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

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Key words: Body composition; Interstitial lung disease; Idiopathic pulmonary fibrosis; Body mass index

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Short title: Clinical outcomes in IPF by BMI and weight loss (47/80 characters)

Number of tables: 3 tables (4 supplementary tables)

Number of figures: 3 figures (1 supplementary figure)

Word count: 4492 words (no limit specified)

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Abstract [248/250 words]

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

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

Methods: Data were included from placebo patients enrolled in ASCEND (NCT01366209) and CAPACITY (NCT00287716, NCT00287729), and all patients in INSPIRE (NCT00075998) and RIFF Cohort A (NCT01872689). An additional analysis included data from pirfenidone-treated patients. Outcomes (annualized change in percent predicted forced vital capacity [%FVC], percent predicted carbon monoxide diffusing capacity, 6-min walk distance, St. George's Respiratory Questionnaire total score, hospitalization, mortality, and serious adverse events) were analyzed by baseline BMI (<25 kg/m^2, 25 kg/m^2–<30 kg/m^2, or ≥30 kg/m^2) and annualized percent change in body weight (no loss, >0–<5% loss, or ≥5% loss).

Results: Placebo-treated patients with baseline BMI <25 kg/m^2 or annualized weight loss may experience worse outcomes, versus those with baseline BMI ≥25 kg/m^2 or no weight loss. The proportion of placebo-treated patients who experienced a relative decline of ≥10% in %FVC or death up to 1 year post-randomization was highest in patients with baseline BMI <25 kg/m^2. Pirfenidone-treated patients with annualized weight loss ≥5% may also experience worse outcomes versus those with no weight loss.

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Conclusions: Patients with baseline BMI <25 kg/m^2 or annualized weight loss of >0–<5% or ≥5% may experience worse outcomes over 1 year versus those with baseline BMI ≥25 kg/m^2 or no weight loss.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease that is associated with a survival rate lower than that reported for many cancers [1-4]. Patients with IPF experience a progressive decline in lung function and exercise capacity, ending in respiratory failure and death; however, the disease course can be variable [1, 2, 5, 6]. Identification of potential indicators of disease severity and prognosis in patients with IPF, including those receiving antifibrotic therapy, are therefore active areas of interest [7, 8].

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

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

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

Materials and Methods

Patient Population

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

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

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

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Predictors

In our post hoc analyses of clinical outcomes at 1 year, patients were stratified by baseline BMI and annualized percent change in body weight. Baseline BMI was categorized based on World Health Organization (WHO) standards, with some categories combined to increase patient numbers per group, as follows: <25 kg/m^2 (WHO normal weight or underweight), 25 kg/m^2–<30 kg/m^2 (WHO pre-obesity), or ≥30 kg/m^2 (WHO obesity, Class I–III) [22]. Annualized percent change in body weight was categorized based on the United States Food and Drug Administration (FDA) Guidance for Developing Products for Weight Management, which recommends an annualized weight loss of ≥5% for use as a primary endpoint [23]. We adapted this guidance and categorized annualized percent change in body weight as follows: no loss, >0–<5% loss, or ≥5% loss. Weight measurements were collected for patients at site visits during each trial.

Outcomes

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

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

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Statistical Analyses

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

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

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

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

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

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

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

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

Results

Patients

In total, 1604 patients from the placebo arms of ASCEND and CAPACITY and both treatment arms of INSPIRE and RIFF (Cohort A) were included in the main analysis population, with a mean (standard deviation [SD]) baseline BMI of 29.68 (4.70) kg/m^2 (baseline BMI: <25 kg/m^2, *n* = 227; 25 kg/m^2–<30 kg/m^2, *n* = 703; ≥30 kg/m^2, *n* = 674). Other than weight and BMI, there were some differences between baseline characteristics when analyzed by baseline BMI, including a higher proportion of males in the 25 kg/m^2–<30 kg/m^2 category compared with the <25 kg/m^2 category and a higher proportion of never-smokers in the <25 kg/m^2 category compared with the ≥30 kg/m^2 category. The proportion of patients using supplemental oxygen increased, while 6MWD decreased, with increasing BMI category (Table 1).

A total of 623 patients from the pirfenidone arms of ASCEND and CAPACITY were included in the additional analysis population and had a mean (SD) baseline BMI of 29.87 (4.43) kg/m^2 (baseline BMI: <25 kg/m^2, *n* = 73; 25 kg/m^2–<30 kg/m^2, *n* = 265; ≥30 kg/m^2, *n* = 285). There were differences between baseline characteristics when analyzed by baseline BMI, such as a higher proportion of males in the 25 kg/m^2–<30 kg/m^2 and ≥30 kg/m^2 categories compared with the <25 kg/m^2 category, a higher proportion of never-smokers in the <25 kg/m^2 category compared with the 25 kg/m^2–<30 kg/m^2 and ≥30 kg/m^2 categories, and a reduced 6MWD in the ≥30 kg/m^2 category compared with the <25 kg/m^2 and 25 kg/m^2–<30 kg/m^2

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

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

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

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

Patients with baseline BMI <25 kg/m^2 had a greater estimated annualized decline in percent predicted FVC than patients with baseline BMI 25 kg/m^2–<30 kg/m^2 or baseline BMI ≥30 kg/m^2 (Table 2). Patients with baseline BMI <25 kg/m^2 also had greater estimated annualized worsening of percent predicted DLco and SGRQ total score than patients with baseline BMI ≥30 kg/m^2 (Table 2). Furthermore, estimated annualized 6MWD decline was numerically greater in patients with baseline BMI <25 kg/m^2 versus 25 kg/m^2–<30 kg/m^2 and ≥30 kg/m^2.

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

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

In total, 1558 patients from the placebo arms of ASCEND and CAPACITY and both treatment arms of INSPIRE and RIFF (Cohort A) were included in this analysis (no weight loss, *n* = 849; >0–<5% loss, *n* = 610; ≥5% loss, *n* = 99 [21 (21.2%) patients who experienced ≥5% loss also had a baseline BMI <25 kg/m^2]).

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

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

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

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

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

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

In total, 623 pirfenidone-treated patients from ASCEND and CAPACITY were included in this analysis (baseline BMI: <25 kg/m^2, *n* = 73; 25 kg/m^2–<30 kg/m^2, *n* = 265; ≥30 kg/m^2, *n* = 285; annualized percent change in body weight: no weight loss, *n* = 374; >0–<5% loss, *n* = 165; ≥5% loss, *n* = 84).

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

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stratified by baseline BMI. However, patients with baseline BMI <25 kg/m^2 experienced an improvement in SGRQ total score, whereas patients with baseline BMI 25 kg/m^2–<30 kg/m^2 or baseline BMI ≥30 kg/m^2 experienced a worsening of SGRQ total score (see Table E3 in the online supplementary material).

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

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

Discussion

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

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

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

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

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

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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/kg^2 versus patients with BMI
318 ≥25 mg/kg^2 [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/m^2 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

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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

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

Limitations of this analysis include that this was a post hoc analysis from studies that were not designed to assess the effects of BMI or weight loss on outcomes, nor was the type I error controlled for positive findings—prospective datasets are required to evaluate whether weight loss is independently associated with clinical outcomes. It is also important to note that the strict inclusion and exclusion criteria of the original clinical trials may have resulted in a patient population that is not entirely representative of clinical practice. Furthermore, although the annualized percentage weight change was similar between the active and placebo arms of INSPIRE and RIFF (Cohort A), the drug effects of IFN-γ-1b and lebrikizumab may also have played a role in body weight, appetite, and related endpoints [20, 21]; however, the occurrence of gastrointestinal AEs such as diarrhea was similar across the placebo and treatment arms of INSPIRE and RIFF (Cohort A) [20, 21]. Given that antifibrotic treatment can result in weight loss in patients with IPF [39], it is possible that pirfenidone may have influenced body weight in patients included in the pirfenidone analysis, thereby impacting the measured outcomes [18, 19]. As this study only looked at outcomes over 1 year, further research is required to assess the impact of weight loss on outcomes over a longer time period.

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

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

Conclusions

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

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

Acknowledgments

Medical writing support was provided by Ceilidh McConnachie, MSc, of CMC AFFINITY, McCann Health Medical Communications, funded by Genentech, Inc. and F. Hoffmann-La Roche, Ltd.

Statement of Ethics

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

Conflict of Interest Statement

S.J. has received fees, funding, or reimbursement for participation at meetings from Actelion, AIRB, AstraZeneca, Bellerophon Therapeutics, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, F. Hoffmann-La Roche, Ltd., Galecto Biotech, Gilead, GlaxoSmithKline, LVL, Mundipharma, Novartis, Pfizer, Pharm-Olam, Pliant Therapeutics, and Savara-Serendex.

B.C. has received personal fees and non-financial support from AstraZeneca; grants, personal fees, and non-financial support from Boehringer Ingelheim and F. Hoffmann-La Roche, Ltd.; grants and personal fees from Sanofi; and personal fees from Bristol-Myers Squibb outside the submitted work.

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R.T. has received royalties for designing the Simple Evaluation of Food Intake (SEFI®) tool (K'noë Groupe GET, le Kremlin Bicêtre, France), and consulting fees from F. Hoffmann-La Roche, Ltd.

M.L. has received fees, funding, or reimbursement for participation at meetings from AstraZeneca, Boehringer Ingelheim, Fresenius-Kabi, Guerbet, Roche SAS, and Siemens Healthcare.

L.V. has received funding for research projects from Boehringer Ingelheim.

M.Y. is an employee of Genentech, Inc. and a shareholder of F. Hoffmann-La Roche, Ltd.

E.M. retired from employment at Genentech, Inc. in December 2020 and is a shareholder of F. Hoffmann-La Roche, Ltd.

K.-U.K. is an employee and shareholder of F. Hoffmann-La Roche, Ltd.

V.C. reports personal fees and non-financial support from Actelion; grants, personal fees, and non-financial support from Boehringer Ingelheim; personal fees from AstraZeneca, Bayer/MSD, Celgene, Galapagos, Galecto, Novartis, Sanofi, and Shionogi; and personal fees and non-financial support from F. Hoffmann-La Roche, Ltd. and Promedior (now a fully owned subsidiary of F. Hoffmann-La Roche, Ltd.) outside the submitted work.

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Funding Sources

This analysis was sponsored by Genentech, Inc. and F. Hoffmann-La Roche, Ltd.

Author Contributions

All authors were involved in the conception and/or design of the work and interpretation of study results, contributed to the manuscript from the outset, and read and approved the final draft. The analyses presented in this manuscript were performed by M.Y. and E.M. All authors vouch for the accuracy of the content included in the final manuscript.

Data Sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (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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Figure Legends

Fig. 1. Proportion of patients from the placebo arms of ASCEND and CAPACITY and all patients from INSPIRE and RIFF (Cohort A) with an absolute or relative decline of ≥10% in percent predicted FVC or death up to 1 year post-randomization, stratified by baseline BMI category (**a**) and annualized percent change in body-weight category (**b**).
BMI, body mass index; FVC, forced vital capacity.

Fig. 2. Time-to-event analysis of first all-cause hospitalization up to 1 year post-randomization, 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).

Fig. 3. Time-to-event analysis of all-cause mortality up to 1 year post-randomization, 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).

Table Legends

Table 1. Demographic and baseline characteristics by baseline BMI category

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

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

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

Demographic/characteristic*	Baseline BMI		
	<25 kg/m²	**25–<30 kg/m²**	**≥30 kg/m²**
	***n* = 227**	***n* = 703**	***n* = 674**
Age at randomization, years	68.3 (7.5)	67.9 (7.6)	65.2 (7.6)
Male, *n* (%)	142 (62.6)	552 (78.5)	484 (71.8)
White, *n* (%)	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, *n* (%)			
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)

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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, *n* (%)	20 (8.8)	106 (15.1)	160 (23.8)
Smoking status at screening, *n* (%)			
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)

*Data are presented as mean (SD) unless specified otherwise. [†]*n* = 165. [‡]*n* = 537. [§]*n* = 526. 6MWD, 6-min walk distance; BMI, body mass index; DLco, carbon monoxide diffusing capacity; FEV_1, 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.

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

Outcome	Baseline BMI		
	<25 kg/m^2	**25–<30 kg/m^2**	**≥30 kg/m^2**
	***n* = 227**	***n* = 703**	***n* = 674**
Annualized change from baseline in percent predicted FVC, %*			
Observed, *n*	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, *n*	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)

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Annualized change from baseline in 6MWD, m*			
Observed, *n*	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, *n*	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, *n*	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)

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Relative decline in percent predicted FVC ≥10% or death up to 1 year post-randomization, %[§]			
Observed, *n*	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, *n*	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, *n*	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)

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

*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. 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.

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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	**>0–<5% loss**	**≥5% loss**
	***n* = 849**	***n* = 610**	***n* = 99**
Annualized change from baseline in percent predicted FVC, %*			
Observed, *n*	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, *n*	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)

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Annualized change from baseline in 6MWD, m*			
Observed, *n*	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, *n*	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, *n*	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)

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Relative decline in percent predicted FVC ≥10% death up to 1 year post-randomization, %[§]			
Observed, *n*	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, *n*	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, *n*	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)

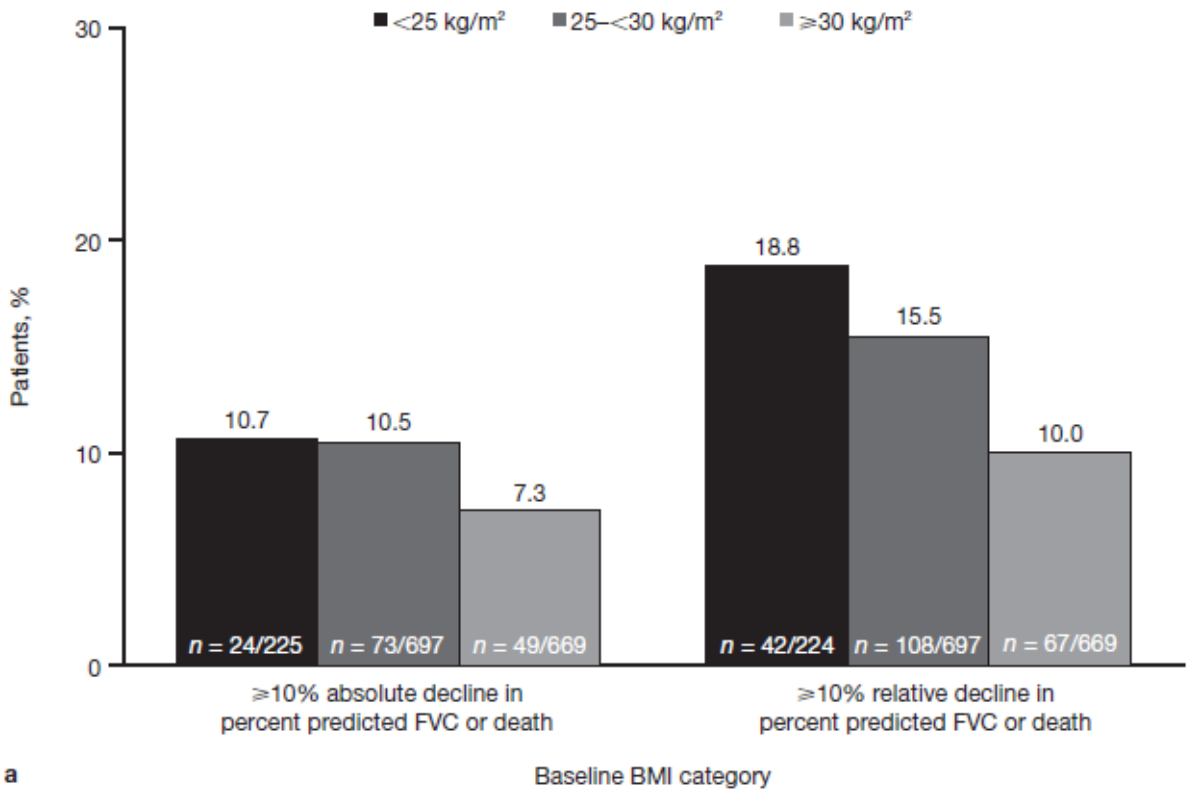
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Any treatment-emergent SAEs up to 1 year post-randomization, %[§]			
Observed, *n*	847	600	99
Estimate (95% CI)	23.3 (17.8, 28.8)	27.3 (21.3, 33.2)	52.0 (41.3, 62.7)
Difference (95% CI)[†]		4.0 (-0.3, 8.2)	28.7 (18.4, 39.0)

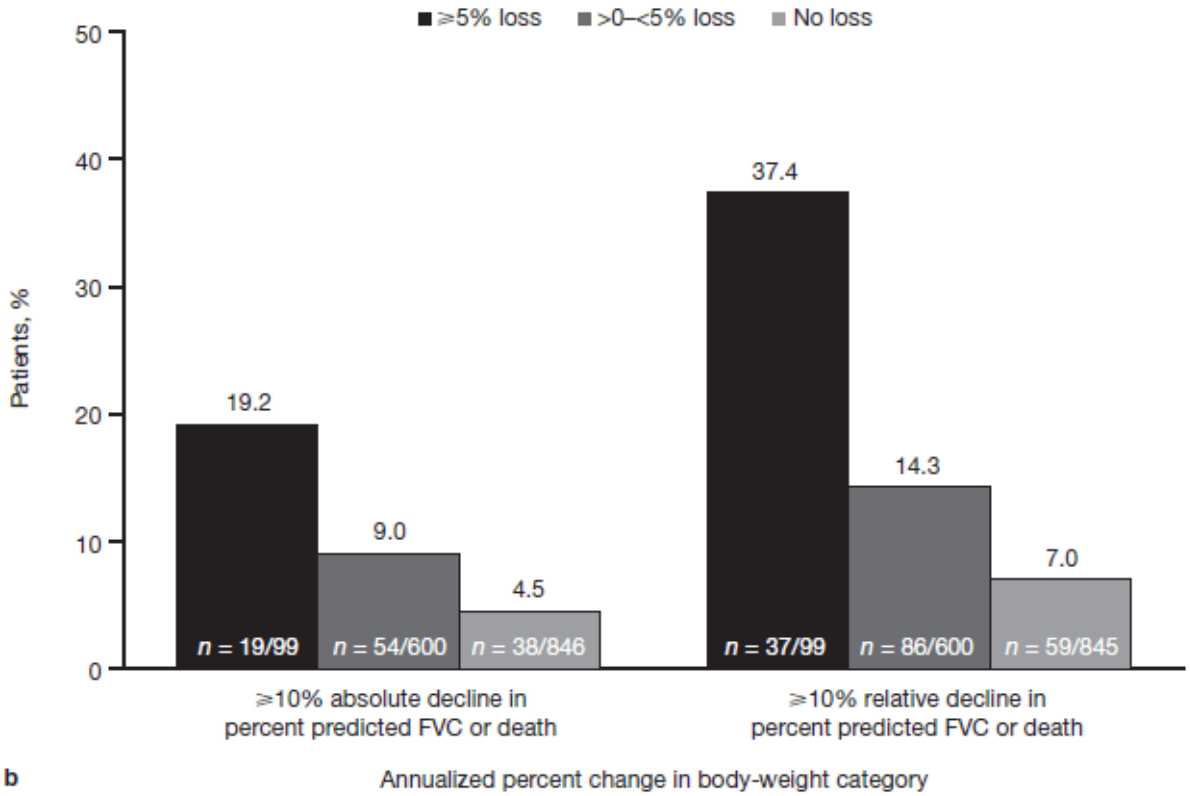
*Estimates (95% CI) based on repeated-measures analysis of covariance with study, age, sex, race, baseline HRCT status, years since IPF diagnosis, baseline oxygen use, baseline smoking status, annualized percent change category, time, and annualized percent change category*time as fixed-effect covariates, 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.

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637 **Fig. 1.**



a

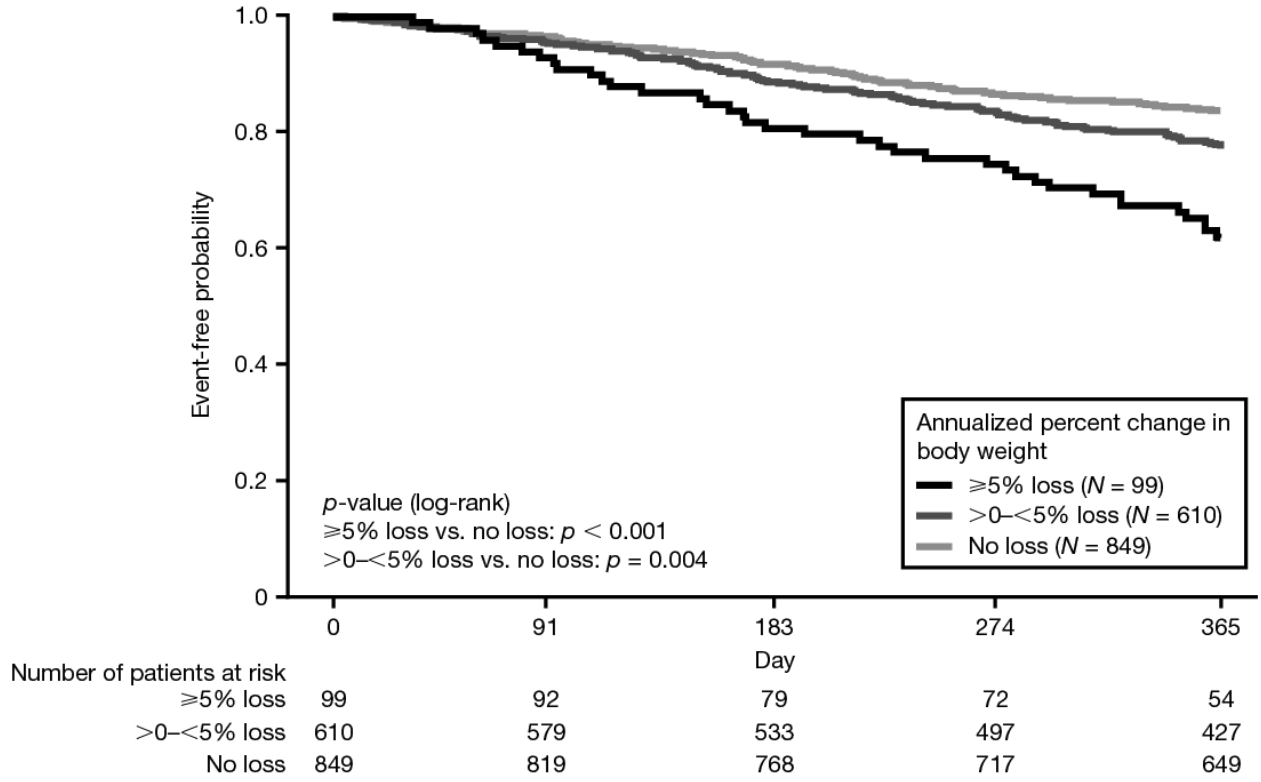


b

638

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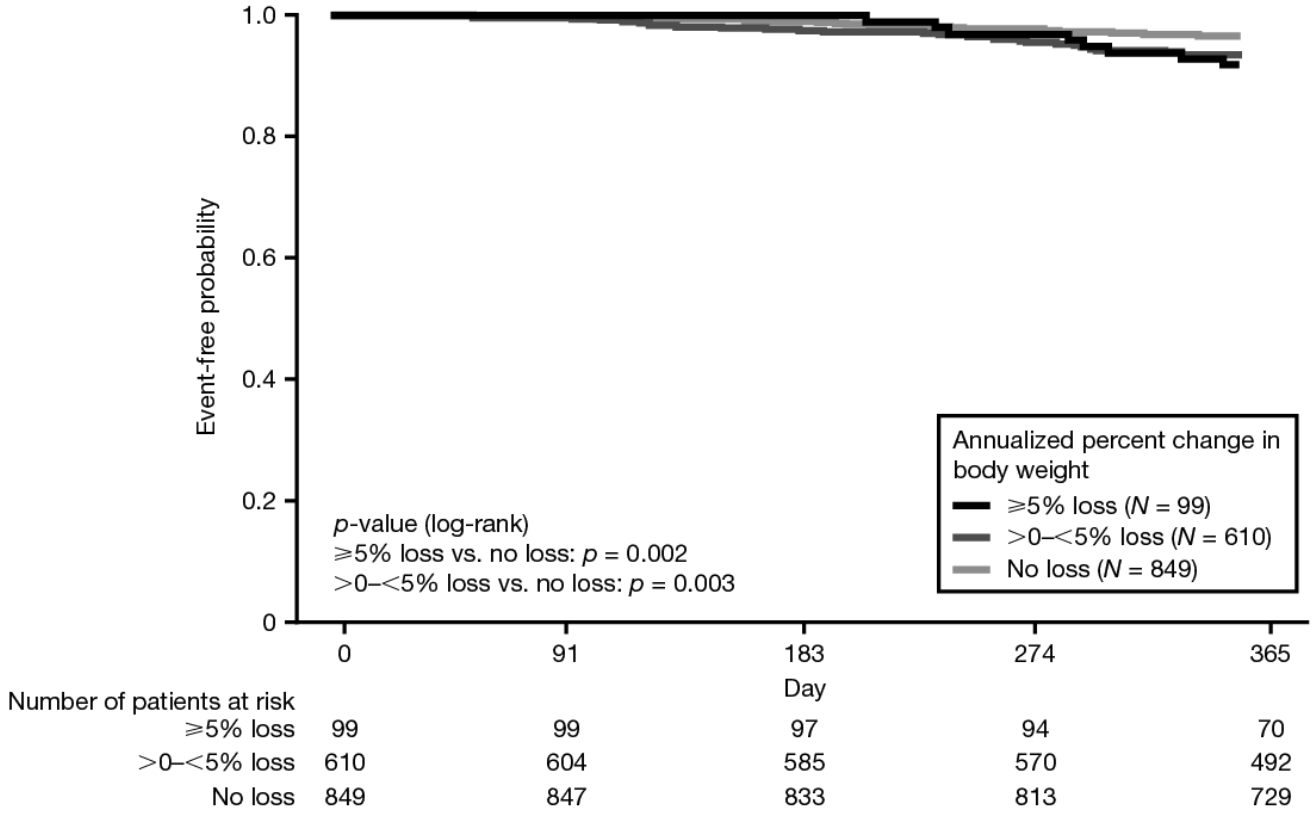
639 **Fig. 2.**



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Fig. 3.



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