ORIGINAL ARTICLE

# Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

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## ABSTRACT

### BACKGROUND

Pulmonary arterial hypertension is a progressive disease involving proliferative remodeling of the pulmonary vessels. Despite therapeutic advances, the disease-associated morbidity and mortality remain high. Sotatercept is a fusion protein that traps activins and growth differentiation factors involved in pulmonary arterial hypertension.

### METHODS

We conducted a multicenter, double-blind, phase 3 trial in which adults with pulmonary arterial hypertension (World Health Organization [WHO] functional class II or III) who were receiving stable background therapy were randomly assigned in a 1:1 ratio to receive subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was the change from baseline at week 24 in the 6-minute walk distance. Nine secondary end points, tested hierarchically in the following order, were multicomponent improvement, change in pulmonary vascular resistance, change in N-terminal pro–B-type natriuretic peptide level, improvement in WHO functional class, time to death or clinical worsening, French risk score, and changes in the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) Physical Impacts, Cardiopulmonary Symptoms, and Cognitive–Emotional Impacts domain scores; all were assessed at week 24 except time to death or clinical worsening, which was assessed when the last patient completed the week 24 visit.

### RESULTS

A total of 163 patients were assigned to receive sotatercept and 160 to receive placebo. The median change from baseline at week 24 in the 6-minute walk distance was 34.4 m (95% confidence interval [CI], 33.0 to 35.5) in the sotatercept group and 1.0 m (95% CI, −0.3 to 3.5) in the placebo group. The Hodges–Lehmann estimate of the difference between the sotatercept and placebo groups in the change from baseline at week 24 in the 6-minute walk distance was 40.8 m (95% CI, 27.5 to 54.1; P<0.001). The first eight secondary end points were significantly improved with sotatercept as compared with placebo, whereas the PAH-SYMPACT Cognitive–Emotional Impacts domain score was not. Adverse events that occurred more frequently with sotatercept than with placebo included epistaxis, dizziness, telangiectasia, increased hemoglobin levels, thrombocytopenia, and increased blood pressure.

### CONCLUSIONS

In patients with pulmonary arterial hypertension who were receiving stable background therapy, sotatercept resulted in a greater improvement in exercise capacity (as assessed by the 6-minute walk test) than placebo. (Funded by Acceleron Pharma, a subsidiary of MSD; STELLAR ClinicalTrials.gov number, NCT04576988.)

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*The complete list of the STELLAR Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Pulmonary arterial hypertension is a disease characterized by proliferative remodeling of the small pulmonary arteries and progressive luminal narrowing.[1] The resulting elevations in pulmonary artery pressure strain the heart, eventually culminating in right ventricular failure and death. Currently available treatments include phosphodiesterase-5 inhibitors, endothelin-receptor antagonists, soluble guanylate cyclase stimulators, and compounds targeting the prostacyclin pathway.[2,3] When administered alone or in combination, these treatments improve pulmonary hemodynamics, exercise capacity, and progression-free survival in patients with pulmonary arterial hypertension. Median survival ranges from 5 to 7 years after diagnosis, but no substantial improvements in survival have been realized during the past decade.[4] The continued high morbidity and mortality underscore the need for additional treatment options that target new pathways involved in pulmonary vascular remodeling.

Pulmonary vascular remodeling affects all layers of the vessel wall and is driven predominantly by enhanced proliferation and diminished apoptosis of endothelial and smooth-muscle cells.[5] Recent research has highlighted the role of altered signal transduction by members of the transforming growth factor $\beta$ (TGF-$\beta$) superfamily, including bone morphogenetic protein receptor type II, activin receptor type IIA (ActRIIA), and the ActRIIA ligands activin A, activin B, growth differentiation factor 8 (GDF8), and GDF11. A shift toward proliferative and antiapoptotic signaling by these TGF-$\beta$ superfamily members is thought to be a prominent mechanism driving pulmonary vascular remodeling in patients with pulmonary arterial hypertension.[6-8]

Sotatercept is a first-in-class fusion protein consisting of the Fc domain of human IgG linked to the extracellular domain of human ActRIIA, which acts as a ligand trap for selected TGF-$\beta$ superfamily members. Inhibition of these ligands by sotatercept is proposed to rebalance pulmonary vascular homeostasis toward growth-inhibiting and proapoptotic signaling. In animal models of pulmonary hypertension, sotatercept inhibited cell proliferation, promoted apoptosis, and alleviated inflammation in the vessel walls, leading to reverse remodeling and restoration of vessel patency.[8-10]

In the phase 2 PULSAR trial, which involved 106 patients receiving background therapy for pulmonary arterial hypertension, 24 weeks of treatment with sotatercept administered subcutaneously every 3 weeks at doses of either 0.3 or 0.7 mg per kilogram of body weight improved pulmonary hemodynamics (including pulmonary vascular resistance and pulmonary artery pressure), serum levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP), and exercise capacity (as assessed by 6-minute walk distance).[11] Improvements were observed within the first 24 weeks of treatment and maintained over a period of 18 to 24 months with continued sotatercept therapy.[12] In the phase 3 STELLAR trial, we further investigated the efficacy, safety, and adverse-event profile of sotatercept in combination with stable background therapy in adult patients with symptomatic pulmonary arterial hypertension (World Health Organization [WHO] functional class II or III; classes range from I to IV, with higher numbers indicating greater functional limitations).

## METHODS

### TRIAL DESIGN AND OVERSIGHT

STELLAR was a phase 3, multicenter, double-blind, randomized, placebo-controlled trial (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). After completion of the trial, patients were eligible to roll over into the ongoing SOTERIA trial (ClinicalTrials.gov number, NCT04796337). Unless otherwise specified, we report the main results from the first 24 weeks of treatment for all efficacy and safety variables. The results of the analysis of time to first occurrence of death or nonfatal clinical worsening event and supplementary safety analyses are reported through the data-cutoff date of August 26, 2022.

A steering committee designed the trial in collaboration with the sponsor, Acceleron Pharma, a subsidiary of MSD. An institutional review board or independent ethics committee at each trial center approved the protocol. An independent data and safety monitoring committee reviewed unblinded safety data collected 21 days after administration of the first dose of sotatercept or placebo and every 3 months thereafter. The responsibilities of the committee included review of accumulating unblinded safety and

limited efficacy data (i.e., 6-minute walk distance, pulmonary vascular resistance, and WHO functional class) to ensure the safety of trial patients as well as to evaluate benefit as compared with risk of treatment without potential stopping for efficacy or alpha adjustment. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the ethical guidelines of the Council for International Organizations of Medical Sciences, the Good Clinical Practice guidelines of the International Council for Harmonisation, and all applicable laws and regulations.[13-15]

In addition to its role in the design of the trial, the sponsor selected the participating trial centers, oversaw the conduct and monitoring of the trial (performed by a contract research organization, PPD), and received and maintained the trial database. The investigators worked under confidentiality agreements with the sponsor. TechData Service performed all statistical analyses. No independent analyses of the data were performed. The authors had the authority to request ad hoc analyses. All the authors participated in interpretation of the data, critical review of the manuscript, and the decision to submit the manuscript for publication. The first author assumes responsibility for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and the statistical analysis plan, which are available at NEJM.org.

### PATIENTS

Eligible patients had a confirmed diagnosis of pulmonary arterial hypertension (idiopathic, heritable, drug-induced, connective-tissue disease–associated, or after shunt correction) in WHO functional class II or III, excluding subtypes associated with portopulmonary disease, schistosomiasis, human immunodeficiency virus infection, or veno-occlusive disease.[2,3] A list of the inclusion and exclusion criteria is provided in the Supplementary Appendix. All the patients were receiving stable background therapy for pulmonary arterial hypertension for at least 90 days before enrollment and continued receiving background therapy throughout the trial. Baseline hemodynamic measurements were obtained during the screening period (i.e., ≤4 weeks before randomization). Background treatments consisted of monotherapy, double therapy, or triple therapy with currently available medications for pulmonary arterial hypertension. All the patients provided written informed consent.

### PROCEDURES

Eligible patients were stratified according to baseline WHO functional class (II vs. III) and background therapy for pulmonary arterial hypertension (monotherapy or double therapy vs. triple therapy) and were randomly assigned with the use of a computerized interactive response technology system in a 1:1 ratio to receive either sotatercept or placebo in combination with stable background therapy. Sotatercept or placebo (saline) was administered by subcutaneous injection every 21 days. Sotatercept was administered at a starting dose of 0.3 mg per kilogram at visit 1 and was escalated to the target dose of 0.7 mg per kilogram at visit 2 (day 21, with a window of ±3 days). Patients continued to receive a dose of 0.7 mg per kilogram for the duration of the trial unless a reduction was warranted according to the protocol (see the Supplementary Appendix for dosing guidance).

Safety and efficacy were assessed at inclusion and every 3 weeks thereafter for 24 weeks. Adverse events were recorded from the signing of informed consent until the final trial visit. We report adverse events that occurred up to and including day 56 after the last dose of sotatercept or placebo; such events were followed until a return to screening baseline, resolution, or the data-cutoff date. Serious adverse events were followed until resolution or until the event was deemed to be chronic or stable.

### END POINTS

The primary end point was the change from baseline at week 24 in the 6-minute walk distance. Secondary end points were ranked in hierarchical order: multicomponent improvement measured by the percentage of patients meeting all three criteria at week 24 relative to baseline (i.e., improvement in 6-minute walk distance [increase of ≥30 m], improvement in NT-proBNP level [decrease of ≥30%] or maintenance or achievement of an NT-proBNP level of <300 pg per milliliter, and improvement in WHO functional class [class III to II or I, or II to I] or maintenance of class II), change from baseline at week 24 in pulmonary vascular resistance, change from baseline at week 24 in NT-proBNP level, improvement in WHO functional class from

**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 |

**Table 1. (Continued.)**

| Characteristic | Sotatercept (N=163) | Placebo (N=160) | Total (N=323) |
|---|---|---|---|
| Mixed venous oxygen saturation — % | 66.8±7.1 | 67.4±7.9 | 67.1±7.5 |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The length of time since diagnosis of pulmonary arterial hypertension was calculated by adding the number of days from the date of diagnosis to the date of informed consent (enrollment) plus 1 day, then dividing by 365.25.
¶ World Health Organization (WHO) functional classes range from I to IV, with higher numbers indicating greater functional limitations.
‖ Background therapy was not prespecified in the protocol; rather, patients were treated according to their respective physicians and countries. Treatments included monotherapy, double therapy, or triple therapy with combinations of endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin-receptor agonists. Patients who were receiving prostacyclin infusion therapy were also included in one of the other categories of therapy.
** Prostacyclin infusion therapy includes intravenous epoprostenol and intravenous or subcutaneous treprostinil.

baseline at week 24, time to first occurrence of death or nonfatal clinical worsening event defined by death from any cause or specified nonfatal clinical worsening events (worsening-related listing for lung or heart–lung transplantation, initiation or rescue therapy with an approved background treatment or increase in the prostacyclin dose by ≥10%, atrial septostomy, hospitalization [≥24 hours] for worsening of pulmonary arterial hypertension, or worsening of pulmonary arterial hypertension relative to baseline as defined by both a worsened WHO functional class and a decrease in 6-minute walk distance by ≥15% [confirmed by two tests ≥4 hours but ≤1 week apart], with all clinical worsening events, including death, up to the end of the trial adjudicated by an independent committee whose members were unaware of the trial-group assignments), a low French risk score (defined by the meeting of all three criteria for low risk: WHO functional class I or II, 6-minute walk distance of >440 m, and NT-proBNP level of <300 pg per milliliter[16]) at week 24, change from baseline at week 24 in the Physical Impacts domain score of the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire,[17,18] change from baseline at week 24 in the Cardiopulmonary Symptoms domain score of the PAH-SYMPACT questionnaire, and change from baseline at week 24 in the Cognitive/Emotional Impacts domain score of the PAH-SYMPACT questionnaire. PAH-SYMPACT is a disease-specific patient-reported outcome instrument. Domain scores range from 0 to 4, with higher scores indicating greater severity of symptoms. A complete list of trial end points is provided in Table S2.

### STATISTICAL ANALYSIS

The sample size was determined with the use of estimates of treatment effect from previous studies.[11,19] The statistical power for the primary end point (change in 6-minute walk distance) was approximately 96% under the Wilcoxon rank-sum test, with the assumption of a 1:1 randomization ratio, a two-sided 0.05 type I error rate, a between-group difference of 25 m (sotatercept group minus placebo group), a common standard deviation of 50 m, and 121 patients per group. All sample-size calculations were performed with the use of nQuery software (Statistical Solutions). All efficacy analyses were performed in the intention-to-treat population, defined as all the patients who underwent randomization.

The prespecified analysis of the primary end point used the aligned-rank stratified Wilcoxon test with randomization factors as strata.[20] The Hodges–Lehmann location-shift estimate of the between-group difference with 95% confidence interval was calculated with the corresponding P value from the aligned-rank stratified Wilcoxon test. The worst-rank score was used to impute nonexistent data owing to the death of a patient, and the next worst-rank score was used to impute missing data owing to a nonfatal clinical worsening event. Sensitivity analyses of the primary end point were performed if there was a significant treatment effect (see the Supplementary Appendix). At the request of the editors, an

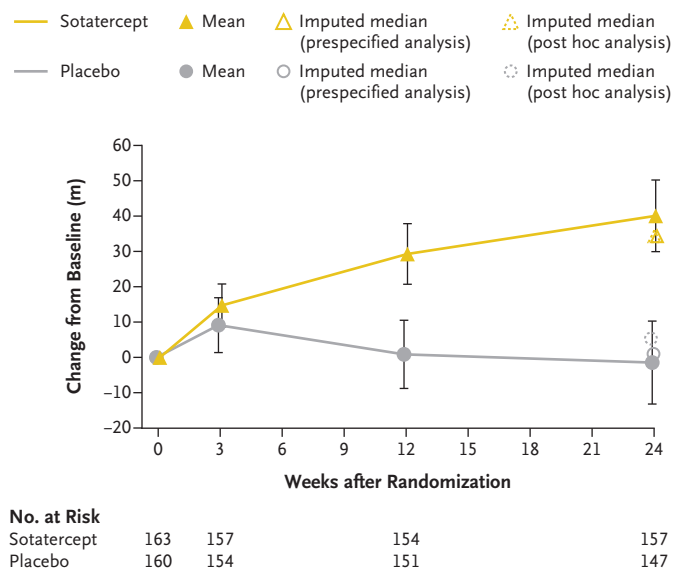



**Figure 1. Change in 6-Minute Walk Distance through Week 24.**

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.

additional post hoc analysis for continuous primary and secondary efficacy end points was performed wherein missing data at week 24 owing to death were not imputed and missing data at week 24 owing to a nonfatal clinical worsening event were imputed as the overall mean change from baseline at week 24 among the patients with observed data. Additional details are provided in the Supplementary Appendix. A gatekeeping method was used to control the type I error rate for the prespecified analyses by testing hierarchically beginning with the primary end point and proceeding in the order of the secondary end points described above. Testing was performed with the use of a two-sided alpha level of 0.05 by proceeding successively only after each of the preceding end points was tested and the between-group difference was found to be significant.

The safety analyses were performed in the safety population, defined as all randomly assigned patients who received at least one dose of sotatercept or placebo. Safety results were summarized with descriptive statistics. For selected safety data, 95% confidence intervals for the between-group difference were also provided with the use of the Miettinen and Nurminen method.[21]

## RESULTS

### BASELINE CHARACTERISTICS AND FOLLOW-UP

Of the 434 patients who were assessed for eligibility, 323 underwent randomization and received sotatercept or placebo at 91 sites in 21 countries (see Table S1 for the representativeness of the trial population). The first patient was screened on January 25, 2021; the first patient underwent randomization on February 16, 2021; and the last patient completed the 24-week primary end-point assessment on August 26, 2022. The database was locked and unblinded on September 27, 2022.

Eligible patients were randomly assigned (in a 1:1 ratio) to receive sotatercept (163 patients) or placebo (160 patients) in combination with stable background therapy (Fig. S2). Reasons for screening failure for the 111 excluded patients are provided in Table S4. The demographic and clinical characteristics of the patients at baseline were generally similar in the two groups. The trial population was relatively young (mean [±SD] age, 47.9±14.8 years), with a mean length of time since diagnosis of 8.8 years. In total, 198 of the 323 randomly assigned patients (61.3%) were receiving triple therapy and 129 (39.9%) were receiving prostacyclin infusion therapy at inclusion (Table 1).

### PRIMARY END POINT

The observed mean change from baseline at week 24 in 6-minute walk distance was 40.1 m

(95% confidence interval [CI], 29.9 to 50.2) in the sotatercept group and –1.4 m (95% CI, –13.2 to 10.3) in the placebo group (Fig. 1). For the prespecified analysis of the primary end point, the median change from baseline value for 6-minute walk distance was 34.4 m (95% CI, 33.0 to 35.5) in the sotatercept group and 1.0 m (95% CI, –0.3 to 3.5) in the placebo group. The Hodges–Lehmann location shift was 40.8 m (95% CI, 27.5 to 54.1; P<0.001), favoring sotatercept (Table 2). The results of a post hoc analysis of 6-minute walk distance were aligned with those of the prespecified analysis: the median change from baseline at week 24 was 34.4 m (95% CI, 33.0 to 35.5) in the sotatercept group and 5.4 m (95% CI, 3.0 to 7.3) in the placebo group. The Hodges–Lehmann location shift for the post hoc analysis was 36.8 m (95% CI, 24.1 to 49.4; P<0.001), favoring sotatercept (Table S8). The magnitude of the treatment effect on 6-minute walk distance was similar irrespective of the handling of missing data owing to death or nonfatal clinical worsening (Table S9) and across most prespecified subgroups (Fig. S4).

#### SECONDARY END POINTS

The number of patients who met all three criteria of the multicomponent improvement end point at week 24 was 63 of 162 (38.9%) in the sotatercept group and 16 of 159 (10.1%) in the placebo group (P<0.001) (Fig. S6 and Table 2). The numbers of patients who met each individual criterion are presented in Table S10.

Relative to placebo, significant improvements were observed with sotatercept treatment for the change from baseline at week 24 in pulmonary vascular resistance, NT-proBNP levels, WHO functional class (Fig. S11), and the simplified French risk model (Fig. S12). Changes in exploratory hemodynamic end points are reported in Table S12.

There was a significant difference in the distribution of time to first occurrence of death or nonfatal clinical worsening event in the sotatercept and placebo groups (P<0.001 by log-rank test) (Fig. 2). Kaplan–Meier curves showed that separation occurred early (at approximately week 10) and continued for the remainder of the trial. After a median follow-up of 32.7 weeks across the groups, the hazard ratio in the sotatercept group as compared with the placebo group was 0.16 (95% CI, 0.08 to 0.35).

With respect to the PAH-SYMPACT quality-of-life questionnaire, changes from baseline at week 24 in the Physical Impacts and Cardiopulmonary Symptoms domain scores showed greater improvements with sotatercept than with placebo. No significant between-group difference was observed for the PAH-SYMPACT Cognitive/Emotional Impacts score (P=0.16). For all secondary end points, the corresponding results from the post hoc analyses that excluded patients who died are shown in Table S8.

#### SAFETY

Data on cumulative exposure to sotatercept or placebo during the 24-week treatment period are provided in Table S13. In total, 162 of 163 patients (99.4%) assigned to the sotatercept group received the maximum dose of 0.7 mg per kilogram during the trial period. Of the 163 patients assigned to receive sotatercept, 145 (89.0%) had no dose reductions or dose delays throughout the 24-week trial period (Table S14). Ten patients (6.1%) in the sotatercept group had at least one dose reduction as specified by the dosing guidance. Adherence to the trial regimen was 98.4% in the sotatercept group and 99.0% in the placebo group (Table S15).

Adverse events that were reported in at least 10% of the patients in either group during the 24-week treatment period are listed in Table 3, and those that occurred up to the data-cutoff date are listed in Table S16. Epistaxis, telangiectasia, and dizziness were more frequent in the sotatercept group than in the placebo group. Serious adverse events occurred in 23 patients (14.1%) in the sotatercept group and 36 patients (22.5%) in the placebo group (Table S17). Serious adverse events that were considered by the investigator to be related to sotatercept or placebo were infrequent (2 patients [1.2%] in the sotatercept group and 2 patients [1.2%] in the placebo group). Severe adverse events were reported in 13 patients (8.0%) in the sotatercept group and 21 patients (13.1%) in the placebo group (Table S18). An overall summary of safety through the data-cutoff date is shown in Table S19.

Prespecified adverse events of interest occurred in 80 patients (49.1%) in the sotatercept group and 58 patients (36.2%) in the placebo group through week 24 (Table S20; see Table S21 for adverse events of interest up to the data-cutoff date). The most common adverse events of

**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) | |

* All analyses were performed in the intention-to-treat population with the prespecified multiple-imputation methods for handling missing data. Missing values at week 24 owing to death or nonfatal clinical worsening events were assigned worst and second-worst rank scores, respectively. Missing values at week 24 owing to reasons other than death or nonfatal clinical worsening events were populated with the use of a fully conditional specification regression model in which the data were assumed to be missing at random (see the Statistical Analyses section in the Supplementary Appendix). The widths of the confidence intervals have not been adjusted for multiple comparisons; the intervals should therefore not be used to infer definitive treatment effects for the secondary end points.

† Shown is the average of the medians across the imputed data sets (with 95% confidence interval) if missing data were imputed.

‡ The Hodges–Lehmann location shift from placebo estimate is the median of all paired differences.

§ P<0.001 for the comparison of sotatercept with placebo on the basis of the aligned-rank stratified Wilcoxon test with randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III) as strata.

¶ P<0.05 as derived by means of a gatekeeping method to control the type I error rate for secondary end points by hierarchical testing that proceeded successively in the order of the end points listed in the table with a two-sided alpha level of 0.05.

‖ One patient in the group had missing data owing to coronavirus disease 2019 (Covid-19) and was excluded from the analysis.

** P<0.001 for the comparison of sotatercept with placebo on the basis of a Cochran–Mantel–Haenszel method stratified according to randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

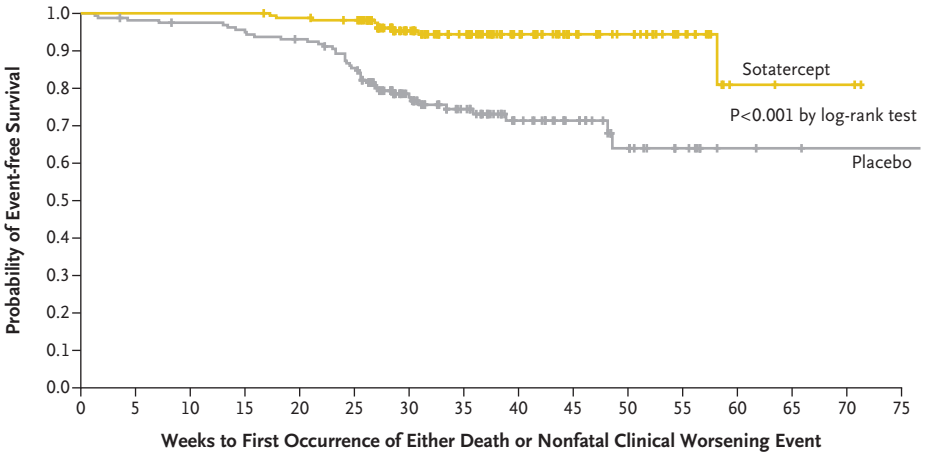
†† The hazard ratio (sotatercept vs. placebo) was derived from a Cox proportional-hazards model with trial group as the covariate and stratification according to the randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

‡‡ P<0.001 for the comparison of sotatercept with placebo on the basis of a Cox proportional-hazards model with trial group as the covariate and stratification according to randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III).

§§ A low French risk score was defined by the meeting of all three criteria for low risk: a WHO functional class of I or II, a 6-minute walk distance of more than 440 m, and an NT-proBNP level of less than 300 pg per milliliter.

¶¶ The Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire is a disease-specific patient-reported outcome instrument. Domain scores range from 0 to 4, with higher scores indicating greater severity of symptoms.

‖‖ P<0.05 for the comparison of sotatercept with placebo on the basis of the aligned-rank stratified Wilcoxon test with randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline WHO functional class (II vs. III) as strata.




**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sotatercept | 163 | 163 | 163 | 163 | 160 | 157 | 111 | 89 | 60 | 37 | 28 | 15 | 3 | 2 | 2 | 0 |
| Placebo | 160 | 156 | 154 | 151 | 146 | 133 | 83 | 59 | 38 | 27 | 16 | 9 | 3 | 2 | 1 | 1 |

| | Sotatercept (N=163) | Placebo (N=160) |
|---|---|---|
| | *no. (%)* | |
| Total no. of patients who died or had ≥1 clinical worsening event | 9 (5.5) | 42 (26.2) |
| Assessment of first occurrence of either death or nonfatal clinical worsening event | | |
| Death as first event | 2 (1.2) | 6 (3.8) |
| Worsening-related listing for lung or heart–lung transplantation | 1 (0.6) | 1 (0.6) |
| Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10% | 2 (1.2) | 17 (10.6) |
| Atrial septostomy | 0 | 0 |
| Pulmonary arterial hypertension–related hospitalization for ≥24 hr | 0 | 7 (4.4) |
| Worsening of pulmonary arterial hypertension | 4 (2.5) | 15 (9.4) |

**Figure 2. Time to First Occurrence of Death or Nonfatal Clinical Worsening Event (Intention-to-Treat Population).**

Shown are Kaplan–Meier curves for the probability of a first adjudicated end-point event, presented according to trial group, through the data-cutoff date (August 26, 2022) in the intention-to-treat population. The adjudicated end point in this time-to-event analysis was the first event of clinical worsening, which was defined as a composite of death from any cause, worsening-related listing for lung or heart–lung transplantation, initiation of rescue therapy with an approved medication for pulmonary arterial hypertension or increase in the prostacyclin dose by at least 10%, atrial septostomy, hospitalization for worsening pulmonary arterial hypertension (≥24 hours), or worsening of pulmonary arterial hypertension. The hatch marks on each curve represent censored data. The incidence of death and nonfatal clinical worsening events at the data-cutoff date are shown below the graph. No formal between-group comparisons were performed for death or any of the nonfatal clinical worsening events. The log-rank test of sotatercept as compared with placebo was stratified according to the randomization factors of background therapy (monotherapy or double therapy vs. triple therapy) and baseline World Health Organization functional class (II vs. III). Dates and times of reported adverse events were used by the adjudication committee to determine death or first nonfatal clinical worsening event. Patients could have more than one assessment for the first occurrence of death or nonfatal clinical worsening event. A single patient could have more than one clinical worsening event but was counted only once for the analysis.

interest included bleeding events (in 35 patients [21.5%] in the sotatercept group and 20 [12.5%] in the placebo group; mostly nonserious epistaxis and gingival bleeding) and thrombocytopenia (in 10 patients [6.1%] in the sotatercept group and 4 [2.5%] in the placebo group).

The mean hemoglobin level increased by 1.3 g per deciliter in the sotatercept group and decreased by 0.1 g per deciliter in the placebo group at week 24. In the sotatercept group, hemoglobin increased by more than 2.0 g per deciliter in 20 patients (12.3%) through the data-cutoff date (Table S22). No patients in either group had increases in the hemoglobin level above 4.0 g per deciliter through the data-cutoff date. The mean platelet count decreased by $15.9\times10^9$ per liter in the sotatercept group and increased by $1.1\times10^9$ per liter in the placebo group at week 24 (further details on platelet counts through the data-cutoff date are provided in Table S23).

**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) |

* Shown are adverse events that occurred up to and including day 56 after the last dose of sotatercept or placebo. The safety population includes all randomly assigned patients who received at least one dose of sotatercept or placebo. NR denotes not reported.

† Shown is the point estimate for the between-group difference. The 95% confidence intervals were calculated with the use of the Miettinen and Nurminen method. The confidence interval is not provided when the incidence is less than 4 in both trial groups.

‡ These events were suspected to be related to sotatercept or placebo by the trial investigator.

§ A severe adverse event was any adverse event that was deemed to be severe in intensity by the trial investigator.

¶ A serious adverse event was defined as any untoward medical event that results in death, is life-threatening, warrants hospitalization or causes prolongation of existing hospitalization, results in persistent or clinically significant disability or incapacity, may have caused a congenital abnormality or birth defect, or warrants intervention to prevent permanent impairment or damage.

‖ Adverse events of interest (bleeding events, cardiac events, embryo or fetal toxic effects, hepatic toxic effects, immunogenicity, increased blood pressure, increased hemoglobin levels, leukopenia, neutropenia, renal toxic effects, suppression of follicle-stimulating hormone, thrombocytopenia, and thromboembolic events) and special interest (telangiectasia) were predefined variables that were monitored to assess the overall safety profile of sotatercept. Only those adverse events of interest and special interest in which the point estimate for the between-group difference excluded zero in the 24-week analysis (Table S20), the cumulative analysis (Table S21), or both are shown here. These two supplementary tables include details on the prespecified search strategies for adverse events of interest and special interest.

A total of 17 patients (10.4%) in the sotatercept group and 5 patients (3.1%) in the placebo group had telangiectasia, a predefined adverse event of special interest. None of these events were severe or serious. Increased blood pressure was more frequently reported in the sotatercept group than in the placebo group through the data-cutoff date.

In accordance with protocol-specified criteria, 13 patients (3 [1.8%] in the sotatercept group and 10 [6.2%] in the placebo group) discontinued the trial regimen during the 24-week treatment period owing to adverse events. There were no discontinuations due to thrombocytopenia or increased hemoglobin levels.

Two patients (1.2%) in the sotatercept group and seven patients (4.4%) in the placebo group died through the data-cutoff date. The causes of death are listed in Table S25.

## DISCUSSION

In the STELLAR trial, the addition of 24-week treatment with sotatercept to background therapy with currently available medications improved exercise capacity as assessed by 6-minute walk distance in patients with pulmonary arterial hypertension. Improvements were also observed in pulmonary vascular resistance, WHO functional class, NT-proBNP levels, risk of death assessed by means of the simplified French risk model, and the Physical Impacts and Cardiopulmonary Symptoms domain scores of the PAH-SYMPACT quality-of-life tool. The risk of death or nonfatal clinical worsening events, assessed up to the end of the trial, was 84% lower with sotatercept than with placebo. The safety profile of sotatercept was consistent with that observed in the phase 2 PULSAR trial,[11,12] including its extension study, with the most notable side effects being telangiectasia and bleeding (mainly epistaxis and gingival bleeding).

The benefit of sotatercept on 6-minute walk distance was observed across most prespecified subgroups, including patients receiving triple background therapy with subcutaneous or intravenous prostacyclin analogues. Triple therapy is currently considered to be the maximum therapy for patients with pulmonary arterial hypertension.

The first secondary efficacy variable was clinical improvement defined by a multicomponent measurement, which encompasses treatment effects on 6-minute walk distance, NT-proBNP levels, and WHO functional class. In a recent registry analysis, multicomponent improvement was associated with a more than 50% reduction in the relative risk of death.[22] Whether multicomponent improvement represents a robust surrogate end point for clinical outcomes (including functional impairment, clinical worsening events, and death) is not known and will require validation in larger prospectively designed studies.

The adverse-event profile that was observed with sotatercept treatment was generally consistent with that reported in previous studies of sotatercept.[11,12] Increases in hemoglobin levels, a known effect of sotatercept, were reported as adverse events in 5.5% and 6.1% of the patients who received the trial drug through week 24 and trial completion, respectively. These increases were manageable with dose interruptions or reductions and were not associated with treatment discontinuations. The 24-week incidence of telangiectasia, an adverse event of special interest first noted during the PULSAR open-label extension,[13] was 10.4% among patients who received sotatercept and 3.1% among those who received placebo. Epistaxis and gingival bleeding were also more common among patients who received sotatercept. These adverse events were mostly considered to be mild by the investigators. Ongoing and future studies will continue to evaluate the incidence and clinical relevance of telangiectasia with longer-term treatment.

Limitations that affect the generalizability of these trial results to a broader population include the enrollment of only WHO functional class II or III patients with certain forms of pulmonary arterial hypertension. Patients with pulmonary arterial hypertension that is associated with connective-tissue disease, congenital heart disease, or drugs and toxins were underrepresented, as were minority groups and patients from outside North America and Europe. Furthermore, only patients with baseline pulmonary vascular resistance values of at least 400 dyn·sec·cm$^{-5}$ (≥5 Wood units) were eligible for enrollment, which is not reflective of the broader hemodynamic definition of pulmonary arterial hypertension in

the updated 2022 European Society of Cardiology–European Respiratory Society guidelines.[2,3] The clinical importance of the improvements observed in the PAH-SYMPACT Physical Impacts and Cardiopulmonary Symptoms domain scores is unknown because minimal clinically important differences have not been established. In addition, there was potential for unblinding owing to side effects such as telangiectasia or hematologic changes. The median treatment period of 7.5 months reported here precluded the ability to establish the long-term durability of the treatment response, including safety and adverse-event profile during long-term administration. These aspects will be further explored in the ongoing, open-label SOTERIA trial. Finally, STELLAR was neither designed nor powered to study the effects of sotatercept on mortality.

In this trial, treatment with sotatercept improved exercise capacity as determined by the 6-minute walk distance and showed clinical benefit across multiple efficacy end points. Sotatercept had a favorable benefit–risk ratio, findings that confirm and extend the results of previous studies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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## APPENDIX

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