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

Marius M. Hoeper, MD

Marius M. Hoeper, David B. Badesch, H. Ardeschir Ghofrani, J. Simon R. Gibbs, Mardi Gomberg-Maitland, Vallerie V. McLaughlin, Ioana R. Preston, Rogerio Souza, Aaron B. Waxman, Ekkehard Grünig, Grzegorz Kopeć, Gisela Meyer, Karen M. Olsson, Stephan Rosenkranz, Yayun Xu, Barry Miller, Marcie Fowler, John Butler, Janethe de Oliveira Pena, Marc Humbert, for the STELLAR Trial Investigators

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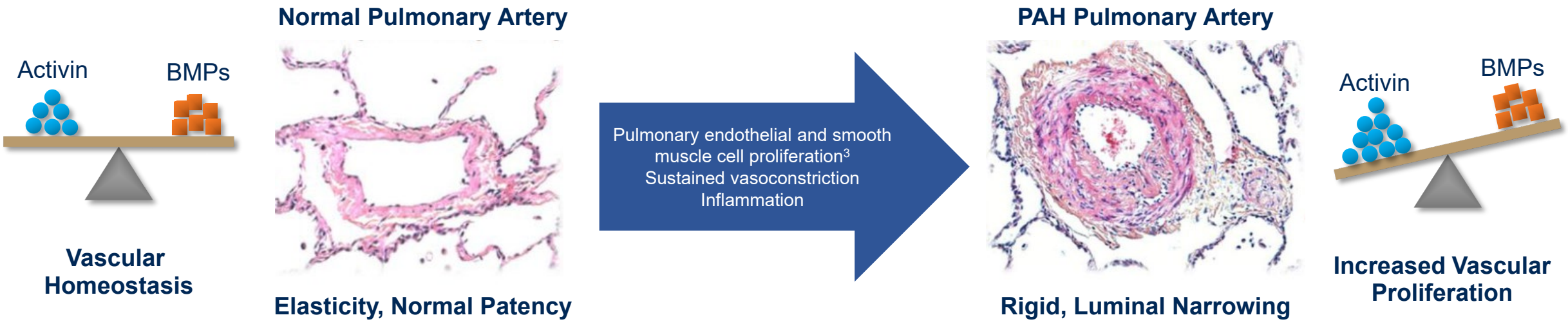
Disclosures

- Marius M. Hoeper is consultant for Acceleron Pharma Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
- This study was funded by Acceleron Pharma Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

PAH Pathobiology: Imbalance in BMPR-II– and ActRIIA-Mediated Signaling

PAH is a progressive disease driven by pulmonary vascular remodeling due in part to an imbalance in anti-proliferative (BMPR-II-mediated) and pro-proliferative (ActRIIA-mediated) signaling pathways, resulting in hyperproliferation of vessel wall cells.[1,2]



Adapted from Guignabert C, Humbert M. *Eur Respir J*. 2021;57(2):2002341.

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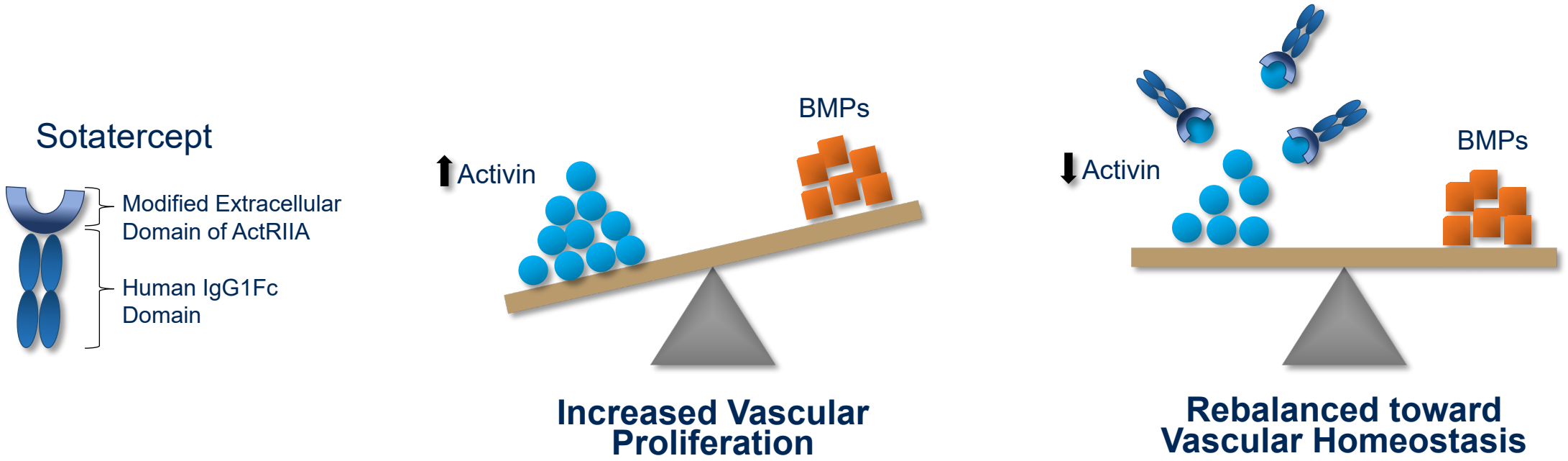
ActRIIA: activin receptor IIA; BMP: bone morphogenetic protein; BMPR-II: bone morphogenetic protein receptor type II; PAH: pulmonary arterial hypertension.

1. Tielemans B, et al. *Drug Discov Today*. 2019;24(3):703-716. 2. Rol N, et al. *Int J Mol Sci*. 2018;19(9):2585; 3. Schermuly RT, et al. *Nat Rev Cardiol*. 2011;8(8):443-455.

Sotatercept is Proposed as a Reverse-Remodeling Agent

- Sotatercept, an activin signaling inhibitor, is proposed to act as a reverse-remodeling agent through rebalancing of anti-proliferative and pro-proliferative signaling pathways.[1,2]



ActRIIA: activin receptor type 2A; BMP: bone morphogenetic protein; IgG1Fc: human immunoglobulin G1 Fc domain.

1. Humbert M, et al. *N Engl J Med*. 2021;384(13):1204–1215; 2. Yung LM, et al. *Sci Transl Med*. 2020;12(543):eeaz5660.

STELLAR: Study Design

- A Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study (NCT04576988) to evaluate sotatercept on top of background PAH therapy* in adult participants with PAH with WHO FC II or III
- Efficacy/safety data through treatment week 24; cumulative safety and time to death or clinical worsening as of Aug 26, 2022 are reported

Inclusion Criteria:
- WHO Group 1 PAH
- WHO FC II or III
- Adult ≥18 years
- Baseline PVR ≥400 dynes·sec·cm^{-5} and PCWP or LVEDP ≤15 mmHg
- 6MWD 150 - 500 meters
- Stable treatment with background PAH therapy*

Randomization 1:1

Stratified by baseline WHO FC and background PAH therapy

Total randomized: 323

Double-blind primary treatment period (24 weeks)

Double-blind extension

Placebo every 3 weeks (N=160)

Sotatercept 0.3 mg/kg starting dose to 0.7 mg/kg every three weeks (N=163)

Primary Endpoint: Change from baseline at week 24 in 6MWD

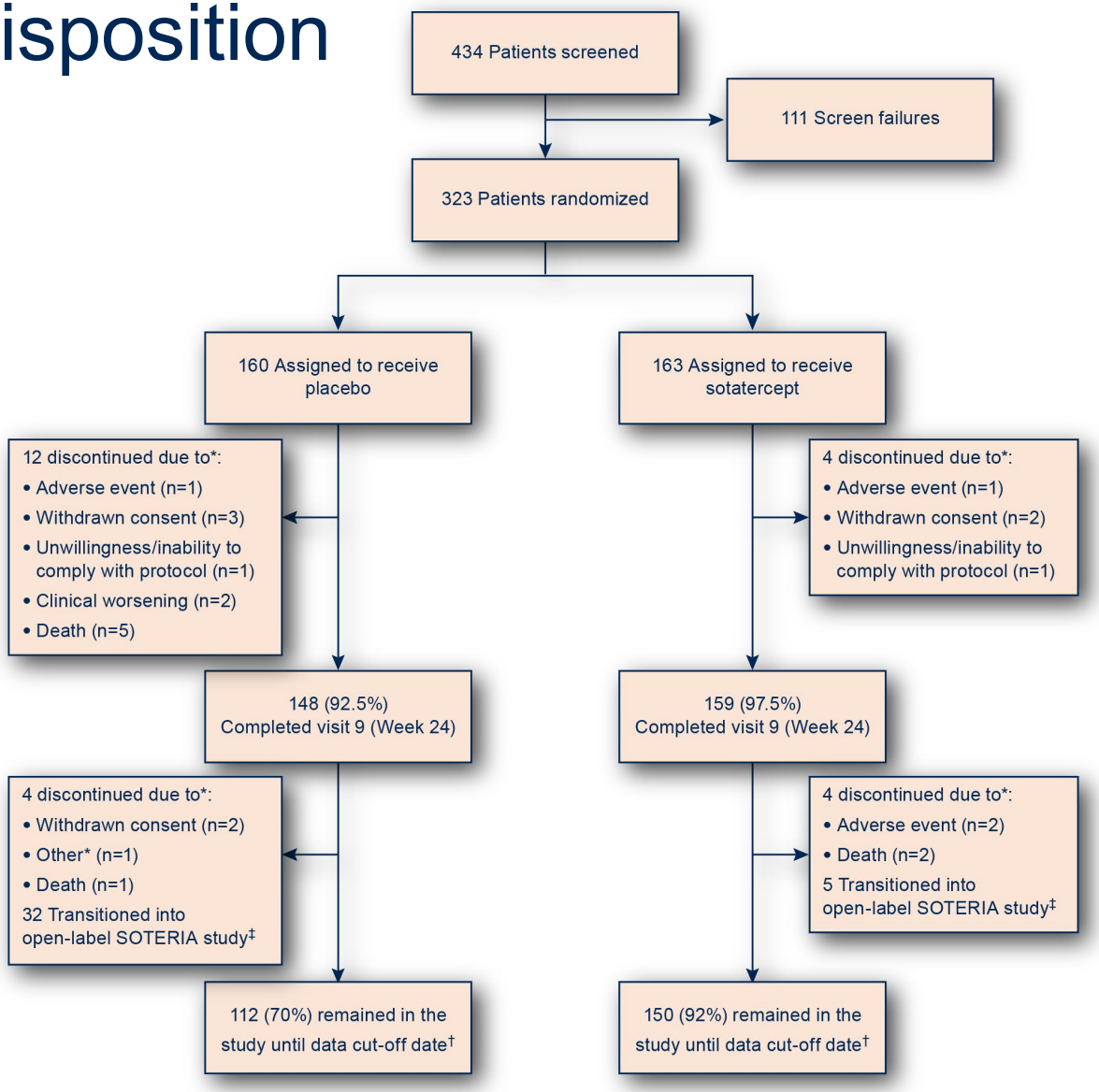
Secondary Endpoints (Tested hierarchically to control type 1 error)

Change from baseline at week 24 in
- Multicomponent clinical improvement
  - Increase ≥30 meters in 6MWD
  - NT-proBNP ≥30%↓ or maintenance/ achievement of NT-proBNP <300 pg/mL
  - Improvement in WHO FC or maintenance of WHO FC II
- PVR, NT-proBNP, WHO FC
- Time to death or first clinical worsening event though study completion (Aug 26, 2022)
- French Risk Score
- 3 domains of PAH-SYMPACT®

*Background PAH therapy included monotherapy, double therapy or triple therapy with one or more of the following:
An endothelin receptor antagonist, a phosphodiesterase-5 inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin (including intravenous).

6MWD: 6-minute walk distance; LVEDP: left ventricular end-diastolic pressure; N: number of patients in the treatment group or overall; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAH: pulmonary arterial hypertension; PAH SYMPACT®: pulmonary arterial hypertension symptoms and impact patient-reported questionnaire; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; WHO: World Health Organization; WHO FC: World Health Organization functional class; WHO FC II: slight limitation of activity (ordinary activities cause some symptoms); WHO FC III: marked limitation of activity (less than ordinary activity causes symptoms).

STELLAR: Patient Disposition



*Patients may have only one primary reason for discontinuation and withdrawal.
†Data cut-off date August 26, 2022.
‡Patients were allowed to roll over to SOTERIA trial if they experienced a clinical worsening event and completed week 24 assessments.

STELLAR: Patient Characteristics

Characteristic	Placebo (N = 160)	Sotatercept (N = 163)	Total (N = 323)
Female sex — no. (%)	127 (79.4)	129 (79.1)	256 (79.3)
Age — yr, mean ± SD	48.3 ± 15.5	47.6 ± 14.1	47.9 ± 14.8
Race — no. (%)			
White	141 (88.1)	147 (90.2)	288 (89.2)
Black or African American	5 (3.1)	2 (1.2)	7 (2.2)
Asian	6 (3.8)	1 (0.6)	7 (2.2)
Other	6 (3.8)	7 (4.3)	13 (4.0)
Missing	2 (1.3)	6 (3.7)	8 (2.5)
Time since PAH diagnosis — yr, mean ± SD	8.3 ± 6.7	9.2 ± 7.3	8.8 ± 7.0
WHO Group 1 PAH Classification — no. (%)			
Idiopathic	106 (66.3)	83 (50.9)	189 (58.5)
Heritable	24 (15.0)	35 (21.5)	59 (18.3)
Associated with connective-tissue disease	19 (11.9)	29 (17.8)	48 (14.9)
Drug-induced or toxin-induced	4 (2.5)	7 (4.3)	11 (3.4)
Associated with corrected congenital shunts	7 (4.4)	9 (5.5)	16 (5.0)
WHO FC — no. (%)			
II	78 (48.8)	79 (48.5)	157 (48.6)
III	82 (51.3)	84 (51.5)	166 (51.4)
Background therapy for PAH — no. (%)			
Prostacyclin infusion therapy	64 (40.0)	65 (39.9)	129 (39.9)
Monotherapy	4 (2.5)	9 (5.5)	13 (4.0)
Double therapy	56 (35.0)	56 (34.4)	112 (34.7)
Triple therapy	100 (62.5)	98 (60.1)	198 (61.3)
6MWD — meter, mean ± SD	404.7 ± 80.6	397.6 ± 84.3	401.1 ± 82.4
NT-proBNP — pg/mL, mean ± SD	1207.8 ± 2694.4	1037.5 ± 2498.6	1121.1 ± 2593.8
PVR — dyn·sec·cm^{-5}, mean ± SD	745.8 ± 313.5	781.3 ± 398.5	763.7 ± 358.8
Mean pulmonary artery pressure — mmHg, mean ± SD	52.2 ± 13.0	53.0 ± 14.6	52.6 ± 13.8

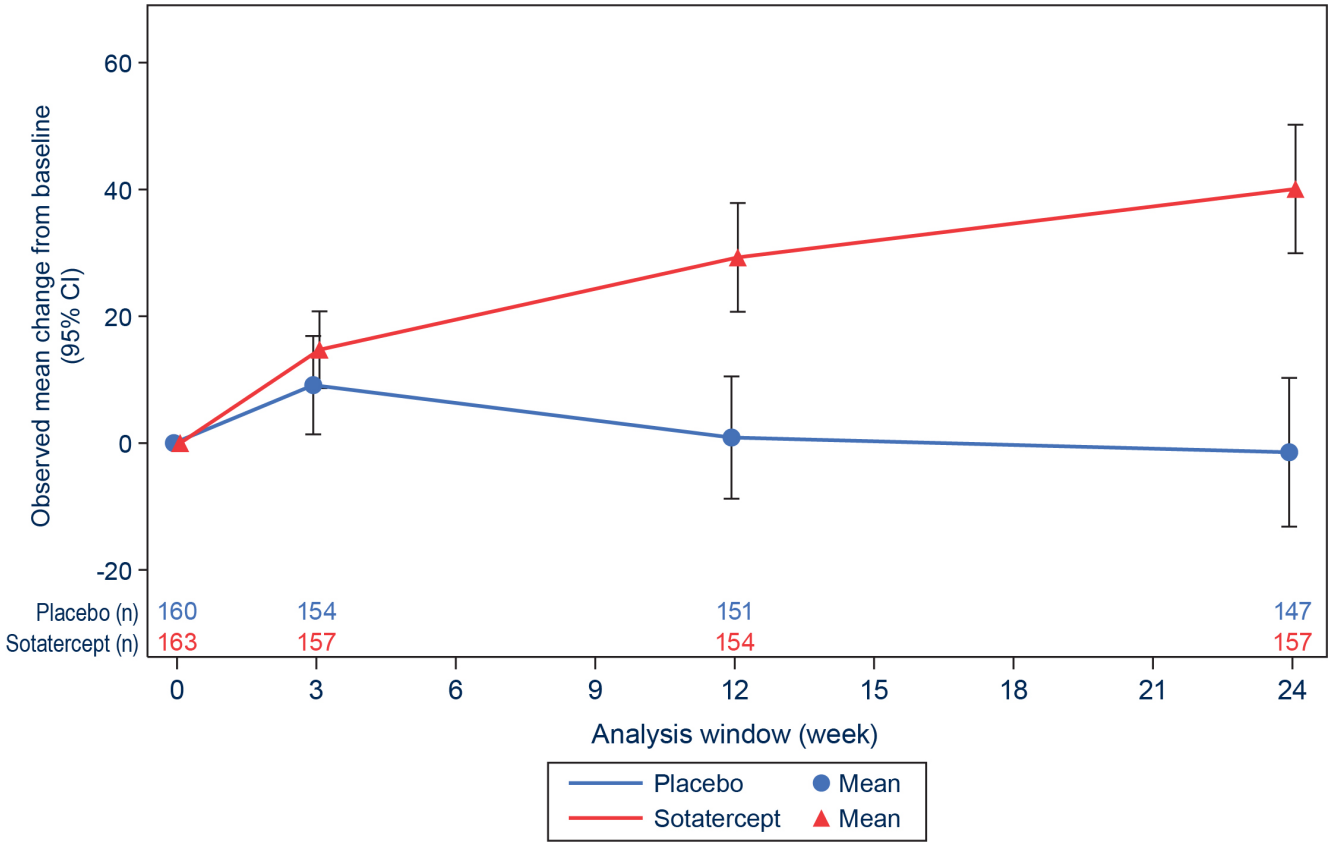
- The study population was relatively young (mean [(SD] 47.9(14.8 years) with an average length of time since PAH diagnosis of 8.8 years; 61% of patients were on triple therapy and 40% were on prostacyclin infusion therapy at inclusion.

6MWD: 6-minute walk distance; N: number of patients in the treatment group or overall; no.: number of patients in the category; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAH: pulmonary arterial hypertension; PAH SYMPACT®: pulmonary arterial hypertension symptoms and impact patient-reported questionnaire; PVR: pulmonary vascular resistance; SD: standard deviation; WHO: World Health Organization; WHO FC: World Health Organization functional class; WHO FC II: slight limitation of activity (ordinary activities cause some symptoms); WHO FC III: marked limitation of activity (less than ordinary activity causes symptoms).

Primary Endpoint: Change from Baseline in 6MWD at Week 24

	Placebo (N=160)	Sotatercept (N=163)
Observed mean change from baseline (95% CI)*	-1.4 (-13.2 to 10.3)	40.1 (29.9 to 50.2)
Hodges-Lehmann location shift (95% CI)†		40.8 (27.5 to 54.1)
Wilcoxon p-value‡		< 0.001

*No imputation of missing data.
†Hodges-Lehmann location shift (95% CI) represents the location shift from placebo estimate (median of the differences in change from baseline at week 24 [sotatercept vs. placebo]).
‡From the aligned rank stratified Wilcoxon test with randomization factors as strata.



6MWD: 6-minute walk distance; CI: confidence interval; N: number of patients in the treatment group or overall; n: number of patients in the category; SD: standard deviation.

Summary of Secondary Endpoints

8 of 9 Secondary hypothesis tests also were significant (accounting for testing strategy):

	Secondary Endpoint	Placebo (N = 160)	Sotatercept (N = 163)	Sotatercept vs. Placebo	
				HL Location Shift (95% CI)	p-value*
1	Multicomponent Improvement†, n/N (%)	16 (10.1)‡	63 (38.9)‡	--	<0.001
2	PVR – dyn·sec·cm^{-5}			-234.6 (-288.4 to -180.8)	<0.001
3	NT-proBNP – pg/mL			-441.6 (-573.5 to -309.6)	<0.001
4	WHO FC, n/N (%)	22 (13.8)‡	48 (29.4)‡	--	<0.001
5	TTCW or all-cause death			0.16 (0.08 to 0.35)†	<0.001†
6	French low-risk score, n/N (%)	29 (18.2)‡	64 (39.5)‡	--	<0.001
7	PAH-SYMPACT® Physical Impacts			-0.26 (-0.49 to -0.04)	0.010
8	PAH-SYMPACT® Cardiopulmonary			-0.13 (-0.26 to -0.01)	0.028
9	PAH-SYMPACT® Cognitive/Emotional			-0.16 (-0.40 to 0.08)	0.156

*Based on aligned rank stratified Wilcoxon test for continuous parameters or Cochran-Mantel-Haenszel method for dichotomous variables, both stratified by randomization factors.
† Defined as meeting all 3 of the following criteria at week 24: improvement in 6MWD [increase of ≥30 meters]; improvement in NT-proBNP level [decrease of ≥30%] or maintenance/achievement of NT-proBNP level <300 pg/mL; and improvement in WHO FC [shift from class III to II or I, or class II to I] or maintenance of class II.
‡For multicomponent improvement and French risk score, N= 159 (placebo) and N= 162 (sotatercept) due to one patient in each treatment group with missing data due to COVID-19 and excluded from analysis. For WHO FC, N= 159 (placebo) and N= 163 (sotatercept) due to a placebo-treated patient with missing data due to COVID-19 and excluded from analysis.
†Expressed as hazard ratio (95% CI) and log-rank test p-value.

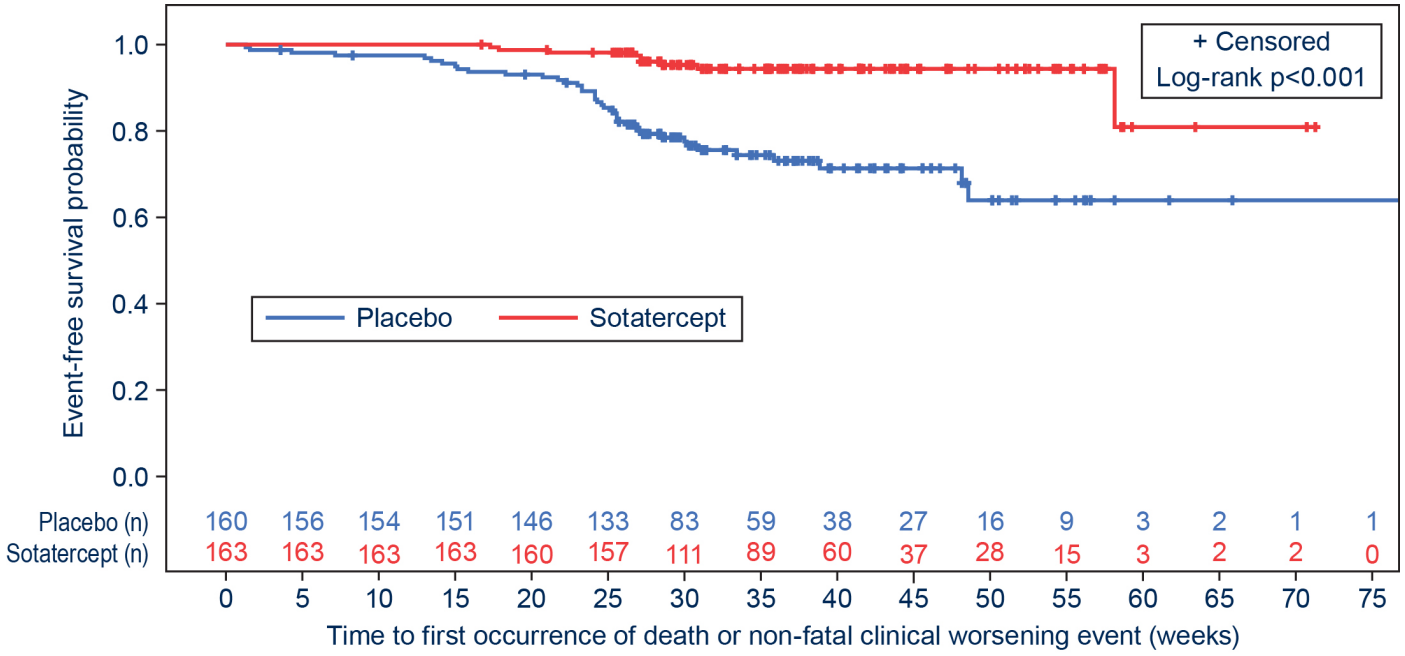
- The between-group reduction from baseline in least-squares mean pulmonary artery pressure (exploratory endpoint) at week 24 was -13.9 mmHg (95% CI: -16.0 to -11.8)

6MWD: 6-minute walk distance; CI: confidence interval; COVID-19: coronavirus of 2019; HL: Hodges-Lehmann; N: number of patients in the treatment group or overall; n: number of patients in the category; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAH SYMPACT®: pulmonary arterial hypertension symptoms and impact patient-reported questionnaire; PVR: pulmonary vascular resistance; TTCW: time to clinical worsening; WHO: World Health Organization; WHO FC: World Health Organization functional class; WHO FC II: slight limitation of activity (ordinary activities cause some symptoms); WHO FC III: marked limitation of activity (less than ordinary activity causes symptoms).

Time to First Occurrence of Death or Non-Fatal Clinical Worsening Event (TTCW)

	Placebo (N=160)	Sotatercept (N=163)
Total number of patients who died or experienced at least one clinical worsening event, n (%)	42 (26.3)	9 (5.5)
Assessment of first occurrence of death or non-fatal clinical worsening event*:		
Death as first event	6 (3.8)	2 (1.2)
Worsening-related listing for lung or heart-lung transplant	1 (0.6)	1 (0.6)
Need to initiate rescue therapy or need to increase dose of infusion prostacyclin by 10% or more	17 (10.6)	2 (1.2)
Need for atrial septostomy	0	0
PAH-related hospitalization (≥24 hours)	7 (4.4)	0
Deterioration of PAH	15 (9.4)	4 (2.5)

*Dates and times of reported adverse events were used by the adjudication committee to determine death or first non-fatal clinical worsening event. Patients could have more than one assessment for their first occurrence of non-fatal clinical worsening event or death. A single patient could have more than one non-fatal clinical worsening event but was only counted once for the time to event analysis.



- After a median follow-up of 32.7 weeks across the treatment groups, the hazard ratio in the sotatercept group as compared with the placebo group was 0.16 (95% CI: 0.08 to 0.35).

N: number of patients in the intention-to-treat population; n: number of patients in the category; PAH: pulmonary arterial hypertension; TTCW: time to clinical worsening.

Overall Summary of Safety

Cumulative results through data cut-off date*

Number of patients with any	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)
Treatment-Emergent adverse events (TEAEs)	147 (91.9)	148 (90.8)
TEAEs related to treatment	43 (26.9)	77 (47.2)
TEAEs leading to treatment discontinuation	11 (6.9)	6 (3.7)
TEAEs leading to study discontinuation	9 (5.6)	8 (4.9)
TEAEs leading to death	7 (4.4)	2 (1.2)
Severe TEAEs	29 (18.1)	21 (12.9)
Serious TEAEs	44 (27.5)	36 (22.1)
Serious TEAEs related to treatment	2 (1.3)	3 (1.8)

*Data cut-off date August 26, 2022.
A TEAE has a start date on or after the first dose of treatment and up to 56 days after the last dose of treatment.

CI: confidence interval; N: number of patients in the treatment group or overall; n: number of patients in the category; TEAE: treatment-emergent adverse event.

Overall Summary of Safety Continued

Cumulative results through data cut-off date*

Number of patients with any	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)
TEAEs of interest†	72 (45.0)	97 (59.5)
Bleeding events	25 (15.6)	52 (31.9)
Telangiectasia	6 (3.8)	23 (14.1)
Increased hemoglobin (increased hematocrit, increased RBC count)	0	10 (6.1)
Thrombocytopenia	5 (3.1)	14 (8.6)
Increased blood pressure	1 (0.6)	7 (4.3)
TEAEs with incidence ≥10% in one or more treatment groups		
Epistaxis	3 (1.9)	33 (20.2)
Telangiectasia	6 (3.8)	23 (14.1)
Dizziness	7 (4.4)	24 (14.7)

*Data cut-off date August 26, 2022.
†TEAE of interest (bleeding events, cardiac events, embryo-fetal toxicity, hepatic toxicity, immunogenicity, increased blood pressure, increased hemoglobin, leukopenia, neutropenia, renal toxicity, suppression of follicle stimulating hormone, thrombocytopenia, thromboembolic events) and special interest (telangiectasia) were predefined parameters that were monitored to assess the overall safety profile of sotatercept. Only those TEAEs in which the point estimate(s) for the between-group differences excluded zero are shown in this table.
A TEAE has a start date on or after the first dose of treatment and up to 56 days after the last dose of treatment.

CI: confidence interval; N: number of patients in the treatment group or overall; n: number of patients in the category; RBC: red blood cell; TEAE: treatment-emergent adverse event.

Summary and Conclusions

STELLAR is the first Phase 3 trial of sotatercept, an activin signaling inhibitor, in adults with PAH and WHO FC II-III.

Sotatercept improved 6MWD (+40.8 m, 95% CI, 27.5 to 54.1; p<0.001) and delivered broad clinical benefit across multiple domains including hemodynamics, WHO functional class, disease biomarkers, risk scores and patient-reported outcomes.

Sotatercept reduced the risk of death and non-fatal clinical worsening events by 84% vs placebo (HR: 0.16 [95% CI: 0.08 to 0.35]).

Sotatercept was generally well tolerated.

- Adverse events more frequent with sotatercept *vs* placebo: minor bleeding events, telangiectasia, dizziness, increased hemoglobin levels, thrombocytopenia and increased blood pressure.

These results establish the clinical utility of sotatercept, administered in combination with approved PAH therapies, as a new treatment for PAH.

6MWD: 6-minute walk distance; CI: confidence interval; HR: hazard ratio; PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class; WHO FC II: slight limitation of activity (ordinary activities cause some symptoms); WHO FC III: marked limitation of activity (less than ordinary activity causes symptoms)..

- The authors thank the patients and their families, the study investigators, and site personnel.
- The STELLAR study paper is available on NEJM.org.

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