**Online Supplementary Material**

***for***

**Post hoc Analysis of Clinical Outcomes in Placebo- and Pirfenidone-treated Patients with IPF Stratified by BMI and Weight Loss**

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**Table E1.** Demographic and baseline characteristics by baseline BMI category in patients from the pirfenidone arms of ASCEND and CAPACITY

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Baseline BMI** | | |
| **Demographic/characteristic\*** | **<25 kg/m2**  ***n* = 73** | **25–<30 kg/m2**  ***n* = 265** | **≥30 kg/m2**  ***n* = 285** |
| Age at randomization, years | 69.8 (7.5) | 68.2 (7.1) | 65.6 (7.7) |
| Male, *n* (%) | 42 (57.5) | 215 (81.1) | 206 (72.3) |
| White, *n* (%) | 58 (79.5) | 226 (85.3) | 259 (90.9) |
| Weight at baseline, kg | | | |
| Male | 69.0 (8.0) | 84.0 (9.0) | 102.8 (14.5) |
| Female | 58.6 (7.3) | 70.3 (6.1) | 85.7 (11.4) |
| BMI at baseline | | | |
| Male | 23.4 (1.5) | 27.7 (1.4) | 33.6 (3.2) |
| Female | 23.2 (1.5) | 27.5 (1.6) | 33.8 (3.3) |
| HRCT diagnosis group at baseline, *n* (%) | | | |
| Definite UIP | 71 (97.3) | 247 (93.6)† | 256 (89.8) |
| Probable/possible UIP | 2 (2.7) | 17 (6.4)† | 27 (9.5) |
| Uncertain with UIP | 0 (0) | 0 (0) | 2 (0.7) |
| Time from IPF diagnosis to randomization, years | 1.7 (1.1) | 1.5 (1.1) | 1.4 (1.0) |
| Percent predicted FVC | 72.5 (15.9) | 72.3 (13.8) | 70.7 (11.8) |
| FEV1/FVC ratio | 0.9 (0.1) | 0.8 (0.0) | 0.8 (0.0) |
| Percent predicted DLco | 44.6 (10.4) | 44.8 (9.9) | 46.5 (10.3) |
| Baseline 6MWD, m | 410.5 (99.0)‡ | 424.2 (95.5)† | 383.0 (86.2)§ |
| Baseline SGRQ score | 30.9 (12.2)‖ | 35.9 (17.6)\*\* | 40.6 (17.4)†† |
| Supplemental oxygen use at baseline, *n* (%) | 11 (15.1) | 50 (18.9) | 94 (33.0) |
| Smoking status at screening, *n* (%) | | | |
| Current | 0 (0.0) | 3 (1.1) | 5 (1.8) |
| History | 38 (52.1) | 173 (65.3) | 195 (68.4) |
| Never | 35 (47.9) | 89 (33.6) | 85 (29.8) |

\*Data are presented as mean (SD) unless specified otherwise. †*n* = 264. ‡*n* = 71. §*n* = 282. ‖*n* = 32. \*\**n* = 127. ††*n* = 170. 6MWD, 6-min walk distance; BMI, body mass index; DLco, carbon monoxide diffusing capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SD, standard deviation; SGRQ, St. George’s Respiratory Questionnaire; UIP, usual interstitial pneumonia.

**Table E2.** Sensitivity analysis of clinical outcomes at 1 year stratified by annualized percent change in body weight, excluding 19 patients with no post-baseline body-weight measurement after Day 90, in patients from the placebo arms of ASCEND and CAPACITY, and all patients from INSPIRE and RIFF (Cohort A)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Annualized percent change in body weight** | | |
| **Outcome** | **No loss**  ***n* = 841** | **>0–<5% loss**  ***n* = 599** | **≥5% loss**  ***n* = 99** |
| **Annualized change from baseline in percent predicted FVC, %\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 838  -4.2 (-4.6, -3.8) | 589  -5.5 (-6.0, -5.0)  -1.3 (-1.9, -0.6) | 99  -9.5 (-10.7, -8.2)  -5.2 (-6.6, -3.9) |
| **Annualized change from baseline in percent predicted DLco, %\*,‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 699  -4.1 (-4.6, -3.7) | 489  -5.2 (-5.7, -4.6)  -1.0 (-1.7, -0.3) | 67  -6.9 (-8.5, -5.3)  -2.8 (-4.4, -1.1) |
| **Annualized change from baseline in 6MWD, m\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 839  -25.7 (-31.0, -20.4) | 589  -37.3 (-43.8, -30.8)  -11.6 (-20.0, -3.2) | 99  -81.1 (-98.7, -63.6)  -55.5 (-73.8, -37.1) |
| **Annualized change from baseline in SGRQ total score\*,‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 699  3.5 (2.8, 4.2) | 487  5.0 (4.2, 5.9)  1.5 (0.4, 2.6) | 67  9.6 (7.2, 12.0)  6.1 (3.5, 8.6) |
| **Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 838  8.0 (3.1, 12.8) | 589  12.3 (6.9, 17.8)  4.3 (0.4, 8.2) | 99  21.9 (12.6, 31.1)  13.9 (4.9, 22.8) |
| **Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 837  8.8 (4.0, 13.6) | 589  16.0 (10.7, 21.4)  7.2 (3.5, 11.0) | 99  37.4 (27.0, 47.8)  28.5 (18.6, 38.5) |
| **Any all-cause hospitalization up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 839  19.3 (14.1, 24.6) | 589  24.5 (18.8, 30.3)  5.2 (1.2, 9.2) | 99  39.7 (29.5, 49.9)  20.4 (10.5, 30.2) |
| **All-cause mortality up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 839  7.6 (2.8, 12.4) | 589  10.4 (4.7, 16.2)  2.9 (-1.5, 7.2) | 99  12.0 (3.1, 20.9)  4.4 (-4.0, 12.8) |
| **Any treatment-emergent SAEs up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 839  22.1 (16.6, 27.6) | 589  25.4 (19.5, 31.3)  3.3 (-0.9, 7.6) | 99  51.0 (40.4, 61.7)  28.9 (18.7, 39.2) |

\*Estimates (95% CI) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, annualized percent change category, time, and annualized percent change category\*time as fixed-effect covariates, with random intercept and random slope for time for each patient. †Estimated difference from first category. ‡Excludes ASCEND study. §Estimates (95% CI) based on logistic regression with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, and annualized percent change in body-weight category as model factors. 6MWD, 6‑min walk distance; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George’s Respiratory Questionnaire.

**Table E3.** Clinical outcomes at 1 year stratified by baseline BMI category in patients from the pirfenidone arms of ASCEND and CAPACITY

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Baseline BMI** | | |
| **Outcome** | **<25 kg/m2**  ***n* = 73** | **25–<30 kg/m2**  ***n* = 265** | **≥30 kg/m2**  ***n* = 285** |
| **Annualized change from baseline in percent predicted FVC, %\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  -4.3 (-5.7, -2.9) | 264  -4.4 (-5.1, -3.7)  -0.1 (-1.7, 1.4) | 285  -3.6 (-4.3, -3.0)  0.7 (-0.8, 2.2) |
| **Annualized change from baseline in percent predicted DLco, %\*,****‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 33  -4.8 (-6.7, -2.9) | 134  -5.5 (-6.4, -4.6)  -0.7 (-2.8, 1.4) | 177  -5.0 (-5.8. -4.3)  -0.2 (-2.3, 1.8) |
| **Annualized change from baseline in 6MWD, m\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  -22.1 (-41.2, -3.0) | 264  -26.5 (-36.2, -16.8)  -4.4 (-25.8, 17.1) | 285  -25.2 (-34.3, -16.2)  -3.1 (-24.2, 18.0) |
| **Annualized change from baseline in SGRQ total score\*,‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 33  -0.8 (-4.1, 2.4) | 134  4.5 (2.8, 6.1)  5.3 (1.7, 9.0) | 177  2.8 (1.4, 4.1)  3.6 (0.0, 7.1) |
| **Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§,‖** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  3.3 (0.7, 14.6) | 264  5.4 (1.7, 16.3)  2.1 (-9.8, 13.3) | 285  2.9 (0.8, 9.7)  -0.4 (-11.9, 6.8) |
| **Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§,‖** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  11.9 (4.8, 26.7) | 264  13.3 (6.9, 24.1)  1.3 (-14.8, 14.3) | 285  7.8 (3.8, 15.5)  -4.1 (-19.4, 6.4) |
| **Any all-cause hospitalization up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  12.4 (5.7, 24.8) | 264  14.7 (8.4, 24.5)  2.4 (-11.6, 14.2) | 285  16.1 (9.4, 26.0)  3.7 (-10.4, 15.7) |
| **All-cause mortality up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  1.9 (0.3, 11.8) | 264  2.9 (0.7, 11.9)  1.1 (-9.1, 10.2) | 285  1.3 (0.3, 6.3)  -0.5 (-10.5, 4.7) |
| **Any treatment-emergent SAEs up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 73  18.3 (9.5, 32.4) | 264  18.0 (10.9, 28.3)  -0.3 (-16.1, 13.2) | 285  18.7 (11.5, 28.8)  0.3 (-15.4, 13.8) |

\*Estimates (95% CI) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, baseline BMI category, time, and baseline BMI category\*time as fixed-effect covariates, with random intercept and random slope for time for each patient. †Estimated difference from first category. ‡Excludes ASCEND study. §Estimates (95% CI) based on logistic regression with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, and baseline BMI category as model factors. ‖Endpoint was derived from estimated annual change in percent predicted FVC for each patient based on a simple random slopes and intercepts model. 6MWD, 6-min walk distance; BMI, body mass index; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George’s Respiratory Questionnaire.

**Table E4.** Clinical outcomes at 1 year stratified by annualized percent change in body weightin patients from the pirfenidone arms of ASCEND and CAPACITY

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Annualized percent change in body weight** | | |
| **Outcome** | **No weight loss**  ***n* = 374** | **>0–<5% loss**  ***n* = 165** | **≥5% loss**  ***n* = 84** |
| **Annualized change from baseline in percent predicted FVC, %\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  -3.5 (-4.0, -2.9)‡ | 165  -4.1 (-5.0, -3.2)  -0.6 (-1.7, 0.4) | 84  -6.8 (-8.1, -5.5)  -3.4 (-4.8, -1.9) |
| **Annualized change from baseline in percent predicted DLco, %\*, ‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 223  -4.6 (-5.2, -3.9) | 89  -5.6 (-6.7, -4.4)  -1.0 (-2.4, 0.3) | 32  -9.1 (-11.1, -7.1)  -4.5 (-6.7, -2.4) |
| **Annualized change from baseline in 6MWD, m\*** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  -18.0 (-25.8, -10.2) | 165  -25.2 (-37.2, -13.2)  -7.2 (-21.5, 7.1) | 84  -67.5 (-86.1, -49.0)  -49.6 (-69.6, -29.5) |
| **Annualized change from baseline in SGRQ total score\*, ‡** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 223  2.4 (1.2, 3.7) | 89  3.6 (1.6, 5.6)  1.2 (-1.2, 3.5) | 32  6.6 (3.1, 10.1)  4.2 (0.5, 7.9) |
| **Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§, ‖** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  2.4 (0.7, 7.9) | 165  4.3 (1.2, 14.0)  1.9 (-4.5, 11.8) | 84  14.6 (4.4, 39.0)  12.2 (0.6, 36.6) |
| **Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %§, ‖** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  5.9 (2.9, 12.0) | 165  12.1 (5.8, 23.3)  6.1 (-2.5, 17.7) | 84  34.8 (18.8, 55.2)  28.8 (11.8, 49.4) |
| **Any all-cause hospitalization up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  11.3 (6.4, 19.0) | 165  20.3 (11.7, 32.8)  9.0 (-2.5, 22.5) | 84  26.2 (14.4, 42.8)  14.9 (0.9, 32.2) |
| **All-cause mortality up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  1.4 (0.3, 6.1) | 165  2.1 (0.4, 9.5)  0.7 (-4.3, 8.2) | 84  6.0 (1.3, 24.2)  4.6 (-2.1, 22.8) |
| **Any treatment-emergent SAEs up to 1 year post-randomization, %§** | | | |
| Observed, *n*  Estimate (95% CI)  Difference (95% CI)† | 373  14.0 (8.4, 22.3) | 165  22.5 (13.6, 34.9)  8.6 (-3.6, 22.1) | 84  35.3 (21.5, 52.1)  21.3 (5.2, 39.0) |

\*Estimates (95% CIs) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, annualized percent change in body-weight category, time, and annualized percent change in body-weight category\*time as fixed-effect covariates, with random intercept and random slope for time for each patient. †Estimated difference from first category. ‡Excludes ASCEND study. §Estimates (95% CIs) based on logistic regression with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, and annualized percent change in body-weight category as model factors. ‖Endpoint was derived from estimated annual change in percent predicted FVC for each patient based on a simple random slopes and intercepts model.6MWD, 6-min walk distance; CI, confidence interval; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SAE, serious adverse event; SGRQ, St. George’s Respiratory Questionnaire.

**Figure E1.** Sensitivity analysis of time to first all-cause hospitalization up to 1 year post‑randomization (with death as competing risk), stratified by annualized percent change in body-weight categories, in patients from the placebo arms of ASCEND and CAPACITY, and all patients from INSPIRE and RIFF (Cohort A).

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