  - 34.4m in Sotatercept group
  - 1.0m in placebo

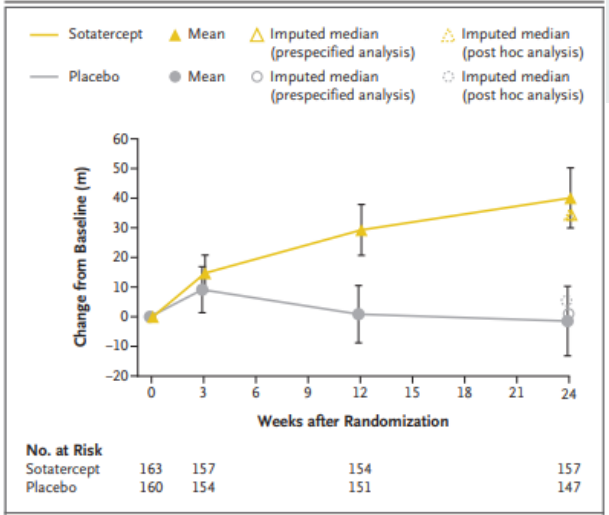

Figure 1. Change in 6-Minute Walk Distance through Week 24.

The line graph shows the observed mean changes from baseline in 6-minute walk distance (in meters) in the sotatercept group (solid triangles) and placebo group (solid circles) with 95% confidence intervals (indicated by I bars). Walking distance was recorded at prespecified trial visits (i.e., week 0 [baseline], week 3, week 12, and week 24) during the first 24 weeks of the trial. The data shown are for patients with available data (observed) over time. The imputed median changes from baseline at week 24 for the prespecified and post hoc analyses are plotted as open symbols (open triangle for sotatercept and open circle for placebo). The prespecified and post hoc imputed medians are shown as open symbols with solid and dashed lines, respectively. For the prespecified analysis, missing values at week 24 owing to death or nonfatal clinical worsening events were assigned worst and second-worst rank scores, respectively. For the post hoc analysis, patients with missing values at week 24 owing to death were excluded from the analysis, whereas missing values owing to nonfatal clinical worsening events were imputed as the overall mean. For both the prespecified and post hoc analyses, missing values at week 24 owing to reasons other than death or nonfatal clinical worsening events were imputed with the use of standard multiple imputation with a fully conditional specification model in which the data were assumed to be missing at random (see the Statistical Analyses section in the Supplementary Appendix). The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Secondary endpoints

- Multicomponent improvement measured by the percentage of patients meeting all three criteria at week 24 relative to baseline:
  - 6MWD (increase of ≥30 m)
  - improvement in NT-proBNP level (decrease of ≥30%) or maintenance or achievement of an NT-proBNP level of <300 pg/mL
  - improvement in WHO functional class
- Significant improvements were observed in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to first occurrence of death or nonfatal clinical worsening
- No significant between-group difference was observed for the PAH-SYMPACT Cognitive/Emotional Impacts domain score

Table 2. Change from Baseline at Week 24 in Primary and Secondary Efficacy End Points (Intention-to-Treat Population).*

End Point	Sotatercept (N=163)	Placebo (N=160)
Primary end point		
6-Minute walk distance — m		
Median change estimate (95% CI) from baseline at wk 24†	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	40.8 (27.5 to 54.1)§¶	
Secondary end points		
Multicomponent improvement		
Patients who met all three criteria for 6-min walk distance, NT-proBNP level, and WHO functional class — no./total no.	63/162‖	16/159‖
Percentage of patients (95% CI)	38.9 (31.3 to 46.9)¶**	10.1 (5.9 to 15.8)
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (95% CI) from baseline at wk 24†	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−234.6 (−288.4 to −180.8)§¶	
NT-proBNP — pg/ml		
Median change estimate (95% CI) from baseline at wk 24†	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−441.6 (−573.5 to −309.6)§¶	
WHO functional class		
Patients with improvement at wk 24 from baseline — no./total no.	48/163¶**	22/159‖
Percentage of patients (95% CI)	29.4 (22.6 to 37.1)	13.8 (8.9 to 20.2)
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)††	0.16 (0.08 to 0.35)¶‡‡	
French risk score§§		
Patients with a low-risk score with the use of the simplified French model at wk 24 — no./total no.	64/162‖	29/159‖
Percentage of patients (95% CI)	39.5 (31.9 to 47.5)¶**	18.2 (12.6 to 25.1)
PAH-SYMPACT Physical Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.26 (−0.49 to −0.04)¶‖	
PAH-SYMPACT Cardiopulmonary Symptoms domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.13 (−0.26 to −0.01)¶‖	
PAH-SYMPACT Cognitive/Emotional Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.16 (−0.40 to 0.08)	

Safety

- Severe (8% vs. 13.1%) and serious (14.1% vs. 22.5%) adverse events were less common in the sotatercept group than in the placebo group
- Adverse events noted with sotatercept included bleeding events (epistaxis and gingival bleeding; 21.5%), telangiectasias (10.4%), thrombocytopenia (6.1%), increase in hemoglobin level (5.5%), and increase in blood pressure (3.7%).

Table 3. Adverse Events through Week 24 (Safety Population).*

Variable	Sotatercept (N=163)	Placebo (N=160)	Difference†
	number (percent)		*percentage points*
Adverse events			
Any	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
Related to sotatercept or placebo‡	67 (41.1)	41 (25.6)	15.5 (5.2 to 25.5)
Leading to discontinuation of sotatercept or placebo	3 (1.8)	10 (6.2)	−4.4 (−9.5 to −0.1)
Leading to withdrawal from the trial	3 (1.8)	5 (3.1)	−1.3 (−5.5 to 2.5)
Leading to death	0	6 (3.8)	−3.8 (−7.9 to −1.4)
Severe adverse event§	13 (8.0)	21 (13.1)	−5.1 (−12.2 to 1.6)
Serious adverse events¶			
Any	23 (14.1)	36 (22.5)	−8.4 (−16.9 to 0.1)
Related to sotatercept or placebo‡	2 (1.2)	2 (1.2)	−0.0 (NR)
Leading to discontinuation of sotatercept or placebo	1 (0.6)	8 (5.0)	−4.4 (−9.0 to −1.0)
Leading to withdrawal from the trial	1 (0.6)	5 (3.1)	−2.5 (−6.6 to 0.6)
Adverse events of interest or special interest‖			
Increased hemoglobin level: increased hematocrit or increased red-cell count	9 (5.5)	0	5.5 (2.9 to 10.2)
Thrombocytopenia	10 (6.1)	4 (2.5)	3.6 (−0.9 to 8.8)
Bleeding events	35 (21.5)	20 (12.5)	9.0 (0.8 to 17.2)
Increased blood pressure	6 (3.7)	1 (0.6)	3.1 (−0.2 to 7.3)
Telangiectasia	17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
Adverse events reported in ≥10% of patients in either group	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
Headache	33 (20.2)	24 (15.0)	5.2 (−3.1 to 13.6)
Covid-19	24 (14.7)	21 (13.1)	1.6 (−6.1 to 9.3)
Nausea	16 (9.8)	18 (11.2)	−1.4 (−8.4 to 5.4)
Diarrhea	20 (12.3)	12 (7.5)	4.8 (−1.8 to 11.6)
Fatigue	17 (10.4)	12 (7.5)	2.9 (−3.5 to 9.5)
Epistaxis	20 (12.3)	3 (1.9)	10.4 (5.2 to 16.6)
Telangiectasia	17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
Dizziness	17 (10.4)	3 (1.9)	8.6 (3.6 to 14.4)

References

Hoeper MM, Badesch DB, Ghofrani HA, et al.; STELLAR Trial Investigators. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med 2023;388:1478-90.