## SUPPLEMENTARY TABLES

**Supplementary Table 1.** Reasons for not completing treatment and exclusions from the per protocol set for analyses of primary endpoint variables.

**Supplementary Table 2** Actual dose of study treatment received on and after week 8 (Visit 4, full analysis set excluding patients with incorrectly assigned doses)

**Supplementary Table 3.** Additional baseline characteristics

**SupplementaryTable 4** Sensitivity analysis: baseline correction of primary endpoint analysis (Per protocol sets)

**Supplementary Table 5** Change from baseline in primary analysis variables (per protocol analysis sets for NT-proBNP and LAV) and heart rate (full analysis set excluding patients with incorrectly assigned doses) based on heart rhythm at baseline

**Supplementary Table 6** Echocardiography (full analysis set excluding patients with incorrectly assigned doses)

**Supplementary Table 7** Biomarkers (full analysis set excluding patients with incorrectly assigned doses)

**Supplementary Methods**

**Supplementary Table 1.** Reasons for not completing treatment and exclusions from the per protocol set for analyses of primary endpoint variables.

| | | Vericiguat | | | |
|---|---|---|---|---|---|
| | **Placebo** | **1.25 mg** | **2.5 mg** | **2.5 to 5 mg** | **2.5 to 10 mg** |
| Randomized to receive treatment | 93 | 96 | 96 | 96 | 96 |
| Completed treatment | 80 | 82 | 83 | 80 | 86 |
| Not completed treatment | 13 | 14 | 13 | 16 | 10 |
| Primary reason | | | | | |
| Adverse event | 3 | 4 | 8 | 6 | 5 |
| Death | 0 | 0 | 0 | 3 | 1 |
| Logistical difficulties | 0 | 1 | 1 | 0 | 0 |
| Protocol decision points | 1 | 3 | 0 | 0 | 0 |
| Protocol violation | 0 | 0 | 0 | 2 | 0 |
| Withdrawal by patient | 9 | 6 | 4 | 5 | 4 |
| Valid for Per protocol set for NT-proBNP* | 73 | 77 | 78 | 57 | 60 |
| Excluded from analysis | 20 | 19 | 18 | 39 | 36 |
| Non-adherence with study drug | 1 | 3 | 1 | 5 | 2 |
| Discontinued study drug >10 d before completing 12 weeks | 11 | 14 | 14 | 15 | 10 |
| Patient did not reach Visit 5 (day 84) | 13 | 14 | 13 | 16 | 10 |
| Visit 1 was done but no NT-proBNP value | 3 | 1 | 2 | 2 | 3 |
| Visit 5 was done but no NT-proBNP value | 6 | 6 | 6 | 12 | 4 |
| Incorrect medication assigned on Visit 3 | 0 | 0 | 0 | 4 | 23 |
| Incorrect medication assigned on Visit 4 | 0 | 0 | 0 | 19 | 24 |
| Concomitant nitrates or NO donors | 6 | 4 | 3 | 5 | 2 |
| Valid for Per protocol set analysis set for LAV* | 67 | 77 | 78 | 57 | 59 |
| Excluded from analysis | 26 | 19 | 18 | 39 | 37 |
| Non-adherence with study drug | 1 | 3 | 1 | 5 | 2 |
| Discontinued study drug >10 d before completing 12 weeks | 11 | 14 | 14 | 15 | 10 |
| Patient did not reach Visit 5 (day 84) | 13 | 14 | 13 | 16 | 10 |
| No valid LAV value at visit 1 | 5 | 2 | 0 | 3 | 2 |
| No valid LAV value at visit 5 | 13 | 9 | 7 | 11 | 6 |
| Incorrect medication assigned on Visit 3 | 0 | 0 | 0 | 4 | 23 |
| Incorrect medication assigned on Visit 4 | 0 | 0 | 0 | 19 | 24 |

| | | | | | |
|---|---|---|---|---|---|
| Concomitant nitrates or NO donors | 6 | 4 | 3 | 5 | 2 |

LAV, left atrial volume; NO, nitric oxide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*More than one reason may apply

**Supplementary Table 2.** Actual dose of study treatment received on and after week 8 (Visit 4, full analysis set excluding patients with incorrectly assigned doses)

| | | Vericiguat | | | |
|---|---|---|---|---|---|
| | **Placebo** | **1.25 mg** | **2.5 mg** | **2.5 to 5 mg** | **2.5 to 10 mg** |
| **Patients treated N (%)** | 82 (100) | 83 (100) | 86 (100) | 62 (100) | 62 (100) |
| 0 mg | 82 (100) | 0 | 1 (1.2) | 0 | 0 |
| 1.25 mg | 0 | 83 (100) | 1 (1.2) | 1 (1.6) | 0 |
| 2.5 mg | 0 | 0 | 84 (97.7) | 9 (14.5) | 1 (1.6) |
| 5 mg | 0 | 0 | 0 | 52 (83.9) | 14 (22.6) |
| 10 mg | 0[1] | 0 | 0 | 0 | 47 (75.8) |

Data are displayed as n (%). [1] Blinded sham titration to highest dose step in 77.5% of patients in placebo arm.

**Supplementary Table 3.** Additional baseline characteristics

| | | Vericiguat | | | | |
|---|---|---|---|---|---|---|
| | **Placebo** | **1.25 mg** | **2.5 mg** | **2.5 mg to 5 mg** | **2.5 mg to 10 mg** | **Total** |
| | **(n = 93)** | **(n = 96)** | **(n = 96)** | **(n = 96)** | **(n = 96)** | **(n= 477)** |
| Region, N (%) | | | | | | |
| Eastern Europe | 27 (29.0%) | 31 (32.3%) | 27 (28.1%) | 24 (25.0%) | 29 (30.2%) | 138 (28.9%) |
| Western Europe | 45 (48.4%) | 50 (52.1%) | 42 (43.8%) | 46 (47.9%) | 45 (46.9%) | 228 (47.8%) |
| Asia/Pacific | 17 (18.3%) | 9 (9.4%) | 17 (17.7%) | 15 (15.6%) | 17 (17.7%) | 75 (15.7%) |
| North America | 4 (4.3%) | 6 (6.3%) | 10 (10.4%) | 11 (11.5%) | 5 (5.2%) | 36 (7.5%) |
| Arterial hypertension, N (%) | 85 (91.4%) | 86 (89.6%) | 85 (88.5%) | 86 (89.6%) | 90 (93.8%) | 432 (90.6%) |
| Chronic kidney disease, N (%) | 43 (46.2%) | 48 (50.0%) | 34 (35.4%) | 33 (34.4%) | 38 (39.6%) | 196 (41.1%) |
| LVEF at baseline, n (%) | | | | | | |
| ≤50% | 12 (12.9) | 13 (13.5) | 12 (12.5) | 13 (13.5) | 9 (9.4) | 59 (12.4) |
| >50% | 77 (82.8) | 80 (83.3) | 83 (86.5) | 79 (82.3) | 85 (88.5) | 404 (84.7) |
| Missing | 4 (4.3) | 3 (3.1) | 1 (1.0) | 4 (4.2) | 2 (2.1) | 14 (2.9) |
| KCCQ-CSS, median (IQR) | 52.8 (37.5–73.7) | 58.1 (40.6–72.4) | 58.3 (39.6–75.0) | 58.9 (33.3–72.9) | 52.3 (36.5–71.4) | 55.7 (38.0–73.4) |
| EQ-5D US index score, median (IQR) | 0.78 (0.69–0.84) | 0.77 (0.59–0.83) | 0.77 (0.59–0.84) | 0.78 (0.69–0.84) | 0.78 (0.59–0.84) | 0.78 (0.59–0.84) |
| Atrial fibrillation in baseline ECG (N) | 35 | 41 | 40 | 38 | 36 | 190 |
| NT-proBNP (n) | 33 | 40 | 39 | 38 | 35 | 185 |
| NT-proBNP (pg/mL), median (IQR) | 2254 (932–3644) | 1877 (1157–2636) | 1729 (1065–3260) | 2301 (1381–4517) | 2407 (1492–4246) | 1983 (1170–3754) |
| LAV (n) | 32 | 40 | 39 | 37 | 35 | 183 |

| | | | | | | |
|---|---|---|---|---|---|---|
| LAV (mL), mean (SD) | 104 (67) | 107 (54) | 101 (32) | 95 (27) | 89 (27) | 99 (44) |
| No atrial fibrillation in baseline ECG (N) | 58 | 55 | 56 | 58 | 60 | 287 |
| NT-proBNP (n) | 57 | 55 | 55 | 56 | 58 | 281 |
| NT-proBNP (pg/mL), median (IQR) | 678 (298–1661) | 616 (279–2441) | 629 (185–1743) | 577 (305–1513) | 733 (314–1593) | 650 (279–1619) |
| LAV (n) | 56 | 54 | 56 | 55 | 59 | 280 |
| LAV (mL), mean (SD) | 79 (26) | 74 (28) | 77 (26) | 76 (30) | 83 (25) | 78 (27) |
| Initial presentation for worsening HF | | | | | | |
| Hospitalization (n) | 72 | 73 | 68 | 75 | 70 | 358 |
| Time from stabilization to randomization (days), mean (SD) | 11.6 (8.8) | 11.6 (8.7) | 13.3 (14.3) | 14.3 (9.0) | 13.5 (9.9) | 12.9 (9.0) |
| Intravenous diuretic (n) | 20 | 23 | 27 | 21 | 26 | 117 |
| Time from stabilization to randomization (days), mean (SD) | 10.6 (7.1) | 13.0 (8.2) | 10.7 (6.0) | 15.5 (8.9) | 14.2 (8.6) | 12.8 (7.9) |

ECG, electrocardiogram; EQ-5D, 5-dimension EuroQol questionnaire; IQR, interquartile range; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAV, left atrial volume; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

**Supplementary Table 4.** Primary endpoints: Model A, NT-proBNP with adjustment for baseline values. Model B, LAV with adjustment for baseline values. ANCOVA with dose group as explanatory variable and additional covariates.

| **Model A** | | **1.25mg** | **2.5mg** | **2.5 to 5mg** | **2.5 to 10mg** |
|---|---|---|---|---|---|
| Covariate: baseline NT-proBNP | Covariate effect: *P* <0.0001 | | | | |
| | LS-Mean Differences relative to Placebo | 0.03 | 0.13 | 0.19 | 0.14 |
| | *P*-value | 0.7716 | 0.2827 | 0.1394 | 0.2541 |
| covariates: baseline NT-proBNP A. Fib. vs. No A. Fib. | Covariate effect: *P* <0.0001 (baseline NT-proBNP) *P* = 0.0001 (A. Fib. vs. No A. Fib.) | | | | |
| | LS-Mean Differences to Placebo | 0.04 | 0.13 | 0.16 | 0.14 |
| | *P*-value | 0.7159 | 0.2743 | 0.1964 | 0.2444 |

| **Model B** | | **1.25mg** | **2.5mg** | **2.5 to 5mg** | **2.5 to 10mg** |
|---|---|---|---|---|---|
| Covariate: baseline LAV | Covariate effect: *P* <0.0001 | | | | |
| | LS-Mean Differences to Placebo | 1.24 | 0.97 | 1.83 | 1.55 |
| | *P*-value | 0.4988 | 0.5976 | 0.3559 | 0.4291 |
| covariates: baseline LAV A. Fib. vs. No A. Fib. | Covariate effect: *P* <0.0001 *P* = 0.0427 | | | | |
| | LS-Mean Differences to Placebo | 1.32 | 1.00 | 1.49 | 1.44 |
| | *P*-value | 0.4709 | 0.5836 | 0.4532 | 0.4618 |

A. Fib., atrial fibrillation; ANCOVA, analysis of covariance; LAV, left atrial volume; LS, least-squares; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**Supplementary Table 5** Change from baseline in primary analysis variables (per protocol analysis sets for NT-proBNP and LAV) and heart rate (full analysis set excluding patients with incorrectly assigned doses) based on heart rhythm at baseline

| Endpoint | Dose group | Heart rhythm at baseline | n | Mean change from baseline (SD) |
|---|---|---|---|---|
| **LAV (mL)** | Placebo | A.fib. | 28 | −5.36 (18.6) |
| | | No A. Fib. | 39 | −1.92 (5.17) |
| | Pooled 2.5/5/10 mg | A.fib. | 89 | −1.59 (15.5) |
| | | No A. Fib. | 105 | −1.85 (10.1) |
| | | | | **Mean log scale (SD – log scale)** |
| **log(NT-proBNP) (pg/mL)** | Placebo | A.fib. | 31 | 0.075 (0.368) |
| | | No A. Fib. | 42 | −0.227 (0.961) |
| | Pooled 2.5/5/10 mg | A.fib. | 89 | −0.026 (0.757) |
| | | No A. Fib. | 106 | 0.092 (0.802) |
| | | | | **LS-mean change from baseline (95% CI)** |
| **Heart Rate (bpm)** | Placebo | A.fib. | | −1.2 (−4.9–2.5) |
| | | No A. Fib. | | 6.6 (3.1–10.1) |
| | Vericiguat 2.5–10 mg | A.fib. | | −3.4 (−7.4–0.5) |
| | | No A. Fib. | | −1.9 (−6.0–2.3) |

A.fib., atrial fibrillation; bpm, beats per minute; LAV, left atrial volume; LS, least-squares; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |
| **LV Structure** | | | | | | | | | | | | | | | | | | | | | |
| LV end-diastolic volume (mL) | 89 | 90.9 (31.4) | 75 | −2.69 (21.6) | 93 | 88.1 (28.6) | 80 | −2.15 (19.7) | 95 | 87.1 (30.0) | 81 | −1.25 (22.8) | 73 | 82.7 (28.7) | 59 | 0.63 (15.6) | 67 | 90.8 (34.6) | 59 | −0.58 (21.1) | 0.25 |
| | | **Difference of means vs. placebo:** | | | | | | 0.55 | | | | 1.44 | | | | 3.32 | | | | 2.11 | |
| | | **(95% CI of difference):** | | | | | | (−6.01–7.10) | | | | (−5.60–8.48) | | | | (−3.28–9.93) | | | | (−5.26–9.47) | (−0.36–0.86) |
| LV end-systolic volume (mL) | 89 | 39.0 (17.3) | 75 | −1.36 (10.9) | 93 | 38.5 (14.8) | 80 | −1.27 (9.4) | 95 | 38.2 (17.0) | 82 | −1.49 (11.2) | 73 | 35.6 (13.7) | 59 | −0.41 (7.4) | 67 | 40.6 (19.0) | 59 | −1.21 (10.5) | 0.06 |
| | | **Difference of means vs. placebo:** | | | | | | 0.09 | | | | −0.13 | | | | 0.95 | | | | 0.15 | |
| | | **(95% CI of difference):** | | | | | | (−3.14–3.31) | | | | (−3.62–3.36) | | | | (−2.33–4.22) | | | | (−3.54–3.83) | (−0.24–0.36) |
| LV mass index (g/m$^2$) | 77 | 124.3 (36.7) | 61 | −1.72 (16.0) | 75 | 119.5 (25.6) | 55 | −1.95 (12.1) | 77 | 128.8 (38.0) | 60 | −1.00 (15.1) | 62 | 115.9 (33.8) | 46 | −0.65 (15.1) | 54 | 126.3 (35.9) | 45 | −1.43 (14.9) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.24 | | | | 0.72 | | | | 1.07 | | | | 0.29 | |
| | | **(95% CI of difference):** | | | | | | (−5.51–5.04) | | | | (−4.89–6.33) | | | | (−4.98–7.12) | | | | (−5.78–6.35) | |
| LVED inter-ventricular septum thickness (mm) | 77 | 12.9 (2.00) | 61 | 0.004 (0.46) | 75 | 12.8 (1.79) | 55 | −0.12 (0.44) | 77 | 13.3 (2.11) | 60 | −0.09 (0.54) | 62 | 12.9 (2.10) | 46 | −0.06 (0.51) | 54 | 13.4 (2.72) | 45 | −0.19 (0.56) | −0.01 |
| | | **Difference of means vs. placebo:** | | | | | | −0.13 | | | | −0.09 | | | | −0.06 | | | | −0.19 | |
| | | **(95% CI of difference):** | | | | | | (−0.29–0.04) | | | | (−0.27–0.09) | | | | (−0.25–0.13) | | | | (−0.39–0.01) | (−0.03–0.005) |
| LVED posterior wall thickness (mm) | 77 | 12.5 (1.92) | 61 | 0.02 (0.61) | 75 | 12.5 (1.44) | 55 | −0.10 (0.56) | 77 | 12.9 (2.04) | 60 | −0.08 (0.78) | 62 | 12.6 (2.07) | 46 | −0.12 (0.55) | 54 | 12.9 (2.44) | 45 | −0.23 (0.83) | −0.02 |
| | | **Difference of means vs. placebo:** | | | | | | −0.13 | | | | −0.10 | | | | −0.14 | | | | −0.25 | |
| | | **(95% CI of difference):** | | | | | | (−0.34–0.09) | | | | (−0.35–0.15) | | | | (−0.36–0.09) | | | | (−0.52–0.03) | (−0.04–0.003) |

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |
| **Diastolic function** | | | | | | | | | | | | | | | | | | | | | |
| E-wave (m/sec) | 86 | 1.07 (0.40) | 72 | −0.01 (0.23) | 93 | 0.99 (0.33) | 77 | 0.05 (0.20) | 94 | 0.99 (0.36) | 80 | 0.02 (0.20) | 72 | 1.04 (0.39) | 58 | 0.08 (0.22) | 63 | 1.01 (0.33) | 56 | 0.03 (0.21) | 0.003 |
| | | **Difference of means vs. placebo:** | | | | | | 0.06 | | | | 0.03 | | | | 0.09 | | | | 0.04 | |
| | | **(95% CI of difference):** | | | | | | (−0.01–0.13) | | | | (−0.04–0.10) | | | | (0.02–0.17) | | | | (−0.03–0.12) | (−0.003–0.010) |
| A-wave (m/sec) | 50 | 0.88 (0.32) | 37 | 0.03 (0.22) | 52 | 0.76 (0.24) | 41 | 0.08 (0.17) | 51 | 0.77 (0.29) | 40 | 0.03 (0.14) | 38 | 0.83 (0.31) | 25 | 0.04 (0.13) | 30 | 0.73 (0.35) | 24 | −0.05 (0.21) | −0.01 |
| | | **Difference of means vs. placebo:** | | | | | | 0.05 | | | | 0.0005 | | | | 0.01 | | | | −0.08 | |
| | | **(95% CI of difference):** | | | | | | (−0.04–0.13) | | | | (−0.08–0.08) | | | | (−0.09–0.10) | | | | (−0.19–0.03) | (−0.02–−0.004) |
| E/A ratio | 50 | 1.26 (0.74) | 37 | −0.14 (0.45) | 52 | 1.27 (0.67) | 41 | −0.09 (0.40) | 51 | 1.38 (0.95) | 40 | −0.08 (0.53) | 38 | 1.40 (0.94) | 25 | −0.004 (0.52) | 30 | 1.42 (0.77) | 24 | 0.13 (0.61) | 0.04 |
| | | **Difference of means vs. placebo:** | | | | | | 0.04 | | | | 0.05 | | | | 0.13 | | | | 0.26 | |
| | | **(95% CI of difference):** | | | | | | (−0.15–0.23) | | | | (−0.17–0.28) | | | | (−0.12–0.38) | | | | (−0.01–0.53) | (0.02–0.06) |
| Deceleration time (DT, msec) | 86 | 209.3 (59.9) | 70 | 1.31 (60.0) | 92 | 198.9 (58.4) | 75 | 0.57 (55.6) | 94 | 193.9 (58.8) | 80 | 3.81 (59.6) | 71 | 187.8 (59.3) | 57 | −5.14 (63.0) | 63 | 186.6 (63.2) | 56 | −9.6 (55.1) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.74 | | | | 2.49 | | | | −6.45 | | | | −10.91 | |
| | | **(95% CI of difference):** | | | | | | (−19.7–18.2) | | | | (−16.8–21.8) | | | | (−28.1–15.2) | | | | (−31.5–9.63) | |
| Isovolumetric relaxation time (IVRT, msec) | 85 | 101.3 (31.6) | 65 | −6.32 (24.0) | 89 | 101.5 (27.8) | 69 | −3.88 (23.4) | 91 | 101.9 (26.5) | 74 | 0.24 (28.1) | 71 | 93.0 (22.4) | 53 | −0.61 (22.2) | 59 | 98.0 (27.4) | 49 | −5.93 (29.3) | |
| | | **Difference of means vs. placebo:** | | | | | | 2.44 | | | | 6.56 | | | | 5.72 | | | | 0.39 | |
| | | **(95% CI of difference):** | | | | | | (−5.67–10.55) | | | | (−2.28–15.41) | | | | (−2.80–14.23) | | | | (−9.52–10.30) | |
| Medial e′ (cm/sec) | 88 | 6.48 (1.93) | 74 | 0.38 (1.68) | 91 | 7.18 (2.89) | 76 | −0.24 (2.16) | 93 | 6.64 (2.78) | 79 | 0.45 (2.17) | 72 | 7.05 (2.89) | 56 | 0.06 (2.16) | 63 | 6.80 (2.35) | 55 | 0.91 (2.73) | 0.079 |
| | | **Difference of means vs. placebo:** | | | | | | −0.621 | | | | 0.068 | | | | −0.319 | | | | 0.534 | |
| | | **(95% CI of difference):** | | | | | | (−1.25–−0.00) | | | | (−0.55–0.69) | | | | (−0.99–0.35) | | | | (−0.24–1.31) | (0.018–0.139) |

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |
| Lateral e′ (cm/sec) | 88 | 8.95 (2.73) | 74 | 0.15 (1.99) | 92 | 9.59 (3.31) | 77 | 0.05 (2.98) | 92 | 9.43 (4.14) | 79 | 0.04 (3.06) | 73 | 9.95 (3.66) | 58 | 0.28 (2.27) | 62 | 9.11 (3.14) | 54 | 0.61 (2.44) | 0.048 |
| | | **Difference of means vs. placebo:** | | | | | | −0.096 | | | | −0.111 | | | | 0.132 | | | | 0.461 | |
| | | **(95% CI of difference):** | | | | | | (−0.91–0.72) | | | | (−0.94–0.72) | | | | (−0.60–0.87) | | | | (−0.32–1.24) | (−0.03–0.12) |
| Medial E/e′ | 86 | 18.4 (9.75) | 72 | −0.70 (5.57) | 91 | 15.9 (8.24) | 76 | 0.79 (3.86) | 93 | 16.7 (8.59) | 77 | −1.07 (4.91) | 71 | 16.4 (8.1) | 56 | 0.64 (4.09) | 63 | 16.1 (7.02) | 55 | −1.02 (3.83) | |
| | | **Difference of means vs. placebo:** | | | | | | 1.49 | | | | −0.37 | | | | 1.33 | | | | −0.33 | |
| | | **(95% CI of difference):** | | | | | | (−0.06–3.04) | | | | (−2.07–1.32) | | | | (−0.42–3.09) | | | | (−2.06–1.41) | |
| Lateral E/e′ | 86 | 13.5 (7.66) | 72 | −0.28 (3.88) | 92 | 11.5 (5.03) | 77 | 0.48 (4.40) | 92 | 11.9 (6.55) | 77 | −0.06 (3.56) | 72 | 12.0 (7.27) | 58 | 0.47 (4.3) | 62 | 12.6 (6.95) | 54 | −0.08 (4.71) | |
| | | **Difference of means vs. placebo:** | | | | | | 0.75 | | | | 0.22 | | | | 0.75 | | | | 0.20 | |
| | | **(95% CI of difference):** | | | | | | (−0.59–2.10) | | | | (−0.98–1.43) | | | | (−0.67–2.17) | | | | (−1.32–1.71) | |
| PV S (m/sec) | 46 | 0.45 (0.17) | 25 | 0.01 (0.12) | 48 | 0.46 (0.17) | 29 | −0.02 (0.14) | 57 | 0.45 (0.19) | 31 | 0.02 (0.21) | 41 | 0.45 (0.17) | 18 | −0.03 (0.19) | 35 | 0.45 (0.18) | 21 | −0.02 (0.15) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.03 | | | | 0.01 | | | | −0.04 | | | | −0.03 | |
| | | **(95% CI of difference):** | | | | | | (−0.10–0.04) | | | | (−0.08–0.11) | | | | (−0.13–0.06) | | | | (−0.11–0.05) | |
| PV D (m/sec) | 62 | 0.62 (0.28) | 39 | −0.04 (0.27) | 65 | 0.58 (0.22) | 44 | −0.03 (0.24) | 72 | 0.59 (0.26) | 52 | 0.07 (0.21) | 59 | 0.66 (0.26) | 42 | 0.03 (0.16) | 47 | 0.62 (0.22) | 36 | 0.05 (0.20) | |
| | | **Difference of means vs. placebo:** | | | | | | 0.01 | | | | 0.11 | | | | 0.07 | | | | 0.10 | |
| | | **(95% CI of difference):** | | | | | | (−0.10–0.12) | | | | (0.01–0.22) | | | | (−0.03–0.17) | | | | (−0.01–0.21) | |
| PV Ar (m/sec) | 34 | 0.27 (0.11) | 17 | 0.01 (0.11) | 29 | 0.27 (0.08) | 17 | 0.01 (0.07) | 33 | 0.25 (0.06) | 24 | 0.02 (0.08) | 25 | 0.26 (0.06) | 14 | 0.001 (0.06) | 18 | 0.26 (0.08) | 14 | −0.01 (0.05) | −0.003 |
| | | **Difference of means vs. placebo:** | | | | | | 0.01 | | | | 0.02 | | | | −0.004 | | | | −0.01 | |
| | | **(95% CI of difference):** | | | | | | (−0.06–0.07) | | | | (−0.04–0.08) | | | | (−0.07–0.06) | | | | (−0.08–0.05) | (−0.01–0.002) |

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |
| **Systemic and vascular** | | | | | | | | | | | | | | | | | | | | | |
| Left ventricular stroke volume (mL) | 89 | 51.8 (17.4) | 75 | −1.34 (13.2) | 93 | 49.6 (16.8) | 80 | −0.88 (11.2) | 95 | 48.9 (15.3) | 81 | 0.14 (12.2) | 73 | 47.1 (17.4) | 59 | 1.04 (9.1) | 67 | 50.3 (17.6) | 59 | 0.63 (12.8) | 0.19 |
| | | **Difference of means vs. placebo:** | | | | | | 0.46 | | | | 1.47 | | | | 2.38 | | | | 1.96 | |
| | | **(95% CI of difference):** | | | | | | (−3.41–4.33) | | | | (−2.54–5.48) | | | | (−1.60–6.35) | | | | (−2.51–6.44) | (−0.16–0.54) |
| Aortic valve – velocity time integral – antegrade flow (cm) | 86 | 37.2 (14.9) | 70 | −0.20 (7.61) | 87 | 31.8 (10.9) | 70 | 0.76 (7.26) | 89 | 32.6 (11.9) | 75 | −0.85 (10.38) | 72 | 32.9 (12.1) | 55 | 0.42 (6.86) | 63 | 32.0 (11.5) | 55 | 2.05 (5.38) | |
| | | **Difference of means vs. placebo:** | | | | | | 0.96 | | | | −0.65 | | | | 0.62 | | | | 2.25 | |
| | | **(95% CI of difference):** | | | | | | (−1.53–3.44) | | | | (−3.65–2.35) | | | | (−1.98–3.21) | | | | (−0.15–4.64) | |
| Systemic arterial compliance (SAC, mL/mmHg) | 89 | 0.89 (0.35) | 74 | −0.04 (0.27) | 93 | 0.87 (0.35) | 80 | −0.02 (0.28) | 94 | 0.9 (0.39) | 79 | −0.01 (0.39) | 70 | 0.83 (0.34) | 56 | 0.07 (0.33) | 67 | 0.89 (0.38) | 59 | −0.002 (0.42) | 0.005 |
| | | **Difference of means vs. placebo:** | | | | | | 0.02 | | | | 0.02 | | | | 0.11 | | | | 0.04 | |
| | | **(95% CI of difference):** | | | | | | (−0.07–0.11) | | | | (−0.08–0.13) | | | | (0.00–0.21) | | | | (−0.08–0.16) | (−0.005,0.01) |
| Effective arterial elastance ($E_a$, mmHg/mL) | 89 | 2.57 (0.97) | 74 | 0.13 (0.79) | 93 | 2.67 (0.93) | 80 | 0.08 (0.87) | 94 | 2.66 (0.98) | 79 | −0.05 (0.75) | 71 | 2.76 (1.09) | 57 | −0.07 (0.92) | 67 | 2.64 (0.84) | 59 | −0.05 (0.71) | −0.01 |
| | | **Difference of means vs. placebo:** | | | | | | −0.04 | | | | −0.18 | | | | −0.19 | | | | −0.18 | |
| | | **(95% CI of difference):** | | | | | | (−0.31–0.22) | | | | (−0.42–0.07) | | | | (−0.49–0.10) | | | | (−0.44–0.08) | (−0.04–0.01) |
| LVES elastance ($E_{es}$, mmHg/mL) | 80 | 1.32 (0.74) | 63 | 0.12 (0.61) | 84 | 1.3 (0.70) | 70 | 0.01 (0.56) | 93 | 1.31 (0.69) | 75 | −0.07 (0.54) | 67 | 1.47 (0.74) | 51 | 0.03 (0.65) | 58 | 1.49 (0.88) | 50 | −0.16 (0.73) | −0.01 |
| | | **Difference of means vs. placebo:** | | | | | | −0.11 | | | | −0.20 | | | | −0.09 | | | | −0.28 | |
| | | **(95% CI of difference):** | | | | | | (−0.31–0.09) | | | | (−0.39–−0.00) | | | | (−0.33–0.14) | | | | (−0.53–−0.03) | (−0.03–0.005) |
| $E_a/E_{es}$ | 80 | 2.59 (2.22) | 63 | 0.37 (5.75) | 84 | 1.86 (3.35) | 70 | −0.24 (3.55) | 93 | 2.71 (5.8) | 75 | −1.29 (6.85) | 67 | 2.01 (2.64) | 51 | 0.52 (3.48) | 58 | 1.68 (9.49) | 50 | 1.53 (11.1) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.61 | | | | −1.67 | | | | 0.14 | | | | 1.16 | |
| | | **(95% CI of difference):** | | | | | | (−2.23–1.01) | | | | (−3.82–0.49) | | | | (−1.67–1.96) | | | | (−2.05–4.36) | |

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |
| **Right heart** | | | | | | | | | | | | | | | | | | | | | |
| Right atrial pressure (mmHg) | 66 | 7.35 (4.06) | 41 | 0.81 (3.43) | 74 | 6.93 (3.34) | 43 | 0.72 (3.75) | 74 | 7.39 (3.87) | 51 | 0.33 (3.76) | 52 | 9.25 (4.23) | 31 | −0.03 (3.53) | 55 | 8.35 (4.23) | 34 | 0.03 (3.88) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.08 | | | | −0.47 | | | | −0.84 | | | | −0.78 | |
| | | **(95% CI of difference):** | | | | | | (−1.65–1.48) | | | | (−1.98–1.03) | | | | (−2.48–0.81) | | | | (−2.46–0.91) | |
| TAPSE (mm) | 86 | 18.9 (3.99) | 70 | 0.04 (2.52) | 89 | 19.1 (4.16) | 73 | 0.36 (2.47) | 91 | 18.5 (4.10) | 73 | 0.01 (2.89) | 71 | 18.6 (4.85) | 56 | 0.02 (2.43) | 62 | 18.2 (4.13) | 54 | 0.78 (2.39) | |
| | | **Difference of means vs. placebo:** | | | | | | 0.32 | | | | −0.03 | | | | −0.02 | | | | 0.74 | |
| | | **(95% CI of difference):** | | | | | | (−0.51–1.14) | | | | (−0.93–0.87) | | | | (−0.90–0.86) | | | | (−0.14–1.63) | |
| RVFAC (%) | 50 | 40.5 (7.97) | 28 | 0.38 (4.52) | 53 | 40.5 (7.66) | 33 | 0.29 (4.50) | 60 | 38.4 (8.93) | 37 | 1.7 (4.08) | 52 | 40.4 (8.17) | 33 | 0.25 (3.34) | 42 | 38.5 (9.45) | 28 | −1.24 (4.90) | |
| | | **Difference of means vs. placebo:** | | | | | | −0.09 | | | | 1.33 | | | | −0.13 | | | | −1.62 | |
| | | **(95% CI of difference):** | | | | | | (−2.41–2.23) | | | | (−0.81–3.47) | | | | (−2.15–1.89) | | | | (−4.14–0.91) | |
| RVSP (mmHg) | 56 | 40.8 (13.9) | 30 | 1.15 (11.3) | 66 | 39.5 (13.8) | 38 | 3.42 (12.2) | 67 | 38.3 (13.6) | 40 | 3.17 (9.5) | 43 | 48.2 (15.9) | 26 | −2.15 (13.1) | 45 | 45.9 (13.7) | 26 | 0.87 (14.9) | |
| | | **Difference of means vs. placebo:** | | | | | | 2.27 | | | | 2.02 | | | | −3.3 | | | | −0.28 | |
| | | **(95% CI of difference):** | | | | | | (−3.48–8.02) | | | | (−2.94–6.97) | | | | (−9.83–3.24) | | | | (−7.30–6.73) | |

**Supplementary Table 6. Echocardiography at rest: change from baseline to Week 12**

| Measurement | Placebo | | | | Vericiguat | | | | | | | | | | | | Regression analysis[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to10 mg | | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | |

A, late ventricular filling; BL, baseline; CI, confidence interval; D, diastolic peak velocity – antegrade flow, Ar, atrial reversal peak velocity; DT, deceleration time; E, mitral valve early diastolic filling - antegrade flow; e′, mitral valve annulus - peak early diastolic tissue velocity; ES, end-systolic; FAS, full analysis set; IVRT, isovolumetric relaxation time; LV, left ventricular: LVED, left ventricular end-diastolic; LVES, left ventricular end-systolic; PV, pulmonary veins; RVFAC, right ventricular fractional area change; RVSP, right ventricular systolic peak gradient; S, systolic peak velocity – antegrade flow; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

[1] Linear regression with dose group as explanatory variable and baseline value as additional covariate

**Supplementary Table 7. Summary statistics for efficacy biomarkers and change from baseline to Week 12 (full analysis set excluding patients with incorrectly assigned doses)**

| Biomarker | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to 10 mg | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change |
| Osteopontin (ng/mL) | 91 | 53.9 (40.8) | 79 | 3.60 (39.7) | 95 | 59.5 (51.3) | 80 | 9.33 (55.2) | 93 | 48.1 (47.7) | 79 | 4.33 (45.2) | 75 | 50.7 (40.4) | 60 | 12.8 (44.7) | 68 | 42.3 (31.5) | 60 | 6.31 (35.4) |
| Median (IQR) | | 44.9 (20.0–81.1) | | | | 50.1 (20.0–81.3) | | | | 20.0 20.0–62.9 | | | | 44.3 (20.0–71.9) | | | | 20.0 (20.0-55.6) | | |
| Difference of means vs. placebo: | | | | | | | | 5.73 | | | | 0.73 | | | | 9.15 | | | | 2.71 |
| (95% CI of difference): | | | | | | | | (−9.36–20.81) | | | | (−12.64–14.10) | | | | (−5.06–23.36) | | | | (−10.13–15.55) |
| TIMP-4* (log pg/mL) | 90 | 7.88 (0.46) | 78 | −0.023 (0.399) | 94 | 7.90 (0.504) | 80 | 0.026 (0.390) | 93 | 7.86 (0.45) | 81 | 0.077 (0.405) | 75 | 7.95 (0.43) | 60 | −0.014 (0.450) | 68 | 7.89 (0.38) | 61 | 0.013 (0.370) |
| Difference of log-transformed means vs. | | | | | | | | 0.048 | | | | 0.099 | | | | 0.008 | | | | 0.035 |
| (95% CI of difference): | | | | | | | | (−0.07–0.17) | | | | (−0.03–0.22) | | | | (−0.13–0.15) | | | | (−0.09–0.16) |
| cGMP (pmol/mL) | 91 | 152.9 (99.2) | 79 | 10.3 (113.7) | 95 | 165.7 (95.8) | 80 | 11.1 (99) | 93 | 162.3 (104.8) | 79 | 19.4 (146) | 75 | 148.5 (102.5) | 60 | 17.7 (135.8) | 68 | 148.7 (115) | 60 | 40.2 (156.4) |
| Median (IQR) | | 146.5 (79.9–196.8) | | | | 156.9 (93.0–219.1) | | | | 146.0 (96.0–200.8) | | | | 116.2 (73.4–190.8) | | | | 117.3 (74.8–184.7) | | |
| Difference of means vs. placebo: | | | | | | | | 0.88 | | | | 9.19 | | | | 7.45 | | | | 29.97 |
| (95% CI of difference): | | | | | | | | (−32.5–34.3) | | | | (−31.9–50.3) | | | | (−34.4–49.3) | | | | (−15.3–75.3) |
| PIIINP (µg/L) | 91 | 10.2 (6.91) | 79 | 0.05 (3.67) | 93 | 11.0 (6.39) | 79 | −0.56 (4.69) | 92 | 11.2 (9.39) | 80 | −1.41 (7.07) | 74 | 12.1 (13.38) | 58 | −1.72 (13.22) | 68 | 12.1 (10.98) | 61 | −0.91 (7.90) |
| Median (IQR) | | 8.9 (6.5–11.7) | | | | 9.2 (7.0–13.1) | | | | 8.2 (6.2–12.4) | | | | 9.6 (6.7–13.7) | | | | 9.3 (7.5–13.2) | | |
| Difference of means vs. placebo: | | | | | | | | −0.61 | | | | −1.46 | | | | −1.77 | | | | −0.96 |
| (95% CI of difference): | | | | | | | | (−1.93–0.71) | | | | (−3.22–0.31) | | | | (−4.85–1.32) | | | | (−2.95–1.03) |

**Supplementary Table 7. Summary statistics for efficacy biomarkers and change from baseline to Week 12 (full analysis set excluding patients with incorrectly assigned doses)**

| Biomarker | Placebo | | | | Vericiguat | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.25 mg | | | | 2.5 mg | | | | 2.5 to 5 mg | | | | 2.5 to 10 mg | | | |
| | n | BL | n | Change (SD) | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change | n | BL | n | Change |
| GDF-15* (log pg/mL) | 91 | 7.86 (0.65) | 79 | −0.015 (0.380) | 95 | 7.82 (0.57) | 80 | 0.048 (0.394) | 93 | 7.71 (0.66) | 79 | −0.007 (0.377) | 75 | 7.89 (0.64) | 60 | 0.010 (0.439) | 68 | 7.73 (0.71) | 60 | 0.025 (0.346) |
| **Difference of log-transformed means vs.** | | | | | | | | 0.063 | | | | 0.008 | | | | 0.114 | | | | 0.039 |
| **(95% CI of difference):** | | | | | | | | (−0.06–0.18) | | | | (−0.11–0.13) | | | | (−0.02–0.25) | | | | (−0.08–0.16) |
| sST2* (log pg/mL) | 90 | 10.03 (0.58) | 78 | 0.084 (0.608) | 94 | 9.92 (0.63) | 80 | 0.131 (0.622) | 93 | 9.96 (0.69) | 81 | 0182 (0.575) | 75 | 10.04 (0.61) | 60 | 0.046 (0.554) | 68 | 9.96 (0.80) | 61 | 0.051 (0.618) |
| **Difference of log-transformed means vs.** | | | | | | | | −0.48 | | | | 0.098 | | | | −0.038 | | | | −0.032 |
| **(95% CI of difference):** | | | | | | | | (−0.15–0.24) | | | | (−0.09–0.28) | | | | (−0.24–0.16) | | | | (−0.24–0.17) |
| Gal-3 (pg/mL) Median (IQR) | 90 | 15.2 (10.60) 13.4 (8.6–18.8) | 78 | −2.22 (8.21) | 93 | 14.0 (6.37) 14.1 (8.4–17.6) | 79 | −0.16 (7.33) | 91 | 12.6 (5.77) 12.6 (7.9–15.9) | 79 | −0.70 (3.81) | 75 | 15.5 (11.09) 13.8 (8.6–19.2) | 60 | 1.26 (11.14) | 68 | 12.9 (7.72) 11.6 (7.7–15.8) | 61 | −2.01 (6.60) |
| **Difference of means vs. placebo:** | | | | | | | | 2.06 | | | | 1.52 | | | | 3.48 | | | | 0.21 |
| **(95% CI of difference):** | | | | | | | | (−0.40–4.51) | | | | (−0.49–3.53) | | | | (0.22–6.73) | | | | (−2.34–2.76) |

BL, baseline; cGMP, cyclic guanosine monophosphate; CI, confidence interval; Gal-3, Galectin-3; GDF-15, growth differentiation factor 15; PIIINP, N-terminal pro-collagen III propeptide; SD, standard deviation; sST2, soluble suppression of tumorigenicity; TIMP-4, tissue metallopeptidase inhibitor 4.

Analyses were only performed if at least 2 patients per subgroup/treatment combination were available for analysis.

*Data were log-transformed to derive normal distribution of data.

**Supplementary Methods.**

Patients received background therapy for comorbidities at the physician's discretion. Total treatment duration was 12 weeks, followed by a safety follow-up visit 16 weeks after randomization.

Statistical methods:

Two secondary analyses of the two primary endpoints were pre-specified: pairwise comparisons of each individual vericiguat treatment group with placebo, to be tested hierarchically with two-sample t-tests at the one-sided significance level $\alpha = 2.5\%$, from highest to lowest treatment group, in case a positive result for the respective endpoint was observed in the respective primary analysis of the respective endpoint. In addition, a linear regression analysis across all dose arms was specified to check for a general trend of dose-response. If the primary analysis of a primary endpoint was non-significant, the corresponding secondary analyses were to be deemed exploratory.

Several transformations of biomarker endpoints were assessed with QQ-plots and Kolmogoroff-Smirnov goodness-of-fit tests to derive approximately normally distributed data (data not shown). For GDF-15, sST2 and TIMP-4, the log-transformation resulted in approximately normally distributed changes from baseline and comparisons are hence displayed on the log-transformed scale.