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1 **Post hoc Analysis of Clinical Outcomes in Placebo- and Pirfenidone-treated**
2 **Patients with IPF Stratified by BMI and Weight Loss (126/130 characters)**

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27 **Abstract [248/250 words]**

28 **Background:** Weight loss is frequently reported in patients with idiopathic pulmonary
29 fibrosis (IPF), and may be associated with worse outcomes in these patients.

30 **Objective:** To investigate the relationships between body mass index (BMI) and weight loss,
31 and outcomes over 1 year in patients with IPF.

32 **Methods:** Data were included from placebo patients enrolled in ASCEND (NCT01366209)
33 and CAPACITY (NCT00287716, NCT00287729), and all patients in INSPIRE (NCT00075998)
34 and RIFF Cohort A (NCT01872689). An additional analysis included data from pirfenidone-
35 treated patients. Outcomes (annualized change in percent predicted forced vital capacity
36 [%FVC], percent predicted carbon monoxide diffusing capacity, 6-min walk distance,
37 St. George's Respiratory Questionnaire total score, hospitalization, mortality, and serious
38 adverse events) were analyzed by baseline BMI (<25 kg/m², 25 kg/m²–<30 kg/m², or
39 ≥30 kg/m²) and annualized percent change in body weight (no loss, >0–<5% loss, or ≥5%
40 loss).

41 **Results:** Placebo-treated patients with baseline BMI <25 kg/m² or annualized weight loss
42 may experience worse outcomes, versus those with baseline BMI ≥25 kg/m² or no weight
43 loss. The proportion of placebo-treated patients who experienced a relative decline of ≥10%
44 in %FVC or death up to 1 year post-randomization was highest in patients with baseline BMI
45 <25 kg/m². Pirfenidone-treated patients with annualized weight loss ≥5% may also
46 experience worse outcomes versus those with no weight loss.

47 **Conclusions:** Patients with baseline BMI $<25 \text{ kg/m}^2$ or annualized weight loss of >0 – $<5\%$ or
48 $\geq 5\%$ may experience worse outcomes over 1 year versus those with baseline BMI $\geq 25 \text{ kg/m}^2$
49 or no weight loss.

50 **Introduction**

51 Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease that is associated
52 with a survival rate lower than that reported for many cancers [1-4]. Patients with IPF
53 experience a progressive decline in lung function and exercise capacity, ending in
54 respiratory failure and death; however, the disease course can be variable [1, 2, 5, 6].

55 Identification of potential indicators of disease severity and prognosis in patients with IPF,
56 including those receiving antifibrotic therapy, are therefore active areas of interest [7, 8].

57 Body mass index (BMI) and body weight are routinely assessed in clinical practice, and
58 associations between BMI and prognosis have been reported in patients with chronic
59 obstructive pulmonary disease (COPD) and rheumatoid arthritis [9, 10]. Many patients with
60 IPF experience weight loss, which has been associated with an increased risk of early
61 treatment termination [11] and reductions in transplant-free and overall survival [12-14].
62 Furthermore, weight loss has been suggested as a longitudinal marker of disease
63 progression and a predictor of mortality in IPF; however, there are limitations associated
64 with these retrospectively acquired data [12, 14]. Prospective studies evaluating the
65 association between weight loss and poor prognosis in IPF are warranted in the future.

66 It should be acknowledged that weight loss is only one factor within the wider context of
67 disease-associated malnutrition; however, there are limited clinical studies in IPF that
68 collect detailed data on malnutrition. BMI and weight loss are two practical proxies for
69 investigation that can be measured quickly with minimal equipment in clinical practice [15-
70 17].

71 This post hoc analysis aimed to investigate the relationships between BMI and weight loss
72 and individual clinical outcomes over 1 year in patients with IPF.

73 **Materials and Methods**

74 *Patient Population*

75 This post hoc analysis included pooled data from five randomized controlled trials of
76 patients with IPF (ASCEND [NCT01366209], CAPACITY [NCT00287716 and NCT00287729],
77 INSPIRE [NCT00075998], and RIFF [NCT01872689]). The designs of these trials have been
78 published previously. Briefly, ASCEND and CAPACITY were Phase III, double-blind trials of
79 pirfenidone versus placebo [18, 19]; INSPIRE was a Phase III, placebo-controlled trial that
80 evaluated the efficacy of interferon (IFN)- γ -1b [20]; and RIFF (Cohort A) assessed
81 lebrikizumab monotherapy versus placebo in a Phase II study [21].

82 The analysis presented here included patients from the placebo arms of ASCEND and
83 CAPACITY, and all patients from INSPIRE and RIFF (Cohort A). All patients from the INSPIRE
84 and RIFF (Cohort A) trials were included as no treatment effect was detected in the active
85 treatment arms of these trials [20, 21]. The lack of treatment difference observed during
86 these trials enabled the inclusion of all patients to provide a larger pooled population than
87 would be obtained by including patients in the placebo group only. Furthermore, the
88 annualized percentage weight change was similar between the two treatment groups in
89 each of these studies.

90 An additional analysis included patients who received pirfenidone 2403 mg/day during
91 ASCEND and CAPACITY (patients who received 1197 mg/day in CAPACITY 004 were not
92 included in this analysis).

93 *Predictors*

94 In our post hoc analyses of clinical outcomes at 1 year, patients were stratified by baseline
95 BMI and annualized percent change in body weight. Baseline BMI was categorized based on
96 World Health Organization (WHO) standards, with some categories combined to increase
97 patient numbers per group, as follows: $<25 \text{ kg/m}^2$ (WHO normal weight or underweight),
98 25 kg/m^2 – $<30 \text{ kg/m}^2$ (WHO pre-obesity), or $\geq 30 \text{ kg/m}^2$ (WHO obesity, Class I–III) [22].

99 Annualized percent change in body weight was categorized based on the United States Food
100 and Drug Administration (FDA) Guidance for Developing Products for Weight Management,
101 which recommends an annualized weight loss of $\geq 5\%$ for use as a primary endpoint [23]. We
102 adapted this guidance and categorized annualized percent change in body weight as follows:
103 no loss, >0 – $<5\%$ loss, or $\geq 5\%$ loss. Weight measurements were collected for patients at site
104 visits during each trial.

105 *Outcomes*

106 Outcomes assessed in patients from the placebo arms of ASCEND and CAPACITY, and all
107 patients from INSPIRE and RIFF (Cohort A), included annualized changes from baseline in
108 percent predicted forced vital capacity (FVC), percent predicted carbon monoxide diffusing
109 capacity (DLco), 6-min walk distance (6MWD), and the St. George’s Respiratory
110 Questionnaire (SGRQ) total score. The proportion of patients with an absolute or relative
111 decline of $\geq 10\%$ in percent predicted FVC or death up to 1 year post-randomization was
112 evaluated. All-cause hospitalization and mortality were evaluated using time-to-event
113 analyses. Treatment-emergent serious adverse events (SAEs) were also assessed.

114 The same outcomes were assessed in patients from the pirfenidone treatment arms of
115 ASCEND and CAPACITY.

116 *Statistical Analyses*

117 Baseline demographics and characteristics, stratified by baseline BMI category, were
118 reported descriptively.

119 For each patient with a baseline and at least one post-baseline measurement of body
120 weight, an annualized percent change in body weight was determined from a linear mixed
121 model for repeated measures of body weight versus actual time since baseline weight
122 assessment (Day 1). The model included both random intercept and random slope terms
123 (assuming different change pattern among patients). For each patient, the predicted 1-year
124 weight change was estimated and percent change calculated using the baseline weight.
125 Patients who discontinued or died prior to 1 year were included in the analyses if weight
126 data were available. Any patient with missing baseline weight or no post-baseline
127 measurement was excluded. All available body weights for each patient were included in
128 the repeated-measures model.

129 The proportions of patients with an absolute or relative decline of $\geq 10\%$ in percent
130 predicted FVC or death up to 1 year post-randomization, stratified by baseline BMI category
131 and annualized percent change in body weight, were reported descriptively.

132 Clinical outcomes up to 1 year were presented as estimates (with 95% confidence intervals
133 [CIs]) and estimated differences (with 95% CIs), from the reference category. For
134 assessment according to BMI, the reference category was baseline BMI $< 25 \text{ kg/m}^2$, and for
135 assessment according to annualized percent change in body weight, the reference category
136 was no weight loss. For continuous data (changes in percent predicted FVC, percent
137 predicted DLco, 6MWD, and SGRQ total score), estimates were based on repeated-
138 measures analysis of covariance, with study, age, sex, race, baseline high-resolution

139 computed tomography (HRCT) status, years since IPF diagnosis, baseline oxygen use,
140 baseline smoking status, the categorical variable of interest (baseline BMI category or
141 annualized percent change in body-weight category), time, and annualized categorical
142 variable of interest*time as fixed-effect covariates, with random intercept and random
143 slope for time for each patient. For these outcomes, estimated annual rates of change were
144 obtained for patients who dropped out or died prior to 1 year if the baseline assessment
145 and at least one post-baseline assessment were available. For binary data (any
146 hospitalization, mortality, absolute or relative decline of $\geq 10\%$ in percent predicted FVC or
147 death, and treatment-emergent SAEs), estimates were based on logistic regression with
148 study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use,
149 baseline smoking status, and the categorical variable of interest as model factors. For these
150 outcomes, patients who dropped out or died prior to 1 year were categorized based on
151 available data to the point of discontinuation or death.

152 Time-to-event analyses of first all-cause hospitalization and mortality are also presented by
153 stratified annualized percent change in body weight. Kaplan-Meier curves were used to
154 display event times and the number of patients at risk, which were compared using the log-
155 rank test.

156 For the analysis population including patients from the placebo arms of ASCEND and
157 CAPACITY, and all patients from INSPIRE and RIFF (Cohort A), a sensitivity analysis was
158 performed for clinical outcomes at 1 year, stratified by annualized percent change in body
159 weight, which excluded patients with no post-baseline body-weight measurement after
160 Day 90. A sensitivity analysis was also performed for time to first all-cause hospitalization, in

161 which death that occurred without a prior hospitalization event was treated as a competing
162 risk event. Gray's test was used to compare cumulative incidence functions [24].

163 **Results**

164 *Patients*

165 In total, 1604 patients from the placebo arms of ASCEND and CAPACITY and both treatment
166 arms of INSPIRE and RIFF (Cohort A) were included in the main analysis population, with a
167 mean (standard deviation [SD]) baseline BMI of 29.68 (4.70) kg/m² (baseline BMI:
168 <25 kg/m², *n* = 227; 25 kg/m²–<30 kg/m², *n* = 703; ≥30 kg/m², *n* = 674). Other than weight
169 and BMI, there were some differences between baseline characteristics when analyzed by
170 baseline BMI, including a higher proportion of males in the 25 kg/m²–<30 kg/m² category
171 compared with the <25 kg/m² category and a higher proportion of never-smokers in the
172 <25 kg/m² category compared with the ≥30 kg/m² category. The proportion of patients
173 using supplemental oxygen increased, while 6MWD decreased, with increasing BMI
174 category (Table 1).

175 A total of 623 patients from the pirfenidone arms of ASCEND and CAPACITY were included in
176 the additional analysis population and had a mean (SD) baseline BMI of 29.87 (4.43) kg/m²
177 (baseline BMI: <25 kg/m², *n* = 73; 25 kg/m²–<30 kg/m², *n* = 265; ≥30 kg/m², *n* = 285). There
178 were differences between baseline characteristics when analyzed by baseline BMI, such as a
179 higher proportion of males in the 25 kg/m²–<30 kg/m² and ≥30 kg/m² categories compared
180 with the <25 kg/m² category, a higher proportion of never-smokers in the <25 kg/m²
181 category compared with the 25 kg/m²–<30 kg/m² and ≥30 kg/m² categories, and a reduced
182 6MWD in the ≥30 kg/m² category compared with the <25 kg/m² and 25 kg/m²–<30 kg/m²

183 categories. The proportion of patients using supplemental oxygen at baseline and SGRQ
184 score at baseline increased with increasing BMI category (Table E1).

185 *Clinical Outcomes up to 1 Year Post-Randomization Stratified by Baseline BMI in Patients*
186 *from the Placebo Arms of ASCEND and CAPACITY, and all Patients from INSPIRE and RIFF*
187 *(Cohort A)*

188 A total of 1604 patients from the placebo arms of ASCEND and CAPACITY and both
189 treatment arms of INSPIRE and RIFF (Cohort A) were included in this analysis (baseline BMI:
190 $<25 \text{ kg/m}^2$, $n = 227$; 25 kg/m^2 – $<30 \text{ kg/m}^2$, $n = 703$; $\geq 30 \text{ kg/m}^2$, $n = 674$).

191 The proportion of patients with a relative decline of $\geq 10\%$ in percent predicted FVC or death
192 up to 1 year post-randomization was highest in patients with baseline BMI $<25 \text{ kg/m}^2$
193 (estimate, 19.0% [95% CI 12.7, 25.4]) and lowest in those with BMI $\geq 30 \text{ kg/m}^2$ (estimate,
194 9.4% [95% CI 4.8, 14.1]; shown in Fig. 1a [observed data]; shown in Table 2 [model
195 estimates]).

196 Patients with baseline BMI $<25 \text{ kg/m}^2$ had a greater estimated annualized decline in percent
197 predicted FVC than patients with baseline BMI 25 kg/m^2 – $<30 \text{ kg/m}^2$ or baseline BMI
198 $\geq 30 \text{ kg/m}^2$ (Table 2). Patients with baseline BMI $<25 \text{ kg/m}^2$ also had greater estimated
199 annualized worsening of percent predicted DLco and SGRQ total score than patients with
200 baseline BMI $\geq 30 \text{ kg/m}^2$ (Table 2). Furthermore, estimated annualized 6MWD decline was
201 numerically greater in patients with baseline BMI $<25 \text{ kg/m}^2$ versus 25 kg/m^2 – $<30 \text{ kg/m}^2$ and
202 $\geq 30 \text{ kg/m}^2$.

203 Estimated all-cause hospitalization and mortality rates, and the proportion of patients
204 experiencing an SAE up to 1 year, were similar across the subgroups stratified by baseline
205 BMI (Table 2).

206 *Clinical Outcomes up to 1 Year Post-Randomization Stratified by Annualized Percent Change*
207 *in Body Weight in Patients from the Placebo Arms of ASCEND and CAPACITY, and all Patients*
208 *from INSPIRE and RIFF (Cohort A)*

209 In total, 1558 patients from the placebo arms of ASCEND and CAPACITY and both treatment
210 arms of INSPIRE and RIFF (Cohort A) were included in this analysis (no weight loss, $n = 849$;
211 >0 – $<5\%$ loss, $n = 610$; $\geq 5\%$ loss, $n = 99$ [21 (21.2%) patients who experienced $\geq 5\%$ loss also
212 had a baseline BMI <25 kg/m²]).

213 Patients with no weight loss experienced the lowest rate of $\geq 10\%$ relative decline in percent
214 predicted FVC or death up to 1 year post-randomization (estimate, 9.5% [95% CI 5.0, 14.1];
215 shown in Fig. 1b [observed data]; Table 3 [model estimates]).

216 Patients who experienced no weight loss also had reduced estimated annualized worsening
217 of percent predicted FVC, percent predicted DLco, 6MWD, and SGRQ total score compared
218 with those who experienced a >0 – $<5\%$ loss or a $\geq 5\%$ loss (Table 3).

219 Compared with patients who experienced no weight loss, a greater percentage of patients
220 with a >0 – $<5\%$ loss or a $\geq 5\%$ loss were hospitalized in 1 year, and mortality was numerically
221 higher in patients with weight loss versus those without weight loss (Table 3). Patients with
222 a $\geq 5\%$ weight loss were also more likely to experience any SAE during the study than those
223 with no weight loss.

224 Results from the sensitivity analysis that excluded 19 patients with no post-baseline body-
225 weight measurement after Day 90 (see Table E2 in the online supplementary material) were
226 consistent with those seen in the main analysis (Table 3).

227 In time-to-event analyses, patients with no weight loss had a significantly lower risk of
228 experiencing a first incidence of all-cause hospitalization or experiencing all-cause mortality
229 over 1 year compared with patients with a >0 – $<5\%$ loss or a $\geq 5\%$ loss (shown in Fig. 2 and 3,
230 respectively). Results from the sensitivity analysis of time to first all-cause hospitalization,
231 which treated any death that occurred without a prior hospitalization as a competing risk
232 event, were consistent with the main analysis (see Fig. E1 in the online supplementary
233 material).

234 *Clinical Outcomes up to 1 Year Post-Randomization Stratified by Baseline BMI and*
235 *Annualized Percent Change in Body Weight in Patients from the Pirfenidone Treatment Arms*
236 *of ASCEND and CAPACITY*

237 In total, 623 pirfenidone-treated patients from ASCEND and CAPACITY were included in this
238 analysis (baseline BMI: <25 kg/m², $n = 73$; 25 kg/m²– <30 kg/m², $n = 265$; ≥ 30 kg/m², $n = 285$;
239 annualized percent change in body weight: no weight loss, $n = 374$; >0 – $<5\%$ loss, $n = 165$;
240 $\geq 5\%$ loss, $n = 84$).

241 In pirfenidone-treated patients, the proportion of patients with a relative decline of $\geq 10\%$ in
242 percent predicted FVC or death up to 1 year post-randomization, and annualized change in
243 percent predicted FVC, percent predicted DLco, and 6MWD, were generally similar across
244 subgroups stratified by baseline BMI (see Table E3 in the online supplementary material).
245 Estimated all-cause hospitalization and mortality rates, and the proportion of patients who
246 experienced an SAE up to 1 year post-randomization, were also similar across subgroups

247 stratified by baseline BMI. However, patients with baseline BMI $<25 \text{ kg/m}^2$ experienced an
248 improvement in SGRQ total score, whereas patients with baseline BMI 25 kg/m^2 – $<30 \text{ kg/m}^2$
249 or baseline BMI $\geq 30 \text{ kg/m}^2$ experienced a worsening of SGRQ total score (see Table E3 in the
250 online supplementary material).

251 When stratified by annualized percent change in body weight, patients with no weight loss
252 experienced a lower rate of $\geq 10\%$ absolute or relative decline in percent predicted FVC or
253 death up to 1 year post-randomization compared with those who experienced a $\geq 5\%$ loss
254 (see Table E4 [model estimates] in the online supplementary material). When compared
255 with patients who experienced a $\geq 5\%$ loss, patients who experienced no weight loss had
256 reduced estimated worsening of percent predicted FVC, percent predicted DLco, 6MWD,
257 and SGRQ total score, and lower estimated rates of any all-cause hospitalization and any
258 SAE up to 1 year post-randomization. Patients who experienced no weight loss also had
259 numerically lower rates of all-cause mortality compared with those who experienced a $\geq 5\%$
260 loss (see Table E4 in the online supplementary material).

261 In time-to-event analyses, patients who experienced no weight loss had a lower risk of
262 experiencing a first incidence of all-cause hospitalization over 1 year compared with patients
263 who experienced a >0 – $<5\%$ loss or a $\geq 5\%$ loss ($p < 0.01$ and $p < 0.001$, respectively). Patients
264 who experienced no weight loss also had a significantly lower risk of experiencing all-cause
265 mortality over 1 year compared with patients who experienced a $\geq 5\%$ loss ($p < 0.05$).

266 **Discussion**

267 The results of the pooled post hoc analysis including patients from the placebo arms of
268 ASCEND and CAPACITY, and all patients from INSPIRE and RIFF (Cohort A), suggest that

269 patients with IPF who have baseline BMI $<25 \text{ kg/m}^2$ or who lose weight in 1 year may
270 experience worse clinical outcomes, up to 1 year compared with those with baseline BMI
271 $\geq 25 \text{ kg/m}^2$ or who experience no weight loss. No significant relationships were observed
272 between baseline BMI and the incidence of hospitalization, mortality, or SAEs; however, a
273 greater percentage of patients with weight loss experienced all-cause hospitalization versus
274 patients with no weight loss, and a greater percentage of patients with $\geq 5\%$ loss
275 experienced an SAE versus patients with no weight loss. Interestingly, in time-to-event
276 analyses, patients with no weight loss had a significantly lower risk of first incidence of all-
277 cause hospitalization and all-cause mortality up to 1 year post-randomization compared
278 with patients with weight loss, and results from the sensitivity analysis were consistent with
279 the hospitalization finding.

280 The results of the post hoc analysis including patients from the pirfenidone arms of ASCEND
281 and CAPACITY highlight that outcomes were similar across all subgroups stratified by
282 baseline BMI, with the exception of patients with baseline BMI $<25 \text{ kg/m}^2$, who experienced
283 an improvement in SGRQ total score, whereas patients with baseline BMI 25 kg/m^2 –
284 $<30 \text{ kg/m}^2$ or $\geq 30 \text{ kg/m}^2$ experienced a worsening of SGRQ total score. Patients in this
285 analysis with $\geq 5\%$ weight loss experienced worse clinical outcomes up to 1 year, compared
286 with patients with no weight loss. Furthermore, patients in this analysis who experienced no
287 weight loss had lower estimated rates of all-cause hospitalization and SAEs up to 1 year
288 post-randomization versus patients who experienced a $\geq 5\%$ loss, and had numerically lower
289 rates of all-cause mortality versus those who experienced a $\geq 5\%$ loss. As each analysis
290 population was comprised of different patient populations from several clinical trials, and
291 the size of the placebo population was increased by combining all patients from INSPIRE and
292 RIFF (Cohort A) with the placebo patients from ASCEND and CAPACITY, it is not possible to

293 directly compare outcomes between analysis populations. However, generally, patients
294 included in the placebo analysis population experienced worse outcomes compared with
295 pirfenidone-treated patients across baseline BMI and annualized weight-change subgroups,
296 with the exception of percent predicted DLco.

297 Our findings expand on results from other studies that have assessed the relationship
298 between BMI, weight loss, and outcomes in IPF [12-14, 25-27]. A single-center cohort study
299 that used bioelectrical impedance analysis found that BMI was independently associated
300 with mortality in IPF [27], and data from a US registry identified a relationship between
301 longitudinal reductions in BMI and risk of mortality [12]. A further study highlighted that
302 weight loss and BMI are associated with increased risk of mortality in patients with IPF, with
303 weight loss being regarded as a longitudinal marker of disease progression [14]. In a
304 multicenter cohort study of patients from the UK and Japan, patients who experienced >5%
305 weight loss experienced increased FVC decline over 1 year and had worse survival rates
306 versus patients with no weight loss, similar to the results observed in our post hoc analysis
307 [13]. Additionally, in line with the results from our post hoc analysis and the results from a
308 real-world registry [26], post hoc analyses of data from the INPULSIS trials of nintedanib
309 identified that rates of adverse events (AEs) and mortality were similar between BMI
310 subgroups [25]. Moreover, the rates of AEs over 52 weeks were also numerically greater in
311 placebo-treated patients with >5% weight loss versus ≤5% weight loss [25], similar to the
312 results of our post hoc analysis. However, in contrast to our findings and the findings from a
313 real-world registry [26], the rate of mortality in the INPULSIS studies was numerically lower
314 in placebo-treated patients with >5% weight loss versus ≤5% weight loss [25].

315 Furthermore, post hoc analyses of data from the INPULSIS trials identified that the rate of
316 FVC decline (mL/year) and worsening of SGRQ scores over 52 weeks were numerically
317 greater in placebo-treated patients with BMI <25 mg/kg² versus patients with BMI
318 ≥25 mg/kg² [25]. Moreover, in the INPULSIS studies, the rate of FVC decline (mL/year) and
319 worsening of SGRQ scores over 52 weeks were numerically greater in placebo-treated
320 patients with >5% weight loss versus ≤5% weight loss [25], similar to the results of our post
321 hoc analysis. The results from our post hoc analysis are generally in line with the results
322 from previous studies and suggest that a BMI of <25 kg/m² and weight loss may be
323 associated with worse clinical outcomes in patients with IPF.

324 Reduced appetite and weight loss are frequently reported as AEs in patients with IPF,
325 including those treated with placebo. Post hoc analyses of data from the INPULSIS trials of
326 nintedanib revealed that in patients in the placebo arm, the rate of decreased appetite was
327 greater in patients who experienced a >5% weight loss compared with patients with a ≤5%
328 weight loss [25]. However, it is difficult to generate an estimate of treatment effect on
329 clinical outcomes in groups of patients stratified by weight loss. As weight-loss subgroups
330 are defined by measurements taken after treatment initiation rather than at baseline, these
331 measurements may be an intermediate result of treatment initiation, and may lead to a
332 biased estimate of treatment effect on other clinical outcomes. Furthermore, while
333 treatment with antifibrotics can lead to weight-loss-related AEs and associated poor
334 outcomes, patients may also experience a reduction in lung-function decline irrespective of
335 weight loss, as shown in a post hoc analysis of the INPULSIS study [25].

336 It is important to look beyond appetite and weight loss and consider the complexities of
337 disease-associated malnutrition. Reduced appetite may not necessarily lead to malnutrition

338 if the patient does not reduce their food intake as a result; likewise, even when appetite is
339 not reduced, patients may report decreased food intake due to factors such as nausea from
340 use of specific medications [28]. Furthermore, in a primary care setting, reduced food intake
341 (regardless of cause) is thought to be correlated with the diagnosis of malnutrition, and can
342 easily be measured using the Simple Evaluation of Food Intake (SEFI®; K'noë Groupe GET, le
343 Kremlin Bicêtre, France) [29]. Additionally, as the disease progresses, symptoms such as
344 breathlessness and cough worsen [30, 31], and subsequently eating becomes more difficult
345 for patients [32]. IPF itself may also be associated with changes in metabolism regulation
346 (e.g., autophagy, oxidative stress, mitochondrial dysfunction, and death-receptor-induced
347 pathways, including tumor necrosis factor [TNF]-alpha), which may also have an effect on
348 muscle mass and function, general health status, IPF severity, and further weight loss [33-
349 36]. Levels of profibrotic mediators such as TNF-alpha are known to be increased in the
350 fibrotic lung [36], and the role of these in influencing food intake is not clear.

351 From a broader perspective, it is clear that body weight and percentage loss should be
352 measured regularly, and that clinicians should be alert to the criteria and risk factors for
353 malnutrition. In patients with IPF, prospective studies involving repeated body composition
354 measurements are needed in order to better understand the ways in which weight loss
355 impacts on outcomes. Future studies in IPF should incorporate validated methods to assess
356 body composition and muscle function to better understand the relationship between
357 weight loss/BMI and poor outcomes. Low baseline BMI has been suggested as a predictor of
358 poor antifibrotic tolerance [37]; however, this was not assessed in our post hoc analysis.
359 Therefore, it may be of value for future studies to also investigate BMI-adjusted doses of
360 antifibrotics in patients with IPF. Furthermore, it may also be important for future studies to

361 consider the association between pleuroparenchymal fibroelastosis (PPFE), which can often
362 be misdiagnosed as IPF or other forms of ILD, and weight loss [38].

363 Limitations of this analysis include that this was a post hoc analysis from studies that were
364 not designed to assess the effects of BMI or weight loss on outcomes, nor was the type I
365 error controlled for positive findings—prospective datasets are required to evaluate
366 whether weight loss is independently associated with clinical outcomes. It is also important
367 to note that the strict inclusion and exclusion criteria of the original clinical trials may have
368 resulted in a patient population that is not entirely representative of clinical practice.

369 Furthermore, although the annualized percentage weight change was similar between the
370 active and placebo arms of INSPIRE and RIFF (Cohort A), the drug effects of IFN- γ -1b and
371 lebrikizumab may also have played a role in body weight, appetite, and related endpoints
372 [20, 21]; however, the occurrence of gastrointestinal AEs such as diarrhea was similar across
373 the placebo and treatment arms of INSPIRE and RIFF (Cohort A) [20, 21]. Given that
374 antifibrotic treatment can result in weight loss in patients with IPF [39], it is possible that
375 pirfenidone may have influenced body weight in patients included in the pirfenidone
376 analysis, thereby impacting the measured outcomes [18, 19]. As this study only looked at
377 outcomes over 1 year, further research is required to assess the impact of weight loss on
378 outcomes over a longer time period.

379 A further limitation of this analysis is that because annualized weight loss was measured
380 over the same 1-year period as the outcomes investigated and took into account all data
381 available during this time period, it is not possible to determine if IPF is causative of weight
382 loss and/or if other factors, such as SAEs, hospitalization, or declining functional status, need
383 to be considered. Therefore, although factors associated with weight loss in IPF have been

384 identified previously [39], further studies that assess weight loss prior to the outcome event
385 are required. Additionally, because BMI and annualized weight loss were not analyzed as
386 continuous variables, it is not possible to comment on whether a linear relationship exists
387 between these predictors and the outcomes in this analysis. Categories of BMI were used,
388 rather than BMI as a continuous variable, as these correspond to the definitions of normal
389 weight, overweight, and obese. Moreover, it is thought that weight-loss categories may be
390 more applicable in the clinic compared with weight loss as a continuous variable. Another
391 limitation is that factors that may be associated with worse outcomes in patients with IPF,
392 such as the presence of anxiety and depression, were unmeasured in this analysis. As this
393 analysis only considered the relationship between outcomes and baseline BMI and
394 annualized weight loss, we cannot comment on any causal relationship between disease-
395 associated malnutrition and outcomes.

396 **Conclusions**

397 The results of this pooled post hoc analysis suggest that placebo patients with a baseline
398 BMI $<25 \text{ kg/m}^2$ or who lose >0 – $<5\%$ or $\geq 5\%$ of their body weight in 1 year may experience
399 worse clinical outcomes up to 1 year compared with those with baseline BMI 25 kg/m^2 –
400 $<30 \text{ kg/m}^2$ (overweight) or $\geq 30 \text{ kg/m}^2$ (obese), or who experience no weight loss.
401 Additionally, pirfenidone-treated patients who lose $\geq 5\%$ of their body weight in 1 year may
402 experience worse clinical outcomes compared with those who experience no weight loss.
403 The clinical relevance of these findings warrants further research to increase the
404 understanding of the relationship between body weight and individual clinical outcomes,
405 and the relative importance of individual factors on overall prognosis. Future trials should

406 aim to demonstrate whether dedicated management to prevent malnutrition and weight
407 loss can improve clinical outcomes in patients with IPF.

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412 **Statement of Ethics**

413 No prospective data were collected during this post hoc analysis, therefore ethical approval
414 was not required; however, during the original trials, all patients provided informed consent
415 and the protocols were approved by the institutional review boards or ethics committees at
416 each participating center.

417 **Conflict of Interest Statement**

418 S.J. has received fees, funding, or reimbursement for participation at meetings from
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445 **Author Contributions**

446 All authors were involved in the conception and/or design of the work and interpretation of
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448 final draft. The analyses presented in this manuscript were performed by M.Y. and E.M. All
449 authors vouch for the accuracy of the content included in the final manuscript.

450 **Data Sharing**

451 Qualified researchers may request access to individual patient-level data through the clinical
452 study data request platform (<https://vivli.org/>). Further details on Roche's criteria for
453 eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further
454 details on Roche's Global Policy on the Sharing of Clinical Information and how to request
455 access to related clinical study documents, see here
456 ([https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)
457 [_trials/our_commitment_to_data_sharing.htm](https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)).

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591

592 **Figure Legends**

593 **Fig. 1.** Proportion of patients from the placebo arms of ASCEND and CAPACITY and all
594 patients from INSPIRE and RIFF (Cohort A) with an absolute or relative decline of $\geq 10\%$ in
595 percent predicted FVC or death up to 1 year post-randomization, stratified by baseline BMI
596 category **(a)** and annualized percent change in body-weight category **(b)**.

597 BMI, body mass index; FVC, forced vital capacity.

598 **Fig. 2.** Time-to-event analysis of first all-cause hospitalization up to 1 year post-
599 randomization, stratified by annualized percent change in body-weight categories, in
600 patients from the placebo arms of ASCEND and CAPACITY and all patients from INSPIRE and
601 RIFF (Cohort A).

602 **Fig. 3.** Time-to-event analysis of all-cause mortality up to 1 year post-randomization,
603 stratified by annualized percent change in body-weight categories, in patients from the
604 placebo arms of ASCEND and CAPACITY, and all patients from INSPIRE and RIFF (Cohort A).

605 **Table Legends**

606 **Table 1.** Demographic and baseline characteristics by baseline BMI category

607 **Table 2.** Clinical outcomes at 1 year, stratified by baseline BMI category, in patients from the
608 placebo arms of ASCEND and CAPACITY and all patients from INSPIRE and RIFF (Cohort A)

609 **Table 3.** Clinical outcomes at 1 year, stratified by annualized percent change in body weight,
610 in patients from the placebo arms of ASCEND and CAPACITY and all patients from INSPIRE
611 and RIFF (Cohort A)

612

613 **Table 1.** Demographic and baseline characteristics by baseline BMI category

Demographic/characteristic*	Baseline BMI		
	<25 kg/m ²	25–<30 kg/m ²	≥30 kg/m ²
	<i>n</i> = 227	<i>n</i> = 703	<i>n</i> = 674
Age at randomization, years	68.3 (7.5)	67.9 (7.6)	65.2 (7.6)
Male, <i>n</i> (%)	142 (62.6)	552 (78.5)	484 (71.8)
White, <i>n</i> (%)	185 (81.5)	620 (88.8)	612 (91.1)
Weight at baseline, kg			
Male	70.5 (7.6)	83.4 (8.7)	102.5 (13.3)
Female	59.3 (6.4)	69.8 (7.3)	89.0 (12.7)
BMI at baseline			
Male	23.5 (1.2)	27.7 (1.4)	33.6 (3.2)
Female	22.9 (1.7)	27.6 (1.4)	34.9 (4.5)
HRCT diagnosis group at baseline, <i>n</i> (%)			
Definite UIP	212 (93.4)	643 (91.5)	590 (87.7)
Probable/possible UIP	15 (6.6)	60 (8.5)	83 (12.3)
Uncertain with UIP	0 (0)	0 (0)	0 (0)

Time from IPF diagnosis to randomization, years	1.4 (1.2)	1.2 (1.1)	1.1 (1.0)
Percent predicted FVC	73.3 (13.3)	72.1 (13.5)	72.1 (13.0)
FEV ₁ /FVC ratio	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
Percent predicted DLco	45.3 (10.2)	45.5 (10.9)	47.2 (9.6)
Baseline 6MWD, m	434.5 (111.4)	414.2 (109.8)	389.5 (105.7)
Baseline SGRQ score [†]	38.8 (17.6) [†]	37.5 (18.0) [‡]	43.9 (17.3) [§]
Supplemental oxygen use at baseline, <i>n</i> (%)	20 (8.8)	106 (15.1)	160 (23.8)
Smoking status at screening, <i>n</i> (%)			
Current	7 (3.1)	21 (3.0)	25 (3.7)
History	131 (57.7)	442 (62.9)	475 (70.5)
Never	89 (39.2)	240 (34.1)	174 (25.8)

614 *Data are presented as mean (SD) unless specified otherwise. [†]*n* = 165. [‡]*n* = 537. [§]*n* = 526.
615 6MWD, 6-min walk distance; BMI, body mass index; DLco, carbon monoxide diffusing
616 capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-
617 resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SD, standard
618 deviation; SGRQ, St. George's Respiratory Questionnaire; UIP, usual interstitial pneumonia.

619 **Table 2.** Clinical outcomes at 1 year, stratified by baseline BMI category, in patients from the placebo arms of ASCEND and CAPACITY and all
 620 patients from INSPIRE and RIFF (Cohort A)

Outcome	Baseline BMI		
	<25 kg/m ² <i>n</i> = 227	25–<30 kg/m ² <i>n</i> = 703	≥30 kg/m ² <i>n</i> = 674
Annualized change from baseline in percent predicted FVC, %*			
Observed, <i>n</i>	225	697	669
Estimate (95% CI)	-6.6 (-7.5, -5.8)	-5.4 (-5.9, -5.0)	-4.1 (-4.6, -3.7)
Difference (95% CI) [†]		1.2 (0.2, 2.2)	2.5 (1.5, 3.5)
Annualized change from baseline in percent predicted DLco, %*,‡			
Observed, <i>n</i>	180	575	559
Estimate (95% CI)	-5.5 (-6.4, -4.5)	-5.0 (-5.5, -4.5)	-4.0 (-4.5, -3.5)
Difference (95% CI) [†]		0.4 (-0.6, 1.5)	1.5 (0.4, 2.5)

Annualized change from baseline in 6MWD, m*			
Observed, <i>n</i>	225	698	669
Estimate (95% CI)	-42.8 (-53.8, -31.9)	-32.5 (-38.6, -26.4)	-30.5 (-36.7, -24.3)
Difference (95% CI) [†]		10.3 (-2.2, 22.8)	12.3 (-0.2, 24.9)
Annualized change from baseline in SGRQ total score*,[‡]			
Observed, <i>n</i>	178	575	558
Estimate (95% CI)	5.8 (4.3, 7.2)	5.2 (4.4, 6.0)	3.1 (2.3, 4.0)
Difference (95% CI) [†]		-0.6 (-2.2, 1.1)	-2.6 (-4.3, -1.0)
Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	225	697	669
Estimate (95% CI)	11.0 (5.8, 16.2)	10.1 (6.1, 14.1)	7.0 (3.2, 10.8)
Difference (95% CI) [†]		-0.9 (-5.7, 3.8)	-4.0 (-8.8, 0.7)

Relative decline in percent predicted FVC \geq10% or death up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	224	697	669
Estimate (95% CI)	19.0 (12.7, 25.4)	15.1 (10.4, 19.8)	9.4 (4.8, 14.1)
Difference (95% CI) [†]		-3.9 (-9.8, 1.9)	-9.6 (-15.4, -3.8)
Any all-cause hospitalization up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	225	698	669
Estimate (95% CI)	23.8 (16.6, 30.9)	25.4 (19.7, 31.1)	24.5 (19.2, 29.9)
Difference (95% CI) [†]		1.7 (-4.3, 7.6)	0.8 (-5.4, 7.0)
All-cause mortality up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	225	698	669
Estimate (95% CI)	6.7 (2.0, 11.5)	7.9 (4.3, 11.6)	6.2 (2.8, 9.6)
Difference (95% CI) [†]		1.2 (-2.5, 4.9)	-0.5 (-4.2, 3.2)

Any treatment-emergent SAEs up to 1 year post-randomization, %[§]

Observed, <i>n</i>	225	698	669
Estimate (95% CI)	26.7 (19.2, 34.2)	30.6 (24.5, 36.7)	27.0 (21.4, 32.6)
Difference (95% CI) [†]		3.9 (-2.5, 10.3)	0.3 (-6.3, 6.9)

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

628 **Table 3.** Clinical outcomes at 1 year, stratified by annualized percent change in body weight, in patients from the placebo arms of ASCEND and
 629 CAPACITY and all patients from INSPIRE and RIFF (Cohort A)

Outcome	Annualized percent change in body weight		
	No weight loss <i>n</i> = 849	>0–<5% loss <i>n</i> = 610	≥5% loss <i>n</i> = 99
Annualized change from baseline in percent predicted FVC, %*			
Observed, <i>n</i>	846	600	99
Estimate (95% CI)	-4.2 (-4.7, -3.8)	-5.5 (-6.0, -5.0)	-9.5 (-10.7, -8.2)
Difference (95% CI) [†]		-1.3 (-2.0, -0.7)	-5.2 (-6.6, -3.9)
Annualized change from baseline in percent predicted DLco, %*,‡			
Observed, <i>n</i>	706	496	67
Estimate (95% CI)	-4.1 (-4.6, -3.7)	-5.2 (-5.7, -4.6)	-6.9 (-8.5, -5.3)
Difference (95% CI) [†]		-1.0 (-1.7, -0.3)	-2.8 (-4.4, -1.1)

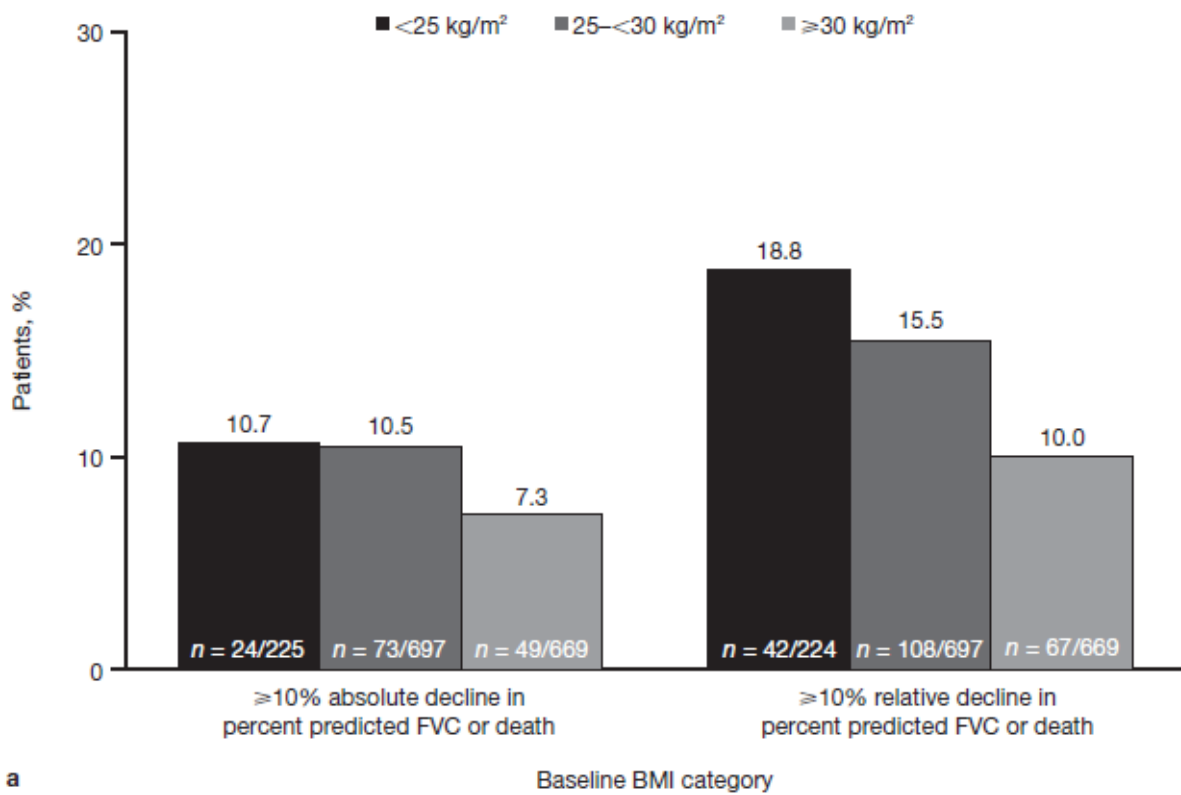
Annualized change from baseline in 6MWD, m*			
Observed, <i>n</i>	847	600	99
Estimate (95% CI)	-25.6 (-31.0, -20.3)	-37.2 (-43.7, -30.7)	-81.1 (-98.6, -63.5)
Difference (95% CI) [†]		-11.6 (-20.0, -3.2)	-55.5 (-73.8, -37.1)
Annualized change from baseline in SGRQ total score*,[‡]			
Observed, <i>n</i>	706	494	67
Estimate (95% CI)	3.5 (2.8, 4.2)	5.0 (4.2, 5.9)	9.6 (7.2, 12.0)
Difference (95% CI) [†]		1.5 (0.4, 2.6)	6.1 (3.6, 8.6)
Absolute decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	846	600	99
Estimate (95% CI)	7.6 (3.8, 11.4)	12.2 (7.7, 16.8)	21.7 (13.1, 30.3)
Difference (95% CI) [†]		4.6 (1.4, 7.9)	14.1 (5.7, 22.5)

Relative decline in percent predicted FVC \geq10% death up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	845	600	99
Estimate (95% CI)	9.5 (5.0, 14.1)	16.8 (11.6, 22.0)	38.0 (27.7, 48.3)
Difference (95% CI) [†]		7.3 (3.6, 11.0)	28.4 (18.5, 38.3)
Any all-cause hospitalization up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	847	600	99
Estimate (95% CI)	20.4 (15.2, 25.7)	26.2 (20.5, 32.0)	40.6 (30.3, 50.9)
Difference (95% CI) [†]		5.8 (1.8, 9.9)	20.2 (10.3, 30.0)
All-cause mortality up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	847	600	99
Estimate (95% CI)	7.6 (3.7, 11.5)	10.6 (5.6, 15.6)	11.7 (3.7, 19.7)
Difference (95% CI) [†]		3.0 (-0.6, 6.7)	4.1 (-3.4, 11.6)

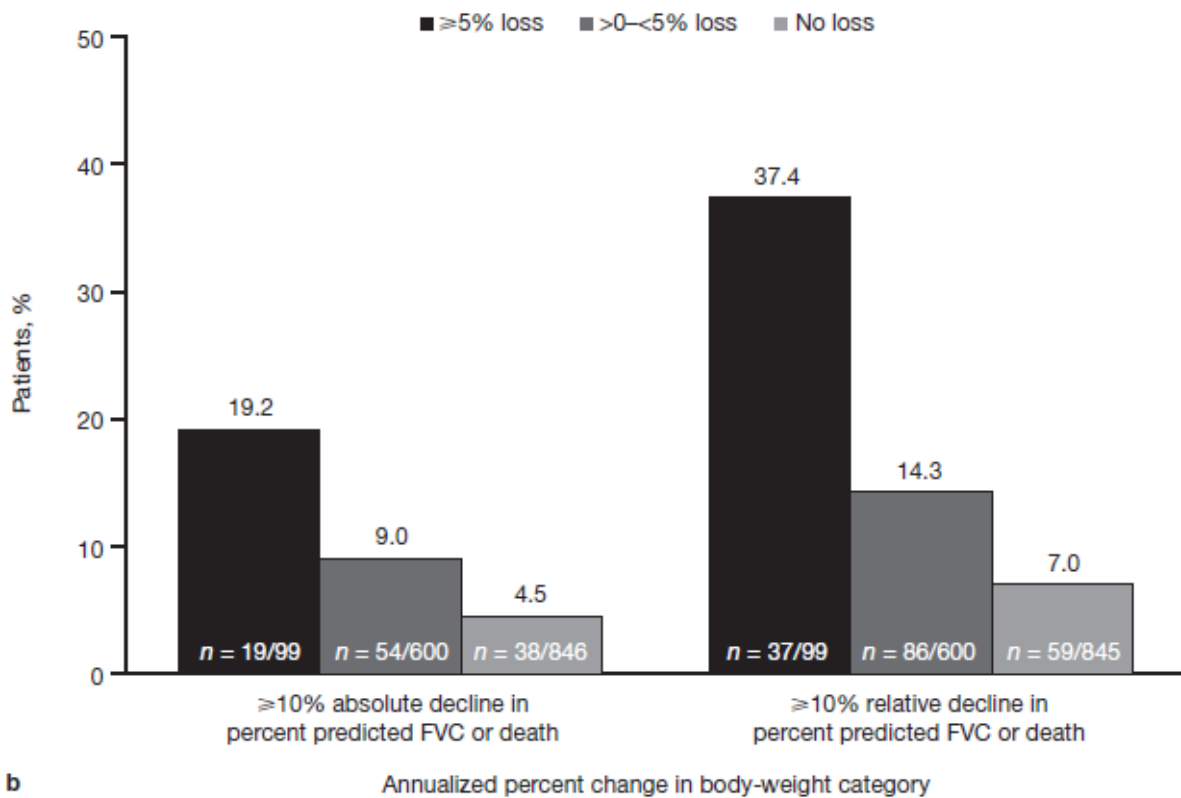
Any treatment-emergent SAEs up to 1 year post-randomization, %[§]			
Observed, <i>n</i>	847	600	99
Estimate (95% CI)	23.3 (17.8, 28.8)	27.3 (21.3, 33.2)	52.0 (41.3, 62.7)
Difference (95% CI) [†]		4.0 (-0.3, 8.2)	28.7 (18.4, 39.0)

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

637 Fig. 1.



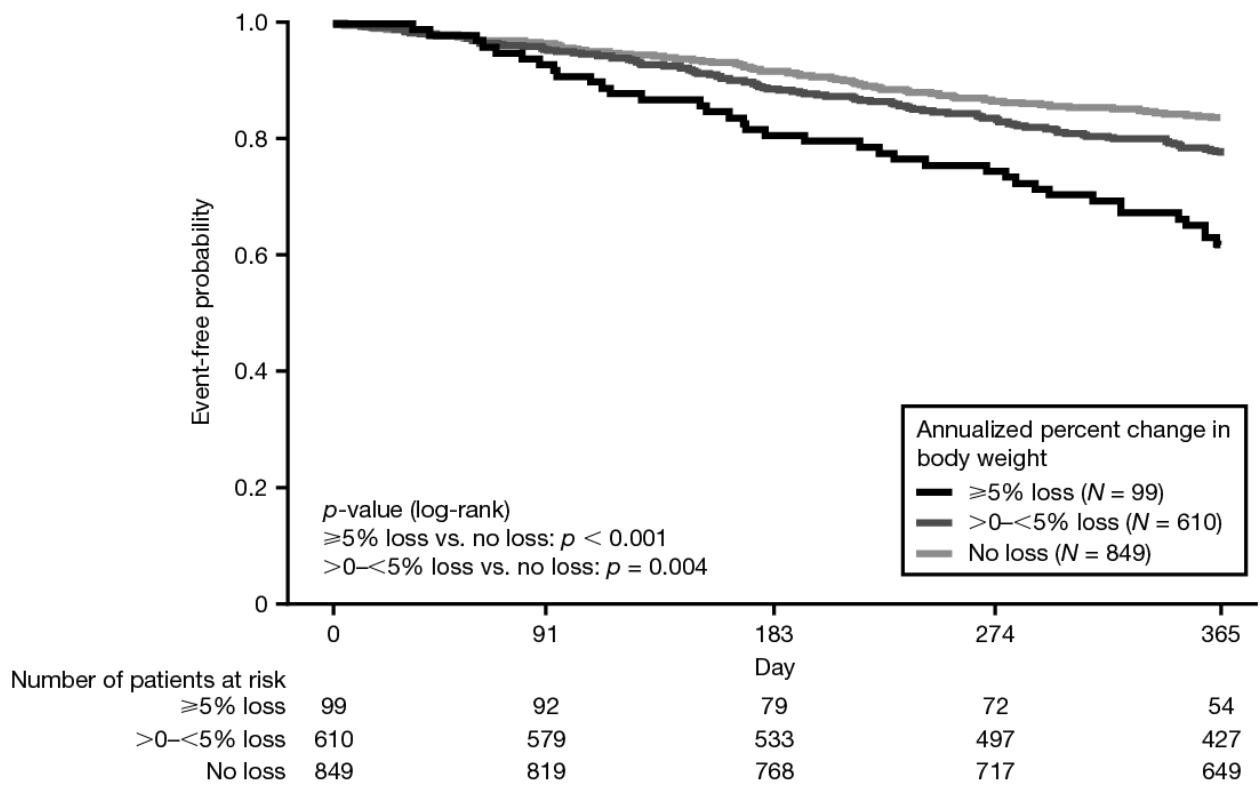
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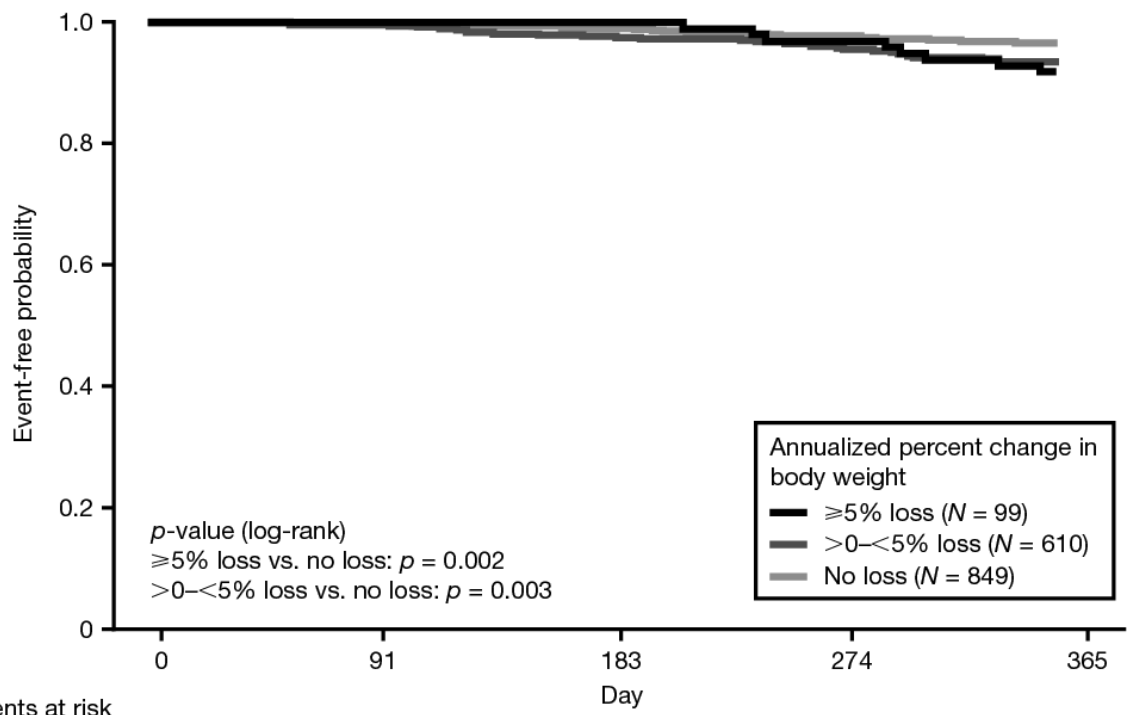
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639 Fig. 2.



640

641 **Fig. 3.**



Number of patients at risk		0	91	183	274	365
$\geq 5\%$ loss		99	99	97	94	70
$>0 - <5\%$ loss		610	604	585	570	492
No loss		849	847	833	813	729

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