| Dosing Day         | BID/QD (N=10)                  | QD/QD (N=10)                  | Overall (N=20)                |
|-------------------|--------------------------------|--------------------------------|--------------------------------|
| **Day 7**         | **20 mg BID**                  | **40 mg QD**                  |                                |
| $T_{\text{max}}$ (h) | 1.0 (1.0, 3.0)                 | 1.0 (1.0, 6.0)                 | 1.0 (1.0, 6.0)                 |
| $C_{\text{max}}$ (ng/mL) | 117 (33)                      | 242 (80)                      |                                |
| $C_{\text{max}}$/ Dose (ng/mL/mg) | 5.84 (1.63)                  | 6.05 (2.00)                   |                                |
| $AUC_{\text{tau}}$ (h-ng/mL) | 795 (186)                    | 2200 (591)                    |                                |
| $AUC_{\text{tau}}$/ Dose (h-ng/mL/mg) | 39.7 (9.3)                  | 54.9 (14.8)                   |                                |
| $C_{\text{trough}}$ (ng/mL) | 52.4 (12.8)                  | 57.2 (14.9)                   |                                |
| $C_{\text{trough}}$ (ng/mL) | 1.69 (0.72)                  | 1.66 (0.91)                   |                                |
| RAUC$_{\text{tau}}$ | 2.22 (0.25)                  | 1.96 (0.38)                   |                                |
| RC$_{\text{trough}}$ | 2.76 (0.68)                  | 3.77 (0.45)                   |                                |
| **Day 14**        | **40 mg QD**                   | **40 mg QD**                   | **Overall (N=20)**             |
| $T_{\text{max}}$ (h) | 1.0 (1.0, 3.0)                 | 1.0 (1.0, 3.0)                 | 1.0 (1.0, 3.0)                 |
| $C_{\text{max}}$ (ng/mL) | 181 (47)                      | 250 (139)                     | 217 (109)                     |
| $C_{\text{max}}$/ Dose (ng/mL/mg) | 4.53 (1.17)                  | 6.25 (3.48)                   | 5.44 (2.73)                   |
| $AUC_{\text{tau}}$ (h-ng/mL) | 2080 (442)                   | 2910 (770)                    | 2520 (750)                    |
| $AUC_{\text{tau}}$/ Dose (h-ng/mL/mg) | 52.1 (11.0)                  | 72.7 (19.2)                   | 62.9 (18.7)                   |
| $AUC_{\text{last}}$ (h-ng/mL) | 17100 (6980)                 | 23600 (8950)                  | 20500 (8530)                  |
| $C_{\text{trough}}$ (ng/mL) | 65.7 (23.0)                  | 90.7 (26.2)                   | 78.9 (27.3)                   |
| $C_{\text{trough}}$ (ng/mL) | 1.69 (0.72)                  | 1.66 (0.91)                   |                                |
| RAUC$_{24}^c$ | 3.29 (0.80)                  | 2.60 (0.54)                   | 2.93 (0.74)                   |
| RC$_{\text{trough}}^d$ | 3.45 (1.54)                  | 6.02 (1.27)                   | 4.74 (1.90)                   |
| CL/F (L/h)        | 20.0 (4.3)                    | 14.7 (3.9)                    | 17.2 (4.8)                    |
| V/F (L)           | 5570 (1530)                   | 3880 (1370)                   | 4680 (1650)                   |
| Terminal $t_{1/2}$ (h) | 197 (57.4)                   | 183 (43)                      | 190 (50)                      |
| Effective $t_{1/2}$ (h) | 45.8 (13.5)                  | 34.2 (9.1)                    | 39.7 (12.6)                   |

%CV=intersubject variability [percent]; $AUC_{\text{tau}}$=area under the plasma concentration-time curve during a dosing interval; CL/F=apparent total body clearance after oral administration; $C_{\text{max}}$=maximum observed plasma concentration, occurring at $T_{\text{max}}$; $C_{\text{trough}}$=plasma concentration observed at the end of a dosing interval (collected before the next administration); Effective $t_{1/2}$=one-compartment elimination rate that would lead to the observed degree of $AUC$ accumulation; RAUC$_{24}^c$=accumulation ratio calculated from 24-hour $AUC$ on Day 14 relative to Day 1; RAUC$_{\text{tau}}$=accumulation ratio calculated from $AUC_{\text{tau}}$ on Day 7 relative to Day 1; RC$_{\text{max}}$=accumulation ratio calculated from $C_{\text{max}}$ on Day 14 relative to Day 1; RC$_{\text{trough}}^d$=accumulation ratio calculated from $C_{\text{trough}}$ on Day 14 relative to Day 1; Terminal $t_{1/2}$=apparent terminal elimination phase half-life; $T_{\text{max}}$=time of maximum observed plasma concentration; $V/F$=apparent volume of distribution during the terminal phase.

a  Median (minimum, maximum)
b  $T_{\text{last}}$=38 days post-final dose (Day 42)
c  Day 14 $AUC_{\text{tau}}$ / Day 1 $AUC_{\text{tau}}$ for QD/QD regimen; Day 14 $AUC_{\text{tau}}$ / Day 1 $AUC_{\text{tau}}$ for BID/QD regimen

d  Day 14 24-hour postdose concentration / Day 2 morning predose concentration
### Supplemental Table 2. Biomarker Assessments

| Biomarker                                         | Placebo (N=6) | Praliciguat (N=20) | LS mean difference between praliciguat and placebo (95% CI) |
|---------------------------------------------------|---------------|--------------------|-------------------------------------------------------------|
|                                                   | Baseline      | LS mean change (95% CI) | Baseline | LS mean change (95% CI) |                                                   |
| Cyclic guanosine monophosphate (ng/mL)            | 0.82 ± 0.26   | 0.09 (-0.19, 0.38) | 0.93 ± 0.36 | 0.33 (0.18, 0.49) | 0.24 (-0.08, 0.56) |
| Arginine (µg/mL)                                  | 12.52 ± 3.94  | 0.04 (-1.19, 1.27) | 13.23 ± 2.82 | 0.82 (0.15, 1.49) | 0.78 (-0.63, 2.18) |
| Asymmetric dimethylarginine (ng/mL)               | 115.10 ± 18.20| 1.97 (-4.97, 8.91) | 104.94 ± 9.03 | -8.68 (-12.34, -5.02) | -10.65 (-18.68, -2.61) |
| Arginine/asymmetric dimethylarginine ratio<sup>a</sup> | 107.67 ± 24.02| -1.99 (-14.67, 10.69) | 125.77 ± 23.16 | 20.17 (13.42, 26.91) | 22.16 (7.52, 36.79) |
| Lipoprotein (a) (µg/mL)                           | 291.4 ± 172.0 | 80.6 (-4.9, 166.1) | 257.6 ± 269.8 | 62.0 (18.2, 105.9) | -18.6 (-114.7, 77.6) |
| Apolipoprotein B (µg/mL)                          | 1147 ± 346.4  | -50.5 (-204.1, 103.0) | 1012.2 ± 274.1 | -169.5 (-252.7, -86.4) | -119.0 (-294.9, 56.9) |
| Apolipoprotein C3 (µg/mL)                         | 451.8 ± 188.0 | -104.3 (-158.6, -50.0) | 417.1 ± 186.9 | -105.0 (-134.7, -75.3) | -0.8 (-62.7, 61.2) |
| Soluble intercellular adhesion molecule 1 (µg/mL) | 0.57 ± 0.27   | 0.03 (-0.07, 0.14) | 0.39 ± 0.09 | -0.03 (-0.09, 0.02) | -0.07 (-0.19, 0.06) |
| Soluble vascular cell adhesion molecule 1 (µg/ml) | 0.64 ± 0.26   | 0.03 (-0.09, 0.15) | 0.56 ± 0.16 | -0.02 (-0.08, 0.05) | -0.04 (-0.18, 0.09) |
| Interleukin 6 (pg/ml)<sup>b</sup>                 | 1.61 ± 0.70   | 0.18 (-0.72, 1.08) | 1.40 ± 0.73 | 0.67 (0.12, 1.23) | 0.49 (-0.57, 1.56) |
| Interleukin 8 (pg/ml)                             | 6.55 ± 3.20   | 0.75 (-1.86, 3.36) | 12.11 ± 29.12 | 0.49 (-0.93, 1.92) | -0.26 (-3.24, 2.73) |
| Tumor necrosis factor alpha (pg/ml)               | 4.11 ± 1.67   | -0.06 (-0.72, 0.61) | 3.60 ± 1.18 | -0.06 (-0.42, 0.30) | -0.04 (-0.76, 0.75) |
| Interferon gamma (pg/ml)                          | 15.15 ± 21.95 | -0.22 (-3.85, 3.41) | 4.91 ± 2.58 | -0.39 (-2.34, 1.56) | -0.17 (-4.41, 4.07) |
| Serum amyloid A (µg/ml)<sup>c</sup>               | 19.75 ± 23.38 | 1.56 (0.78, 3.11) | 9.36 ± 7.84 | 1.04 (0.72, 1.51) | 0.67 (0.30, 1.48) |
| C-reactive protein (µg/ml)<sup>c</sup>            | 7.26 ± 6.57   | 1.22 (0.57, 2.60) | 3.52 ± 3.30 | 1.35 (0.90, 2.03) | 1.11 (0.46, 2.64) |

<sup>a</sup>Arginine/asymmetric dimethylarginine ratio was calculated post hoc by first converting arginine in µg/ml to ng/ml; <sup>b</sup>Interleukin-6 was detectable in 7 out of 20 patients in the treatment group and 5 out of 6 patients in the placebo group. No imputations were performed; <sup>c</sup>C-reactive protein and serum amyloid A were log-transformed prior to analysis. LS mean values were exponentiated back to original scale.