Online supplementary material

Exclusion criteria

Patients were excluded from the study if they had: >15% difference in 6MWD between the 14-day screening period and Week 0; participated in another clinical trial in the last 30 days; had previously been treated with riociguat; had been treated with prostanoids ≤90 days before baseline; or if they were receiving ongoing therapy with concomitant PDE5i, non-specific phosphodiesterase inhibitors or NO donors.

Statistical analysis

The full analysis set included all patients who received ≥1 dose of riociguat. All variables were analysed descriptively. No formal hypothesis testing was planned owing to the exploratory nature of the study. In addition, exploratory, missing data sensitivity analyses were performed, and data imputed using the following rules: for 6MWD, where a patient died or withdrew due to clinical worsening with no termination visit measurement, the worst-possible value (0 m) was imputed. In the case of withdrawal for other reasons, the termination visit or last post-baseline measurement was used. For WHO FC, in the case of withdrawal due to clinical worsening with no termination visit measurement, the worst-possible score (IV) was used, and in the case of death, the worst-possible value plus one (V). For pulmonary haemodynamics, in the case of missing post-baseline values, the baseline absolute value (change of 0) was imputed. For EQ-5D VAS, in the case of withdrawal due to clinical worsening with no termination visit measurement, the worst possible score (0) was imputed.

Post hoc calculation of statistical significance of changes from baseline to Week 24 was performed using an analysis of covariance with calculation of 95% confidence intervals (CIs) for 6MWD, PVR and cardiac index. The relative changes in geometric mean and 95% CI were calculated for the change from baseline to Week 24 for NT-proBNP level and the statistical significance of change from baseline to Week 24 in WHO FC was calculated using a sign test.

A *post hoc* analysis was performed to determine whether patients had changed their ESC/ERS risk category at Week 24 using the following thresholds: WHO FC I or II, 6MWD >440 m, NT-proBNP <300 pg/mL, right atrial area <18 cm^2, right atrial pressure <8 mmHg, cardiac index ≥2.5 L/min/m^2 and mixed-venous oxygen saturation >65% (data for signs of right heart failure, progression of symptoms, syncope, cardiopulmonary exercise testing and echocardiography were not included in the analysis). For the purpose of this analysis, we assumed an overall low-risk profile when patients had an arbitrary majority (>50%) of available variables that met the above thresholds.

SUPPLEMENTARY TABLE S1. Sensitivity analyses for change in 6MWD, NT-ProBNP, and WHO FC according to imputation rules

Parameter	n	Value at Last Visit	Change from Baseline to Last Visit	95% CI p value for change from baseline
6MWD, m [a]	61	371 (120)	+14 (98)	–11 to +39 p=0.281
NT-proBNP, pg/mL[b,c]	61	1083 (1904)	–100 (1478)	0.7 to 1.03 p=0.0932
WHO FC, %[c,d]	60	**I/II/III/IV/V** 2/45/50/2/2	**Improved/stable/worsened** 47/50/3	p=<0.0001

Data are mean (standard deviation) unless otherwise stated

Last Visit = last observed value post-baseline.

[a]Where a patient died or withdrew due to clinical worsening with no termination visit measurement, the worst possible value (0 m) was imputed. In the case of withdrawal for other reasons, the termination visit or last post-baseline measurement was imputed (LOCF).

[b]95% CIs and p value are for relative change from baseline.

[c]Where a patient died or withdrew, the termination visit or last post-baseline measurement was imputed (LOCF). Patients who died or withdrew with no post-baseline measurement were excluded from the analysis.

[d]Where a patient withdrew due to clinical worsening with no termination visit measurement, the worst possible score (IV) was used, and in the case of death, the worst possible value plus one (V) was used.

6MWD: 6-minute walking distance; CI: confidence interval; LOCF: last observation carried forward; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; WHO FC: World Health Organisation functional class.

SUPPLEMENTARY TABLE S2 Change from baseline (the last documented value while still receiving PDE5i) to Week 24 for EQ-5D measures, including last observation carried forward sensitivity analysis

Parameter	n	Value at Week 24/Last Visit	Change to Week 24/Last Visit[a,b]
EQ-5D VAS score[c]	52	69 (17)	+7 (19)
EQ-5D utility score[d]	52	0.76 (0.20)	+0.07 (0.28)
EQ-5D VAS score (Last Visit)	61	67 (22)	+5 (21)
EQ-5D utility score (Last visit)	61	0.70 (0.34)	+0.03 (0.39)

Data are mean (standard deviation).

Last Visit = last observed value post-baseline. Where a patient died or withdrew due to clinical worsening with no termination visit measurement, the worst possible score (0) was imputed.

[a]An increase in EQ-5D VAS or utility scores denotes improvement.

[b]This table includes only those patients for whom the respective variables were available at baseline and at Week 24.

[c]MID: 7–12 [32].

[d]MID: 0.074 [33].

EQ-5D: EuroQol 5-Dimensions questionnaire; LOCF: last observation carried forward; MID: minimally important difference; PDE5i: phosphodiesterase-5 inhibitors; VAS: visual analogue scale.

SUPPLEMENTARY TABLE S3 Change from baseline (the last documented value while still receiving PDE5i) to Week 24 in 6MWD, NT-proBNP and haemodynamics in patients receiving monotherapy and combination therapy at baseline

Parameter	Monotherapy		Combination therapy	
	n	**Change from baseline to Week 24[a]**	**n**	**Change from baseline to Week 24[a]**
6MWD, m	10	+33 (63)	41	+30 (64)
NT-proBNP, pg/mL	11	–813 (2024)	40	–219 (909)
Cardiac index, L/min/m^2	11	+0.40 (0.54)	37	+0.29 (0.53)
PVR, dyn·s·cm^{-5}	11	–142 (260)	38	–92 (307)

Data are mean (standard deviation).

[a]This table includes only those patients for whom the respective variables were available at baseline and at Week 24.

6MWD: 6-minute walking distance; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PDE5i: phosphodiesterase-5 inhibitors; PVR: pulmonary vascular resistance.

SUPPLEMENTARY TABLE S4 Change from baselinea (the last documented value while still receiving PDE5i) to Week 24 in 6MWD, NT-proBNP and haemodynamics in the overall ERA, bosentan and macitentan/ambrisentan combined subgroups

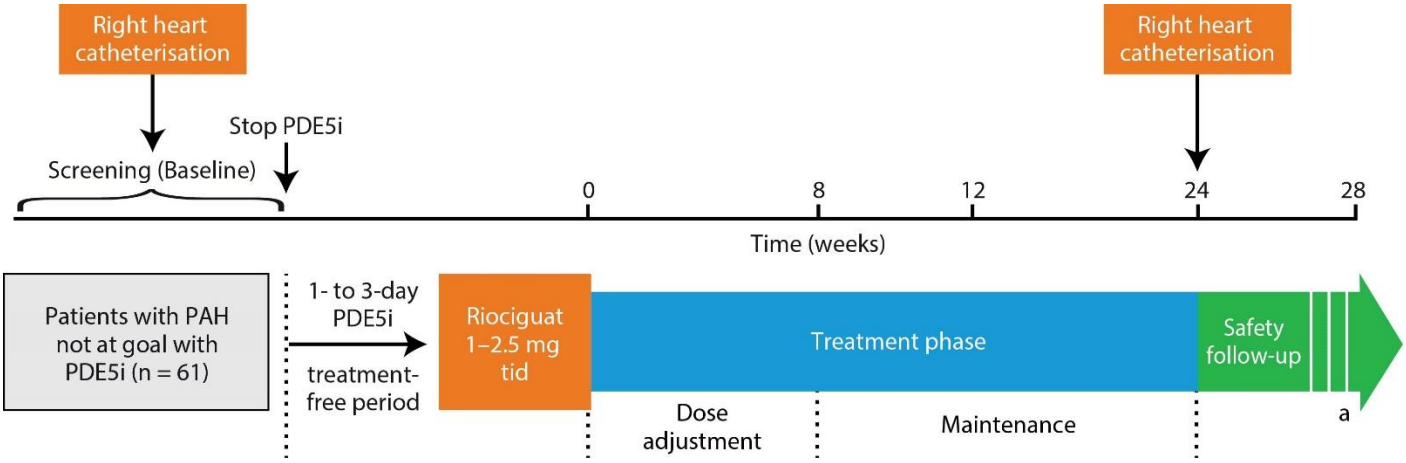
Parameter	**ERAs (overall)**		**Bosentan**		**Macitentan/ambrisentan**	
	n	**Change from baseline to Week 24**	**N**	**Change from baseline to Week 24**	**n**	**Change from baseline to Week 24**
6MWD, m	42	+28 (65)	13	+58 (64)	29	+15 (61)
NT-proBNP, pg/mL	41	–369 (1316)	12	–856 (1403)	29	–168 (1249)
Cardiac index, L/min/m^2	38	+0.30 (0.53)	12	+0.37 (0.72)	26	+0.28 (0.42)
PVR, dyn·s·cm^{-5}	39	–96 (305)	12	–45 (450)	27	–119 (220)

Data are mean (standard deviation).

[a]This table includes only those patients for whom the respective variables were available at baseline and at Week 24.

6MWD: 6-minute walking distance; ERA: endothelin receptor antagonist; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PDE5i: phosphodiesterase-5 inhibitors; PVR: pulmonary vascular resistance.

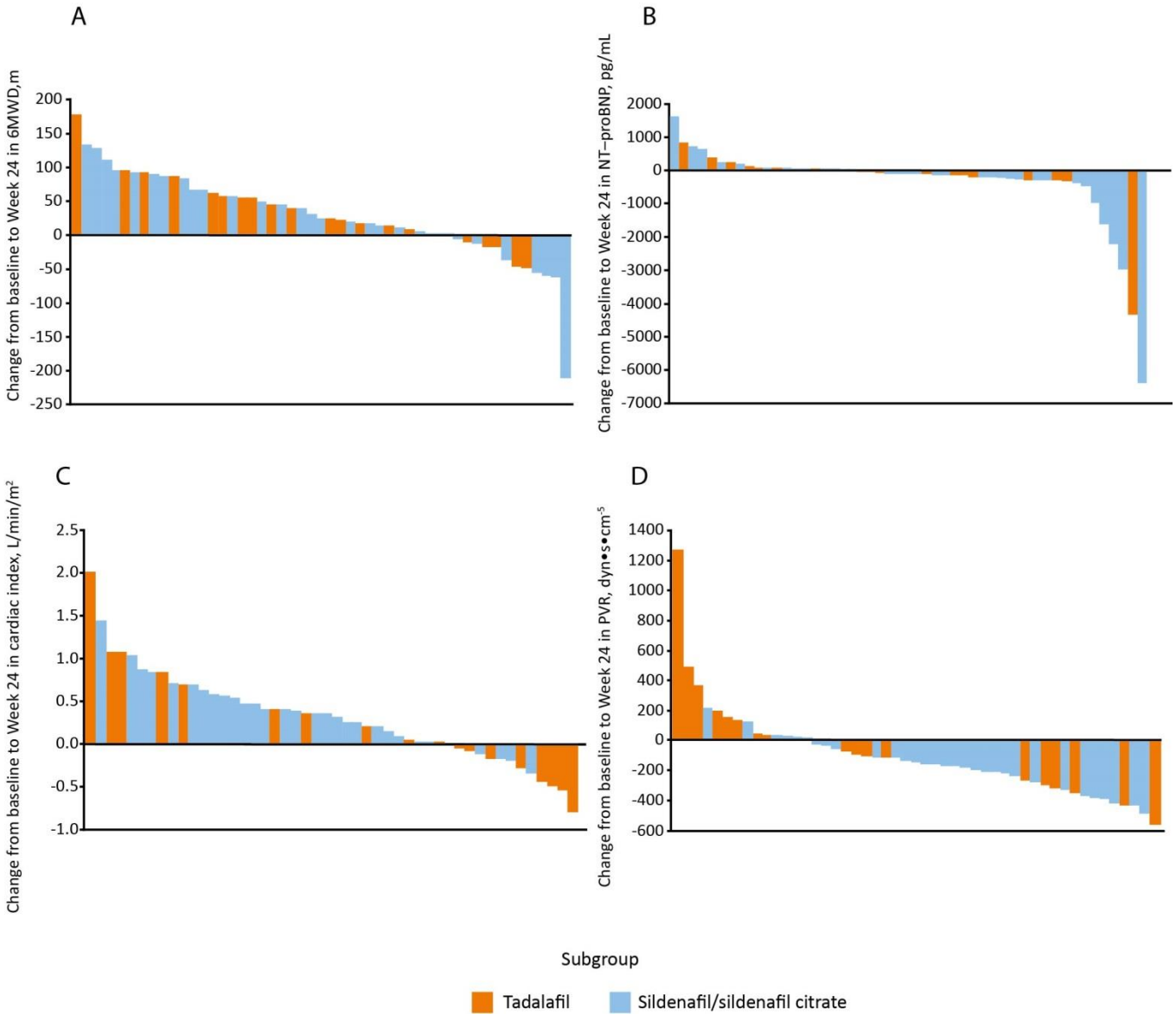
SUPPLEMENTARY FIGURE S1 RESPITE study design.



[a]Patients may participate in an extended drug-supply phase for 18 months or until reimbursement.

PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase-5 inhibitors; tid: three times daily.

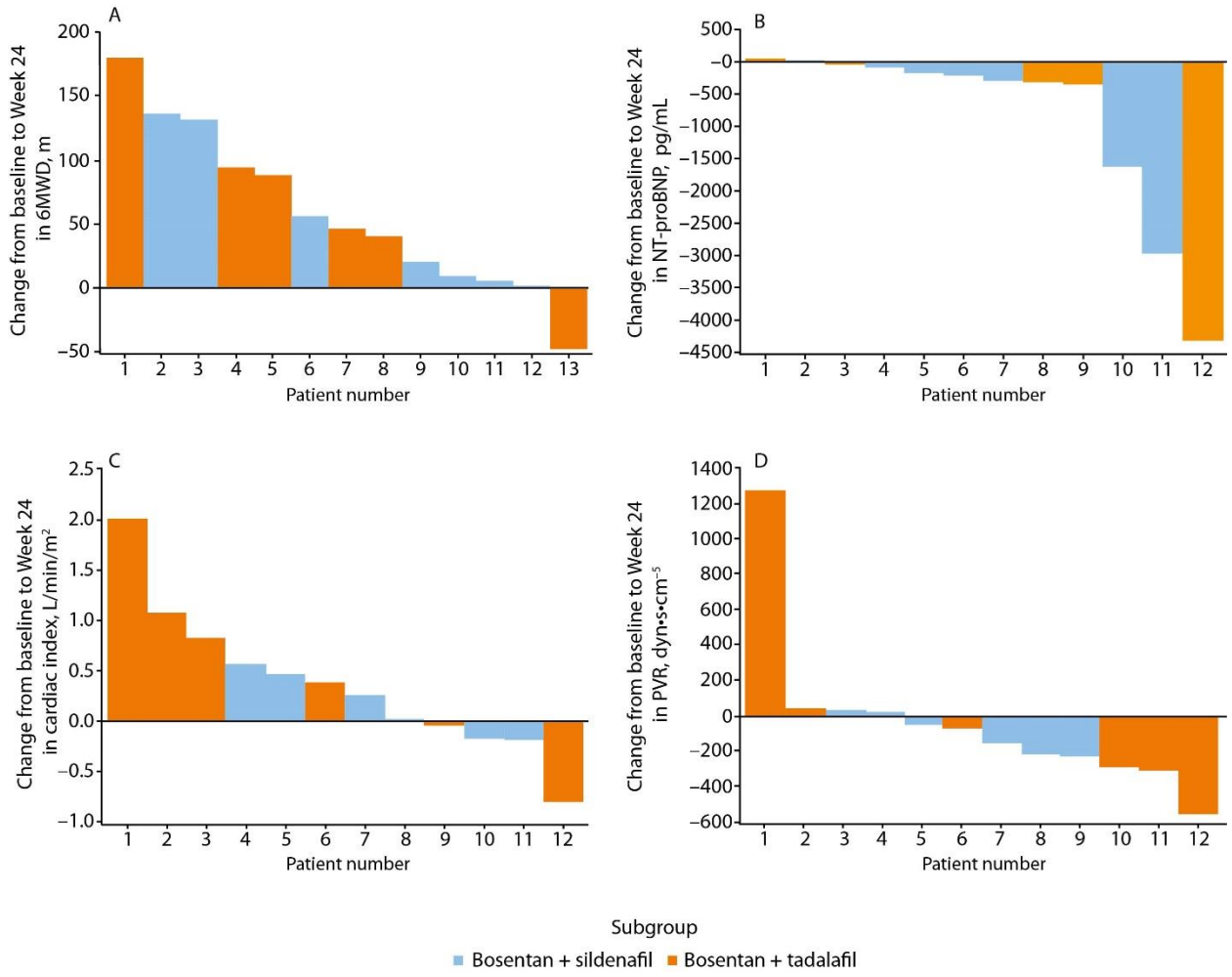
SUPPLEMENTARY FIGURE S2 Waterfall plots of individual patient data for changes from baseline (the last documented value while still receiving PDE5i) to Week 24 in (A) 6MWD, (B)



NT-proBNP, (C) cardiac index and (D) PVR by prior PDE5i treatment.

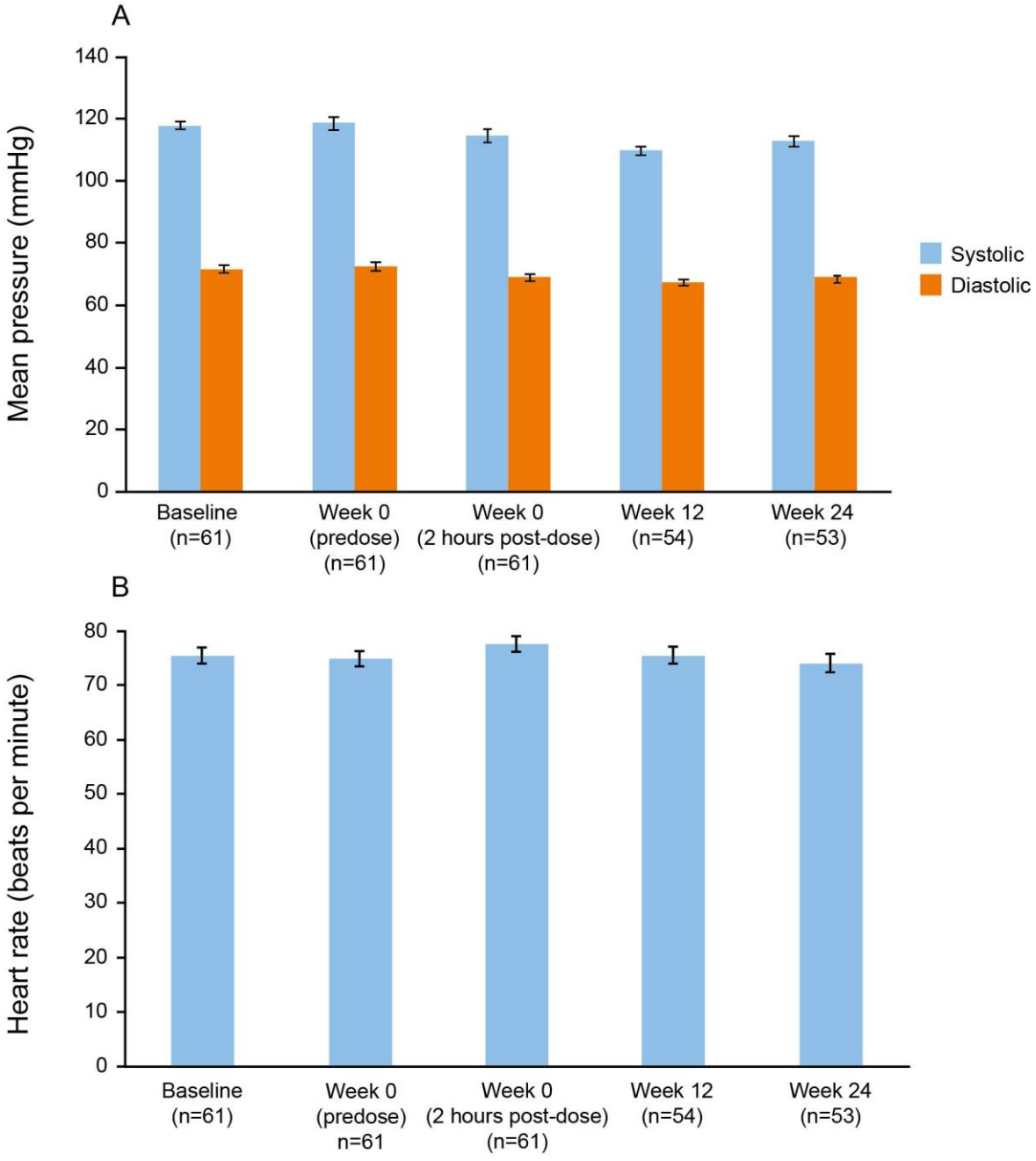
6MWD: 6-minute walking distance; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PDE5i: phosphodiesterase-5 inhibitors; PVR: pulmonary vascular resistance.

SUPPLEMENTARY FIGURE S3 Waterfall plots of individual patient data for changes from baseline (the last documented value while still receiving PDE5i) to Week 24 in (A) 6MWD, (B) NT-proBNP, (C) cardiac index and (D) PVR in patients receiving concomitant bosentan, by prior PDE5i treatment.



6MWD: 6-minute walking distance; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PDE5i: phosphodiesterase-5 inhibitors; PVR: pulmonary vascular resistance.

SUPPLEMENTARY FIGURE S4 (A) Systolic and diastolic blood pressure and (B) heart rate at baseline (the last documented value while still receiving PDE5i), Week 0 (the last documented value before starting riociguat treatment after the PDE5i treatment-free period), Week 12 and Week 24.



PDE5i: phosphodiesterase-5 inhibitors.