

Supplementary Table 1. Changes in WHO FC over time.

| Time | Change in WHO FC, n (%) | | | | | | | | |
|-------------------------------|-------------------------|-----------|-------------|-------------|-----------|----------|---|-------------|-------------|
| | -3 | -2 | -1 | 0 | 1 | 2 | 3 | Missing | ≤-1 |
| 4 months (n=1,027) | 3 (0.3%) | 38 (3.7%) | 233 (22.7%) | 536 (52.2%) | 11 (1.1%) | 0 | 0 | 206 (20.1%) | 274 (26.7%) |
| 1 year (n=723) | 3 (0.4%) | 44 (6.1%) | 197 (27.2%) | 296 (40.9%) | 21 (2.9%) | 0 | 0 | 162 (22.4%) | 244 (33.7%) |
| 2 years (n=503) | 2 (0.4%) | 38 (7.6%) | 150 (29.8%) | 178 (35.4%) | 19 (3.8%) | 0 | 0 | 116 (23.1%) | 190 (37.8%) |
| Last observation (n=1,027) | 6 (0.6%) | 68 (6.6%) | 284 (27.7%) | 451 (43.9%) | 44 (4.3%) | 1 (0.1%) | 0 | 173 (16.8%) | 358 (34.9%) |

WHO FC: World Health Organization functional class.

Supplementary Table 2. Key effectiveness parameters for riociguat in patients with and without BPA during the study (data from effectiveness analysis set: n=1,027).

| Parameter | Without BPA ^a | | | With BPA ^b | | |
|-----------------------------|--------------------------|---------------|--|-----------------------|---------------|--|
| | n | Baseline | Change from baseline to last observation | n | Baseline | Change from baseline to last observation |
| mPAP, mmHg | 137 | 38.8 (10.6) | -7.0 (10.0)** | 263 | 39.9 (10.1) | -13.9 (11.2)** |
| PVR, dyn·s·cm ⁻⁵ | 98 | 678.5 (490.1) | -207.0 (495.5)** | 197 | 717.6 (365.0) | -367.5 (477.7)** |
| PAWP, mmHg | 133 | 9.7 (5.2) | 0.3 (6.2) | 250 | 8.6 (3.7) | -0.1 (4.3) |
| RAP, mmHg | 131 | 6.2 (4.3) | -1.0 (4.4)* | 243 | 6.5 (4.1) | -2.1 (4.8)** |
| CO, L/minute | 131 | 4.1 (1.4) | 0.6 (1.4)** | 250 | 4.0 (1.4) | 0.8 (1.4)** |

| | | | | | | |
|----------------------|-----|-------------------|---------------------|-----|-----------------|------------------|
| SvO ₂ , % | 61 | 64.1 (10.6) | 2.9 (11.4) | 158 | 62.9 (10.4) | 6.7 (12.0)** |
| 6MWD, m | 138 | 337.3 (121.3) | 35.3 (84.3)** | 167 | 337.2 (111.1) | 57.2 (94.1)** |
| Borg CR 10 Score | 95 | 4.5 (2.4) | -0.5 (2.6) | 86 | 4.5 (3.2) | -1.4 (2.6)** |
| BNP, pg/mL | 317 | 256.6 (419.8) | -118.8 (385.9)** | 286 | 263.8 (383.2) | -213.5 (375.9)** |
| NT-proBNP, pg/mL | 36 | 2,106.3 (3,426.0) | -1,483.5 (3,399.4)* | 25 | 922.9 (1,501.5) | -762.5 (1443.1)* |
| TRPG, mmHg | 317 | 63.1 (23.8) | -10.3 (21.0)** | 243 | 66.8 (22.0) | -26.7 (22.8)** |

* $P <$

0.01; ** $P <$ 0.001 (paired t-test)

^aPatients who have not received BPA during the study. Patients who underwent PEA during the study were excluded from this analysis.

^bPatients who had BPA after starting riociguat administration. Patients who underwent PEA during the study were excluded from this analysis.

Data are mean (SD) for patients with data at baseline and at last observation (any time point after starting riociguat administration).

6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; BPA: balloon pulmonary angioplasty; CO: cardiac output; CR: category ratio; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAWP: pulmonary arterial

wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SvO₂: systemic venous oxygen saturation; TRPG: tricuspid regurgitation pressure gradient.

Supplementary Table 3. Key effectiveness parameters for riociguat in patients who did not undergo BPA or receive PAH-targeted therapy other than riociguat during the study (data from effectiveness analysis set : n=1,027).

| | n | Baseline | Last observation | Change from baseline to last observation |
|-----------------------------|-----|---------------|------------------|--|
| mPAP, mmHg | 68 | 37.7 (10.2) | 30.7 (9.1) | -7.0 (10.0)** |
| PVR, dyn·s·cm ⁻⁵ | 49 | 649.4 (313.2) | 412.0 (215.2) | -237.5 (246.5)** |
| PAWP, mmHg | 67 | 8.8 (4.7) | 9.8 (5.0) | 1.0 (5.7) |
| RAP, mmHg | 64 | 6.0 (4.4) | 5.2 (2.9) | -0.8 (4.3) |
| CO, L/minute | 65 | 3.8 (1.1) | 4.4 (1.4) | 0.6 (0.9)** |
| SvO ₂ , % | 30 | 63.9 (10.7) | 67.1 (12.0) | 3.2 (14.8) |
| 6MWD, m | 75 | 331.5 (119.9) | 371.4 (118.3) | 39.9 (81.8)** |
| Borg CR 10 Score | 55 | 4.6 (2.3) | 3.7 (1.9) | -0.9 (2.5)* |
| BNP, pg/mL | 163 | 247.5 (463.7) | 111.0 (196.5) | -136.5 (431.1)** |

| | | | | |
|------------------|-----|-----------------|---------------|-------------------|
| NT-proBNP, pg/mL | 15 | 3206.1 (4651.7) | 622.6 (733.0) | -2583.5 (4536.1)* |
| TRPG, mmHg | 165 | 62.0 (23.2) | 51.5 (22.0) | -10.5 (19.5)** |

*P < 0.01; **P < 0.001 (paired t-test)

Patients who underwent PEA during the study were excluded during the study from this analysis.

Data are mean (SD) for patients with data at baseline and at last observation.

6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; CO: cardiac output; CR: category ratio; mPAP: mean pulmonary arterial pressure; NT-proBNP: *N*-terminal prohormone of brain natriuretic peptide; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SD: standard deviation; SvO₂: systemic venous oxygen saturation; TRPG: tricuspid regurgitation peak gradient.