ORIGINAL ARTICLE

Sotatercept for Pulmonary Arterial Hypertension within the First Year after Diagnosis

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ABSTRACT

BACKGROUND

Sotatercept, an activin-signaling inhibitor, reduces morbidity and mortality among patients with long-standing pulmonary arterial hypertension. Its effects in patients with pulmonary arterial hypertension within the first year after diagnosis are unclear.

METHODS

In this phase 3 trial, we enrolled adult patients with World Health Organization functional class II or III pulmonary arterial hypertension who had received the diagnosis less than 1 year earlier, had an intermediate or high risk of death, and were receiving double or triple background therapy. Patients were randomly assigned to receive add-on therapy with subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; escalated to target dose, 0.7 mg per kilogram) or placebo every 21 days. The primary end point was clinical worsening, a composite of death from any cause, unplanned hospitalization lasting at least 24 hours for worsening of pulmonary arterial hypertension, atrial septostomy, lung transplantation, or deterioration in performance in exercise testing due to pulmonary arterial hypertension, assessed in a time-to-first-event analysis.

RESULTS

The trial was stopped early owing to loss of clinical equipoise after the reporting of positive results from previous sotatercept trials. A total of 320 patients were included (160 each in the sotatercept and placebo groups). The median duration of follow-up was 13.2 months. At least one primary end-point event occurred in 17 patients (10.6%) in the sotatercept group and in 59 patients (36.9%) in the placebo group (hazard ratio, 0.24; 95% confidence interval, 0.14 to 0.41; P<0.001). Deterioration in performance in exercise testing due to pulmonary arterial hypertension occurred in 8 patients (5.0%) in the sotatercept group and in 46 patients (28.8%) in the placebo group; unplanned hospitalization for worsening of pulmonary arterial hypertension occurred in 3 patients (1.9%) and 14 patients (8.8%), respectively; and death from any cause occurred in 7 patients (4.4%) and 6 patients (3.8%). No cases of atrial septostomy or lung transplantation occurred. The most common adverse events with sotatercept were epistaxis (31.9%) and telangiectasia (26.2%).

CONCLUSIONS

Among adults with pulmonary arterial hypertension who had received the diagnosis less than 1 year earlier, the addition of sotatercept to background therapy resulted in a lower risk of clinical worsening than placebo. (Funded by Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]; HYPERION ClinicalTrials.gov number, NCT04811092.)

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*A complete list of the HYPERION trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Pulmonary arterial hypertension is a life-threatening condition characterized by progressive pulmonary vascular remodeling, luminal narrowing, and increased pulmonary vascular resistance, ultimately leading to right ventricular failure and death.[1,2] Established medical treatments for pulmonary arterial hypertension include endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin-pathway agents.[3] Despite treatment, disease progression, exercise limitation, and death can still occur in patients with pulmonary arterial hypertension.

Sotatercept, a first-in-class activin-signaling inhibitor, offers a novel approach in the management of pulmonary arterial hypertension by targeting ligands in the transforming growth factor β superfamily that are implicated in pulmonary vascular remodeling and cellular proliferation.[4-6] By improving the balance between proliferative and antiproliferative signaling, sotatercept is proposed to address one of the underlying causes of the disease.[4] Previous studies[7-13] — including the STELLAR trial[10] and the ZENITH trial[12] — have shown that sotatercept, when added to standard regimens for pulmonary arterial hypertension, increases exercise capacity and reduces morbidity and mortality among patients with long-standing pulmonary arterial hypertension who are receiving stable background therapy. These results suggest that sotatercept may affect disease progression in patients with pulmonary arterial hypertension. However, these studies predominantly enrolled patients with long-standing pulmonary arterial hypertension who were receiving stable background therapy — with a mean duration of 8 years since diagnosis — leaving a gap in the understanding of the effect of treatment with sotatercept in patients with pulmonary arterial hypertension within the first year after diagnosis.

In the event-driven HYPERION trial, we assessed the effects of early initiation of sotatercept in patients with World Health Organization (WHO) functional class II or III pulmonary arterial hypertension who had received the diagnosis less than 1 year earlier, had an intermediate or high risk of death, and were receiving double or triple background therapy.

Methods

Trial Design and Oversight

HYPERION was a phase 3, double-blind, parallel-group, randomized, placebo-controlled trial. Patients were randomly assigned in a 1:1 ratio to receive add-on therapy with subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; escalated to target dose, 0.7 mg per kilogram) or placebo every 21 days. Randomization was stratified according to WHO functional class (II vs. III) and background therapy (double vs. triple). Dose adjustments followed prespecified criteria that were based on hemoglobin levels and platelet counts, with dose modifications indicated for the occurrence of telangiectasia and serious bleeding. Patients were considered to have completed the trial when they had a primary endpoint event that was confirmed by an independent adjudication committee or when the trial was terminated, at which point they were given the option to transition into the long-term, open-label follow-up study of sotatercept, SOTERIA (ClinicalTrials.gov number, NCT04796337) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The trial was conducted in accordance with the principles of Good Clinical Practice originating from the Declaration of Helsinki. Written informed consent was obtained from all the patients before enrollment. The protocol (available at NEJM.org) and all amendments were approved by the appropriate ethics body at each participating site. An independent data monitoring committee provided oversight and had the authority to recommend trial modifications or termination.

The sponsor (Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]) and an external steering committee designed the trial. The sponsor oversaw the monitoring of the trial and performed the analyses. All the authors participated in the interpretation of the data, review of the manuscript, and the decision to submit the manuscript for publication. The academic authors had full access to the data. All the authors had the authority to request ad hoc analyses. The first author drafted the initial manuscript with editorial support from a sponsor-employed medical writer. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Eligible patients were adults (≥18 years of age) with WHO functional class II or III group 1 pulmonary arterial hypertension (idiopathic, heritable, induced by drugs or toxins, associated with connective-tissue disease, or associated with simple congenital systemic-to-pulmonary shunts occurring ≥1 year after repair) who had received the diagnosis less than 1 year earlier and had an intermediate or high risk of death, which was defined as a REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) Lite 2 risk score of 6 or higher or a COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) 2.0 risk score of 2 or higher. The REVEAL Lite 2 risk score is based on six noninvasively measured variables: WHO or New York Heart Association functional class, systolic blood pressure, heart rate, 6-minute walk distance, N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, and renal function. Scores range from 1 to 14, with higher scores indicating a greater 1-year risk of death.[14,15] The COMPERA 2.0 risk score is based on WHO functional class, 6-minute walk distance, and NT-proBNP level. Scores of 1, 2, 3, and 4 correspond to a low, intermediate–low, intermediate–high, and high risk of transplantation-free death within 1 year, respectively.[16]

Hemodynamic measurements had been obtained at the time of the diagnosis of pulmonary arterial hypertension by means of right heart catheterization. If the diagnostic right heart catheterization did not provide all the necessary hemodynamic measurements to meet the inclusion criteria, then right heart catheterization was conducted as a screening procedure. The date of diagnosis was defined as the date on which the diagnostic right heart catheterization had been performed. Key inclusion criteria were a pulmonary vascular resistance of at least 320 dyn·sec·cm^{-5} (≥4 Wood units) and a pulmonary artery wedge pressure or left ventricular end-diastolic pressure of 15 mm Hg or lower. Patients were required to have received stable doses of double or triple therapy for pulmonary arterial hypertension for at least 90 days before screening. Key exclusion criteria were pulmonary arterial hypertension associated with portal hypertension, human immunodeficiency virus infection, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis; pulmonary hypertension other than group 1 pulmonary arterial hypertension; a left ventricular ejection fraction of less than 50%; clinically significant mitral- or aortic-valve disease; or other clinically significant coexisting conditions or laboratory abnormalities.

EFFICACY END POINTS

The primary efficacy end point was clinical worsening, a composite of death from any cause, unplanned hospitalization lasting at least 24 hours for worsening of pulmonary arterial hypertension, atrial septostomy, lung transplantation, or deterioration in performance in exercise testing due to pulmonary arterial hypertension, assessed in a time-to-first-event analysis. Deterioration in performance in exercise testing due to pulmonary arterial hypertension was defined as any decrease from baseline in the mean 6-minute walk distance on two consecutive tests performed at least 4 hours apart, accompanied by one or more of the following: worsening of the WHO functional class, symptoms or signs of increased right ventricular failure, the initiation of a new background therapy for pulmonary arterial hypertension, or a change in the delivery route of background therapy to parenteral. Events other than death were recorded only during the trial, whereas deaths were recorded both during and after the trial, up to the day of the final database lock. All potential primary endpoint events were adjudicated by an independent adjudication committee whose members were unaware of the trial-group assignments.

Secondary end points were the following: multicomponent improvement (an increase from baseline in the 6-minute walk distance by ≥30 m, a decrease from baseline in the NT-proBNP level by ≥30% or an NT-proBNP level of <300 pg per milliliter, and improvement from baseline in WHO functional class or maintenance of WHO functional class II) at week 24; a low REVEAL Lite 2 risk score (≤5) at week 24; a low simplified French risk score at week 24; the change from baseline in the NT-proBNP level at week 24; improvement from baseline in WHO functional class or maintenance of WHO functional class II at week 24; the change from baseline in the 6-minute walk distance at week 24; overall survival, assessed

in a time-to-event analysis; and the change from baseline in the PAH-SYMPACT (Pulmonary Arterial Hypertension–Symptoms and Impact) domain scores at week 24. The simplified French risk score is a binary disease-specific risk-assessment measure that is based on three noninvasively measured variables: WHO functional class, 6-minute walk distance, and NT-proBNP level.[17] The presence of all three of the following criteria indicates a low risk of death: WHO functional class I or II, 6-minute walk distance of more than 440 m, and NT-proBNP level of less than 300 pg per milliliter. PAH-SYMPACT domain scores are disease-specific patient-reported outcome measures in physical, cardiopulmonary, and cognitive and emotional domains; scores range from 0 to 4, with higher scores indicating a greater severity of symptoms.

SAFETY END POINTS

Safety assessments included adverse events, laboratory test results, vital signs, and physical examination findings. Adverse events of interest (increased hemoglobin level, thrombocytopenia, immunogenicity, increased blood pressure or hypertension, thromboembolic events, bleeding events, renal toxic effects, hepatic toxic effects, and cardiac events) and an adverse event of special interest (telangiectasia) were identified with the use of predefined standardized *Medical Dictionary for Regulatory Activities* (MedDRA) queries or grouped preferred terms. These events were selected on the basis of the mechanism of action of sotatercept, preclinical data, and previous clinical findings.

STATISTICAL ANALYSIS

The planned sample size was 444 patients. Assuming a hazard ratio of 0.55 for the primary efficacy end point, we estimated that 121 events would need to occur by the time of the final analysis (anticipated to occur at 44 months) to provide the trial with 90% power (with a one-sided type I error rate of 0.025). An interim analysis was planned to be performed after approximately 61 events had accrued.

However, while the HYPERION trial was ongoing, a prespecified interim analysis of the ZENITH trial showed a statistically significant and clinically meaningful reduction in morbidity and mortality with sotatercept as compared with placebo among adults with WHO functional class III or IV pulmonary arterial hypertension who had a high risk of death.[12] The results of the ZENITH trial, in addition to the totality of data from previous sotatercept studies, led the sponsor and the external steering committee to conclude that the HYPERION trial had lost clinical equipoise and needed to be stopped before its interim analysis so that all eligible patients could receive sotatercept either in the extension study (SOTERIA) or through commercial access, where available. Therefore, after notifying the data monitoring committee, the sponsor and steering committee decided to close the HYPERION trial,[18] forgoing the interim analysis and proceeding to the final analysis using all available patient data. The sponsor and steering committee remained unaware of the trial-group assignments at the time that the decision was made, and blinding was continued until after the database lock.

For the final analysis, an alpha level of 0.025 (one-sided) or 0.05 (two-sided) was used. The type I error rate was controlled with the use of a hierarchical testing strategy, starting with the primary end point and continuing with the secondary end points in the order presented above, and stopping at the first nonsignificant result. For end points that were ineligible for statistical testing, unadjusted 95% confidence intervals are provided. These 95% confidence intervals should not be interpreted as definitive evidence of an effect in the absence of statistical testing. No formal comparisons between the trial groups were made for the individual components of the primary end point.

Efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization, except for one patient who withdrew from the trial immediately after randomization and before receiving any doses of sotatercept or placebo. Patients who had not reached week 24 at the time of the premature trial termination were excluded from analyses of secondary end points, which were assessed at week 24. Safety analyses included all the patients who had undergone randomization and had received at least one dose of sotatercept or placebo.

Time-to-event analyses were performed with the log-rank test and Cox proportional-hazards regression model, with stratification according to randomization factors (WHO functional class and background therapy). Continuous end points were analyzed by means of the aligned-rank Wilcoxon test with Hodges–Lehmann location shifts, with stratification according to randomization factors. For continuous end points assessed at

week 24, patients who died before week 24 were assigned the worst-rank score, and those with nonfatal clinical worsening received the next worst-rank score. Multiple imputation was used for other missing data. PAH-SYMPACT domain scores were not eligible for statistical testing if there was low patient participation in the assessment (<50%), as prespecified in the statistical analysis plan, available with the protocol. Dichotomous end points were assessed with the Cochran–Mantel–Haenszel test and the method of Miettinen and Nurminen,[19] with stratification according to randomization factors; patients with missing values were considered to not have a response. Safety data were analyzed descriptively; differences in percentages and 95% confidence intervals were calculated with the method of Miettinen and Nurminen. Prespecified subgroup analyses were performed for the primary efficacy end point and any secondary efficacy end points that had significant results. Further details regarding the trial design and statistical methods are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

The first patient was enrolled on April 8, 2022. The trial was ended early by the sponsor and the external steering committee on January 30, 2025. Afterward, all 233 eligible patients transitioned into the SOTERIA study, with the final rollover occurring on April 3, 2025.

During the screening period, 441 patients were assessed for eligibility, 120 (27.2%) of whom were excluded (Fig. S2). The primary reasons for screening failure were not having a REVEAL Lite 2 risk score of 6 or higher or a COMPERA 2.0 risk score of 2 or higher (Table S1). A total of 321 patients underwent randomization, including 1 patient who was withdrawn from the trial without having received any doses of sotatercept or placebo and was excluded from all analyses. Consequently, 320 patients (160 in the sotatercept group and 160 in the placebo group) were included in the intention-to-treat population (Table S2). The median duration of follow-up was 14.6 months (range, 0.7 to 35.0) in the sotatercept group and 11.5 months (range, 0.7 to 34.4) in the placebo group (Table S3). The overall median duration of follow-up was 13.2 months (range, 0.7 to 35.0).

The demographic and clinical characteristics of the patients at baseline are shown in Table 1 and Table S4. The baseline characteristics were generally similar in the two trial groups. Background therapies for pulmonary arterial hypertension are summarized in Table S5. The representativeness of the trial population is shown in Table S6. Exposure to sotatercept, dose modifications, and adherence to treatment are summarized in Tables S7, S8, and S9, respectively.

PRIMARY EFFICACY END POINT

In the primary analysis, at least one event indicative of clinical worsening occurred in 17 patients (10.6%) in the sotatercept group and in 59 patients (36.9%) in the placebo group (hazard ratio, 0.24; 95% confidence interval [CI], 0.14 to 0.41; P<0.001) (Fig. 1, Table 2, and Table S10). Overall, 76 patients had 80 primary end-point events that were recorded as first events. Four patients in the placebo group each had the same 2 concurrent primary end-point events: deterioration in performance in exercise testing due to pulmonary arterial hypertension and unplanned hospitalization lasting at least 24 hours for worsening of pulmonary arterial hypertension.

Of the 84 primary end-point events that were recorded in the database, 54 were cases of deterioration in performance in exercise testing due to pulmonary arterial hypertension, 17 were cases of unplanned hospitalization for worsening of pulmonary arterial hypertension, and 13 were deaths. No cases of atrial septostomy or lung transplantation occurred in the trial. Of the 54 patients with deterioration in performance in exercise testing due to pulmonary arterial hypertension, 30 had a decrease from baseline in the 6-minute walk distance by 15% or greater, 8 had a decrease by 10% to less than 15%, 11 had a decrease by 5% to less than 10%, and 5 had a decrease by less than 5% (Table S11). A detailed breakdown of primary end-point events according to trial group is provided in Table 3. Four primary end-point events were not recorded as first events: 3 were cases of unplanned hospitalization for worsening of pulmonary arterial hypertension (2 in the placebo group and 1 in the sotatercept group), and 1 was a death (in the placebo group). Findings across all prespecified subgroups appeared to be consistent with the overall treatment effect (Fig. S3).

SECONDARY EFFICACY END POINTS

A total of 33 patients had not reached week 24 at the time of the early trial termination and were excluded from analyses of secondary end points.

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

Characteristic	Sotatercept (N=160)	Placebo (N=160)	Total (N=320)
Female sex — no. (%)	120 (75.0)	112 (70.0)	232 (72.5)
Age			
Mean — yr	57.3±15.4	55.0±17.3	56.2±16.4
≥65 yr — no. (%)	68 (42.5)	62 (38.8)	130 (40.6)
Geographic region — no. (%)			
North America	21 (13.1)	21 (13.1)	42 (13.1)
South America	20 (12.5)	19 (11.9)	39 (12.2)
Europe	96 (60.0)	98 (61.2)	194 (60.6)
Asia–Pacific	23 (14.4)	22 (13.8)	45 (14.1)
Race or ethnic group — no. (%)†			
White	140 (87.5)	136 (85.0)	276 (86.2)
Other	20 (12.5)	24 (15.0)	44 (13.8)
Body-mass index‡			
Mean	27.9±5.9	27.8±6.2	27.8±6.1
≥30 — no. (%)	48 (30.0)	51 (31.9)	99 (30.9)
Time since diagnosis of pulmonary arterial hypertension — mo§			
Mean	7.4±3.1	7.0±2.9	7.2±3.0
Median (range)	7.4 (0.1–14.5)	6.9 (0.3–13.0)	7.1 (0.1–14.5)
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	103 (64.4)	87 (54.4)	190 (59.4)
Heritable	11 (6.9)	8 (5.0)	19 (5.9)
Associated with connective-tissue disease	39 (24.4)	58 (36.2)	97 (30.3)
Induced by drugs or toxins	4 (2.5)	4 (2.5)	8 (2.5)
Associated with corrected congenital shunts	3 (1.9)	3 (1.9)	6 (1.9)
REVEAL Lite 2 risk score — no. (%)¶			
Low: ≤5	29 (18.1)	37 (23.1)	66 (20.6)
Intermediate: 6 or 7	84 (52.5)	79 (49.4)	163 (50.9)
High: ≥8	47 (29.4)	43 (26.9)	90 (28.1)
Missing data	0	1 (0.6)	1 (0.3)
COMPERA 2.0 risk score — no. (%)‖			
Low: 1	1 (0.6)	5 (3.1)	6 (1.9)
Intermediate–low: 2	105 (65.6)	100 (62.5)	205 (64.1)
Intermediate–high: 3	49 (30.6)	54 (33.8)	103 (32.2)
High: 4	5 (3.1)	0	5 (1.6)
Missing data	0	1 (0.6)	1 (0.3)
WHO functional class — no. (%)**			
II	36 (22.5)	32 (20.0)	68 (21.2)
III	124 (77.5)	128 (80.0)	252 (78.8)
Background therapy for pulmonary arterial hypertension — no. (%)††			
Double therapy	116 (72.5)	115 (71.9)	231 (72.2)
Triple therapy	44 (27.5)	45 (28.1)	89 (27.8)
Prostacyclin infusion therapy	26 (16.2)	27 (16.9)	53 (16.6)
6-Minute walk distance — m	357.6±90.9	352.3±95.6	354.9±93.2
Coexisting conditions — no. (%)‡‡			
Diabetes mellitus	35 (21.9)	37 (23.1)	72 (22.5)
Hypertension	66 (41.2)	72 (45.0)	138 (43.1)
Obesity	49 (30.6)	52 (32.5)	101 (31.6)
Coronary heart disease	21 (13.1)	22 (13.8)	43 (13.4)

Table 1. (Continued.)

Characteristic	Sotatercept (N=160)	Placebo (N=160)	Total (N=320)
No. of coexisting conditions — no. (%)			
None	57 (35.6)	51 (31.9)	108 (33.8)
1 or 2	85 (53.1)	91 (56.9)	176 (55.0)
≥3	18 (11.2)	18 (11.2)	36 (11.2)
NT-proBNP level — pg/ml	1123.5±2394.7	788.1±1003.1	956.3±1842.7
Pulmonary vascular resistance — dyn·sec·cm^{-5}§§	939.3±385.7	893.3±406.7	916.3±396.4
Hemoglobin level — g/dl	13.4±1.5	13.4±1.7	13.4±1.6
Estimated glomerular filtration rate — ml/min/1.73 m^2	80.5±27.8	86.3±31.9	83.4±30.0

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The measurements summarized in the table were obtained during the screening visit unless otherwise noted. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.

† Race or ethnic group was reported by the patient. The "other" category includes Black, Asian, American Indian or Alaska Native, or other.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The time since the diagnosis of pulmonary arterial hypertension was determined by counting the number of days from the date of diagnosis to the date of informed consent (enrollment), adding 1 day, and then dividing the sum by 30.4367. Two patients had a protocol deviation with a time since the diagnosis of pulmonary arterial hypertension of more than 1 year (442 days in one patient in the sotatercept group; 397 days in one patient in the placebo group).

¶ The REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) Lite 2 risk score is based on six noninvasively measured variables: World Health Organization (WHO) or New York Heart Association functional class, systolic blood pressure, heart rate, 6-minute walk distance, NT-proBNP level, and renal function. Scores range from 1 to 14, with higher scores indicating a greater 1-year risk of death.

‖ The COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) 2.0 risk score is based on WHO functional class, 6-minute walk distance, and NT-proBNP level. Scores of 1, 2, 3, and 4 correspond to a low, intermediate–low, intermediate–high, and high risk of transplantation-free death within 1 year, respectively.

** WHO functional classes range from I to IV, with higher classes indicating greater functional limitations. The WHO functional class reported in this table was assessed at the first visit before the first dose was administered.

†† Background therapy was not prespecified in the protocol; patients were treated according to the judgment of their respective physicians and local clinical practice. Treatments included double 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 (intravenous epoprostenol and intravenous or subcutaneous treprostinil) were also included in one of the other categories of therapy.

‡‡ Coexisting conditions were identified with the use of standardized *Medical Dictionary for Regulatory Activities* (MedDRA) terms. Diabetes mellitus included the terms diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, and glucose tolerance impaired; hypertension included the terms hypertension and essential hypertension; obesity included the terms obesity and body-mass index ≥30; and coronary heart disease included the terms coronary artery disease, coronary arterial stent insertion, coronary angioplasty, arteriosclerosis coronary artery, coronary artery stenosis, myocardial ischemia, myocardial infarction, acute myocardial infarction, and angina pectoris.

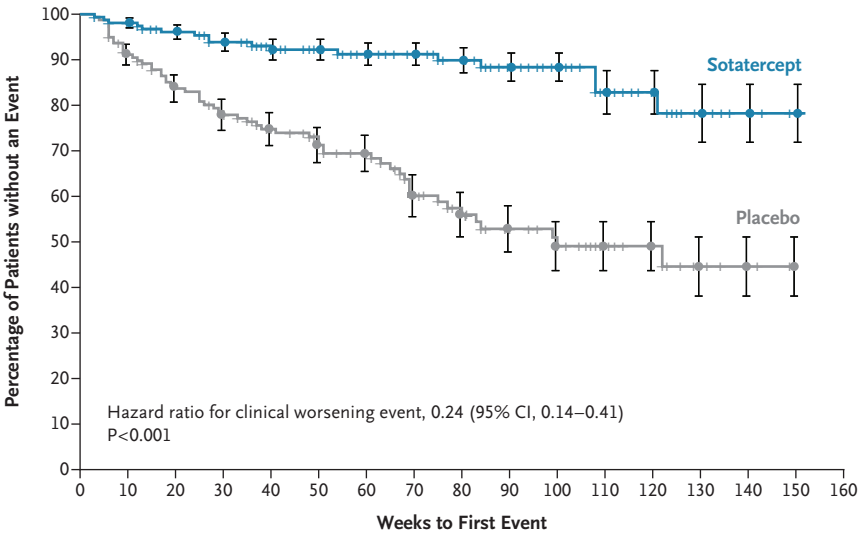
§§ Most measurements had been obtained at the time of the diagnosis of pulmonary arterial hypertension by means of right heart catheterization. If the diagnostic right heart catheterization did not provide all the necessary measurements to meet the inclusion criteria, right heart catheterization was conducted as a screening procedure, with results reported in the database.

Multicomponent improvement at week 24 and a low REVEAL Lite 2 risk score at week 24 occurred in a higher percentage of patients in the sotatercept group than in the placebo group (Table S12). The difference between the two groups in the percentage of patients with a low simplified French risk score at week 24 was not significant, and therefore, subsequent secondary end points in the hierarchy were not eligible for statistical testing (Table 2).

The analysis of overall survival, the analysis of PAH-SYMPACT domain scores, missing data for continuous and binary end points, and post hoc sensitivity analyses of continuous and binary efficacy end points are summarized in Tables S13, S14, S15, and S16, respectively. Results were robust to missing-data assumptions, except those for low REVEAL Lite 2 risk score, which showed sensitivity when the assumption in the imputation was conservative.

SAFETY

The median duration of follow-up was longer in the sotatercept group than in the placebo group (14.6 months vs. 11.5 months). Adverse events were reported in 89.4% of the patients in the sotatercept group and in 90.0% of those in the placebo group (Table 4). Among the adverse events



No. at Risk																	
Sotatercept	160	152	138	125	109	95	87	75	63	53	40	26	21	10	4	2	0
Placebo	160	142	122	107	92	80	70	50	40	31	27	16	11	5	2	1	0
No. of Events																	
Sotatercept	3	3	3	1	1	1	0	1	1	0	2	0	1	0	0	0	0
Placebo	13	11	8	5	2	4	8	2	3	1	1	0	1	0	0	0	0

Figure 1. Primary Efficacy End Point (Intention-to-Treat Population).

The primary efficacy end point was clinical worsening, a composite of death from any cause, unplanned hospitalization lasting at least 24 hours for worsening of pulmonary arterial hypertension, atrial septostomy, lung transplantation, or deterioration in performance in exercise testing due to pulmonary arterial hypertension, assessed in a time-to-first-event analysis. Deterioration in performance in exercise testing due to pulmonary arterial hypertension was defined as any decrease from baseline in the mean 6-minute walk distance on two consecutive tests performed at least 4 hours apart, accompanied by worsening of the World Health Organization (WHO) functional class, symptoms or signs of increased right ventricular failure, the initiation of a new background therapy for pulmonary arterial hypertension, or a change in the delivery route of background therapy to parenteral. All deaths that occurred up to the database lock were included, regardless of adjudication and regardless of whether they occurred during or after the patient's participation in the HYPERION trial, except for deaths that occurred after rollover to the SOTERIA study. Tick marks indicate censored data. I bars indicate 95% confidence intervals. The log-rank test used for comparing the sotatercept group with the placebo group was stratified according to randomization factors: WHO functional class (II vs. III) and background therapy (double vs. triple).

with an incidence of at least 10% in either group, the events with an incidence that was at least 5 percentage points higher with sotatercept than with placebo were epistaxis (in 31.9% vs. 6.9% of the patients) and telangiectasia (in 26.2% vs. 11.2%) (Table S17). Adverse events leading to discontinuation of the trial regimen were reported in 3.1% of the patients in the sotatercept group and in no patients in the placebo group (Table S18).

Adverse events that were considered by the investigator to be related to sotatercept or placebo are shown in Table S19. These events were more common with sotatercept than with placebo (in 57.5% vs. 30.0% of the patients). Serious adverse events occurred in 24.4% of the patients in the sotatercept group and in 28.1% of those in the placebo group (Table S20). Adverse events that were rated by the investigators as severe were reported in 20.0% of the patients in the sotatercept group and in 19.4% of those in the placebo group (Table S21). Serious adverse events leading to discontinuation of the trial regimen were reported in 0.6% of the patients in the sotatercept group and in no patients in the placebo group. Adverse events leading to death occurred in four patients (2.5%) in the sotatercept group and in five patients (3.1%) in the placebo group. The causes of death are listed in Table S22.

Adverse events of interest or special interest that occurred more frequently in the sotatercept group than in the placebo group were bleeding events (in 41.2% vs. 16.2% of the patients), telan-

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Sotatercept (N=160)	Placebo (N=160)	Treatment Effect (95% CI)
Primary end point			
Clinical worsening, time-to-first-event analysis — no. (%)†	17 (10.6)	59 (36.9)	0.24 (0.14 to 0.41)‡§
Secondary end points¶			
Multicomponent improvement at wk 24 — no./total no. (%)‖	42/143 (29.4)	21/144 (14.6)	14.45 (5.12 to 23.92)**††
Low REVEAL Lite 2 risk score at wk 24 — no./total no. (%)‡‡	86/143 (60.1)	69/144 (47.9)	12.34 (0.83 to 23.54)**§§
Low simplified French risk score at wk 24 — no./total no. (%)¶¶	26/143 (18.2)	19/144 (13.2)	4.98 (–3.48 to 13.64)**‖‖
Median change from baseline in NT-proBNP level at wk 24 (range) — pg/ml***	–199.3 (–211 to –188)	–10.3 (–18 to –7)	–308.6 (–434.84 to –182.37)†††
WHO functional class I or II at wk 24 — no./total no. (%)‡‡‡	79/143 (55.2)	56/144 (38.9)	15.62 (4.70 to 26.29)**
Median change from baseline in 6-minute walk distance at wk 24 (range) — m***	29.09 (28.0 to 32.5)	16.07 (14.3 to 19.6)	21.4 (4.65 to 38.24)†††
Death from any cause, time-to-event analysis — no. (%)	7 (4.4)	6 (3.8)	0.94 (0.31 to 2.81)‡

* Analyses were performed in the intention-to-treat population except where otherwise noted. Multiple imputation was used for missing data. Baseline was defined as the last measurement obtained before the first dose of sotatercept or placebo.

† Clinical worsening was a composite of death from any cause, unplanned hospitalization lasting at least 24 hours for worsening of pulmonary arterial hypertension, atrial septostomy, lung transplantation, or deterioration in performance in exercise testing due to pulmonary arterial hypertension, assessed in a time-to-first-event analysis. Deterioration in performance in exercise testing due to pulmonary arterial hypertension was defined as any decrease from baseline in the mean 6-minute walk distance on two consecutive tests performed at least 4 hours apart, accompanied by worsening of the WHO functional class, symptoms or signs of increased right ventricular failure, the initiation of a new background therapy for pulmonary arterial hypertension, or a change in the delivery route of background therapy to parenteral. All deaths that occurred up to the database lock were included, regardless of adjudication and regardless of whether they occurred during or after the patient's participation in the HYPERION trial, except for deaths that occurred after rollover to the SOTERIA study.

‡ The hazard ratio is shown. The hazard ratio was derived from a Cox proportional-hazards model with trial group as the covariate, with stratification according to randomization factors: WHO functional class (II vs. III) and background therapy (double vs. triple).

§ P<0.001 (one-sided) by the log-rank test with trial group as the covariate, with stratification according to randomization factors.

¶ A gatekeeping method was used to control the type I error rate across secondary end points. Secondary end points were tested in a prespecified sequential order; each subsequent test was conducted only if the previous test showed statistical significance, with an alpha level of 0.025 (one-sided) or 0.05 (two-sided). For the secondary efficacy end points that were ineligible for statistical testing, unadjusted 95% confidence intervals are provided. These 95% confidence intervals should not be interpreted as definitive evidence of an effect in the absence of statistical testing.

‖ Multicomponent improvement was defined as an increase from baseline in the 6-minute walk distance by at least 30 m, a decrease from baseline in the NT-proBNP level by at least 30% or an NT-proBNP level of less than 300 pg per milliliter, and WHO functional class I or II.

** The difference in percentage points is shown.

†† P=0.003 (two-sided) by the Cochran–Mantel–Haenszel method, with stratification according to randomization factors.

‡‡ A low REVEAL Lite 2 risk score was 5 or less.

§§ P=0.04 (two-sided) by the Cochran–Mantel–Haenszel method, with stratification according to randomization factors.

¶¶ The simplified French risk score is a binary disease-specific risk-assessment measure that is based on three noninvasively measured variables: WHO functional class, 6-minute walk distance, and NT-proBNP level. The presence of all three of the following criteria indicates a low risk of death: WHO functional class I or II, 6-minute walk distance of more than 440 m, and NT-proBNP level of less than 300 pg per milliliter.

‖‖ The P value did not meet the statistical criterion for superiority.

*** Data were available for 143 patients in the sotatercept group and 144 patients in the placebo group. The mean of medians across imputed datasets (with 95% confidence intervals) is shown if missing data were imputed.

††† The Hodges–Lehmann location shift from placebo estimate, which is the median of all paired differences, is shown.

‡‡‡ The end point was assessed as a change from baseline in WHO functional class from II to I, from III to I, or from III to II or maintenance of WHO functional class II.

giectasia (in 26.2% vs. 11.2%), and an increased hemoglobin level (in 11.2% vs. 1.2%) (Table S23). The imbalance in bleeding events was mostly due to the occurrence of nonserious epistaxis and gingival bleeding. Serious bleeding events occurred in 3.8% of the patients in the sotatercept group and in 1.9% of those in the placebo group (Table S24). Adverse events leading to withdrawal from the trial are summarized in Table S25. The percentage of patients with an upward shift in the hemoglobin level is shown in Table S26. Increased hemoglobin level can also be assessed with longitudinal laboratory data, which is independent of the assessment of investigator-reported adverse events. The mean increase in the hemoglobin level at week 24 was 1.2 g per deciliter in the sotatercept group and 0.0 g per deciliter in the placebo group (Table S27). The percentage of patients with a downward shift in the platelet count is shown in Table S28.

Table 3. Components of the Primary Efficacy End Point.*

Variable	Sotatercept (N=160)	Placebo (N=160)
	no. of patients (%)	
Death from any cause†	7 (4.4)	6 (3.8)
Unplanned hospitalization lasting ≥24 hr for worsening of pulmonary arterial hypertension	3 (1.9)	14 (8.8)
Atrial septostomy	0	0
Lung transplantation	0	0
Deterioration in performance in exercise testing due to pulmonary arterial hypertension‡	8 (5.0)	46 (28.8)

* Each component of the primary end point is shown as a standalone end point. A patient is included under more than one component if multiple events were observed. No formal comparisons between the trial groups were made for the individual components of the primary end point.

† All deaths were included, regardless of adjudication and regardless of whether they occurred during or after the patient's participation in the HYPERION trial, except for deaths that occurred after rollover to the SOTERIA study.

‡ Deterioration in performance in exercise testing due to pulmonary arterial hypertension was defined as any decrease from baseline in the mean 6-minute walk distance on two consecutive tests performed at least 4 hours apart, accompanied by worsening of the WHO functional class, symptoms or signs of increased right ventricular failure, the initiation of a new background therapy for pulmonary arterial hypertension, or a change in the delivery route of background therapy to parenteral.

DISCUSSION

In the HYPERION trial, the addition of sotatercept to standard background therapy within the first year after the diagnosis of pulmonary arterial hypertension resulted in a lower risk of clinical worsening events than placebo among patients at an intermediate or high risk of death, with a hazard ratio of 0.24. This treatment effect appeared to be consistent across all prespecified subgroups, including patients with connective-tissue disease, those receiving double therapy for pulmonary arterial hypertension, and those at intermediate risk according to the REVEAL Lite 2 risk score or at intermediate–low risk according to the COMPERA 2.0 risk score. It is notable that the early and sustained separation of Kaplan–Meier curves for the primary end point indicated that a clinical benefit could be detected after three doses of sotatercept, a finding reminiscent of the early effects observed in the ZENITH trial.[12] In practical terms, at 12 months, the absolute risk reduction was 22 percentage points, and the number needed to treat was 5, which indicated that treatment with sotatercept prevented one additional clinical worsening event for every five patients treated over a 12-month period, as compared with placebo.

The reduction in the risk of clinical worsening events with sotatercept was primarily driven by fewer cases of deterioration in performance in exercise testing due to pulmonary arterial hypertension (any decrease from baseline in the 6-minute walk distance, accompanied by worsening of the WHO functional class, symptoms or signs of increased right ventricular failure, the initiation of a new background therapy for pulmonary arterial hypertension, or a change in the delivery route of background therapy to parenteral) and unplanned hospitalizations for worsening of pulmonary arterial hypertension. Such events are considered to be important because nonfatal clinical worsening events in patients with pulmonary arterial hypertension are associated with an increased risk of subsequent death, a relationship underscoring the need to monitor and prevent disease progression in these patients.[20-24]

The HYPERION trial expands on evidence regarding the benefit–risk balance of sotatercept in patients with pulmonary arterial hypertension by showing its efficacy and safety early in the disease course, given that the STELLAR and ZENITH trials had enrolled patients with more long-standing pulmonary arterial hypertension. The HYPERION trial enrolled patients with pulmonary arterial hypertension who had received the diagnosis less than 1 year earlier and were also older and had more coexisting conditions than the patients enrolled in the STELLAR and ZENITH trials; these features aligned more closely with those of patients in contemporary registries,[25] representing a more real-world population. Although the trial allowed for the inclusion of patients with intermediate–high and high risk, most of the patients were classified as having

Table 4. Adverse Events.*

Event	Sotatercept (N=160)	Placebo (N=160)	Difference (95% CI)†
	no. of patients (%)		*percentage points*
Any adverse event	143 (89.4)	144 (90.0)	–0.6 (–7.5 to 6.3)
Adverse event leading to discontinuation of sotatercept or placebo	5 (3.1)	0	3.1 (0.7 to 7.1)
Adverse event related to sotatercept or placebo‡	92 (57.5)	48 (30.0)	27.5 (16.8 to 37.6)
Adverse event related to sotatercept or placebo leading to discontinuation of sotatercept or placebo‡	5 (3.1)	0	3.1 (0.7 to 7.1)
Adverse event leading to death§	4 (2.5)	5 (3.1)	–0.6 (–4.9 to 3.5)
Adverse event related to sotatercept or placebo leading to death‡	0	0	0.0 (–2.4 to 2.4)
Serious adverse event¶	39 (24.4)	45 (28.1)	–3.8 (–13.4 to 5.9)
Serious adverse event leading to discontinuation of sotatercept or placebo	1 (0.6)	0	0.6 (–1.7 to 3.5)
Serious adverse event related to sotatercept or placebo‡	4 (2.5)	1 (0.6)	1.9 (–1.2 to 5.7)
Serious adverse event related to sotatercept or placebo leading to discontinuation of sotatercept or placebo‡	1 (0.6)	0	0.6 (–1.7 to 3.5)
Adverse event of interest or special interest‖			
Any event	101 (63.1)	79 (49.4)	13.8 (2.9 to 24.3)
Bleeding event**	66 (41.2)	26 (16.2)	25.0 (15.3 to 34.4)
Cardiac event	9 (5.6)	23 (14.4)	–8.8 (–15.7 to –2.3)
Increased blood pressure or hypertension	11 (6.9)	3 (1.9)	5.0 (0.6 to 10.3)
Increased hemoglobin level	18 (11.2)	2 (1.2)	10.0 (5.2 to 16.0)
Telangiectasia	42 (26.2)	18 (11.2)	15.0 (6.6 to 23.5)
Adverse event with an incidence of ≥10% in either group			
Epistaxis	51 (31.9)	11 (6.9)	25.0 (16.8 to 33.3)
Anemia	19 (11.9)	14 (8.8)	3.1 (–3.7 to 10.1)
Palpitations	8 (5.0)	16 (10.0)	–5.0 (–11.2 to 0.8)
Diarrhea	24 (15.0)	23 (14.4)	0.6 (–7.3 to 8.5)
Nausea	14 (8.8)	20 (12.5)	–3.8 (–10.8 to 3.1)
Fatigue	22 (13.8)	15 (9.4)	4.4 (–2.7 to 11.6)
Peripheral edema	15 (9.4)	38 (23.8)	–14.4 (–22.6 to –6.4)
Coronavirus disease 2019	19 (11.9)	16 (10.0)	1.9 (–5.1 to 9.0)
Nasopharyngitis	17 (10.6)	21 (13.1)	–2.5 (–9.8 to 4.7)
Upper respiratory tract infection	19 (11.9)	15 (9.4)	2.5 (–4.4 to 9.5)
Cough	14 (8.8)	20 (12.5)	–3.8 (–10.8 to 3.1)
Dizziness	17 (10.6)	14 (8.8)	1.9 (–4.8 to 8.6)
Headache	22 (13.8)	24 (15.0)	1.2 (–9.1 to 6.6)
Dyspnea	20 (12.5)	32 (20.0)	–7.5 (–15.7 to 0.6)
Pulmonary arterial hypertension††	2 (1.2)	17 (10.6)	–9.4 (–15.3 to –4.7)
Telangiectasia	42 (26.2)	18 (11.2)	15.0 (6.6 to 23.5)

* Adverse events that occurred from the first dose of sotatercept or placebo through 56 days after the last dose were included in the analysis.
† The 95% confidence intervals should not be interpreted as definitive evidence of an effect in the absence of statistical testing.
‡ These adverse events were considered by the trial investigator to be related to sotatercept or placebo.
§ The number of patients who died from an adverse event differs from the number of deaths assessed for the primary and secondary end points that included death from any cause as a component. Adverse events leading to death were evaluated from the first dose of sotatercept or placebo through 56 days after the last dose.
¶ A serious adverse event is 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 major 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 or special interest are medical concepts that were searched with the use of prespecified standardized MedDRA queries or groupings of preferred terms. Adverse events of interest or special interest were selected on the basis of the mechanism of action of sotatercept, preclinical data, or previous clinical findings. Only the adverse events of interest or special interest for which the 95% confidence interval for the between-group difference excluded zero are shown in this table. Complete results and details regarding the prespecified search strategies for adverse events of interest or special interest are provided in the Supplementary Appendix.
** Bleeding events were adverse events identified with the standardized MedDRA query hemorrhages (excluding laboratory terms).
†† This term refers to the worsening of pulmonary arterial hypertension.

intermediate–low risk (64%) according to the COMPERA 2.0 risk score and having intermediate risk (51%) according to the REVEAL Lite 2 risk score at baseline. The majority were receiving double background therapy, with only 17% receiving intravenous prostacyclin therapy. Despite these differences, the HYPERION trial showed a benefit similar to that observed in previous trials of sotatercept.[7,10,12]

Although the ZENITH trial was stopped at the time of the interim analysis, the HYPERION trial was stopped before its interim analysis by the sponsor and external steering committee owing to loss of clinical equipoise after the reporting of positive results from the interim analysis of the ZENITH trial and review of the totality of data from previous sotatercept studies. Despite the early termination and truncated event accrual, the primary analysis showed significant results, indicating a reduction in the risk of clinical worsening events.

Among the secondary end points, multicomponent improvement and a low REVEAL Lite 2 risk score at 24 weeks had significant results, showing the efficacy of sotatercept in reaching or maintaining low-risk status in patients with pulmonary arterial hypertension. The third secondary end point, a low simplified French risk score, did not have significant results, perhaps owing to the older age of the trial population and the higher proportion of patients with coexisting conditions in this trial than in the STELLAR trial,[10] given that the risk tool includes a cutoff for the 6-minute walk distance of 440 m for low risk. The results for the subsequent secondary end points, which were not eligible for statistical testing, are suggestive of a potential benefit of sotatercept treatment on WHO functional class, 6-minute walk distance, and NT-proBNP level, findings consistent with the results of the STELLAR trial. The magnitude of the between-group difference in the change from baseline in the 6-minute walk distance (assessed with the Hodges–Lehmann location shift) was smaller than that observed in the STELLAR trial, possibly owing to differences in the patient population (e.g., age and coexisting conditions) and ongoing improvement resulting from the recent initiation of background therapy.

The safety profile of sotatercept in the HYPERION trial was generally consistent with that seen in previous trials.[7,10,12] The percentages of patients who had serious adverse events, severe adverse events, and adverse events leading to death were generally similar in the sotatercept and placebo groups. These findings are noteworthy, given the longer duration of exposure in the sotatercept group than in the placebo group. Adverse events leading to discontinuation of the trial regimen were infrequent and occurred only in the sotatercept group (3.1%).

Adverse events related to sotatercept included increased hemoglobin levels, bleeding events (mostly nonserious epistaxis and gingival bleeding), and telangiectasia. The percentage of patients who had serious bleeding events was higher in the sotatercept group than in the placebo group. A small mean increase in the hemoglobin level was observed in the sotatercept group, whereas no increase was seen in the placebo group; these findings are generally consistent with results of previous studies. The safety profile reflects the effects of sotatercept on erythropoiesis, hemostasis, and microvascular structure. Reports of thrombocytopenia were balanced between the two trial groups and did not account for the imbalance in the occurrence of bleeding events.

This trial has some limitations. First, early termination of the trial reduced the follow-up duration and limited enrollment, hindering longer-term safety and efficacy assessments and affecting the reporting of subsequent events, including deaths. Second, 33 patients (17 in the sotatercept group and 16 in the placebo group) did not reach the week 24 visit because of the early trial termination. Third, low patient participation (<50%) with the PAH-SYMPACT patient-reported outcome measure restricted the ability to draw conclusions about the effect of sotatercept on this quality-of-life measure. Fourth, secondary end points were tested at 24 weeks, and the results do not reflect longer-term efficacy. The ongoing, open-label SOTERIA study will help characterize the long-term efficacy and safety of sotatercept in patients with pulmonary arterial hypertension.[13] Fifth, although an increased hemoglobin level did not occur in all patients receiving sotatercept, nor did it occur in a predictable or immediate manner, the possibility of unintentional bias in subjective assessments cannot be fully ruled out. Sixth, although the patients in the HYPERION trial had received the diagnosis of pulmonary arterial hypertension closer to the time of enrollment than those in the STELLAR and ZENITH trials,[10,12] this trial population may not have had lower disease severity. Finally, whether sotatercept can be used as first-line therapy for pulmonary arterial hypertension remains to be determined.

Among adults with pulmonary arterial hypertension who had received the diagnosis less than 1 year earlier, the addition of sotatercept to background therapy resulted in a lower risk of clinical worsening than placebo.

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