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| Supplemental Table 1: Baseline Patient Characteristics in the Overall Sensitivity Cohort,  and as Stratified by Therapy Class and Additional PH Risk Factors | | | | | | | |
|  | Overall  (N = 108) | PAH on therapy with ERA  (N = 16) | PAH on therapy with PDE5i  (N = 17) | PAH on therapy with combination ERA and PDE5i  (N = 25) | PAH with concomitant left heart disease  (N =17) | PAH with concomitant lung disease  (N = 20) | CTEPH  (N = 13) |
| Age (yrs) | 60.4±14.4 | 59.9±14.1 | 65.6±13.9 | 49.9±15.5 | 66.1±5.8 | 61.2±11.8 | 65.4±15.9 |
| Years with  PH | 6.2±5.4 | 7.7± 5.5 | 6.8±6.1 | 7.8±7.2 | 5.1±3.8 | 4.3±2.8 | 5.0±3.9 |
| Female | 91 (84%) | 16 (100%) | 14 (82%) | 22 (88%) | 15 (88%) | 15 (75%) | 9 (69%) |
| 6MWD (m) | 386 ± 113  N = 92 | 415 ± 67 | 414 ± 96  N=15 | 444 ± 96  N=23 | 290 ± 108  N=9 | 325 ± 108  N=17 | 357 ± 143  N=12 |
| mPAP  (mmHg) | 39.4± 12.5  N = 57 | 39.5± 12.0  N = 12 | 30.2± 12.8  N = 10 | 43.4± 11.2  N = 13 | 41.5± 7.9  N = 8 | 39.0± 14.4  N = 9 | 44.9± 14.4  N = 5 |
| PVR (WU) | 5.4±3.0  N = 53 | 4.9±1.7  N = 11 | 3.3±1.7  N = 9 | 6.9 ±3.4  N = 11 | 4.9 ±2.8  N = 8 | 6.5±4.0  N = 9 | 6.0 ±2.7  N = 5 |
| DLCO (% predicted) | 60±26  N = 53 | 56±17  N = 10 | 72±27  N = 9 | 72±29  N = 11 | 59±22  N = 4 | 40±18  N = 12 | 66±27  N = 7 |
| RVSP  (mmHg) | 51±18  N = 58 | 56±20  N =7 | 38±15  N = 11 | 55±13  N = 13 | 50±22  N = 8 | 52±23  N = 11 | 55±15  N = 8 |
| PH Therapy  ERA  PDE5i  ERA+PDE5i  sGC | 26 (24%)  34 (32%)  44 (41%)  4 (4%) | 16 (100%)  0 (0%)  0 (0%)  0 (0%) | 0 (0%)  15 (88%)  0 (0%)  2 (12%) | 0 (0%)  0 (0%)  24 (96%)  1 (4%) | 6 (35%)  6 (35%)  5 (29%)  0 (0%) | 2 (10%)  11 (55%)  7 (35%)  0 (0%) | 2 (15%)  2 (15%)  8 (62%)  1 (8%) |
| WHO = World Health Organization; CpC = combined post and pre-capillary; PH = pulmonary hypertension; 6MWD = six minute walk distance; m = meters; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; WU = woods units; RVSP = right ventricular systolic pressure  Continuous variables presented as mean ±SD; categorical variables presented as frequency (proportion) | | | | | | | |

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| Supplemental Table 2: Baseline Biomarker Values in the Entire Cohort,  and as Stratified by Therapy Class and Additional PH Risk Factors | | | | | | | |
| Baseline  biomarker | Group 1,  ERA | Group 1,  PDE5i | Group 1,  ERA+PDE5i | PAH with concomitant  left heart disease | PAH with concomitant lung disease | CTEPH | Overall |
| ET-1 (pg/mL) | 3.1 (2.3, 3.9)  N = 14 | 2.2 (1.8, 2.7)  N = 15 | 4.4 (2.5, 6.0)  N = 21 | 3.0 (2.0, 5.9)  N = 15 | 2.8 (1.5, 4.0)  N = 19 | 3.0 (2.0, 5.4)  N = 11 | 2.8 (2.2, 5.1)  N = 95 |
| NTproBNP  (pg/mL) | 386.0 (119.0, 661.0)  N = 15 | 264.0 (89.5,  541.0)  N = 16 | 297.0 (125.0,  592.0)  N = 22 | 699.0 (261.0, 1301.0)  N = 17 | 244.5 (100.0,  462.5)  N = 20 | 461.0 (192.0, 837.0)  N = 13 | 302.0 (122.0, 747.0)  N = 103 |
| RDW (%) | 15.1 (14.2,  16.4)  N = 15 | 14.4 (13.5,  15.0)  N = 15 | 15.4 (14.2,  16.8)  N = 21 | 15.4 (14.4,  16.3)  N = 17 | 14.7 (14.1,  15.5)  N = 20 | 14.3 (13.7,  15.8)  N = 13 | 14.7 (14.0,  16.1)  N = 101 |
| cGMP  (pmoles/mL) | 41.3 (33.1, 109.8)  N = 13 | 60.7 (33.3, 121.3)  N = 15 | 51.0 (39.4,  115.7)  N = 20 | 48.7 (36.1,  85.0)  N = 15 | 44.5 (39.5,  101.2)  N = 19 | 59.5 (36.2,  133.8)  N = 11 | 49.2 (38.3, 107.9)  N = 93 |
| SNO-Hb (moles SNO/mole Hb) | 0.0008  (0.0005,  0.0011)  N = 10 | 0.0010  (0.0008,  0.0014)  N = 12 | 0.0017  (0.0011,  0.0021)  N = 14 | 0.0006  (0.0004,  0.0007)  N = 14 | 0.0006  (0.0004,  0.0011)  N = 13 | 0.0008  (0.0008,  0.0023)  N = 11 | 0.0009  (0.0006,  0.0015)  N = 74 |
| cGMP to NTproBNP ratio (pmoles/pg) | 0.23  (0.10, 0.66)  N = 12 | 0.29  (0.05, 0.69)  N = 14 | 0.27  (0.11, 0.41)  N = 17 | 0.07  (0.02, 0.49)  N = 15 | 0.21  (0.10, 0.46)  N = 19 | 0.10  (0.06, 0.74)  N = 11 | 0.20  (0.07, 0.49)  N = 88 |
| ADMA (nM) | 550.5  (500.0, 556.0)  N = 14 | 526.5  (442.5, 594.0)  16 | 515.0  (432.0, 565.0)  N = 23 | 549.5  (473.0, 643.0)  N = 16 | 523.0  (467.0, 614.0)  N = 17 | 551.0  (458.0, 607.0)  N = 11 | 523.0  (457.0, 576.0)  N = 97 |
| SDMA (nM) | 352.7 (327.0, 402.2)  N = 13 | 453.6 (411.2, 521.0)  N = 14 | 424.9 (353.6, 500.0)  N = 23 | 502.5 (423.2, 785.5)  N = 16 | 543.0 (407.6, 621.0)  N = 17 | 534.5 (377.0, 737.0)  N = 10 | 435.0 (377.0, 561.0)  N = 93 |
| NO2- (nM) | 72.6  (41.0, 163.4)  N = 10 | 39.0  (26.5, 53.2)  N = 8 | 46.9  (35.0, 93.0)  N = 12 | 62.7  (48.1, 84.1)  N = 15 | 41.2  (35.3, 85.4)  N = 13 | 78.3  (44.3, 116.6)  N = 10 | 56.2  (36.2, 94.9)  N = 68 |
| ET-1 = endothelin-1; NTproBNP = N-terminal fragment of brain natriuretic peptide; RDW = red cell distribution width; cGMP = cyclic guanosine monophosphate; SNO-Hb = S-nitrosohemoglobin; ADMA= asymmetric dimethylarginine; SDMA = symmetric dimethylarginine; NO2- = nitrite  Continuous variables presented as median (IQR) | | | | | | | |

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| Supplemental Table 3: Prediction of 6MWD Using Biomarker Value at Previous Visit in larger cohort of pulmonary vascular disease subjects | | | | |
| Biomarker\* | **Estimate** | **Standard Error** | **Standardized model coefficients$** | **P-value** |
| ET -1 (N = 79) | -29.37 | 12.34 | -13.59 | 0.02 |
| NT-proBNP (N = 82) | -8.04 | 3.81 | -10.37 | 0.04 |
| RDW (N = 82) | -111.43 | 53.14 | -11.03 | 0.04 |
| cGMP (N = 77) | 2.64 | 9.15 | 1.49 | 0.77 |
| SNO-Hb (N = 70) | -1914.56 | 4468.35 | -1.53 | 0.67 |
| cGMP/NTproBNP ratio  Log (cGMP/NTproBNP + 1) ≤ 0.75 ϕ  Log (cGMP/NTproBNP + 1) >0.75 ϕ | 55.23 -14.36 | 23.71 23.61 | 22.12  -5.75 | 0.02 0.55 |
| NO2- (N = 72) | -3.10 | 7.97 | -2.68 | 0.70 |
| ADMA (N = 78) | 0.01 | 0.05 | 0.53 | 0.92 |
| SDMA (N= 79) | -0.16 | 13.14 | -0.06 | 0.99 |
| \* All biomarkers were transformed as log(biomarker+1) besides ADMA $ Standarized model coefficients quantify change per 1 standard deviation increase in values of each biomarker  ϕ Per 1 unit increase on log scale | | | | |

**Supplemental Figures**

**Figure S1: Association between 6MWD and Selected Biomarkers at the Previous Visit in larger cohort of pulmonary vascular disease subjects**



p=0.04



p=0.02



p=0.04