Efficacy and safety of the activin signalling inhibitor, sotatercept, in a pooled analysis of PULSAR and STELLAR studies

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Key safety and efficacy findings from a combined analysis of the PULSAR and STELLAR trials in patients with PAH

- This *post hoc*, exploratory, pooled analysis combines data from the double-blind placebo periods of the phase 2 PULSAR (NCT03496207) and phase 3 STELLAR (NCT04576988) studies
- A total of 429 patients with Group 1 PAH were randomised and treated; 237 received sotatercept and 192 received placebo

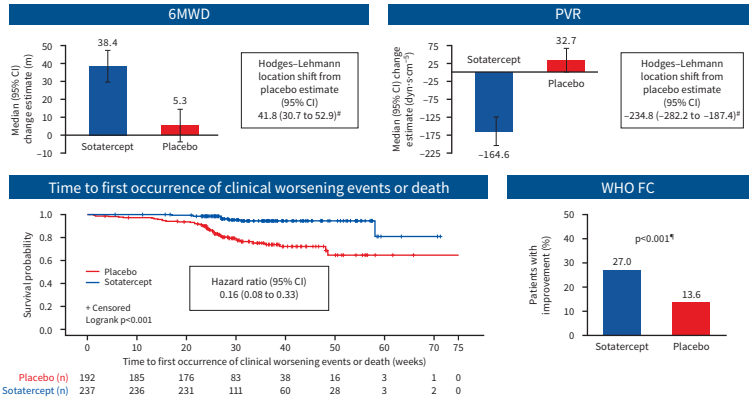
Safety

Sotatercept had favourable safety in patients with PAH

	Sotatercept (n=237)	Placebo (n=192)
Number of patients with any adverse event, n (%)		
Any	202 (85.2)	169 (88.0)
Related to study treatment	104 (43.9)	50 (26.0)
Leading to discontinuation of study treatment	9 (3.8)	11 (5.7)
Leading to death	1 (0.4)	6 (3.1)
Number of patients with an adverse event of interest and special interest, n (%)		
Increased blood pressure	8 (3.4)	3 (1.6)
Increased haemoglobin	18 (7.6)	0
Thrombocytopenia	17 (7.2)	4 (2.1)
Bleeding event	49 (20.7)	28 (14.6)
Telangiectasia	17 (7.2)	5 (2.6)

Efficacy

Adding sotatercept to background PAH therapy for 24 weeks improved exercise capacity (as assessed by 6MWD), PVR and WHO functional class, and delayed time to first occurrence of death or clinical worsening event



Conclusion: sotatercept delivered therapeutic benefit across a range of efficacy end-points and had favourable safety in patients with PAH

GRAPHICAL ABSTRACT Overview of the study. #: p<0.001 for comparison of sotatercept with placebo on the basis of aligned-rank stratified Wilcoxon test, stratified according to randomisation factors of background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline World Health Organization functional class (WHO FC) (II *versus* III); ¶: p<0.001 for comparison of sotatercept with placebo on basis of a Cochran–Mantel–Haenszel method, stratified according to randomisation factors. 6MWD: 6-min walk distance; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance.

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Shareable abstract (@ERSpublications)
The results of this pooled analysis confirm sotatercept delivers therapeutic benefit across a range of efficacy end-points, including exercise capacity and PVR, and has a favourable safety profile in patients with PAH on background standard-of-care therapy https://bit.ly/425DLiV

Cite this article as: Hoeper MM, Gomberg-Maitland M, Badesch DB, *et al*. Efficacy and safety of the activin signalling inhibitor, sotatercept, in a pooled analysis of PULSAR and STELLAR studies. *Eur Respir J* 2025; 65: 2401424 [DOI: 10.1183/13993003.01424-2024].

This article has an editorial commentary: https://doi.org/10.1183/13993003.00322-2025

Received: 22 July 2024
Accepted: 6 Jan 2025

Abstract

Introduction Pulmonary arterial hypertension is a progressive disease associated with significant morbidity and mortality. Sotatercept is a first-in-class activin signalling inhibitor that acts to restore the balance between the growth-promoting and growth-inhibiting signalling pathways.

Methods This *post hoc*, exploratory, pooled analysis combines data from the double-blind placebo periods of the phase 2 PULSAR (NCT03496207) and phase 3 STELLAR (NCT04576988) studies. Both studies were international, multicentre, randomised, double-blind, placebo-controlled trials in patients with pulmonary arterial hypertension. Efficacy and safety parameters common to both studies were analysed.

Results A total of 429 patients were randomised and treated; 237 received sotatercept and 192 received placebo. Adding sotatercept to background pulmonary arterial hypertension therapy for 24 weeks improved exercise capacity (as assessed by 6-min walk distance), pulmonary vascular resistance and World Health Organization functional class, and delayed time to first occurrence of death or clinical worsening event. There were clinically important reductions in both pulmonary and right heart pressures; improvements in right ventricle size during both systole and diastole; and enhancements in right ventricle contractility and right ventricular–pulmonary artery coupling. The number of patients who experienced at least one adverse event of interest or special interest (increased haemoglobin, thrombocytopenia, bleeding events (mostly epistaxis), increased blood pressure and telangiectasia) was higher in the sotatercept group than the placebo group.

Conclusion This pooled analysis confirms that sotatercept delivers therapeutic benefit across a range of efficacy end-points and has favourable safety in patients with pulmonary arterial hypertension. Increased duration of follow-up will provide further insight into long-term outcomes of sotatercept in patients with pulmonary arterial hypertension.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease that leads to increased pulmonary artery (PA) pressure and right ventricular (RV) dysfunction [1–3]. PAH is associated with abnormal changes in signal transduction involving members of the transforming growth factor β receptor superfamily. Specifically, PAH is caused by an imbalance between bone morphogenetic protein receptor type 2-mediated anti-proliferative signalling and activin receptor type IIA-mediated pro-proliferative signalling. This aberrant signalling leads to endothelial dysfunction and endothelial and smooth muscle cell hyperproliferation within the vessel wall, with subsequent pulmonary vascular and right heart remodelling and sustained pulmonary vascular resistance (PVR) elevations [4–11]. Despite treatment advances in the past decade, PAH continues to be associated with significant morbidity and mortality. Therefore, there is a need for novel treatments that target the pathobiology of PAH [1, 2, 12, 13].

Sotatercept is a first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the fragment crystallisable domain of human IgG (supplementary figure S1) [14]. Sotatercept, an activin signalling inhibitor, acts as a selective ligand trap for pro-proliferative activins and related growth differentiation factors; this restores the balance between the growth-promoting and growth-inhibiting signalling pathways [15–17]. In 2024, the US Food and Drug Administration approved sotatercept for the treatment of adults with PAH to increase exercise capacity, improve World Health Organization functional class (WHO FC) and reduce the risk of clinical worsening events [18].

The efficacy and safety of sotatercept added to background therapy for PAH was evaluated in the randomised, double-blind, placebo-controlled phase 2 PULSAR (NCT03496207) and phase 3 STELLAR (NCT04576988) studies conducted in adults with a diagnosis of group 1 PAH with mild-to-moderate symptoms [15, 17]. In both studies, treatment with sotatercept for 24 weeks led to significant improvements in PVR, 6-min walk distance (6MWD) (a measure of exercise capacity) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels [15, 17]. Sotatercept also significantly delayed the time to first occurrence of death or nonfatal clinical worsening event, providing a relative risk reduction of 84% in STELLAR [17]. Moreover, a *post hoc* analysis of STELLAR showed that sotatercept significantly reduced PA pressure, improved PA compliance and RV–PA coupling, reduced tricuspid regurgitation and cardiac workload, and improved right heart dimensions and function [19]. Adverse events (AEs), which occurred more frequently with sotatercept (observed in ⩾10% of patients treated with sotatercept in PULSAR and/or STELLAR) than placebo, comprised headache, COVID-19, diarrhoea, epistaxis, telangiectasia, dizziness, fatigue and haemoglobin increase [15, 17].

The rationale for pooling data from the PULSAR and STELLAR studies stems from the similarity in the study designs, with both featuring 24-week, double-blind, placebo-controlled treatment periods [15, 17]. The studies enrolled similar populations of patients with group 1 PAH with similar disease characteristics, who were on similar approved background PAH therapies. Pooling the results across these two studies offered a robust framework for undertaking the current *post hoc* analysis, allowing for evaluation of the efficacy and safety of sotatercept across a broader population. Combining the datasets enhanced the statistical power to provide greater precision around the estimates of treatment effects. Pooling safety data provided a way to obtain meaningful information on adverse events of interest (AEOIs) occurring in <10% of patients. Thus, benefit–risk assessment of sotatercept based on greater numbers of participants was possible. Furthermore, small sample sizes in certain subgroups in the individual studies may have limited the ability to detect clinically meaningful differences in efficacy or safety. Here, we aim to further describe the patient demographics, efficacy and safety of sotatercept *versus* placebo arms across the two studies and within subgroups.

Methods

Study design

This *post hoc*, exploratory, pooled analysis combines data from the double-blind placebo-controlled periods of the phase 2 PULSAR (NCT03496207) and phase 3 STELLAR (NCT04576988) studies. Both studies were international, multicentre, randomised, double-blind trials, with a 24-week placebo-controlled period [15, 17]. This was followed by an 18-month open-label extension period in PULSAR and a double-blind extension period of up to 72 weeks in STELLAR. The trial designs have been published previously [15, 17].

Both trials were conducted in accordance with the principles of the Declaration of Helsinki, the ethical guidelines of the Council for International Organizations of Medical Sciences, the Good Clinical Practice guidelines of the International Council for Harmonisation, and all applicable laws and regulations. All patients provided written informed consent.

Patients

Patients were eligible for inclusion if they had confirmed PAH (idiopathic, heritable, drug-induced or associated with connective tissue disease or congenital heart disease after shunt correction) in WHO FC II or III. Patients with PAH subtypes associated with portopulmonary disease, schistosomiasis, HIV infection and pulmonary veno-occlusive disease (STELLAR only) were excluded. Patients were receiving approved background PAH therapies including monotherapy, dual therapy or triple therapy with currently available PAH medication(s) in accordance with local treatment guidelines. Concomitant medications included endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues or prostacyclin receptor agonists [15, 17].

Procedures

The procedures for PULSAR (protocol 7962–001) and STELLAR (protocol 7962–003) have been described previously [15, 17].

In PULSAR, patients were initially randomised 1:1:1 to receive placebo, sotatercept 0.3 $mg \cdot kg^{-1}$ or sotatercept 0.7 $mg \cdot kg^{-1}$ administered subcutaneously once every 3 weeks. Sotatercept doses were pooled for this analysis. The randomisation ratio was changed during the trial to 3:3:4 to increase the statistical power with respect to the sotatercept 0.7 mg group [15]. In STELLAR, patients were randomised 1:1 to receive either placebo or sotatercept (starting dose 0.3 $mg \cdot kg^{-1}$ escalated to a target dose of 0.7 $mg \cdot kg^{-1}$) administered subcutaneously once every 3 weeks. Patients continued to receive a dose of 0.7 $mg \cdot kg^{-1}$ unless a reduction was warranted [17].

Patients continued treatment with background PAH therapy during the studies. In STELLAR, the initiation of new therapies was not permitted, and background PAH therapies were to remain unchanged throughout the duration of the study. Adjustments within 10% for infusion prostacyclin doses and changes in existing oral diuretics were allowed to ensure treatment stability.

End-points

The end-point definitions for PULSAR and STELLAR have been described previously [15, 17]. The efficacy end-points for this pooled analysis were change from baseline at week 24 in 6MWD (primary end-point in STELLAR; secondary end-point in PULSAR), PVR (primary end-point in PULSAR; secondary end-point in STELLAR) and NT-proBNP level (secondary end-point in PULSAR and STELLAR). This pooled analysis also included subgroup analyses for 6MWD, PVR and NT-proBNP level in prespecified subgroups.

Multicomponent improvement (secondary end-point in STELLAR only) was another efficacy end-point measured by the percentage of patients meeting all three criteria at week 24 relative to baseline (*i.e.* improvement from baseline in 6MWD (increase of ⩾30 m), in NT-proBNP level (decrease of ⩾30%) or maintenance/achievement of an NT-proBNP level of <300 $pg \cdot mL^{-1}$, and in WHO FC (shift from class III to II or I, or II to I) or maintenance of class II at week 24).

Other efficacy end-points in this analysis included the percentage of patients with improvement in WHO FC (shift from class III to II or I, or II to I between baseline and week 24; secondary end-point in PULSAR and STELLAR), the percentage of patients with improvement in European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk score (based on WHO FC, 6MWD and B-type natriuretic peptide or NT-proBNP variables [3]; exploratory end-point in PULSAR and STELLAR) at week 24, and the percentage of patients with a low French risk score (meeting all three criteria for low risk: WHO FC of I or II, 6MWD >440 m and NT-proBNP level <300 $pg \cdot mL^{-1}$; secondary end-point in STELLAR only) at week 24.

The time to first occurrence of death or nonfatal clinical worsening event (secondary end-point in PULSAR and STELLAR) was evaluated in both studies. Clinical worsening was defined as a composite of prespecified outcomes, including death, worsening-related listing for lung or heart–lung transplantation, initiation of rescue therapy or increase in dose of infusion prostacyclin by ⩾10%, need for atrial septostomy, PAH-related hospitalisation (⩾24 h) and worsening of PAH relative to baseline (worsened WHO FC (shift from II to III, III to IV, II to IV) and a 6MWD decrease of ⩾15%). The time to clinical worsening was assessed up to week 24 in PULSAR and up to week 78 in STELLAR.

Select right heart catheterisation (RHC) parameters (mean pulmonary arterial pressure, pulmonary artery wedge pressure, mean right atrial pressure, cardiac index and cardiac output) and echocardiography (ECHO) parameters (systolic pulmonary arterial pressure (sPAP), estimated right atrial pressure, tricuspid

annular plane systolic excursion (TAPSE), RV fractional area change, RV area in end-diastole, RV area in end-systole and RV–PA coupling (TAPSE/sPAP ratio)) were assessed. Apart from TAPSE, which was a secondary end-point in PULSAR, these RHC and ECHO parameters were exploratory end-points in both PULSAR and STELLAR.

The safety end-points included treatment-emergent AEs (TEAEs), AEOIs and telangiectasia. AEs were documented from the day of informed consent signing through week 24. TEAEs, identified as those AEs occurring after the initial dose of study drug and spanning up to 8 weeks following the last dose, were monitored until they either reverted to baseline, were resolved or the data cut-off point was reached. Serious AEs were tracked until resolution or until they were considered chronic or stable. A severe AE was any AE that was deemed to be severe in intensity by the trial investigator. A serious AE was defined as any untoward medical event that resulted in death, was life-threatening, warranted hospitalisation or caused prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, may have caused a congenital abnormality or birth defect, or warranted intervention to prevent permanent impairment or damage.

In the STELLAR trial, a broad set of prespecified AEOIs was defined based on nonclinical data, mechanism of action, class effects and clinical data from early clinical studies in a variety of indications, including oncology [14, 20–22]. The AEOIs included bleeding events, cardiac events, embryo-foetal toxicity, hepatic toxicity, immunogenicity, increased blood pressure, increased haemoglobin, leukopenia, neutropenia (including febrile neutropenia), renal toxicity, suppression of follicle-stimulating hormone, thrombocytopenia and thromboembolic events; those, and AEs of special interest (AESIs) (telangiectasia) were analysed using predefined search strategies to further assess the safety profile of sotatercept. In the PULSAR trial, AESIs were limited to leukopenia, neutropenia and thrombocytopenia based on findings from earlier clinical studies in which sotatercept was studied in patients with advanced malignancies [20]. This pooled analysis used the AEOIs/AESIs as defined for STELLAR.

Statistical analyses

Efficacy analyses were performed in the full analysis set, which comprised all randomised patients. Safety analyses were performed in the safety population, defined as all randomly assigned patients who received at least one dose of sotatercept or placebo. Continuous variables were summarised with descriptive statistics at baseline and week 24 by treatment group. Analyses of the change from baseline at week 24 for 6MWD, PVR and NT-proBNP used the aligned-rank stratified Wilcoxon test, with background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline WHO FC (II *versus* III) as strata. The Hodges–Lehmann location-shift estimate of the between-group difference in change from baseline with 95% confidence interval (CI) was calculated with the corresponding p-value from the aligned-rank stratified Wilcoxon test. The analysis used a standard multiple-imputation method for missing data, with missing values due to death or nonfatal clinical worsening events assigned the lowest and next-lowest rank scores, respectively.

Categorical values were summarised with descriptive statistics at baseline and week 24 by treatment group. The analysis utilised the Cochran–Mantel–Haenszel method for evaluating differences in proportions, stratifying for background PAH therapy and baseline WHO FC. Individuals with missing results at week 24 were considered nonresponders. Individuals with missing assessments due to COVID-19 were excluded from the denominator.

Time to events were summarised with descriptive statistics at the median follow-up time in weeks for each treatment group. The hazard ratio with 95% CI for the between-group comparison was calculated using the Cox proportional hazards method, with treatment group as the covariate and stratifying for background therapy and baseline WHO FC. Kaplan–Meier plots were generated for the sotatercept and placebo groups. Individuals who did not experience either death or a nonfatal clinical worsening event were censored at their last on-treatment study visit.

Results

Baseline demographics and clinical characteristics

Across the two studies, 429 patients were randomised and treated; 237 received sotatercept and 192 received placebo (supplementary figure S2). This pooled analysis included 106 patients from PULSAR (placebo: n=32; sotatercept 0.3 $mg \cdot kg^{-1}$: n=32; sotatercept 0.7 $mg \cdot kg^{-1}$: n=42) and 323 patients from STELLAR (placebo: n=160; sotatercept 0.3 $mg \cdot kg^{-1}$ then 0.7 $mg \cdot kg^{-1}$: n=163).

Demographics and baseline clinical characteristics were generally comparable across the treatment groups (table 1). The study population mainly comprised adult Caucasian female patients diagnosed with idiopathic PAH, the majority of whom were taking triple combination therapy. The mean±SD ages were 48.2±14.3 years and 47.8±15.2 years in the sotatercept and placebo groups, respectively. The mean±SD lengths of time since diagnosis of PAH were 8.8±6.9 years and 8.2±6.5 years in the sotatercept and placebo groups, respectively.

TABLE 1 Baseline demographics and disease characteristics

	Sotatercept	Placebo	Total
Subjects (n)	237	192	429
Age (years)	48.2±14.3	47.8±15.2	48.0±14.7
Sex			
Male	42 (17.7)	39 (20.3)	81 (18.9)
Female	195 (82.3)	153 (79.7)	348 (81.1)
Race			
White	215 (90.7)	171 (89.1)	386 (90.0)
Black or African American	6 (2.5)	5 (2.6)	11 (2.6)
Asian	1 (0.4)	6 (3.1)	7 (1.6)
American Indian or Alaska Native	0	1 (0.5)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0	2 (1.0)	2 (0.5)
Other	6 (2.5)	4 (2.1)	10 (2.3)
Multiple	3 (1.3)	1 (0.5)	4 (0.9)
Missing	6 (2.5)	2 (1.0)	8 (1.9)
Ethnicity			
Hispanic or Latino	49 (20.7)	41 (21.4)	90 (21.0)
Not Hispanic or Latino	179 (75.5)	145 (75.5)	324 (75.5)
Not reported	8 (3.4)	6 (3.1)	14 (3.3)
Unknown	1 (0.4)	0	1 (0.2)
BMI			
Actual ($kg \cdot m^{-2}$)	26.4±5.8	26.7±6.0	26.6±5.9
$\geqslant$30 $kg \cdot m^{-2}$	53 (22.4)	46 (24.0)	99 (23.1)
Time since PAH diagnosis (years)	8.8±6.9	8.2±6.5	8.5±6.7
Classification of PAH			
Idiopathic	125 (52.7)	125 (65.1)	250 (58.3)
Heritable	45 (19.0)	31 (16.1)	76 (17.7)
Drug or toxin-induced	13 (5.5)	4 (2.1)	17 (4.0)
Associated with connective tissue disease	44 (18.6)	23 (12.0)	67 (15.6)
Associated with corrected congenital shunts	10 (4.2)	9 (4.7)	19 (4.4)
WHO FC			
Class II	119 (50.2)	95 (49.5)	214 (49.9)
Class III	118 (49.8)	97 (50.5)	215 (50.1)
Background PAH therapy			
Monotherapy	17 (7.2)	6 (3.1)	23 (5.4)
Dual therapy	80 (33.8)	69 (35.9)	149 (34.7)
Triple therapy	140 (59.1)	117 (60.9)	257 (59.9)
Prostacyclin infusion therapy	94 (39.7)	74 (38.5)	168 (39.2)
Haemoglobin ($g \cdot dL^{-1}$)	13.7±1.7	13.7±1.6	13.7±1.6
Estimated glomerular filtration rate ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	87.9±32.5	86.4±34.4	87.3±33.3
6MWD (m)	396.0±85.9	405.4±77.9	400.2±82.5
NT-proBNP ($pg \cdot mL^{-1}$)	1002.5±2226.8	1150.3±2505.5	1068.2±2353.0
PVR ($dyn \cdot s \cdot cm^{-5}$)	777.9±386.4	754.4±314.8	767.4±356.0
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.7±0.6	2.7±0.6	2.7±0.6
Cardiac output ($L \cdot min^{-1}$)	4.8±1.2	4.8±1.1	4.8±1.2
Pulmonary artery pressure (mmHg)	52.6±13.9	52.5±13.0	52.6±13.5
Right atrial pressure (mmHg)	7.8±4.1	8.7±4.7	8.2±4.4
Pulmonary artery wedge pressure (mmHg)	9.9±3.2	9.9±3.1	9.9±3.1

Data are presented as mean±SD or n (%), unless otherwise stated. 6MWD: 6-min walk distance; BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; WHO FC: World Health Organization functional class.

At baseline in the sotatercept and placebo groups, 17 (7.2%) and six (3.1%) patients were on monotherapy, 80 (33.8%) and 69 (35.9%) patients were on dual therapy, 140 (59.1%) and 117 (60.9%) patients were on triple therapy, and 94 (39.7%) and 74 (38.5%) patients were on prostacyclin infusion therapy, respectively.

Efficacy

The median change estimate from baseline at week 24 for 6MWD was 38.4 m (95% CI 29.8 to 47.1 m) in the sotatercept group and 5.3 m (95% CI −3.8 to 14.3 m) in the placebo group. The Hodges–Lehmann estimate location shift was 41.8 m (95% CI 30.7 to 52.9 m; p<0.001), favouring sotatercept (table 2). The number of patients who met all three criteria of the multicomponent improvement end-point at week 24 was 100 of 236 (42.4%) in the sotatercept group and 21 of 191 (11.0%) in the placebo group (p<0.001; table 2). Relative to placebo, significant improvements were observed with sotatercept treatment for the change from baseline at week 24 in PVR and NT-proBNP levels (table 2).

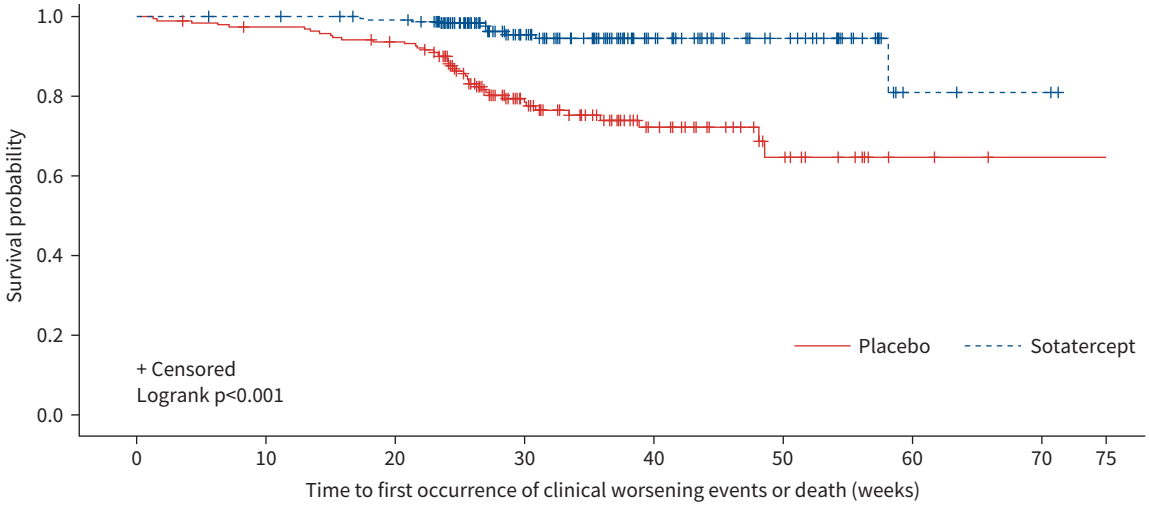
The percentage of patients with a WHO FC improvement, ESC/ERS risk status improvement and low French risk score was also significantly higher with sotatercept *versus* placebo (table 2). There was a

TABLE 2 Change from baseline at week 24 in efficacy end-points

	Sotatercept	Placebo
Subjects (n)	237	192
6MWD (m)		
Median change estimate (95% CI)[#]	38.4 (29.8 to 47.1)	5.3 (−3.8 to 14.3)
Hodges–Lehmann location shift from placebo estimate (95% CI)[¶]	41.8 (30.7 to 52.9)[f]	NA
PVR (dyn·s·cm^{-5})		
Median change estimate (95% CI)	−164.6 (−204.2 to −125.1)	32.7 (−0.1 to 65.6)
Hodges–Lehmann location shift from placebo estimate (95% CI)	−234.8 (−282.2 to −187.4)[f]	NA
NT-proBNP (pg·mL^{-1})		
Median change estimate (95% CI)	−186.8 (−248.5 to −125.2)	44.7 (−6.1 to 95.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)	−420.7 (−536.9 to −304.6)[f]	NA
WHO FC		
Patients with improvement (n/N)	64/237	26/191
Percentage of patients	27.0[##]	13.6
Multicomponent improvement		
Patients who met all three criteria for 6MWD, NT-proBNP level and WHO FC (n/N)	100/236	21/191
Percentage of patients	42.4[##]	11.0
French risk score[+]		
Patients with a low-risk score using the simplified French risk score calculator at week 24 (n/N)	95/236[¶¶]	37/191[¶¶]
Percentage of patients	40.3[##]	19.4
ESC/ERS risk status improvement		
Patients with improvement (n/N)	83/236	21/191
Percentage of patients	35.2[##]	11.0
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)[§]	0.16 (0.08 to 0.33)[++]	NA

All analyses were performed in the full analysis set with the prespecified multiple-imputation methods for handling missing data. Missing values at week 24 owing to death or nonfatal clinical worsening events were assigned worst and second-worst rank scores, respectively. Missing values at week 24 owing to reasons other than death or nonfatal clinical worsening events were populated with the use of a fully conditional specification regression model in which the data were assumed to be missing at random. The widths of the confidence intervals have not been adjusted for multiple comparisons; therefore, the intervals should not be used to infer definitive treatment effects for the secondary end-points. 6MWD: 6-min walk distance; ERS: European Respiratory Society; ESC: European Society of Cardiology; NA: not available; NT-proBNP: N-terminal pro-brain natriuretic peptide; PVR: pulmonary vascular resistance; WHO FC: World Health Organization functional class. [#]: median estimated across the imputed data sets with Statistical Analysis System (SAS) proc quantreg model adjusting for randomisation factors (with 95% confidence intervals) if missing data were imputed; [¶]: the Hodges–Lehmann location shift from placebo estimate is the median of all paired differences; [+]: a low French risk score was defined by meeting all three criteria for low risk: a WHO functional class of I or II, a 6MWD of >440 m and an NT-proBNP level of <300 pg·mL^{-1}; [§]: the hazard ratio (sotatercept *versus* placebo) was derived from a Cox proportional hazards model, with trial group as the covariate and stratification according to the randomisation factors of background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline WHO FC (II *versus* III); [f]: p<0.001 for the comparison of sotatercept with placebo on the basis of the aligned-rank stratified Wilcoxon test, with randomisation factors of background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline WHO FC (II *versus* III) as strata; [##]: p<0.001 for the comparison of sotatercept with placebo on the basis of a Cochran–Mantel–Haenszel method, stratified according to randomisation factors of background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline WHO FC (II *versus* III); [¶¶]: one patient in the group had missing data owing to COVID-19 and was excluded from the analysis; [++]: p<0.001 for the comparison of sotatercept with placebo on the basis of a Cox proportional hazards model, with trial group as the covariate and stratification according to randomisation factors of background therapy (monotherapy or dual therapy *versus* triple therapy) and baseline WHO FC (II *versus* III).

a)



Placebo (n)	192	185	176	83	38	16	3	1	0
Sotatercept (n)	237	236	231	111	60	28	3	2	0

b)

	Placebo (n)	Sotatercept (n)	Sotatercept *versus* placebo Hazard ratio (95% CI)	Sotatercept *versus* placebo Hazard ratio[#] (95% CI)
Overall	192	237		0.16 (0.08 to 0.33)
Sex				
Male	39	42		0.15 (0.03 to 0.67)
Female	153	195		0.18 (0.08 to 0.40)
Background therapy at baseline				
Monotherapy	6	17		0.00 (NE to NE)[¶]
Double	69	80		0.27 (0.09 to 0.85)
Triple	117	140		0.13 (0.05 to 0.34)
Baseline WHO FC				
Class II	95	119		0.13 (0.03 to 0.57)
Class III	97	118		0.17 (0.08 to 0.40)
PAH aetiological subgroups				
iPAH	125	125		0.19 (0.08 to 0.47)
hPAH	31	45		0.21 (0.02 to 2.08)
Drug/toxin-induced PAH	4	13		0.00 (NE to NE)[¶]
Connective tissue disease	23	44		0.13 (0.02 to 0.71)
Corrected congenital heart disease	9	10		0.00 (NE to NE)[¶]
Prostacylin infusion therapy at baseline				
Yes	74	94		0.15 (0.05 to 0.43)
No	118	143		0.18 (0.07 to 0.48)
Baseline PVR				
≤800 dyn·s·cm^{-5}	129	157		0.20 (0.08 to 0.48)
>800 dyn·s·cm^{-5}	63	80		0.11 (0.03 to 0.39)
Region				
North America	63	69		0.27 (0.07 to 1.05)
South America	24	30		0.00 (NE to NE)[¶]
Europe	88	116		0.19 (0.07 to 0.51)
Asia or Pacific	17	22		0.33 (0.03 to 3.19)
Cardiac index				
<2.5 L·min^{-1}·m^{-2} (intermediate/high risk)	84	95		0.21 (0.08 to 0.56)
≥2.5 L·min^{-1}·m^{-2} (low risk)	108	142		0.12 (0.04 to 0.34)

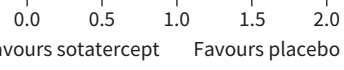
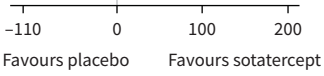


FIGURE 1 a) Kaplan–Meier plot of time to first occurrence of clinical worsening events or death overall and b) forest plot of time to first occurrence of clinical worsening events or death in subgroups (full analysis set). hPAH: heritable PAH; iPAH: idiopathic PAH; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; WHO FC: World Health Organization functional class. [#]: treatment effect is the hazard ratio derived from a Cox proportional hazard model with treatment group as the covariate stratified by WHO FC and PAH background therapy; [¶]: hazard ratio is 0 and confidence interval is not evaluable (NE) due to small number of events, or no events occurring, in the subgroup.

a) 6MWD

	Placebo (n)	Sotatercept (n)	Sotatercept *versus* placebo H-L location shift (95% CI)	Sotatercept *versus* placebo H-L location shift (ASE) (95% CI)
Overall	192	237		41.8 (5.67) (30.69 to 52.93)
Sex				
Male	39	42		47.9 (16.29) (15.96 to 79.82)
Female	153	195		40.8 (6.19) (28.68 to 52.95)
Background therapy at baseline				
Monotherapy	6	17		5.0 (58.24) (−109.15 to 119.16)
Dual	69	80		41.2 (9.50) (22.60 to 59.86)
Triple	117	140		44.6 (7.09) (30.70 to 58.50)
Baseline WHO FC				
Class II	95	119		25.6 (7.07) (11.75 to 39.45)
Class III	97	118		59.2 (8.73) (42.08 to 76.29)
PAH aetiological subgroups				
iPAH	125	125		46.1 (7.94) (30.49 to 61.63)
hPAH	31	45		31.2 (11.13) (9.40 to 53.05)
Drug/toxin-induced PAH	4	13		40.3 (32.27) (−14.73 to 111.78)
Connective tissue disease	23	44		15.6 (14.16) (−12.18 to 43.32)
Corrected congenital heart disease	9	10		103.1 (44.40) (16.04 to 190.11)
Prostacyclin infusion therapy at baseline				
Yes	74	94		47.0 (8.73) (29.91 to 64.14)
No	118	143		38.1 (7.40) (23.58 to 52.57)
Baseline PVR				
≤800 dyn·s·cm^{-5}	129	157		30.2 (6.70) (17.06 to 43.34)
>800 dyn·s·cm^{-5}	63	80		59.1 (10.21) (39.04 to 79.06)
Region				
North America	63	69		34.7 (9.88) (15.35 to 54.07)
South America	24	30		46.4 (24.59) (−1.80 to 94.58)
Europe	88	116		35.8 (7.47) (21.20 to 50.48)
Asia or Pacific	17	22		47.2 (22.61) (2.88 to 91.50)
Cardiac index				
<2.5 L·min^{-1}·m^{-2} (intermediate/high risk)	84	95		50.0 (8.94) (32.46 to 67.50)
≥2.5 L·min^{-1}·m^{-2} (low risk)	108	142		33.9 (7.40) (19.41 to 48.43)



b) PVR

	Placebo (n)	Sotatercept (n)	Sotatercept *versus* placebo H-L location shift (95% CI)	Sotatercept *versus* placebo H-L location shift (ASE) (95% CI)
Overall	192	237		−234.8 (24.18) (−282.16 to −187.36)
Sex				
Male	39	42		−240.8 (51.37) (−341.45 to −140.06)
Female	153	195		−233.8 (27.70) (−288.12 to −179.55)
Background therapy at baseline				
Monotherapy	6	17		−382.6 (188.88) (−752.78 to −12.32)
Dual	69	80		−172.5 (41.00) (−252.87 to −92.13)
Triple	117	140		−267.0 (29.49) (−324.85 to −209.23)
Baseline WHO FC				
Class II	95	119		−176.3 (27.92) (−231.07 to −121.62)
Class III	97	118		−306.9 (43.63) (−392.42 to −221.38)
PAH aetiological subgroups				
iPAH	125	125		−260.1 (32.91) (−324.61 to −195.58)
hPAH	31	45		−187.1 (45.14) (−275.58 to −98.63)
Drug/toxin-induced PAH	4	13		−92.1 (100.86) (−289.10 to 106.28)
Connective tissue disease	23	44		−170.5 (77.09) (−321.63 to −19.43)
Corrected congenital heart disease	9	10		−356.4 (312.52) (−968.90 to 256.17)
Prostacyclin infusion therapy at baseline				
Yes	74	94		−274.4 (38.79) (−350.47 to −198.41)
No	118	143		−202.7 (31.35) (−264.18 to −141.26)
Baseline PVR				
≤800 dyn·s·cm^{-5}	129	157		−164.6 (20.88) (−205.54 to −123.68)
>800 dyn·s·cm^{-5}	63	80		−404.3 (52.12) (−506.43 to −302.11)
Region				
North America	63	69		−236.8 (39.67) (−314.53 to −159.04)
South America	24	30		−286.0 (77.36) (−437.67 to −134.41)
Europe	88	116		−193.1 (33.41) (−258.55 to −127.59)
Asia or Pacific	17	22		−210.1 (98.46) (−403.05 to −17.07)
Cardiac index				
<2.5 L·min^{-1}·m^{-2} (intermediate/high risk)	84	95		−296.3 (48.94) (−392.26 to −200.40)
≥2.5 L·min^{-1}·m^{-2} (low risk)	108	142		−202.8 (26.91) (−255.51 to −150.00)

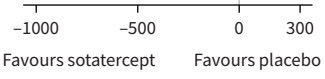


FIGURE 2 Forest plot for change from baseline at week 24 in subgroups in a) 6-min walk distance (6MWD), b) pulmonary vascular resistance (PVR) and c) N-terminal pro-brain natriuretic peptide (NT-proBNP) level (full analysis set). ASE: asymptotic standard error; H-L: Hodges–Lehmann; hPAH: heritable PAH; iPAH: idiopathic PAH; PAH: pulmonary arterial hypertension; WHO FC: World Health Organization functional class.

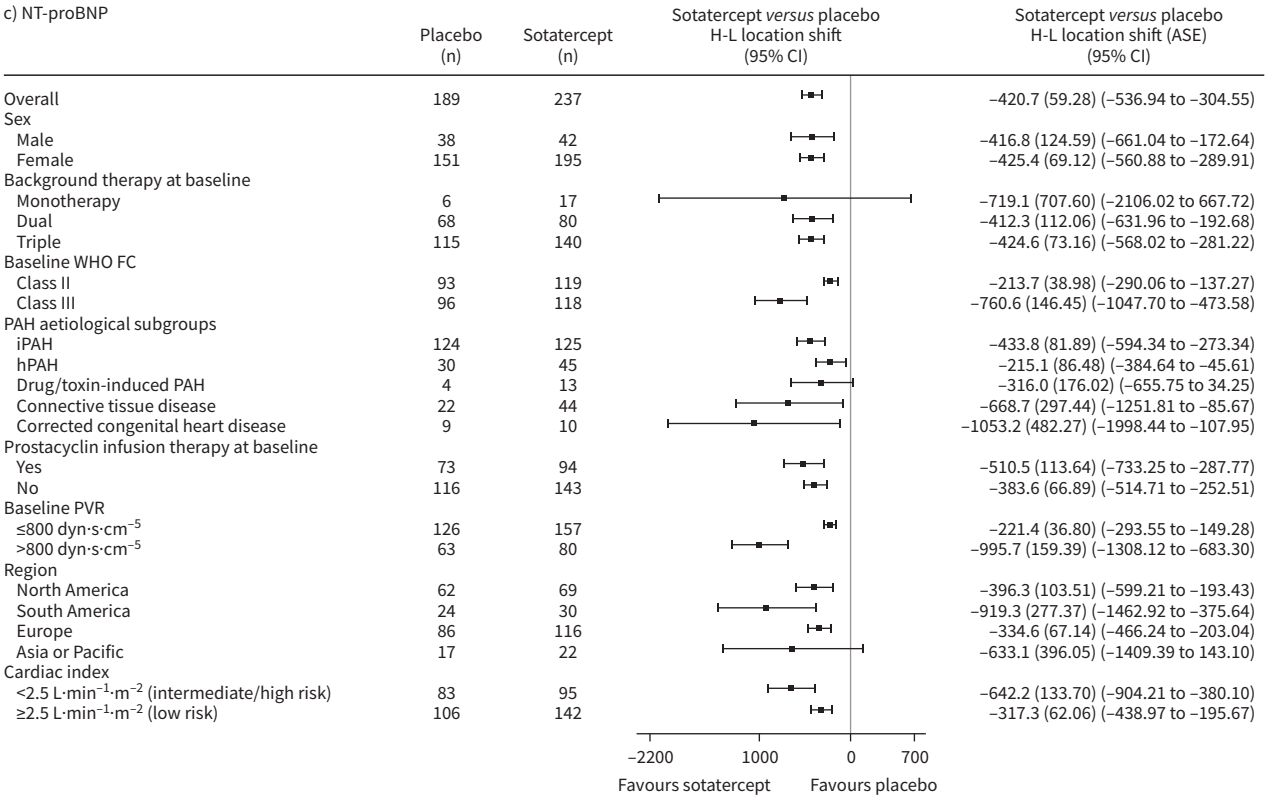


FIGURE 2 Continued.

significant difference in the distribution of time to first occurrence of death or nonfatal clinical worsening event in the sotatercept and placebo groups ($p<0.001$ by log-rank test). The total number of clinical worsening events or death was 10 in the sotatercept group and 47 in the placebo group. The hazard ratio in the sotatercept group, as compared with the placebo group, was 0.16 (95% CI 0.08 to 0.33; table 2), representing a relative risk reduction of 84% favouring sotatercept (figure 1a). The analysis by subgroup for time to first occurrence of death or nonfatal clinical worsening event is shown in figure 1b.

The subgroup analyses for 6MWD, PVR and NT-proBNP level are shown in figure 2. In the subgroups, the results were consistent with the overall analysis and generally favoured sotatercept. In several subgroups (monotherapy at baseline for 6MWD and NT-proBNP; drug/toxin-induced PAH for 6MWD, PVR and NT-proBNP; connective tissue disease for 6MWD; and corrected congenital heart disease for PVR), the point estimate favoured sotatercept, but the confidence intervals were wide and crossed zero.

The change from baseline at week 24 for select RHC and ECHO parameters is shown in table 3. There were clinically important reductions in both pulmonary and right heart pressures (mean pulmonary arterial pressure, systolic pulmonary arterial pressure, mean right atrial pressure, estimated right atrial pressure), improvements in RV size (RV area) during both systole and diastole, and enhancements in RV contractility (RV fractional area change) and RV–PA coupling (TAPSE/sPAP ratio). We observed a small reduction in PA wedge pressure and no meaningful changes in cardiac output or cardiac index.

Safety

While the number of patients experiencing TEAEs in the 24-week placebo-controlled period occurred with comparable frequency across both treatment groups (202 patients (85.2%) in the sotatercept group and 169 patients (88.0%) in the placebo group; table 4), the number of patients experiencing TEAEs related to treatment was higher in the sotatercept group (104 patients (43.9%)) than the placebo group (50 patients (26.0%)). The numbers of patients experiencing serious TEAEs (35 patients (14.8%) *versus* 39 patients (20.3%); supplementary table S1) and TEAEs leading to death (one patient (0.4%) *versus* six patients (3.1%)) were lower in the sotatercept than the placebo group. The number of patients experiencing serious AEs that were considered by the investigator to be related to sotatercept or placebo was low (four patients

TABLE 3 Change from baseline at week 24 in select RHC and ECHO parameters (full analysis set)

	Sotatercept	Placebo
Subjects (n)	237	192
RHC parameters		
Cardiac index (L·min^{-1}·m^{-2})		
Least-squares[#] mean change±SE	−0.0±0.04	−0.1±0.04
Least-squares[#] mean difference *versus* placebo (95% CI)	0.0 (−0.07 to 0.14)	
Mean pulmonary artery pressure (mmHg)		
Least-squares[#] mean change±SE	−12.6±0.61	0.7±0.71
Least-squares[#] mean difference *versus* placebo (95% CI)	−13.4 (−15.19 to −11.54)	
Mean pulmonary artery wedge pressure (mmHg)		
Least-squares[#] mean change±SE	−0.5±0.22	0.3±0.26
Least-squares[#] mean difference *versus* placebo (95% CI)	−0.8 (−1.46 to −0.13)	
Right atrial pressure (mmHg)		
Least-squares[#] mean change±SE	−2.1±0.24	0.4±0.28
Least-squares[#] mean difference *versus* placebo (95% CI)	−2.5 (−3.17 to −1.76)	
Cardiac output (L·min^{-1})		
Least-squares[#]mean change±SE	−0.1±0.07	−0.1±0.08
Least-squares[#] mean difference *versus* placebo (95% CI)	0.0 (−0.16 to −0.24)	
ECHO parameters		
Pulmonary artery systolic pressure (mmHg)		
Least-squares[#] mean change±SE	−19.4±1.66	−0.7±1.75
Least-squares[#] mean difference *versus* placebo (95% CI)	−18.7 (−23.38 to −13.96)	
Estimated right atrial pressure (mmHg)		
Least-squares[#] mean change±SE	−1.1±0.14	0.4±0.17
Least-squares[#] mean difference *versus* placebo (95% CI)	−1.5 (−1.96 to −1.10)	
Tricuspid annular plane systolic excursion (cm)		
Least-squares[#] mean change±SE	−0.0±0.02	−0.0±0.03
Least-squares[#] mean difference *versus* placebo (95% CI)	0.0 (−0.06 to 0.08)	
RV fractional area change (%)		
Least-squares[#] mean change±SE	4.0±0.58	1.4±0.70
Least-squares[#] mean difference *versus* placebo (95% CI)	2.6 (0.85 to 4.39)	
RV area in end-diastole (cm^2)		
Least-squares[#] mean change±SE	−4.3±0.35	0.8±0.42
Least-squares[#] mean difference *versus* placebo (95% CI)	−5.0 (−6.12 to −3.97)	
RV area in end-systole (cm^2)		
Least-squares[#] mean change±SE	−4.1±0.30	0.3±0.36
Least-squares[#] mean difference *versus* placebo (95% CI)	−4.4 (−5.34 to −3.51)	
RV pulmonary artery contractile pressure coupling (mm·mmHg^{-1})		
Least-squares[#] mean change±SE	0.1±0.01	−0.0±0.01
Least-squares[#] mean difference *versus* placebo (95% CI)	0.1 (0.09 to 0.15)	

ECHO: echocardiography; RHC: right heart catheterisation; RV: right ventricular. [#]: derived from ANCOVA model with treatment, randomisation baseline stratification factors of background therapy (monotherapy or double *versus* triple therapy) and baseline World Health Organization functional class (II *versus* III) as fixed factors and the relevant baseline value for the parameter under evaluation as covariate.

(1.7%) in the sotatercept group and three patients (1.6%) in the placebo group). The incidence of patients experiencing severe AEs was similar in the sotatercept group (27 patients (11.4%)) and the placebo group (26 patients (13.5%)). AEOIs and AESIs occurring more frequently with sotatercept than placebo are shown in table 5.

Discussion

The pooled analysis of the PULSAR and STELLAR studies confirms the efficacy of sotatercept *versus* placebo in patients with PAH. Adding sotatercept treatment to background PAH therapy for 24 weeks improved exercise capacity (as assessed by improvement in 6MWD) and cardiac pulmonary haemodynamic parameters (as assessed by PVR) in patients with PAH. For the end-points of WHO FC, multicomponent improvement, ESC/ERS risk status and French risk score, significantly greater proportions of patients achieved improvements with sotatercept *versus* placebo. Sotatercept was also associated with an improvement in NT-proBNP levels and a delay in the time to first occurrence of death or clinical worsening event. Moreover, treatment with sotatercept demonstrated reductions in both pulmonary and

TABLE 4 Summary of adverse events through week 24

	Sotatercept	Placebo
Subjects (n)	237	192
Patients with any adverse event		
Any	202 (85.2)	169 (88.0)
Related to study treatment[#]	104 (43.9)	50 (26.0)
Leading to discontinuation of study treatment	9 (3.8)	11 (5.7)
Leading to death	1 (0.4)	6 (3.1)
Patients with any severe adverse event[¶]	27 (11.4)	26 (13.5)
Patients with any serious adverse event[+]		
Any	35 (14.8)	39 (20.3)
Related to study treatment[#]	4 (1.7)	3 (1.6)
Patients with any adverse event reported in ⩾10% of patients		
Headache	47 (19.8)	30 (15.6)
Diarrhoea	33 (13.9)	17 (8.9)
Epistaxis	29 (12.2)	4 (2.1)
Dizziness	26 (11.0)	6 (3.1)
Nausea	24 (10.1)	23 (12.0)
COVID-19	24 (10.1)	21 (10.9)

Data are presented as n (%), unless otherwise stated. Shown are adverse events that occurred up to and including day 56 after the last dose of sotatercept or placebo. The safety population includes all randomly assigned patients who received at least one dose of sotatercept or placebo. [#]: suspected to be related to sotatercept or placebo by the trial investigator; [¶]: any adverse event that was deemed to be severe in intensity by the trial investigator; [+]: defined as any untoward medical event that resulted in death, was life-threatening, warranted hospitalisation or caused prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, may have caused a congenital abnormality or birth defect, or warranted intervention to prevent permanent impairment or damage.

right heart pressures, improvements in RV size during systole and diastole, and enhancements in RV contractility and RV–PA coupling; this is supportive of RV reverse remodelling.

Although results from this pooled analysis demonstrated that the point estimates favoured sotatercept in several subgroups (monotherapy at baseline for 6MWD and NT-proBNP; drug/toxin-induced PAH for 6MWD, PVR and NT-proBNP; connective tissue disease for 6MWD; and corrected congenital heart disease for PVR), the confidence intervals were wide and crossed zero. These results were consistent with the analyses in the individual PULSAR and STELLAR studies [15, 17]. However, the individual studies were not designed or powered to address differences within subgroups. Small numbers in the subgroups limited interpretation of the results. In addition, connective tissue disease is further complicated by heterogeneity in this subgroup. Therefore, additional data on the effect of sotatercept in these specific patient subgroups are required.

The AE profile observed in this pooled analysis was consistent with that previously reported in the individual PULSAR and STELLAR studies [15, 17], and no new safety signals were observed. Of the AEOIs analysed, bleeding events, increased blood pressure, increased haemoglobin, telangiectasia and thrombocytopenia were more frequently reported with sotatercept than with placebo. The majority of these AEOIs were nonserious. Increased haemoglobin and thrombocytopenia are responsive to dose modification [18]. Because the protocols did not request invasive investigations, the events of telangiectasia reported were localised on the skin. Among bleeding events, epistaxis was, by far, the most frequently reported event. Epistaxis was not associated with reductions in platelet count. There was also no evidence that telangiectasia in the nasal mucosa accounted for epistaxis; however, no systematic endoscopic or other examination of the nasal mucosa was conducted. For the AEOI of cardiac events, embryo-foetal toxicity, hepatic toxicity, leukopenia, neutropenia, renal toxicity, suppression of follicle-stimulating hormone and thromboembolic events, the rates were similar or lower on sotatercept when compared with placebo. Together, these findings support a favourable and manageable safety profile when sotatercept is combined with background therapies for PAH.

There are some strengths and weaknesses associated with this pooled analysis. The fact that it was *post hoc* without adjustment for multiple comparisons increased the likelihood of finding statistically significant results by chance. However, both PULSAR and STELLAR had methods to control for type I error and both studies generally had results favouring sotatercept. In this pooled analysis, all covariates that could

TABLE 5 Adverse events of interest and special interest through week 24

Patients with any adverse event of interest or special interest by category and preferred term[#]	Sotatercept	Placebo
Subjects (n)	237	192
Increased blood pressure	8 (3.4)	3 (1.6)
Hypertension	5 (2.1)	1 (0.5)
Blood pressure increased	1 (0.4)	2 (1.0)
Labile hypertension	1 (0.4)	0
Diastolic blood pressure increased	1 (0.4)	0
Increased haemoglobin	18 (7.6)	0
Haemoglobin increased	15 (6.3)	0
Polycythaemia	3 (1.3)	0
Red blood cell count increased	1 (0.4)	0
Thrombocytopenia	17 (7.2)	4 (2.1)
Thrombocytopenia	15 (6.3)	3 (1.6)
Platelet count decreased	3 (1.3)	1 (0.5)
Bleeding events	49 (20.7)	28 (14.6)
Epistaxis	29 (12.2)	4 (2.1)
Anaemia	5 (2.1)	7 (3.6)
Gingival bleeding	5 (2.1)	1 (0.5)
Haemoptysis	3 (1.3)	2 (1.0)
Haematoma	3 (1.3)	1 (0.5)
Injection-site bruising	3 (1.3)	0
Melaena	2 (0.8)	0
Contusion	1 (0.4)	2 (1.0)
Rectal haemorrhage	1 (0.4)	1 (0.5)
Conjunctival haemorrhage	1 (0.4)	1 (0.5)
Ecchymosis	1 (0.4)	1 (0.5)
Haemorrhoidal haemorrhage	1 (0.4)	1 (0.5)
Post-procedural haematoma	1 (0.4)	1 (0.5)
Vaginal haemorrhage	1 (0.4)	1 (0.5)
Administration-site bruise	1 (0.4)	0
Administration-site haematoma	1 (0.4)	0
Petechiae	1 (0.4)	0
Application-site haematoma	1 (0.4)	0
Cerebral haematoma	1 (0.4)	0
Gastrointestinal haemorrhage	1 (0.4)	0
Upper gastrointestinal haemorrhage	1 (0.4)	0
Vaginal haematoma	1 (0.4)	0
Telangiectasia	17 (7.2)	5 (2.6)

Shown are adverse events that occurred up to and including day 56 after the last dose of sotatercept or placebo. The safety population includes all randomly assigned patients who received at least one dose of sotatercept or placebo. [#]: adverse events of interest (bleeding events, cardiac events, embryo or foetal toxic effects, hepatic toxic effects, immunogenicity, increased blood pressure, increased haemoglobin levels, leukopenia, neutropenia, renal toxic effects, suppression of follicle-stimulating hormone, thrombocytopenia and thromboembolic events) and special interest (telangiectasia) were predefined variables based on standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries or groupings if preferred terms were analysed to assess the overall safety profile of sotatercept.

potentially have different distributions across these studies were included and, hence, additional random effects to account for variability across studies were not needed. The uniformity of study cohorts restricts the generalisability of the findings to a broader population of patients with PAH. Although the primary end-points of the two trials differed (6MWD was the primary end-point in STELLAR but a secondary end-point in PULSAR, and PVR was the primary end-point in PULSAR but a secondary end-point in STELLAR), key secondary end-points, such as NT-proBNP level, WHO FC and time to first occurrence of death or nonfatal clinical worsening event, were shared, allowing for a pooled analysis. Furthermore, similarities in study design allow for end-points classified as primary and secondary to be pooled. The limited duration of 24 weeks (except for the analysis of time to first occurrence of death or nonfatal clinical worsening event in STELLAR) prevented the long-term assessment of sotatercept efficacy and safety.

Although 24 weeks is a relatively limited period for safety analysis, with longer placebo-controlled observation, the group imbalance may increase due to drop-out of patients randomised to placebo experiencing clinical worsening. This analysis relies on previously collected data that may not have been uniformly collected across studies (*i.e.* missing data resulting from missed appointments due to COVID-19 in STELLAR). This could introduce biases and/or reduce statistical power. Confounding variables across the studies may have influenced outcomes, such as differences in treatment protocols, concomitant medications or comorbid conditions that cannot be controlled for and can introduce biases. While an aggregate data meta-analysis could have been performed, the individual patient data for the efficacy end-points allowed for a more comprehensive analysis that would not have been possible or feasible for some of the analyses presented, such as for time to first occurrence of death or nonfatal clinical worsening event.

In conclusion, the results of this pooled analysis confirm that sotatercept delivers therapeutic benefit across a range of efficacy end-points in patients with PAH on background standard-of-care PAH therapy and has a favourable safety profile. These results strengthen the existing evidence base to enable more informed clinical decisions that may lead to optimised therapeutic strategies in patients with PAH. Ongoing double-blind, randomised, controlled, phase 3 trials with sotatercept will generate additional insight into the efficacy and safety profile of sotatercept in subgroups of patients with more severe disease (ZENITH (NCT04896008 [23]) and earlier stage disease (HYPERION (NCT04811092) [24]). In addition, SOTERIA (NCT04796337) [25], an open-label extension follow-up study of patients who completed a prior sotatercept study, will provide longer term follow-up for the efficacy and safety of sotatercept.

Acknowledgements: The authors would like to thank the patients, their families and all investigators involved in this study. Medical writing support, including assisting authors with developing the outline and initial draft and incorporation of comments, was provided by Anastasija Pesevska, and editorial support, including fact checking, referencing, figure preparation, formatting, proofreading and submission was provided by Anastasija Pesevska and Ian Norton, all of Scion (a division of Prime, London, UK), supported by Merck Sharp & Dohme LLC (MSD), a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, according to Good Publication Practice guidelines. The sponsor was involved in the study design and collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions and data interpretation lies with the authors.

Data availability: The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at https://engagezone.msd.com/ds_documentation.php. Requests for access to the study data can be submitted through the Engage Zone site or *via* email to the data access mailbox.

The PULSAR trial was prospectively registered with ClinicalTrials.gov as NCT03496207 and STELLAR as NCT04576988.

Ethics statement: Both trials were conducted in accordance with the principles of the Declaration of Helsinki, the ethical guidelines of the Council for International Organizations of Medical Sciences, the Good Clinical Practice guidelines of the International Council for Harmonisation, and all applicable laws and regulations. All patients provided written informed consent.

Author contributions: J. de Oliveira Pena, J. Strait, A.G. Cornell and L. Perchenet were involved in conceptualisation. J. de Oliveira Pena, B. Miller, A. Xing, S. Manimaran and X. Wang were involved in development or design of methodology. A. Xing, S. Manimaran and X. Wang were involved in programming and software development. B. Miller, A. Xing, S. Manimaran and X. Wang were involved in validation of the results. A. Xing, S. Manimaran and X. Wang were involved in formal analysis of the study data. S. Rosenkranz, J. de Oliveira Pena, A. Xing, E. Grünig and G. Kopeć were involved in the investigation process or data/evidence collection. A. Xing, S. Manimaran and X. Wang were involved in data curation. A. Xing was involved in data visualisation. J. de Oliveira Pena, B. Miller, A. Xing and J. Strait were involved in supervision/oversight of the research. All authors participated in the review and revision of the manuscript. All authors have approved and take responsibility for the final version of the manuscript.

Conflicts of interest: M.M. Hoeper reports fees for lectures or consultations from Acceleron, Actelion, Aerami, Aerovate, AOP Health, Bayer, Ferrer, Gossamer, Janssen, MSD and Novartis. M. Gomberg-Maitland reports scientific consulting for Acceleron Pharma and Merck & Co., Inc., AeramiI, Bayer HealthCare Pharmaceuticals, Janssen Biotech, Jucabio, Keros and United Therapeutics Corporation; and receiving grants or contracts to her institution from Aerovate, Altavant, Acceleron Pharma Gossamer Bio and MSD; her spouse is an employee of Intellia

Therapeutics. D.B. Badesch has served as a steering committee member and consultant to MSD; has received grant support from MSD, AI Therapeutics, Arena/United Therapeutics, Altavant and Liquidia; and is a distinguished advisor to the Pulmonary Hypertension Association's Scientific Leadership Council; his wife is a long-term holder of stock in Johnson & Johnson in a family trust. J.S.R. Gibbs is a consultant for Acceleron Pharma Inc., a wholly owned subsidiary of Merck & Co., Inc., Actelion, Aerovate, Gossamer Bio, Janssen, Merck & Co., Inc., MSD, Keros, LG Chem, Pfizer and United Therapeutics. E. Grünig has received honoraria for serving as a speaker and/or consultant from Bayer HealthCare, Ferrer, GEBRO, GlaxoSmithKline, Janssen Biotech, MSD and OMT; and received research funding for clinical studies from Acceleron, Actelion Pharmaceuticals, Bayer HealthCare, MSD, Bellerophon, Gossamer Bio, Janssen, Novartis, OMT, Pfizer, REATA and United Therapeutics. G. Kopeć reports consulting fees from MSD; and lecture fees from MSD, Janssen, AOP Orphan, Pfizer, Bayer and Aerovate. V.V. McLaughlin reports grant support from Aerovate, Enzyvant, Gossamer Bio, Janssen, Merck & Co., Inc. and Sonovie; and consultancy fees from 35 Pharma, Aerami, Aerovate, Caremark, LLC, Corvista, Enzyvant, Gossamer Bio, Janssen, Keros, Liquidia, Merck & Co., Inc., United Therapeutics, Respira and Vertex. G. Meyer reports grant or contract support from Bayer, Pulmovant, Janssen, Merck & Co., Inc. and Gossamer Bio; consulting fees from Bayer, Gossamer Bio, Janssen and Pulmovant; payment or honoraria for lectures, presentations, manuscript writing or educational events from Bayer, Gossamer Bio, Janssen and Merck & Co., Inc.; support for attending meetings from Janssen, Bayer and Gossamer Bio; and participation on a data safety monitoring board or advisory board from Bayer, Liquidia, Janssen, Pulmovant and Gossamer Bio. K.M. Olsson reports research funding to her institution from Acceleron, MSD and Janssen; consulting fees from Acceleron, Actelion, Janssen, Ferrer, Merck & Co., Inc., AOP Health, Gossamer and Bayer; speaking honoraria from Acceleron, Actelion, AOP Health, Janssen, Bayer, MSD, Ferrer and Gossamer; and travel support from Acceleron/MSD and Janssen/Actelion. I.R. Preston reports grant or contract support from Merck & Co., Inc., Janssen, United Therapeutics, Keros and Tenax; consulting fees from Merck & Co., Inc., Janssen, United Therapeutics, Liquidia, Gossamer, Aerovate and Insmed; and participation in educational events for Medscape and NACE. S. Rosenkranz reports speaker or consultant fees from Abbott, Acceleron, Actelion, Aerovate, Altavant, AOP, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Ferrer, Gossamer, Inari, Janssen, Lilly, MSD and United Therapeutics; and research grants (paid to his institution) from AstraZeneca, Bayer, Janssen, Lempo and MSD. R. Souza reports lecture fees from Bayer, Janssen and MSD; and participation in an advisory board for Bayer, Janssen and MSD. A.B. Waxman has served as a steering committee member/investigator for MSD and United Therapeutics; investigator for OrphAI and ARIA-CV; and data safety monitoring board chair for INSMED. L. Perchenet, J. Strait, A. Xing, S. Manimaran, X. Wang, B. Miller and A.G. Cornell are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. J. de Oliveira Pena was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA, during the conduct and readout of the studies. H.A. Ghofrani reports consultancy fees from Aerovate, Altavant, Bayer AG, Attgeno, Gossamer, Janssen/Actelion, Keros, Liquidia, Morphic, MSD/Acceleron and Pfizer; payment or honoraria for lectures, presentations, manuscript writing or educational events from Bayer AG, Gossamer, Janssen/Actelion, Keros and MSD/Acceleron; participation as an advisory committee member for Aerovate, Altavant, Attgeno, Bayer AG, Janssen/Actelion, MSD/Acceleron and Pfizer; and as a data and safety monitoring board member for Insmed; his spouse is an employee of Liquidia. M. Humbert reports grants or contracts (paid to institution) from Gossamer and Merck & Co., Inc.; consulting fees from 35 Pharma, Aerovate, AOP Orphan, Chiesi, Ferrer, Gossamer, Janssen, Keros, Liquidia, Merck & Co., Inc., Respira and United Therapeutics; payment or honoraria for lectures, presentations, manuscript writing or educational events from Janssen and Merck & Co., Inc.; and participation on a data safety monitoring board or advisory board for 35 Pharma, Aerovate, Janssen, Keros, Merck & Co., Inc. and United Therapeutics.

Support statement: This study was funded by Acceleron Pharma Inc., a wholly owned subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding information for this article has been deposited with the Crossref Funder Registry.

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