

## Appendix

**Table A1: Univariate analysis of patients with IPAH-noLD**

| <b>Characteristic</b>                       | <b>HR<sup>1</sup></b> | <b>95% CI<sup>1</sup></b> | <b>p-value</b> |
|---|-----------------------|---------------------------|----------------|
| CT - Centrilobular Ground Glass (CGG)       | 0.62                  | 0.30, 1.26                | 0.2            |
| CT - Ground Glass Opacification (GGO)       | 0.64                  | 0.32, 1.26                | 0.2            |
| CT - Honeycombing                           |                       |                           |                |
| CT - Consolidation                          | 1.55                  | 0.48, 4.96                | 0.5            |
| Age at diagnosis                            | 1.05                  | 1.03, 1.07                | <0.001         |
| Male Gender                                 | 1.50                  | 0.90, 2.52                | 0.12           |
| WHO Functional Class III & IV (ref: I & II) | 1.78                  | 1.12, 2.81                | 0.014          |
| WHO Functional Class                        |                       |                           |                |
| II  | —                     | —                         |                |
| III   | 2.61                  | 1.02, 6.67                | 0.046          |
| IV  | 5.62                  | 2.07, 15.2                | <0.001         |
| mPAP (mmHg)                                 | 0.99                  | 0.97, 1.01                | 0.3            |
| mRAP (mmHg)                                 | 1.04                  | 1.00, 1.08                | 0.085          |
| PAWP (mmHg)                                 | 1.10                  | 1.00, 1.20                | 0.040          |
| Cardiac output (L/min)                      | 1.00                  | 0.84, 1.18                | >0.9           |
| Cardiac index (L/min/m <sup>2</sup> )       | 0.98                  | 0.70, 1.38                | >0.9           |
| PVR (Wood Units)                            | 0.97                  | 0.92, 1.02                | 0.2            |
| SvO <sub>2</sub> %                          | 0.96                  | 0.94, 0.99                | 0.011          |
| FEV <sub>1</sub> % predicted                | 0.98                  | 0.97, 0.99                | 0.008          |
| FVC % predicted                             | 0.99                  | 0.98, 1.00                | 0.11           |
| FEV <sub>1</sub> /FVC Ratio                 | 0.96                  | 0.94, 0.98                | <0.001         |
| DLco % predicted                            | 0.95                  | 0.93, 0.97                | <0.001         |

Abbreviations: HR - Hazard Ratio, CI - Confidence Interval, IPAH-noLD, Idiopathic Pulmonary Arterial Hypertension with no lung disease, CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO<sub>2</sub> – mixed venous oxygen saturation. FEV<sub>1</sub> – forced expiratory volume in 1 second, FVC – forced vital capacity, DLco – diffusing capacity of carbon monoxide.

Table A2: Baseline characteristics of IPAH-noLD vs IPAH-LD vs PH-CLD

| Characteristic                           | IPAH-noLD,<br>N = 197 | IPAH-LD,<br>N = 138 | PH-CLD,<br>N = 325 | p-value |
|--|-----------------------|---------------------|--------------------|---------|
| Age at diagnosis                         | 54 (18) †‡            | 70 (10) *           | 67 (11) *          | <0.001  |
| Male Gender                              | 59 (30%) †‡           | 72 (52%)*           | 187 (58%)*         | <0.001  |
| WHO Functional Class                     | †‡                    | *                   | *                  | <0.001  |
| 2  | 34 (17%) †‡           | 10 (7.2%)*          | 34 (10%)           |         |
| 3  | 127 (65%)             | 86 (62%)            | 185 (57%)          |         |
| 4  | 34 (17%)              | 42 (30%)            | 105 (32%)          |         |
| CT - Centrilobular Ground Glass (CGG)    | 46 (23%) †‡           | 8 (5.8%)*           | 0 (0%)*            | <0.001  |
| CT - Ground Glass Opacification (GGO)    | 48 (24%) †‡           | 14 (10%)*           | 31 (9.5%)*         | <0.001  |
| CT - Honeycombing                        | 0 (0%)                | 5 (3.6%)            | 10 (3.1%)          | 0.013   |
| CT - Consolidation                       | 7 (3.6%)              | 2 (1.4%) †          | 22 (6.8%) †        | 0.031   |
| CT - Fibrosis                            | 0 (0%) †‡             | 72 (52%)*           | 141 (43%)*         | <0.001  |
| CT - Fibrosis (by severity)              | †‡                    | * ‡                 | * †                | <0.001  |
| Mild                                     | 0 (0%)                | 54 (39%)            | 28 (8.6%)          |         |
| Moderate                                 | 0 (0%)                | 9 (6.5%)            | 44 (14%)           |         |
| None                                     | 197 (100%)            | 66 (48%)            | 184 (57%)          |         |
| Severe                                   | 0 (0%)                | 0 (0%)              | 48 (15%)           |         |
| Unknown                                  | 0 (0%)                | 9 (6.5%)            | 21 (6.5%)          |         |
| CT - Emphysema                           | 0 (0%) †‡             | 98 (71%)*           | 204 (63%)*         | <0.001  |
| CT - Emphysema (by severity)             | †‡                    | * ‡                 | * †                | <0.001  |
| Mild                                     | 0 (0%)                | 48 (35%)            | 29 (8.9%)          |         |
| Moderate                                 | 0 (0%)                | 38 (28%)            | 91 (28%)           |         |
| None                                     | 197 (100%)            | 40 (29%)            | 121 (37%)          |         |
| Severe                                   | 0 (0%)                | 5 (3.6%)            | 64 (20%)           |         |
| Unknown                                  | 0 (0%)                | 7 (5.1%)            | 20 (6.2%)          |         |
| CT - CPFE                                | 0 (0%) †‡             | 32 (23%)*           | 69 (21%)*          | <0.001  |
| mPAP (mmHg)                              | 56 (13) †‡            | 49 (9)* ‡           | 42 (10)* †         | <0.001  |
| mRAP (mmHg)                              | 11.4 (6.1) ‡          | 11.3 (5.3) ‡        | 9.0 (5.1)* †       | <0.001  |
| PAWP (mmHg)                              | 10.6 (3.1) ‡          | 11.1 (3.6)          | 11.8 (4.2)*        | 0.004   |
| Cardiac output (L/min)                   | 4.46 (1.74) ‡         | 4.10 (1.41)         | 5.00 (1.64)        | <0.001  |
| Cardiac index (L/min x m <sup>-2</sup> ) | 2.39 (0.87) ‡         | 2.23 (0.71) ‡       | 2.73 (0.87)* †     | <0.001  |
| PVR (Wood Units)                         | 11.6 (5.7) †‡         | 10.2 (4.4)* ‡       | 7.0 (4.1)* †       | <0.001  |
| SvO <sub>2</sub> %                       | 62 (10) ‡             | 59 (8) ‡            | 65 (8)* †          | <0.001  |
| FEV <sub>1</sub> % predicted             | 83 (17)* ‡            | 83 (20) ‡           | 60 (25)* †         | <0.001  |
| FEV <sub>1</sub> severity                | ‡                     | ‡                   | * †                | <0.001  |
| Normal (>80% predicted)                  | 114 (61%)             | 73 (54%)            | 72 (24%)           |         |

|                             |            |            |            |        |
|-----------------------------|------------|------------|------------|--------|
| Mild (70-80% predicted)     | 29 (16%)   | 24 (18%)   | 34 (11%)   |        |
| Moderate (50-70% predicted) | 39 (21%)   | 31 (23%)   | 69 (23%)   |        |
| Severe (<50% predicted)     | 5 (2.7%)   | 6 (4.5%)   | 129 (42%)  |        |
| FEV <sub>1</sub> / FVC (%)  | 74 (10) †‡ | 67 (10)* ‡ | 61 (18)* † | <0.001 |
| DLco % predicted            | 53 (19) †‡ | 32 (15)* ‡ | 28 (14)* † | <0.001 |

Data are presented as number (percentage) or mean (standard deviation). Between-group comparisons performed using one-Way ANOVA with Bonferroni Post-Hoc Correction. Difference between groups noted: \* significant difference to IPAH-noLD, † significant difference to IPAH-LD, ‡ significant difference to PH-CLD. Abbreviations: IPAH-LD, Idiopathic Pulmonary Arterial Hypertension with lung disease, PH-CLD, PH due to chronic lung disease and/or hypoxia, CT – Computed Tomography, WHO – World Health Organisation, CPFE – Combined Pulmonary Fibrosis and Emphysema, mPAP – mean pulmonary arterial pressure, mRAP – mean right atrial pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, SvO<sub>2</sub> – mixed venous oxygen saturation. FEV<sub>1</sub> – forced expiratory volume in 1 second, FVC – forced vital capacity, DLco – diffusing capacity of carbon monoxide.

**Table A3: Survival of patients with IPAH-noLD, IPAH-LD and PH-CLD**

| Characteristic | 1 Year | 2 Year | 3 Year | 4 Year | 5 Year |
|----------------|--------|--------|--------|--------|--------|
| IPAH-noLD      | 92%    | 85%    | 82%    | 78%    | 70%    |
| IPAH-LD        | 87%    | 60%    | 41%    | 29%    | 21%    |
| PH-CLD         | 69%    | 46%    | 36%    | 28%    | 20%    |

Abbreviations: IPAH-noLD, Idiopathic Pulmonary Arterial Hypertension with no lung disease; IPAH-LD, Idiopathic Pulmonary Arterial Hypertension with lung disease; PH-CLD, PH due to chronic lung disease and/or hypoxia.