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Sotatercept for Combined Post- and Pre-capillary Pulmonary Hypertension Associated With Heart Failure: Results from the Phase 2, Randomized, Placebo-Controlled CADENCE Study

Running title: *Gomberg-Maitland et al.; Sotatercept for CpcPH–HFpEF*

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Abstract

Background: Combined post- and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction (CpcPH–HFpEF) involves remodeling in both the heart and pulmonary vasculature. Despite significant mortality, there are no proven therapies.
Methods: In this multicenter, randomized, placebo-controlled, phase 2 trial, adults received sotatercept (0.3 or 0.7 mg/kg) or placebo every 3 weeks. The primary end point was change in pulmonary vascular resistance at week 24. Hodges–Lehmann shift estimates described placebo-adjusted changes.
Results: 164 patients were randomized 54:55:55 to sotatercept 0.3 mg/kg, 0.7 mg/kg, and placebo, and baseline median pulmonary vascular resistance was 5.2 (interquartile range [IQR] 4.0–6.9) Wood units. The median change from baseline in pulmonary vascular resistance at week 24 was −0.67 Wood units in the sotatercept 0.3 mg/kg group, −0.33 Wood units in the sotatercept 0.7 mg/kg group, and 0.26 Wood units in the placebo group. The Hodges–Lehmann shift estimates in pulmonary vascular resistance were −1.02 Wood units (95% CI, −1.81 to −0.23; *P*=0.004) for 0.3 mg/kg and −0.75 Wood units (95% CI, −1.52 to 0.03; *P*=0.024) for 0.7 mg/kg sotatercept. Reductions were observed in mean pulmonary arterial pressure (0.3 and 0.7 mg/kg: −9.19 mm Hg [95% CI, −13.00 to −5.38] and −9.22 [95% CI, −12.97 to −5.46]) and pulmonary arterial wedge pressure (0.3 and 0.7 mg/kg: −3.04 mm Hg [95% CI, −5.77 to −0.32] and −2.53 [95% CI, −5.33 to 0.28]). Changes in 6-minute walk distance were 20.3 meters (95% CI, 1.5–39.1) for 0.3 mg/kg and 5.8 meters (95% CI, −17.3 to 28.9) for 0.7 mg/kg sotatercept. The most common adverse events with sotatercept (both groups) were increased hemoglobin and diarrhea.
Conclusions: These findings provide proof of concept for improved pulmonary vascular and cardiac hemodynamics following activin signalling inhibition with sotatercept in patients with CpcPH–HFpEF.
Clinical trial registration: https://clinicaltrials.gov/study/NCT04945460, CADENCE ClinicalTrials.gov number: NCT04945460, Date of registration: June 22, 2021.

Key Words: Heart failure with preserved ejection fraction, Combined post- and pre-capillary pulmonary hypertension, Sotatercept, Pulmonary vascular resistance, Phase 2

Non-standard Abbreviations and Acronyms:

6MWD	6-minute walk distance
CI	Confidence interval
CpcPH	Combined post- and pre-capillary pulmonary hypertension
HFpEF	Heart failure with preserved ejection fraction
IQR	Interquartile range
mPAP	Mean pulmonary arterial pressure
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PVR	Pulmonary vascular resistance
sPAP	Systolic pulmonary artery pressure
TAPSE	Tricuspid annular plane systolic excursion
WHO	World Health Organization

Clinical Perspective

What is New?

- The CADENCE study establishes proof of concept for the activin signaling inhibitor sotatercept in patients with CpcPH–HFpEF, a condition without any approved treatments.

What Are the Clinical Implications?

- The CADENCE trial of sotatercept in patients with CpcPH–HFpEF met its primary end point, reducing pulmonary vascular resistance compared with placebo, with hemodynamic findings suggestive of direct pulmonary vascular and cardiac benefits.
- Secondary end points also point to potential benefits of clinical significance, alongside a well-tolerated safety profile.
- The results from CADENCE suggest that sotatercept may meet a significant unmet need in CpcPH–HFpEF and support advancing development into a confirmatory phase 3 trial.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome with substantial morbidity and mortality, for which effective disease-modifying therapies remain limited.[1,2] Some patients may progress to pulmonary hypertension related to HFpEF (World Health Organization [WHO] Group 2 pulmonary hypertension), which is defined as a resting mean pulmonary arterial pressure (mPAP) >20 mm Hg and pulmonary arterial wedge pressure (PAWP) >15 mm Hg.[3-5] There are two distinct subtypes of pulmonary hypertension associated with HFpEF: isolated post-capillary and combined post- and pre-capillary pulmonary hypertension (CpcPH), which are distinguished by the absence or presence of elevations in pulmonary vascular resistance (PVR; ≤2 or >2 Wood units, respectively).[3,4,6-8]

Elevated PVR in CpcPH associated with HFpEF (CpcPH–HFpEF) defines a distinct clinical syndrome and is linked to a worse prognosis;[8] it results from increased left heart and pulmonary venous pressures triggering a cascade of fibrosis, immune cell infiltration, and endothelial dysfunction in pulmonary arterioles and veins, which leads to abnormal pulmonary vascular remodeling, thickening of the vascular walls, luminal narrowing, and, ultimately, increased vascular resistance.[3,4,7,9-11] In turn, this drives increased pulmonary artery pressure, worsening right ventricle–pulmonary artery coupling, and, ultimately, right ventricular dysfunction that, added to the co-existing left ventricular dysfunction, reduces exercise capacity and results in increased hospitalization and mortality.[3,4,7,12-16]

Currently, there is no recommended pharmacological therapy to treat CpcPH–HFpEF.[3,4,7] Vasodilatory treatments proven efficacious in pulmonary arterial hypertension (PAH), the pathophysiology of which is limited to the pulmonary arteries and right side of the heart, have largely failed in HFpEF, and safety findings have suggested possible harm, including the development of edema and significant fluid retention.[3,4,7,12,17-20] Moreover,

guideline-directed medical therapies for HFpEF, although associated with improved outcomes in the overall HFpEF population, are unproven for the treatment of CpcPH.[3,4,7]

The activin signaling inhibitor sotatercept is the first non-vasodilatory therapy approved for the treatment of PAH.[21-24] In a pre-clinical model of pulmonary hypertension associated with HFpEF, a murine analog of sotatercept decreased pathological pulmonary vascular remodeling and improved ventricular function (left and right).[25] In the phase 2 CADENCE trial, we performed the first evaluation of sotatercept in patients with hemodynamically confirmed CpcPH–HFpEF.

Methods

Trial Design and Oversight

CADENCE is a phase 2, multicenter, double-blind, randomized trial that includes a 24-week placebo-controlled treatment period, followed by an active-drug extension period, evaluating the efficacy, safety, and tolerability of sotatercept in patients with CpcPH–HFpEF (Figure S1). Here, we report the main results from the placebo-controlled period. The clinical study protocol and statistical analysis plan are available in the Supplemental Material. This report adheres to the Consolidated Standards of Reporting Trials guidelines.

Patients were randomly assigned to receive subcutaneous sotatercept (0.3 mg/kg or 0.3 mg/kg for three dosing visits before dose was escalated to 0.7 mg/kg [target dose]) or placebo every 3 weeks according to a randomization schedule that was generated using a block size of 6 using a 1:1:1 allocation ratio. Randomization was stratified by baseline New York Heart Association (NYHA) functional class II or III status.[26] Randomization was generated by a computerized interactive response technology system. Dose modifications could be implemented for safety reasons at any time; specific guidelines were also available

to aid management of some specific events (elevated hemoglobin, reduced platelets, moderate telangiectasia, or serious bleeding; Table S1). Only the pharmacist preparing the study treatment was unblinded during the placebo-controlled treatment period. All other study personnel, all participants, and Sponsor personnel remained blinded to treatment assignments throughout the trial. Sotatercept and the matching placebo were supplied as lyophilized powder in labelled, rubber-stoppered Type I glass vials to ensure blinding of study treatments.

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 patients before enrolment. The protocol and all amendments were approved at each institution by the local institutional review board. 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 interpretation of the data, review of the manuscript, and the decision to submit the manuscript for publication. 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. The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is available at https://trialstransparency.msdclinicaltrials.com/policies-perspectives.aspx. Requests for access to the clinical study data can be submitted via email to the Data Access mailbox (dataaccess@msd.com).

Trial Population

Eligible patients were adults (18–85 years of age) with symptomatic CpcPH–HFpEF (NYHA functional class II or III) diagnosed by local investigator assessment of hemodynamics by right heart catheterization: mPAP >20 mm Hg; PAWP >15 and <30 mm Hg; PVR ≥4 Wood units (although CpcPH is clinically defined by PVR >2 Wood units,[3,4] CADENCE used a higher threshold cut-off to promote enrollment of patients with more advanced disease profiles). HFpEF was defined as heart failure with left ventricular ejection fraction ≥50% and no history of left ventricular ejection fraction <45% on more than two consecutive readings. During screening, the investigator also reviewed clinical characteristics, medical records, demographics, and laboratory measurements to confirm eligibility before dosing. This includes a requirement for stable guideline-directed therapies for HFpEF and achieving ≥100 m in two 6-minute walk distance (6MWD) tests (with results within 15% of each other). Key exclusion criteria were diagnosis of another form of pulmonary hypertension (WHO Groups 1, 3, 4, or 5), clinically significant and active lung disease, severe hepatic impairment and/or cirrhosis, and/or hospitalization for worsening medical conditions or significant surgery within 30 days of randomization (visit 1). Additional key inclusion and exclusion criteria are reported in Table S2.

Efficacy End Points

The primary efficacy end point was change from baseline in PVR at week 24. The key secondary efficacy end point was change from baseline in 6MWD at week 24. Other secondary efficacy end points included time to clinical worsening (defined as the time from first dose date to the first occurrence of any of the following events: all-cause death, non-elective hospitalization ≥24 h due to cardiopulmonary indication related to pulmonary hypertension and/or heart failure, administration of intravenous diuretics or subcutaneous

furosemide, or ≥15% decrease from baseline in 6MWD confirmed by two tests), change from baseline to week 24 in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, NYHA functional class, and hemodynamic and echocardiographic parameters. Right heart catheterization data were interpreted by a blinded, central assessor. Analyses used centrally determined values except if either baseline or week 24 tracings were not received by the central assessor, and local assessments were available for both timepoints. Readings considered uninterpretable by the central assessor were excluded.

Safety End Points

Safety assessments included adverse events and discontinuation of study treatment due to adverse events, laboratory test results, vital signs, and physical examination findings. Adverse events of interest were telangiectasia, intrapulmonary right-to-left shunting or pulmonary capillary dilatation (see Supplemental Appendix for a list of terms), increased hemoglobin, thrombocytopenia, and bleeding events, and were identified with the use of pre-defined standardized Medical Dictionary for Regulatory Activities queries or grouped preferred terms.

Statistical Analysis

The sample size was determined based on the primary efficacy end point. Assuming a true mean decrease of 1.15 Wood units for the primary end point in each sotatercept group versus 0 for placebo, and a common standard deviation of 1.9 Wood units, 45 per group was expected to provide 80% power using a one-sided alpha of 0.025. Approximately 150 patients were planned to be enrolled, assuming 10% dropout through to week 24.

Efficacy analyses were performed in the intention-to-treat population, which included all randomized patients, except for one patient who was randomized inadvertently and immediately discontinued (did not receive study treatment). Safety analyses included all

randomized patients who received at least one dose of sotatercept or placebo. An interim futility analysis was performed after approximately 75 patients completed 24 weeks of treatment (or discontinued treatment before 24 weeks).

The present analysis reports all available data from the placebo-controlled period. For PVR, *P*-values for sotatercept versus placebo were computed using the aligned-rank stratified Wilcoxon test,[27] and between-group differences with 95% confidence intervals (CIs) were estimated using Hodges–Lehmann location shifts.[28] For patients without data owing to death, the worst-rank score was imputed; for patients without data owing to a non-fatal clinical worsening event, the next worst-rank score was imputed.[29] For patients without data for other reasons, multiple imputation[30,31] was used. For the primary efficacy end point, subgroup analyses were pre-specified for sex, NYHA functional class, diabetes at baseline, medical history of atrial fibrillation at baseline, and atrial fibrillation type; the effect of cardiac output at baseline and atrial fibrillation status based on baseline electrocardiogram (yes/no) were assessed post-hoc.

The 6MWD, NT-proBNP levels, hemodynamic and echocardiography data were analyzed similarly to the primary end point. The hazard ratio for time to clinical worsening was estimated using a Cox proportional hazards model. Patients who completed the study to visit 9 without a clinical worsening event were censored at visit 9; those who did not reach visit 9 were censored at the last visit while still in the study. The odds ratio of the change from baseline at week 24 in NYHA functional class was analyzed by the Mantel–Haenszel method. All analyses were stratified by NYHA functional class II or III. For the incidence of adverse events, between-group differences and 95% CIs (using the Miettinen and Nurminen method[32]) were computed for terms that occurred in at least four patients in any treatment group.

The type 1 error rate for the primary and key secondary end points was controlled at 0.025 (one-sided) by testing PVR (sotatercept 0.7 mg/kg versus placebo then 0.3 mg/kg versus placebo) followed by 6MWD (sotatercept 0.7 mg/kg versus placebo then 0.3 mg/kg versus placebo), stopping at the first non-significant result. Unadjusted 95% CIs were calculated for other secondary end points; these should not be interpreted as definitive evidence of an effect in the absence of statistical testing.

Further details of the trial design and statistical methods are provided in the Supplementary Methods and Results.

Results

Trial Population

The first patient was randomized on January 19, 2022, and the last patient's last visit was on September 5, 2025. During the screening period, 319 patients were assessed for eligibility, 154 of whom were excluded for not meeting eligibility criteria. Reasons for screening failure are provided in Table S3. A total of 165 patients underwent randomization: one patient was randomized inadvertently (did not receive study treatment) and 164 patients represent the intention-to-treat population; 54 were assigned sotatercept 0.3 mg/kg, 55 were assigned sotatercept 0.7 mg/kg (escalated from 0.3 mg/kg), and 55 were assigned placebo (Figure S2). The median duration of follow-up in the placebo-controlled period was 5.6 months (interquartile range [IQR], 5.5–5.7) in the sotatercept 0.3 mg/kg group, 5.6 months (IQR, 5.5–5.8) in the sotatercept 0.7 mg/kg group, and 5.6 months (IQR, 5.5–5.8) in the placebo group.

The demographics and clinical characteristics of patients at baseline were generally balanced (Table 1). The median age was 75 years (IQR, 69–79) and 69.5% were female.

Baseline median PVR was 5.2 (IQR, 4.0–6.9) Wood units, median of the mPAP was 43.0 (IQR, 38.0–50.0) mm Hg, and median PAWP was 21.0 (IQR, 18.0–25.0) mm Hg. All patients were on guideline-directed medications for HFpEF at baseline (Table 1). The representativeness of the trial population is shown in Table S4. Dose modifications are summarized in Table S5.

Pulmonary Vascular Resistance and Associated Metrics

At week 24, sotatercept treatment resulted in statistically significant reductions in PVR compared with placebo. The median change from baseline was −0.67 Wood units in the sotatercept 0.3 mg/kg group, −0.33 Wood units in the sotatercept 0.7 mg/kg group, and 0.26 Wood units in the placebo group (Figure 1A, Figure S3, Table S6 and Table S7). The Hodges–Lehmann shift estimate versus placebo was −1.02 Wood units (95% CI, −1.81 to −0.23; *P*=0.004) for the sotatercept 0.3 mg/kg group and −0.75 Wood units (95% CI, −1.52 to 0.03; *P*=0.024) for the 0.7 mg/kg group (Table 2 and Figure 1A). Results were generally consistent across subgroups, including by the degree of elevation in PVR at baseline (Figures S4 and S5). Analysis of individual hemodynamic metrics identified decreases in mPAP, PAWP, cardiac output, and transpulmonary gradient, and improvements in several other hemodynamic parameters including measures of left- and right-sided cardiac structure and function (Table 2). Both doses had a similar absolute decrease in mPAP and PAWP, but the reduction in cardiac output was greater in the 0.7 mg/kg group than in the 0.3 mg/kg group compared with placebo. The right atrial pressure-to-PAWP ratio decreased in both sotatercept treatment groups compared with placebo (Table 2). Patients receiving sotatercept had increased hemoglobin levels (Figure S6); decreases in hematocrit-adjusted PVR were observed with both sotatercept dose levels (Table 2). Change from baseline at week 24 in

systemic blood pressure (and analysis of changes over 24 weeks) and heart rate are shown in Table 2, Figure S7, and Table S6.

Additional Secondary End Points

Further hemodynamic, echocardiography, functional and clinical results are summarized in Figure 2, Table 2, and Table 3. For the key secondary end point of week 24 change from baseline in 6MWD, a non-significant change versus placebo was observed in the 0.7 mg/kg group (Hodges–Lehmann shift estimate: 5.80 m [95% CI, −17.33 to 28.92]; *P*=0.295) and a nominal increase versus placebo occurred in the sotatercept 0.3 mg/kg group (Hodges–Lehmann shift estimate: 20.29 m [95% CI, 1.48 to 39.11]; Figure 2A, Figure S3, and Table S7). Analysis of 6MWD changes at week 24 by baseline NYHA functional class is shown in Figure S8. The time to first occurrence of a clinical worsening event was prolonged in sotatercept treatment groups compared with placebo and was more pronounced in the 0.3 mg/kg group (Figure 2C). NT-proBNP levels decreased in both sotatercept treatment groups compared with placebo (Figure 2B), and analysis of NT-proBNP changes at week 24 by baseline cardiac output is shown in Figure S9. In general, echocardiography parameters improved with both sotatercept dose levels compared with placebo. Improvements in right-sided hemodynamics included the tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (sPAP) ratio, measured as a surrogate of right ventricular–pulmonary artery coupling. Left-sided hemodynamic changes were also evident in the 0.3 mg/kg group, with a reduction in the PAWP and left atrial volume index (Table 3).

Safety

Adverse events were reported in 90.7% of patients in the 0.3 mg/kg group, 92.7% of patients in the sotatercept 0.7 mg/kg group, and 87.3% in the placebo group (Table 4, Table S8, and Table S9). Serious adverse events occurred in 20.4% of patients in the 0.3 mg/kg group,

32.7% of patients in the 0.7 mg/kg group, and 21.8% in the placebo group (Table 4 and Table S10). Discontinuation of trial medication because of adverse events occurred in three patients (5.5%) in the sotatercept 0.7 mg/kg group and no patients in the other groups. Adverse events with an incidence of at least 10% in any treatment group and all adverse events of interest or special interest are listed in Table 4. Details of bleeding events are reported in Table S11. Intrapulmonary right-to-left shunting or pulmonary capillary dilatation was not reported in any patients.

Adverse events led to death in one patient (1.8%) in the sotatercept 0.7 mg/kg group and two patients (3.6%) in the placebo group; the events leading to death are listed in Table S12.

Discussion

In this phase 2 study of patients with CpcPH–HFpEF receiving guideline directed therapy, both sotatercept doses (0.3 and 0.7 mg/kg) demonstrated statistically significant reductions in PVR compared with placebo over a 24-week treatment period. PVR is an invasive hemodynamic parameter calculated from the transpulmonary gradient (mPAP minus PAWP), divided by cardiac output. Assessment of these components suggested that decreases with sotatercept were driven by reductions in the transpulmonary gradient. A concordant reduction in right atrial pressure, mPAP, and PAWP indicated lower right- and left-sided filling pressures, and suggested treatment effects on both right and left heart function. The PAWP reduction is especially important, given the critical role of increased PAWP in the development of CpcPH progression in HFpEF. Together, these effects demonstrated a beneficial effect of sotatercept in lowering all three of the defining invasive hemodynamic features of CpcPH (elevated mPAP, PVR, and PAWP).[3,4]

Findings from invasive hemodynamics were corroborated by echocardiography data, with consistent reductions in pulmonary vascular pressure, markers of cardiac congestion (inferior vena cava diameter, estimated right atrial pressure, and left atrial volume index), and improvements in right ventricular–pulmonary artery coupling, as assessed by the TAPSE/sPAP ratio, supporting enhanced right ventricular functional efficiency. Both sotatercept doses were associated with reductions in NT-proBNP levels, which is a biomarker associated with clinical outcomes in pulmonary hypertension and heart failure.[1,3,4,33,34] Functionally, the 0.3 mg/kg dose improved 6MWD versus placebo, accompanied by parallel improvements in NYHA functional class, and showed exploratory evidence for a reduction in clinical worsening events (82% relative risk reduction). These findings provide proof of concept for sotatercept in CpcPH–HFpEF and indicate that the effects of activin signaling- inhibition have both pulmonary vascular and cardiac benefits that may translate into improvements in important clinical outcomes.

Sotatercept has consistently been shown to reduce PVR and improve right ventricular function in PAH.[21,35,36] CADENCE extends these findings to CpcPH–HFpEF and suggests pulmonary vascular selectivity of sotatercept,[35] as the predominant hemodynamic effects were observed in the pulmonary circulation. The magnitude of PVR reduction in patients with CpcPH–HFpEF in CADENCE was less than that reported in PAH sotatercept trials[21] but with a similar decrease in the mPAP. Notably, in the CpcPH–HFpEF patient population, the hemodynamic effect of sotatercept included favorable modulation of left-sided filling pressures, as evidenced by a significant reduction in PAWP. In this context, the more moderate decrease in PVR likely reflects the concomitant lowering of PAWP and should be interpreted within the framework of a broader improvement in cardiopulmonary hemodynamics. Moreover, in post-hoc analyses accounting for blood viscosity, the

reductions in PVR were greater after adjustment for hematocrit,[37] providing additional confirmation of pulmonary vascular benefits.

In addition to improvements in pulmonary and right-sided cardiac hemodynamics, CADENCE provides evidence of benefit in parameters beyond the pulmonary circulation suggestive of left-sided cardiac benefits, as reflected by reduction in PAWP and echocardiographic structural and functional measures, such as decrease in left atrial volume index. Notably, the reduction in PAWP observed in patients with CpcPH–HFpEF treated with sotatercept was of comparable magnitude to the effect of 24-week dapagliflozin treatment in patients with general HFpEF.[38] These observations align with pre-clinical data showing that a murine analog of sotatercept limits pulmonary vascular remodeling and reverses left and right ventricular changes in animal models of pulmonary hypertension associated with HFpEF,[25] providing a biologically plausible mechanism to explain the observed hemodynamic improvements in CADENCE. The distinct mechanism of action of sotatercept as an activin signaling inhibitor may explain these promising results in the CpcPH population, in contrast to other treatments proven beneficial in PAH but neutral or harmful in CpcPH–HFpEF, highlighting the need for novel approaches in this high-risk group. For example, tadalafil, a phosphodiesterase 5 inhibitor, and macitentan, an endothelin receptor antagonist, failed to show clinical benefit and resulted in some safety concerns.[7,17,18]

Recognizing that the hemodynamic response in pulmonary hypertension–HFpEF was potentially different from what has been observed in PAH, CADENCE was designed as a phase 2, dose-finding trial exploring a lower dose range and a titration schema distinct from those used in PAH. In patients with left-sided heart failure, changes in preload (PAWP) and afterload, including hemoglobin-related effects, may have distinct implications for overall cardiac performance compared with PAH, in which right ventricular afterload predominates.

Therefore, the dosing strategy was intended to explore a range that could provide pulmonary vascular benefit while balancing hemodynamic effects and the overall risk–benefit profile in this clinically complex population. The two doses of sotatercept studied in CADENCE did not show a consistent dose–response relationship across efficacy end points. Both were associated with hemodynamic improvements compared with placebo; however, the lack of a clear dose–response relationship may be attributable to factors such as limited sample size, heterogeneity in baseline risk profiles, and a potential ceiling effect at the 0.3 mg/kg dose. These findings also highlight potential differences in dose–response between PAH and CpcPH–HFpEF, and suggest that, in the CpcPH population, a lower dose may optimize the benefit–risk profile; a possibility that requires additional study to confirm the optimal dose. In considering the hemodynamic findings, we note that right heart catheterization was done at rest and, accordingly, these results cannot be extrapolated to any response to exercise hemodynamics.[36] Overall, the relevance of improvements in hemodynamic parameters was largely corroborated by changes in exploratory end points selected to detect clinical improvements. Notably, dose adjustments appeared more frequently at the higher dose, which should be considered when interpreting the comparative outcomes.

As a treatment with a non-vasodilatory mechanism of action, sotatercept differs from vasodilator therapies tried in this setting, for which reductions in PVR are typically accompanied by increases in cardiac output. By contrast, in CADENCE, the PVR decreased despite a decline in cardiac output from baseline in both treatment arms, a pattern consistent with direct pulmonary vascular effects. In the context of improvements in right atrial pressure, PAWP, left atrial volume index, and NT-proBNP levels, which would be expected to be associated with improved cardiac function in a HFpEF population, the decrease in cardiac output does not appear to be deleterious. In addition, improvements in right

ventricular–pulmonary artery coupling further support a beneficial effect on right ventricular–pulmonary vascular interaction. Also, it is significant that in both treatment arms, left ventricular ejection fraction and resting oxygen delivery remained unchanged, the latter in part due to an increase in hemoglobin levels. While there was a decrease in resting cardiac output in the 0.3 mg/kg dose arm, these participants on average walked further in the 6MWD test at 24 weeks, suggesting exercise capacity improved.

This pattern in patients with CpcPH–HFpEF, a decrease in resting cardiac output but improvement in measures of congestion and preservation of exercise capacity with sotatercept treatment, is consistent with a recent report in patients with PAH. Reddy et al. reported, in a study using invasive monitoring at rest and at exercise, that sotatercept treatment led to decreased resting cardiac output with preserved oxygen delivery, decongestion with plasma volume reduction, and subsequent hemo-concentration. During exercise, sotatercept improved right ventricular–pulmonary artery coupling, enhanced cardiac output reserve and increased exercise capacity, findings that may reflect a favorable physiologic adaptation to reduced pulmonary vascular load and higher hemoglobin rather than a harmful depression of cardiac function (inotropy), and contextualize the cardiac output findings in CADENCE.[39]

In CADENCE, post hoc subgroup analyses showed that reductions in NT-proBNP were greatest amongst patients with lower baseline cardiac output, suggesting benefit extended to those with more advanced hemodynamic impairment. Notably, NT-proBNP, PAWP, and left atrial volume index, which are all key prognostic markers in heart failure,[1,34,40,41] decreased, indicating that the overall hemodynamic effects and biomarker profile achieved by sotatercept in CpcPH–HFpEF may translate into favorable cardiovascular clinical outcomes. The concomitant increase in pulmonary arterial compliance and reduction

in the right atrial pressure-to-PAWP ratio with sotatercept are consistent with improved right ventricular–pulmonary vascular coupling, a finding of prognostic relevance given the established association of these measures with adverse outcomes in pulmonary hypertension and heart failure.[42]

Both sotatercept doses were well tolerated over 24 weeks; there were no new safety signals compared with prior studies in PAH,[21-24] and bleeding was relatively low despite multiple comorbidities (ie, age and atrial fibrillation) and high use of anticoagulant and antiplatelet therapies. A modest (1–2 g/dL) and expected increase in hemoglobin occurred with both doses; however, the magnitude of these changes only partially accounts for the observed hemodynamic and clinical benefits. Compared with placebo, the 0.3 mg/kg dose was associated with small increases in systemic vascular resistance with minimal changes in systemic blood pressure, whereas the 0.7 mg/kg dose was associated with larger increases in systemic vascular resistance and modest increases in systolic blood pressure that were not considered clinically meaningful, consistent with findings observed in PAH.

The CADENCE study has some limitations. As a phase 2 study, the sample size was relatively small. Although safety was manageable and no new signals were identified, larger studies are needed to fully characterize the safety profile of sotatercept in this population. Participant inclusion was based on local site readings of PVR to balance real-world practice and clinical trial operations; central assessments did not confirm elevated PVR in a few patients. Although the inclusion criteria enriched for patients with advanced pulmonary vascular disease, subgroup analyses stratified by baseline PVR demonstrated consistent treatment effects, with no meaningful differences in response observed across the subgroups with lower baseline PVR. Apart from the primary and key secondary end points, no correction for type 1 error was applied; therefore, findings for other end points should be

considered hypothesis-generating. Finally, the double-blind, placebo-controlled period was limited to 24 weeks, which precluded assessment of the durability of benefit and long-term safety.

In CADENCE, a proof-of-concept trial, sotatercept had a well-tolerated safety profile, reduced PVR at both doses in CpcPH–HFpEF and demonstrated mechanistic evidence of improvements in both pulmonary vascular and cardiac end points.

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Table 1. Baseline Demographic and Clinical Characteristics*

Characteristic	Sotatercept 0.3 mg/kg (N=54)	Sotatercept 0.7 mg/kg (N=55)	Placebo (N=55)	Total (N=164)
Female sex – no. (%)	35 (64.8)	43 (78.2)	36 (65.5)	114 (69.5)
Age				
Median (IQR) – years	76 (71–79)	74 (68–78)	75 (69–79)	75 (69–79)
≥65 years – no. (%)	50 (92.6)	45 (81.8)	48 (87.3)	143 (87.2)
Geographic region – no. (%)				
North America	18 (33.3)	22 (40.0)	27 (49.1)	67 (40.9)
Europe	30 (55.6)	26 (47.3)	22 (40.0)	78 (47.6)
Asia–Pacific	6 (11.1)	7 (12.7)	6 (10.9)	19 (11.6)
Race– no. (%)†				
White	46 (85.2)	51 (92.7)	52 (94.5)	149 (90.9)
Other	8 (14.8)	4 (7.3)	3 (5.5)	15 (9.1)
Body mass index‡				
Median (IQR) – kg/m^2	32.0 (27.1–37.3)	29.9 (26.2–35.3)	32.1 (28.1–36.6)	31.2 (27.2–36.7)
NYHA functional class – no. (%)				
Class II	17 (31.5)	19 (34.5)	20 (36.4)	56 (34.1)
Class III	37 (68.5)	36 (65.5)	35 (63.6)	108 (65.9)
Time since PH diagnosis – years				
Median (IQR)	1.2 (0.2–2.8)	0.9 (0.2–3.0)	1.2 (0.2–3.3)	1.1 (0.2–3.0)
Time since HF diagnosis – years				
Median (IQR)	1.8 (0.5–3.8)	2.1 (0.9–4.1)	1.9 (0.3–4.1)	1.9 (0.5–4.0)
History of COPD – no. (%)	11 (20.4)	10 (18.2)	6 (10.9)	27 (16.5)
Atrial fibrillation at baseline by electrocardiogram				
Yes – no. (%)	23 (42.6)	18 (32.7)	16 (29.1)	57 (34.8)
Corrected valvular disease				
Yes – no. (%)	3 (5.6)	9 (16.4)	4 (7.3)	16 (9.8)
Background therapy (Class I and IIa) for HFpEF – no. (%)§				
Loop diuretics	43 (79.6)	45 (81.8)	41 (74.5)	129 (78.7)
Thiazide diuretics	9 (16.7)	3 (5.5)	8 (14.5)	20 (12.2)
Sodium–glucose co-transporter 2 inhibitors	32 (59.3)	26 (47.3)	28 (50.9)	86 (52.4)
Other background therapy for HFpEF – no. (%)				
Renin–angiotensin–aldosterone system inhibitors	37 (68.5)	28 (50.9)	28 (50.9)	93 (56.7)
Mineralocorticoid receptor antagonists	28 (51.9)	26 (47.3)	24 (43.6)	78 (47.6)
Anticoagulants	41 (75.9)	40 (72.7)	42 (76.4)	123 (75.0)
Antiplatelets	6 (11.1)	13 (23.6)	12 (21.8)	31 (18.9)

Glucagon-like peptide-1 receptor agonists – no. (%)	7 (13.0)	3 (5.5)	1 (1.8)	11 (6.7)
6MWD – median (IQR) m‖	259.5 (174.5–336.0)	304.0 (216.5–343.5)	270.0 (197.4–346.1)	273.8 (199.5–343.8)
NT-proBNP level – median (IQR) pg/mL	1222.5 (397.0–2848.0)	1215.5 (836.0–2785.0)	980.0 (554.0–1857.0)	1119.0 (554.0–2383.0)
Pulmonary vascular resistance – median (IQR) Wood units¶	5.3 (4.1–7.4)	5.8 (3.9–6.5)	5.0 (4.2–6.5)	5.2 (4.0–6.9)
Mean pulmonary arterial pressure – median (IQR) mm Hg¶**	43.0 (38.0–52.0)	43.0 (37.0–48.0)	44.0 (38.0–49.0)	43.0 (38.0–50.0)
Pulmonary arterial wedge pressure – median (IQR) mm Hg¶	21.0 (18.0–24.0)	20.5 (18.0–24.0)	22.0 (19.0–26.0)	21.0 (18.0–25.0)
Systemic vascular resistance – median (IQR) Wood units¶	22.1 (16.6–26.0)	20.9 (15.7–26.8)	22.0 (16.3–25.0)	21.9 (16.1–25.6)
Cardiac output – median (IQR) L/min¶	4.3 (3.7–4.6)	3.9 (3.3–4.6)	4.1 (3.4–4.8)	4.1 (3.4–4.7)
Hemoglobin level – median (IQR) g/dL	13.7 (12.1–14.9)	13.6 (12.4–14.4)	13.6 (12.5–14.6)	13.7 (12.5–14.6)
Estimated glomerular filtration rate – median (IQR) mL/min/1.73 m^2	58.5 (48.0–70.0)	59.0 (43.0–81.0)	58.0 (48.0–81.0)	58.5 (48.0–79.0)

*Percentages may not total 100 because of rounding. The measurements summarized in the table were obtained during the screening visit unless otherwise noted.
†Race 'other' includes Black or African American.
‡The body mass index is weight in kg divided by the square of height in meters.
§Class 1 and 2a HFpEF medications taken within 30 days of the first administration of study treatment. The total percentage exceeds 100% as some patients received more than one therapy. Patients were required to be receiving guideline-directed medications for HFpEF; patients were treated according to the judgment of their respective physicians and local clinical practice.
‖6MWD is reported as an average from two tests conducted during screening.
¶Parameters were measured by right heart catheterization during screening, except for some patients for whom values from a recent right heart catheterization procedure (within 14 days of initiating screening) were used after review and approval of the Medical Monitor. Local values from right heart catheterization analyzed by site investigators were used to determine eligibility and data were transferred to a central vendor for interpretation. For the right heart catheterization parameters analyzed by the central reader, the values for a participant are from the same reader (central or local), in the following order of preference: (1) central if observed at both baseline and week 24; (2) local if observed at both baseline and week 24; (3) central if observed at baseline; (4) local if observed at baseline. Readings considered uninterpretable by the central assessor were excluded from analyses.
**Mean pulmonary arterial pressure, defined as the time-averaged pulmonary arterial pressure over the cardiac cycle, is reported as median (IQR).
6MWD, 6-minute walk distance; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PH, pulmonary hypertension.

Table 2. Hemodynamic and Functional Parameters: Estimated Change from Baseline to Week 24 with Sotatercept Versus Placebo

Parameter	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	Hodges–Lehmann location shift from placebo estimate (95% CI)	
Primary end point		
Pulmonary vascular resistance, Wood units*,†	−1.02 (−1.81 to −0.23)	−0.75 (−1.52 to 0.03)
P value‡	*P*=0.004	*P*=0.024
Components of pulmonary vascular resistance ([mean pulmonary arterial pressure – pulmonary arterial wedge pressure]/cardiac output)		
Transpulmonary gradient (mean pulmonary arterial pressure – pulmonary arterial wedge pressure), mm Hg*,†	−6.49 (−9.72 to −3.27)	−7.25 (−10.38 to −4.12)
Mean pulmonary arterial pressure, mm Hg*,†	−9.19 (−13.00 to −5.38)	−9.22 (−12.97 to −5.46)
Pulmonary arterial wedge pressure, mm Hg*,†	−3.04 (−5.77 to −0.32)	−2.53 (−5.33 to 0.28)
Cardiac output, L/min*,†	−0.44 (−0.76 to −0.12)	−0.70 (−1.05 to −0.36)
Additional select right heart catheterization parameters		
Mean pulmonary arterial pressure/stroke volume, mL/mm Hg*,†	0.16 (−0.03 to 0.35)	0.05 (−0.16 to 0.25)
Hematocrit-adjusted pulmonary vascular resistance, Wood units*,†,§ $\frac{mPAP}{CO * e^{[2(\varphi_{measured}-\varphi_{ref})]}} - \frac{PAWP}{CO}$	−2.00 (−2.90 to −1.11)	−2.12 (−2.99 to −1.26)
Oxygen delivery, mL/min*,†	13.02 (−55.60 to 81.65)	−5.04 (−76.39 to 66.31)
Pulmonary artery compliance (mL/mm Hg)*,†	0.36 (0.15 to 0.56)	0.43 (0.18 to 0.68)
Right atrial pressure, mm Hg*,†	−3.25 (−5.25 to −1.24)	−3.08 (−5.11 to −1.06)
Right atrial pressure/pulmonary arterial wedge pressure ratio*,†	−0.10 (−0.19 to −0.01)	−0.10 (−0.18 to −0.01)
Systemic vascular resistance, Wood units*,†	4.86 (2.36 to 7.35)	8.45 (5.98 to 10.91)
Systolic pulmonary artery pressure, mm Hg*,†	−16.17 (−21.52 to −10.82)	−18.29 (−24.68 to −11.91)
Vital signs		
Systolic blood pressure, mm Hg‖	−0.25 (−8.50 to 8.50)	4.00 (−4.00 to 12.00)
Diastolic blood pressure, mm Hg‖	−1.00 (−6.00 to 4.00)	2.00 (−3.00 to 7.00)
Heart rate, beats/min‖	1.00 (−3.50 to 5.00)	1.00 (−3.00 to 5.50)
Improved or maintained NYHA functional class at week 24		
Odds ratio for comparison versus placebo estimate (95% CI)¶	3.66 (0.95 to 14.15)	1.51 (0.53 to 4.34)

Baseline and median change from baseline data are reported in Table S6.
*The worst-rank score and next worst-rank score were assigned for patients who did not have week 24 data due to death or a clinical worsening event (other than all-cause mortality), respectively. For patients lacking a value at week 24 due to reasons other than death or clinical worsening, multiple imputation was used to impute missing data at week 24. Patients lacking baseline data were excluded. Hodges–Lehmann location shift point estimates and 95% CIs were stratified by NYHA functional class II or III at baseline.
†Right heart catheterization traces were assessed by site investigators to determine patient eligibility and also transferred to a central assessor for interpretation. For efficacy analyses, values for a

participant are from the same assessor (central or local), in the following order of preference: (1) central if available at both baseline and week 24; (2) local if available at both baseline and week 24; (3) central if available at baseline; (4) local if available at baseline. Readings considered uninterpretable by the central assessor were excluded from analyses.
‡One-sided *P*-value provided using the aligned-rank stratified Wilcoxon test stratified by NYHA functional class II or III at baseline.
§Hematocrit-adjusted pulmonary vascular resistance was calculated as previously described,[37] and noting limitations explained in the supplementary methods.
‖Data as observed (no imputation for missing week 24 data).
¶Patients lacking week 24 data were considered to have a worsened functional class. Odds ratio based on Mantel–Haenszel method stratified by NYHA functional class II or III at baseline.
CI, confidence interval; NYHA, New York Heart Association.

Table 3. Echocardiography Parameters: Estimated Change from Baseline to Week 24 with Sotatercept Versus Placebo

Parameter	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	Hodges–Lehmann location shift from placebo estimate (95% CI)	
Select echocardiography parameters		
Inferior vena cava maximum diameter, cm*,†	−0.33 (−0.59 to −0.07)	−0.43 (−0.69 to −0.16)
Left atrial volume index, mL/m^2*,†	−6.44 (−12.02 to −0.86)	−4.47 (−9.76 to 0.81)
Left ventricular ejection fraction, %*,†	−0.40 (−4.56 to 3.76)	−0.93 (−5.03 to 3.18)
Peak systolic tricuspid regurgitation pressure gradient, mm Hg*,†	−16.36 (−22.94 to −9.78)	−22.36 (−29.73 to −14.98)
Pulmonary arterial systolic pressure, mm Hg*,†	−18.59 (−25.79 to −11.38)	−27.86 (−35.28 to −20.43)
Right atrial pressure, mm Hg*,†	−1.41 (−3.11 to 0.30)	−1.62 (−3.24 to 0.00)
Tricuspid annular plane systolic excursion, cm*,†	0.09 (−0.13 to 0.31)	0.05 (−0.17 to 0.26)
Tricuspid annular plane systolic excursion/systolic pulmonary artery pressure, mm/mm Hg*,†	0.13 (0.06–0.19)	0.17 (0.10–0.25)

Baseline and median change from baseline data are reported in Table S6.
*The worst-rank score and next worst-rank score were assigned for patients who did not have week 24 data due to death or a clinical worsening event (other than all-cause mortality), respectively. For patients lacking a value at week 24 due to reasons other than death or clinical worsening, multiple imputation was used to impute missing data at week 24. Patients lacking baseline data were excluded. Hodges–Lehmann location shift point estimates and 95% CIs were stratified by NYHA functional class II or III at baseline.
†All echocardiography data were centrally-read.
CI, confidence interval; NYHA, New York Heart Association.

Table 4. Adverse Events*

Variable	Sotatercept 0.3 mg/kg (N=54)	Sotatercept 0.7 mg/kg (N=55)	Placebo (N=55)
	No. of Patients (%)		
Any adverse event	49 (90.7)	51 (92.7)	48 (87.3)
Adverse event leading to dose delay of sotatercept or placebo†	10 (18.5)	8 (14.5)	5 (9.1)
Adverse event leading to discontinuation of sotatercept or placebo	0	3 (5.5)	0
Adverse event related to sotatercept or placebo leading to discontinuation of sotatercept or placebo	0	1 (1.8)	0
Adverse event leading to death	0 (0)	1 (1.8)	2 (3.6)
Serious adverse event	11 (20.4)	18 (32.7)	12 (21.8)
Serious adverse event leading to discontinuation of sotatercept or placebo	0	1 (1.8)	0
Adverse event of interest/special interest‡			
Bleeding events§,‖	14 (25.9)	15 (27.3)	13 (23.6)
Epistaxis	7 (13.0)	6 (10.9)	4 (7.3)
Increased blood pressure/hypertension§	1 (1.9)	4 (7.3)	2 (3.6)
Increased hemoglobin§	11 (20.4)	6 (10.9)	1 (1.8)
Telangiectasia	3 (5.6)	2 (3.6)	4 (7.3)
Adverse event with an incidence of ≥10% in any group¶			
Diarrhea	7 (13.0)	7 (12.7)	3 (5.5)
Fatigue	5 (9.3)	6 (10.9)	6 (10.9)
Peripheral edema	8 (14.8)	3 (5.5)	3 (5.5)
Influenza	6 (11.1)	0	1 (1.8)
Nasopharyngitis	6 (11.1)	3 (5.5)	3 (5.5)
Urinary tract infection	6 (11.1)	5 (9.1)	3 (5.5)
Dizziness	6 (11.1)	7 (12.7)	4 (7.3)
Headache	3 (5.6)	8 (14.5)	5 (9.1)
Dyspnea	6 (11.1)	0	5 (9.1)

*Adverse events that occurred up to and including day 56 after the last dose were included in the analysis. Point estimates for the difference in percentage between sotatercept versus placebo treatment groups are provided in Table S8.
†There were no adverse events leading to dose reductions.
‡Select events that occurred in at least four patients in one or more treatment groups.
§Combined terms based on more than one preferred MedDRA term.
‖Bleeding totals do not include events detected by laboratory assessment, or anemia events.
¶Not including terms reported above as adverse events of interest/special interest.
MedDRA, Medical Dictionary for Regulatory Activities.

Figure Legends

Figure 1. RHC Parameters.

Change from baseline to week 24 in (A) pulmonary vascular resistance, (B) mean pulmonary arterial pressure, (C) pulmonary arterial wedge pressure, and (D) transpulmonary gradient.

*Local values from right heart catheterization analyzed by site investigators were used to determine eligibility and data were transferred to a central vendor for interpretation. For the right heart catheterization parameters analyzed by the central reader, the values for a participant are from the same reader (central or local), in the following order of preference: (1) central if observed at both baseline and week 24; (2) local if observed at both baseline and week 24; (3) central if observed at baseline; (4) local if observed at baseline. Readings considered uninterpretable by the central assessor were excluded from analyses.

†The worst-rank score and next worst-rank score were assigned for patients who did not have week 24 data due to death or a clinical worsening event (other than all-cause mortality), respectively. For patients lacking a value at week 24 due to reasons other than death or a clinical worsening event, multiple imputation was used to impute missing data at week 24. Patients lacking baseline data were excluded. For PVR, details of the reasons for missing data, and how each was handled in the analysis, are shown in Table S7. Hodges–Lehmann location shift point estimates and 95% CIs were stratified by NYHA functional class II or III at baseline. Values on the plots report medians; error bars show the lowest and highest of all median values in the imputed data sets when missing data were imputed.

CI, confidence interval; NYHA, New York Heart Association.

Figure 2. Functional and Clinical Outcomes.

Change from baseline to week 24 in (A) 6-minute walk distance and (B) N-terminal pro-B-type natriuretic peptide, and (C) time to first clinical worsening event (placebo-controlled period).

*The worst-rank score and next worst-rank score were assigned for patients who did not have week 24 data due to death or a clinical worsening event (other than all-cause mortality), respectively. For patients lacking a value at week 24 due to reasons other than death or a clinical worsening event, multiple imputation was used to impute missing data at week 24. Patients lacking baseline data were excluded. For 6MWD, details of the reasons for missing data, and how each was handled in the analysis, are shown in Table S7. Hodges–Lehmann location shift point estimates and 95% CIs were stratified by NYHA functional class II or III at baseline. Values on the plots report medians; error bars show the lowest and highest of all median values in the imputed data sets when missing data were imputed.

†A hierarchical testing strategy was used for the primary and key secondary end points to control for type 1 error, in descending order of sotatercept dose group (0.7 mg/kg versus placebo followed by 0.3 mg/kg versus placebo), stopping at the first non-significant result. One-sided *P*-values provided using the aligned-rank stratified Wilcoxon test, both stratified by NYHA functional class II or III at baseline. As the *P* value for the sotatercept 0.7 mg/kg dose group was non-significant for 6MWD, there was no formal testing for the 0.3 mg/kg dose group.

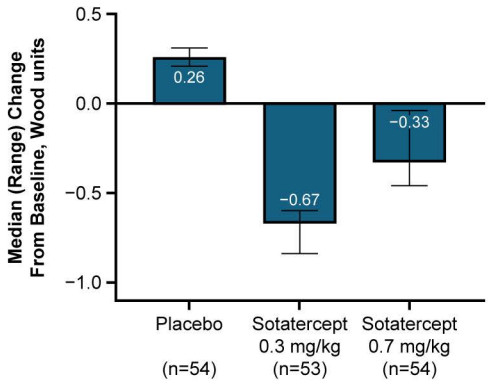
‡Time from first dose to hospitalization due to a cardiopulmonary indication (a non-elective hospitalization lasting at least 24 hours caused by clinical conditions directly related to pulmonary hypertension and/or heart failure), administration of intravenous diuretics or

subcutaneous furosemide, death (all causes), or ≥15% decrease in 6MWD compared with baseline. Hazard ratio by Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by NYHA functional class II or III at baseline. + shows censored patients. Note that the y-axis is abbreviated to show 50–100 to improve visualization of data. Note that the errors bars on the plot indicate 95% CIs. The plot extends past 24 weeks as the study design permitted participants to enter an extension period after the placebo-controlled base period. The follow-up duration of the base period was calculated for each participant up to the time of enrollment into the extension period. In some participants, enrollment into the extension period exceeded 24 weeks.

[§]Each component is shown as a standalone end point. A patient is included under more than one component if multiple events were observed.

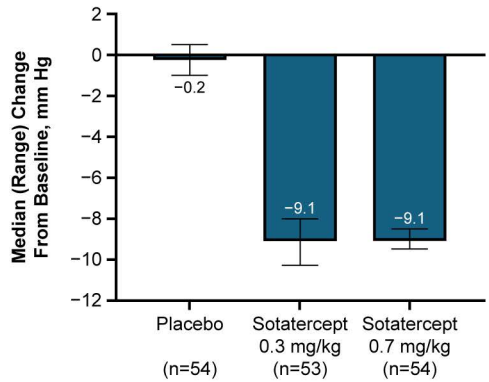
6MWD, 6-minute walk distance; CI, confidence interval; IV, intravenous; n/a, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SC, subcutaneous.

A



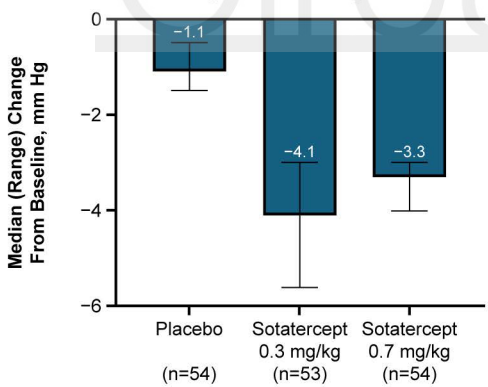
Hodges–Lehmann location shift from placebo estimate (95% CI), Wood units *P* value‡	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	−1.02 (−1.81 to −0.23) *P*=0.004	−0.75 (−1.52 to 0.03) *P*=0.024

B



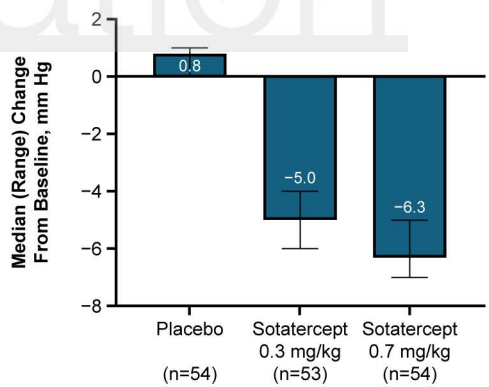
Hodges–Lehmann location shift from placebo estimate (95% CI), mm Hg	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	−9.19 (−13.00 to −5.38)	−9.22 (−12.97 to −5.46)

C



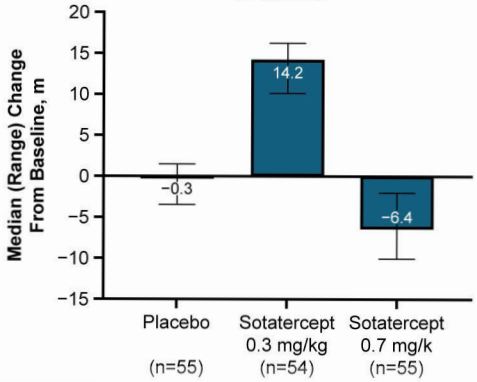
Hodges–Lehmann location shift from placebo estimate (95% CI), mm Hg	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	−3.04 (−5.77 to −0.32)	−2.53 (−5.33 to 0.28)

D



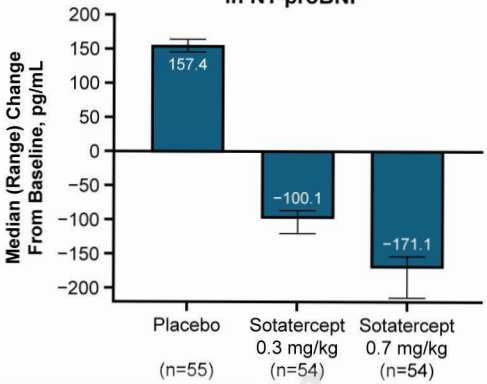
Hodges–Lehmann location shift from placebo estimate (95% CI), mm Hg	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	−6.49 (−9.72 to −3.27)	−7.25 (−10.38 to −4.12)

A



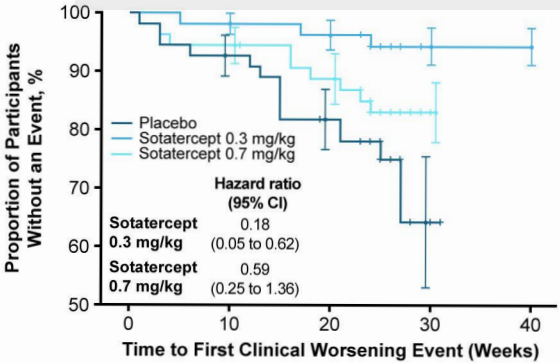
Hodges–Lehmann location shift from placebo estimate (95% CI), m	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	20.29 (1.48 to 39.11)	5.80 (−17.33 to 28.92)

B



Hodges–Lehmann location shift from placebo estimate (95% CI), pg/mL	Sotatercept 0.3 mg/kg	Sotatercept 0.7 mg/kg
	−343.72 (−656.10 to −31.34)	−402.18 (−846.60 to 42.24)

C



Number of participants at risk

Placebo	55	51	44	3	0
Sotatercept 0.3 mg/kg	54	53	52	1	1
Sotatercept 0.7 mg/kg	55	51	47	1	0

	Placebo (n=55)	Sotatercept 0.3 mg/kg (n=54)	Sotatercept 0.7 mg/kg (n=55)
Patients with a first clinical worsening event, n (%)	14 (25.5)	3 (5.6)	9 (16.4)
Patients with any clinical worsening event, n (%)§			
Death	2 (3.6)	0	1 (1.8)
≥1 hospitalization due to a cardiopulmonary indication	1 (1.8)	1 (1.9)	7 (12.7)
≥1 administration of IV diuretics or SC furosemide	7 (12.7)	2 (3.7)	6 (10.9)
≥15% decrease in 6MWD from baseline	6 (10.9)	1 (1.9)	2 (3.6)