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Dose modification and dose intensity during treatment with pirfenidone: analysis of pooled data from three multinational phase III trials

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ABSTRACT

Introduction Temporary dose modifications, such as reductions or interruptions, may allow patients to better manage adverse events (AEs) associated with pirfenidone use and continue treatment for idiopathic pulmonary fibrosis (IPF). However, the impact of such dosing adjustments on efficacy and safety is uncertain.

Methods Patients randomised to receive treatment with pirfenidone 2403 mg/day or placebo in the Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY (Study 004 (NCT00287716)) and Study 006 (NCT00287729))) and Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND (Study 016 (NCT01366209)) trials were included in the analysis (n=1247). Descriptive statistics and a linear mixed-effects model (slope analysis) for annual rate of decline in forced vital capacity (FVC) by dose intensity were performed. Treatment-emergent AEs (TEAEs) were summarised and grouped by dose intensity or body size.

Results Dose reductions and interruptions occurred in 76.9% (95% CI 73.4% to 80.1%) and 46.5% (95% CI 42.6% to 50.6%) of patients receiving pirfenidone vs 72.0% (95% CI 68.3% to 75.4%) and 31.1% (95% CI 27.5% to 34.9%) of patients receiving placebo, respectively. Dose interruptions tended to occur during the first 6 months of treatment, whereas dose reductions exhibited more variability. Less FVC decline from baseline was observed in patients receiving pirfenidone versus placebo at >90% dose intensity ($p<0.001$) or ≤90% dose intensity ($p=0.0191$), showing treatment benefit in both subgroups of dose intensity. No meaningful relationship between weight and TEAEs was observed.

Conclusion Dose interruptions, which may be required to manage TEAEs, mostly occurred during the first 6 months of treatment. Despite dose reductions and interruptions, most patients with IPF maintained relatively high dose intensity on pirfenidone, without compromising its treatment effect compared with placebo.

Trial registration numbers NCT00287729, NCT00287716, NCT01366209.

Key messages

- ► Does adjusting the dose of pirfenidone, used as a management strategy to control common treatment-emergent adverse events (TEAEs), have a significant impact on its efficacy in the treatment of idiopathic pulmonary fibrosis (IPF)?
- ► Dose adjustment occurs early in treatment if required, and efficacy is still evident at a dose intensity of ≤90%; no meaningful relationship with body weight and TEAEs was observed.
- ► This post-hoc analysis is the first to examine data on the effects of dose adjustment on efficacy and safety from three phase III trials of pirfenidone in the treatment of IPF; our findings suggest that dose adjustment is an effective management strategy to help maintain persistence and efficacy in patients with IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive and fatal fibrosing lung disease of ageing.[1] IPF is associated with a poor prognosis, with an estimated median survival of approximately 3 years, when untreated with antifibrotic drugs.[2–5] The incidence and prevalence of IPF increase with age and are higher in men, and rates appear to be rising worldwide.[6 7]

Pirfenidone is an oral antifibrotic agent conditionally recommended for the treatment of IPF in universally accepted treatment guidelines.[1] Three pivotal, multinational, randomised, placebo-controlled, phase III trials evaluated pirfenidone in patients with IPF—the Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY (Study 004 and Study 006)) and the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND (Study 016)) trials.[8 9]

Pooled analyses of data from these three trials demonstrated that treatment with pirfenidone for 1 year slowed the disease progression as measured by changes in forced vital capacity (FVC), an independent predictor of mortality.[10 11] Both pooled and meta-analyses of data from these three trials revealed a reduction in risk of mortality with pirfenidone compared with placebo over 120 weeks.[12] Continuing treatment with pirfenidone after clinically meaningful progression of the disease may reduce the risk of a subsequent ≥10% absolute decline in FVC or death.[13]

An integrated safety analysis from five clinical trials demonstrated that pirfenidone was generally well tolerated (median duration of exposure, 1.7 years (range, 1 week–9.9 years)).[14] In the phase III trials, nearly all patients experienced at least one treatment-emergent adverse event (TEAE) over 1 year (98.7% and 96.5% in the pirfenidone and placebo groups, respectively).[10] Notably, there were fewer serious TEAEs (20.5% vs 22.3% of patients) and fewer treatment-emergent deaths (2.2% vs 5.1% of patients) in the pirfenidone-treated group than in those receiving placebo. More patients in the pirfenidone group compared with the placebo group discontinued treatment prematurely due to TEAEs (11.9% vs 8.7%).[10] Gastrointestinal and skin-related events were the most common TEAEs, which tended to occur early during treatment and decreased over time.[14]

The reduction in the rate of FVC decline reported in patients with IPF treated with pirfenidone is dose dependent and therefore may be affected by dose reductions.[9] Parameters, such as body weight, that may be important for adjusting the pirfenidone dose to manage TEAEs but maintain efficacy have not been examined in detail. This post-hoc analysis evaluated the effects of pirfenidone dose reductions and interruptions on the annual rate of FVC decline in the pooled pirfenidone phase III clinical trial population as a function of dose intensity. Dose intensity using a 90% threshold has been evaluated in prespecified subgroup analyses from other antifibrotic IPF clinical trials to assess the impact of dose intensity on efficacy.[15] In addition to evaluating change in efficacy following dose modifications as a function of dose intensity, the safety of pirfenidone as a function of body size was also assessed.

METHODS

Patients

All patients randomised to receive treatment with pirfenidone 2403 mg/day or placebo in the phase III studies, CAPACITY (Study 004 and 006; NCT00287729 and NCT00287716, respectively) and ASCEND (Study 016; NCT01366209), were included in the analysis. The study designs of CAPACITY and ASCEND have been previously described.[8–10] Briefly, in the two CAPACITY studies, patients were treated for up to 72 weeks and followed up until study closure (maximum of 120 weeks); in ASCEND, patients were treated and followed up for 52 weeks. Treatment was administered orally in three equally divided daily doses with food and escalated to the full dose during a 2-week titration period in all three studies.

Dose reductions and interruptions

Dose reductions and interruptions were analysed using descriptive statistics. A dose reduction was defined as any decrease to a lower dose of study treatment than the protocol-defined full maintenance dose (2403 mg/day) after the first 2 weeks of treatment (excluding a zero dose), as reported by the patient. This reduction was temporary if the dose was then increased back to the protocol-defined full maintenance dose. A dose interruption was defined as any reported dosing gap to a zero dose of study treatment after the first 2 weeks of dose titration. Dose reductions or interruptions had no prespecified duration and could be temporary or permanent. For Kaplan-Meier analyses, the time to first dose reduction or interruption for each patient was used. Patients with no dose reductions or interruptions were censored at 12 months post baseline.

Dose intensity was calculated from the actual dose taken during the randomised treatment period divided by the planned dose that the patient should have received. The assumption was that patients would receive a stable dose of 2403 mg/day throughout the full period on study drug (minus the 2-week titration period). Different threshold rates were explored (ie, >90% vs ≤90%, >80% vs ≤80%) to identify a cut-off that would allow for a reasonable comparison of groups and to characterise adherence patterns in the trials. Previous analyses of pooled data from IPF clinical trials have evaluated a dose intensity threshold of 90%, suggesting that it was a rational cut-off for these analyses.[15]

Post-hoc analyses in subgroups of patients randomly assigned to pirfenidone or placebo were conducted. Within each treatment group, patients who interrupted or reduced their dose were analysed separately.

Efficacy

Efficacy (change in FVC from baseline without imputation (modified intention-to-treat analysis)) was compared between patients receiving pirfenidone and those receiving placebo after stratification by dose intensity (>90% vs ≤90% of the protocol-defined dose until individual end of treatment). The same analysis was conducted within treatment groups.

Efficacy at month 12, as determined by a decline of ≥10% in % predicted FVC or death, or a decline of ≥50 m in 6 min walk distance (6MWD) or death, was analysed by subgroup of dose intensity (based on actual dose). The categorical analysis compared pirfenidone and placebo within each dose intensity subgroup using a X^2 test.

Linear mixed-effects models were used to analyse the annual rate of decline from baseline in FVC. Separate models were designed using data from patients with dose intensity >90% and those with dose intensity ≤90%. In each model, study (CAPACITY 004, CAPACITY 006 and ASCEND 016), treatment, sex, age and height were fixed effects, whereas patient and assessment time were random effects. The models allowed comparisons of modelled mean differences in annual rate of FVC decline between the pirfenidone and placebo groups.

Safety

Safety outcomes were reported as TEAEs that occurred between baseline and 28 days after the last dose of study drug (up to 12 months). These TEAEs were coded to preferred terms in the Medical Dictionary for Regulatory Activities, V.11.0, descriptively summarised and grouped by dose intensity (based on actual dose) or body size (body mass index (BMI), body surface area (BSA) or weight).

RESULTS

Patients

A total of 1247 patients were included in the analyses (n=623, pirfenidone 2403 mg/day; n=624, placebo). The dose intensity thresholds of >90% and ≤90% were selected based on the distribution of dose intensity in the total population; the 90% threshold provided a reasonable sample size for the analyses (online supplementary table 1). Demographics and baseline characteristics across the pooled pirfenidone and placebo populations that received ≤90% or >90% of the target 2403 mg/day dose were generally well balanced (table 1).

The total proportion of women was 25.7% and 25.5% in the pirfenidone and placebo groups, respectively. Women comprised a higher proportion of patients receiving ≤90% dose intensity for either pirfenidone or placebo, at 34.2% and 30.8%, respectively, relative to the total population (25.7% and 25.5%). For patients in the pirfenidone group, the mean and median dose intensity were 88% and 96%, respectively, over 52 weeks. The mean daily actual dose of pirfenidone was 2054.0 mg/day. For the dose intensity subgroups of interest, the mean daily actual dose was 2278.4 mg/day and 1575.9 mg/day for patients with a dose intensity of >90% and ≤90%, respectively.

Dose reductions and interruptions

There was little difference between the pirfenidone and placebo groups in the proportion of patients with temporary dose reductions (59.7% vs 60.1%, respectively). In contrast, more patients receiving pirfenidone had permanent (31.5%) dose reductions versus those receiving placebo (20.8%; table 2).

The median cumulative duration of dose reduction was longer in the pirfenidone group (38.0 (IQR, 9–103) days) than in the placebo group (29.0 (IQR, 7–95) days; table 2).

Dose reductions occurred throughout the 12 months of treatment (figure 1). The median time to the first dose reduction was approximately 95 days (figure 2).

The majority of dose interruptions occurred during the first 6 months of treatment (figure 3). In contrast to the time to first dose reduction, however, dose interruptions were more evenly distributed across 12 months (figure 4).

Table 1 Baseline demographics and clinical characteristics (based on actual dose), modified intention-to-treat population

	Pirfenidone			Placebo		
Characteristics*	Total (n=623)	DI≤90% (n=199)	DI>90% (n=424)	Total (n=624)	DI≤90% (n=65)	DI>90% (n=559)
Age	68.0 (45–80)	68.0 (46–80)	68.0 (45–80)	68.0 (40–80)	68 (48–79)	68.0 (40–80)
Male, n (%)	463 (74.3)	131 (65.8)	332 (78.3)	465 (74.5)	45 (69.2)	420 (75.1)
White, n (%)	592 (95.0)	188 (94.5)	404 (95.3)	590 (94.6)	57 (87.7)	533 (95.3)
Weight, kg	86.5 (40–168)	82.0 (40–157)	87.7 (44–168)	85.7 (40–147)	84.4 (54–138)	86.0 (40–147)
BMI, kg/m^2	29.6 (19–47)	29.4 (19–42)	29.7 (19–47)	29.3 (15–48)	29.0 (23–42)	29.3 (15–48)
Men	29.5 (19–44)	29.6 (19–42)	29.4 (20–44)	29.3 (20–48)	29.3 (23–42)	29.3 (20–48)
Women	29.8 (19–47)	28.9 (19–42)	30.9 (19–47)	29.3 (15–44)	26.9 (23–39)	29.4 (15–44)
FVC, % predicted	71.1 (48–124)	72.8 (48–120)	70.3 (48–124)	70.3 (48–136)	69.3 (50–112)	70.6 (48–136)
6MWD, m	400.0 (112–731)	391.0 (112–619)	405.0 (145–731)	413.5 (163–716)	398.5 (168–573)	416.0 (163–716)

*Values expressed as median (range), unless otherwise stated.
6MWD, 6 min walk distance; BMI, body mass index; DI, dose intensity; FVC, forced vital capacity.

Table 2 Pirfenidone dose reductions and interruptions during 12 months of treatment (based on actual dose)

	Pirfenidone (n=623)	Placebo (n=624)
Daily dose, mean (SD), mg	2054.0 (425.05)	–
Patients with any dose reduction, n (%)*	479 (76.9)	449 (72.0)
Patients with temporary dose reductions, including permanent dose reductions, n (%)	372 (59.7)	375 (60.1)
Patients with only temporary dose reductions, excluding permanent dose reductions, n (%)	283 (45.4)	319 (51.1)
Patients with permanent dose reductions, including temporary dose reductions, n (%)	196 (31.5)	130 (20.8)
Patients with only permanent dose reductions, excluding temporary dose reductions, n (%)	107 (17.2)	74 (11.9)
Cumulative days of dose reduction, median (IQR)	38.0 (9–103)	29.0 (7–95)
Patients with any dose interruption, n (%)†	290 (46.5)	194 (31.1)
Patients with temporary dose interruptions, n (%)	244 (39.2)	145 (23.2)
Patients with permanent dose interruptions (discontinuation), n (%)‡	95 (15.2)	79 (12.7)
Cumulative days of dose interruption, median (IQR)*	14.0 (3–29)	4.0 (1–13)

*Not including patients who discontinued.
†Dose interruption was defined as the patient receiving a zero dose after having previously received a higher dose.
‡Permanent dose interruption was defined as the patient stopping study treatment prematurely.
IQR, interquartile range; SD, standard deviation.

The dropout rate in both pirfenidone and placebo arms was numerically higher in the ≤90% dose intensity groups (17% vs 20%, respectively) than in the >90% dose intensity groups (8% vs 11.6%).

Efficacy

A significantly smaller decrease in the annual rate of FVC decline from baseline was observed in patients treated with pirfenidone compared with those treated with placebo at either >90% dose intensity ($p<0.001$) or ≤90% dose intensity ($p=0.0191$; figure 5). Dropout rates among patients combined with non-imputation of longitudinal FVC analysis resulted in small and asymmetric sample sizes.

Among patients at >90% dose intensity, significantly fewer patients in the pirfenidone group experienced a decline of ≥10% in % predicted FVC (with imputation)

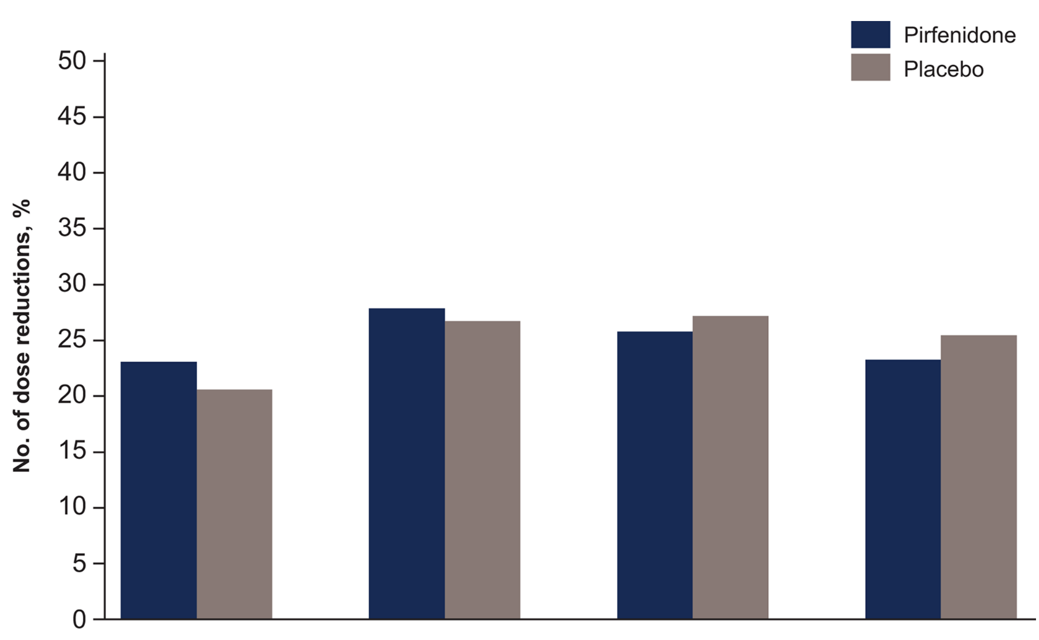

Figure 1 Distribution of any dose reductions over time by treatment. Percentages are based on the total number of dose reductions until 12 months within the respective treatment arm. Based on actual dose, modified intention-to-treat population.

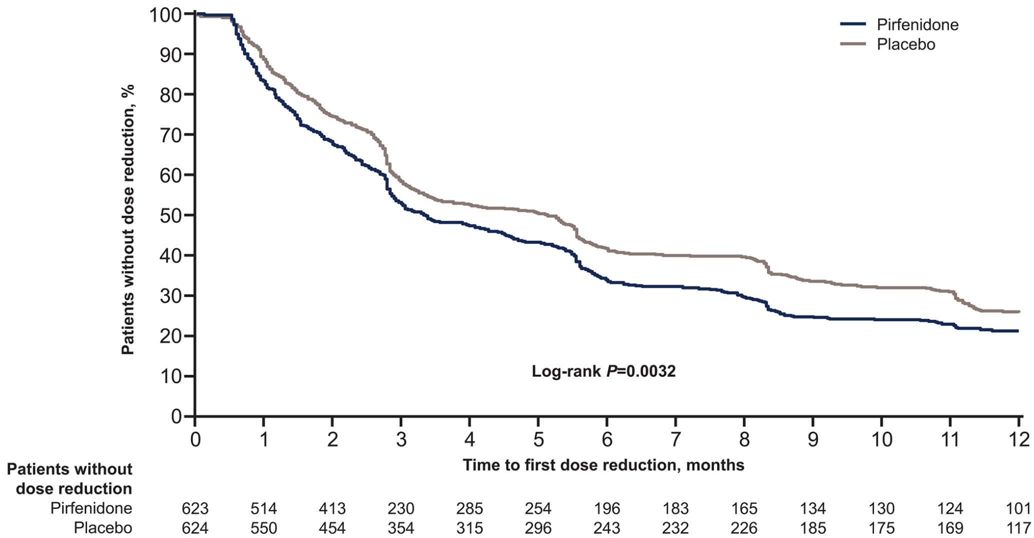

Figure 2 Kaplan-Meier analysis for time to first dose reduction in pirfenidone and placebo groups (based on actual dose).

by month 12 than in the placebo group (11.6% vs 25.6%; p<0.0001; table 3).

Similar results were observed among patients at ≤90% dose intensity, but the difference between the pirfenidone and placebo groups was not statistically significant (21.6% vs 32.3%; p=0.0805). The relative difference between the pirfenidone and placebo groups at >90% dose intensity was −54.8%, and between the pirfenidone and placebo groups at ≤90% dose intensity was −33.1%, a change in magnitude of approximately 20%. Sample sizes of patients at ≤90% dose intensity or >90% dose intensity were asymmetrical (eg, 65 vs 559 in the placebo group and 199 vs 424 in the pirfenidone group, respectively).

Among patients at >90% dose intensity, significantly fewer patients in the pirfenidone group experienced a decline of ≥50 m in 6MWD (with imputation) by month 12 than in the placebo group (24.4% vs 33.4%; p=0.0023); a similar result was observed in patients at ≤90% dose intensity (25.6% vs 46.9%; p=0.0014; table 3). The relative difference between the pirfenidone and placebo groups at >90% dose intensity was −26.9%, and between pirfenidone and placebo groups at ≤90% dose intensity was −45.3%.

To determine if body size affected efficacy, FVC decline and dose intensity were stratified according to body size: BMI, BSA and absolute body weight (online supplementary table 2). No consistent patterns were observed. The

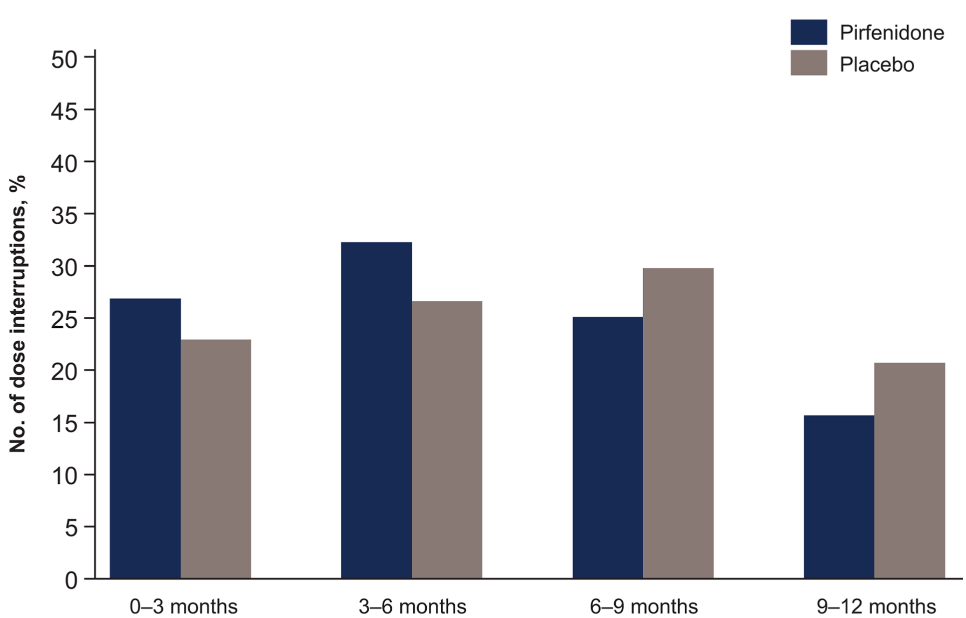

Figure 3 Distribution of any dose interruptions over time by treatment. Percentages are based on the total number of dose interruptions until 12 months within the respective treatment arm. Based on actual dose, modified intention-to-treat population.

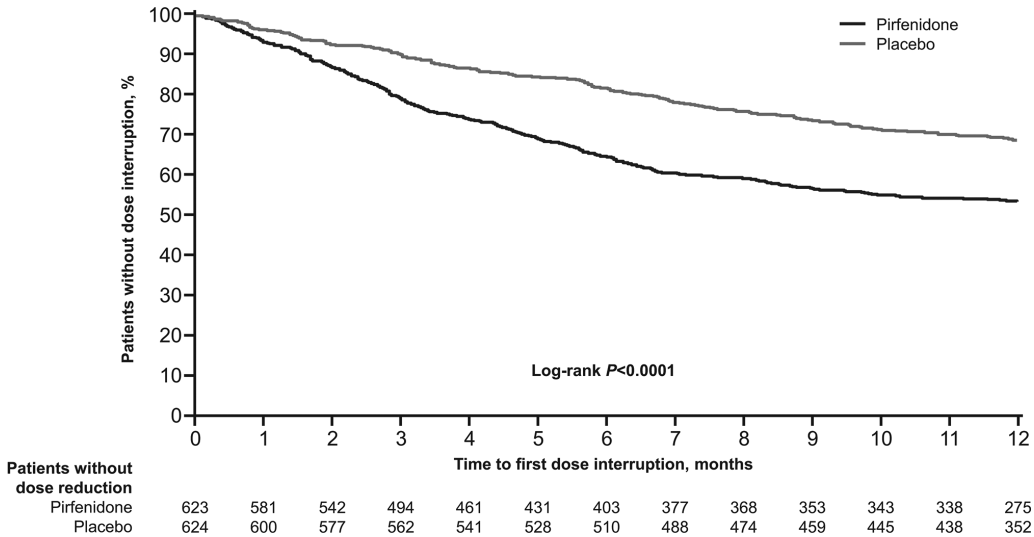

Figure 4 Kaplan-Meier analysis for time to first dose interruption in pirfenidone and placebo groups (based on actual dose).

number of patients with true low body weight was too small and did not allow stratification into body weight groups for analysis.

Safety

Analyses of adverse events leading to dose modification were performed, but there were no clear differences from the overall TEAE rates (data not shown). The number of patients presenting with the most common TEAEs of interest for pirfenidone (eg, diarrhoea, nausea, photosensitivity, rash and vomiting) was compared between subgroups defined according to ≤90% dose intensity or >90% dose intensity within each treatment arm (table 4).

The most frequent TEAE in the pirfenidone group was nausea, which occurred in a higher proportion of patients at ≤90% pirfenidone dose intensity (48.7% of patients (n=199)) than at the >90% dose intensity (30.2% of patients (n=424)). Within the placebo group, nausea was experienced by 29.2% of patients with TEAEs at ≤90% dose intensity and 14.1% of patients at >90% dose intensity. Rash was the second most frequent TEAE in the

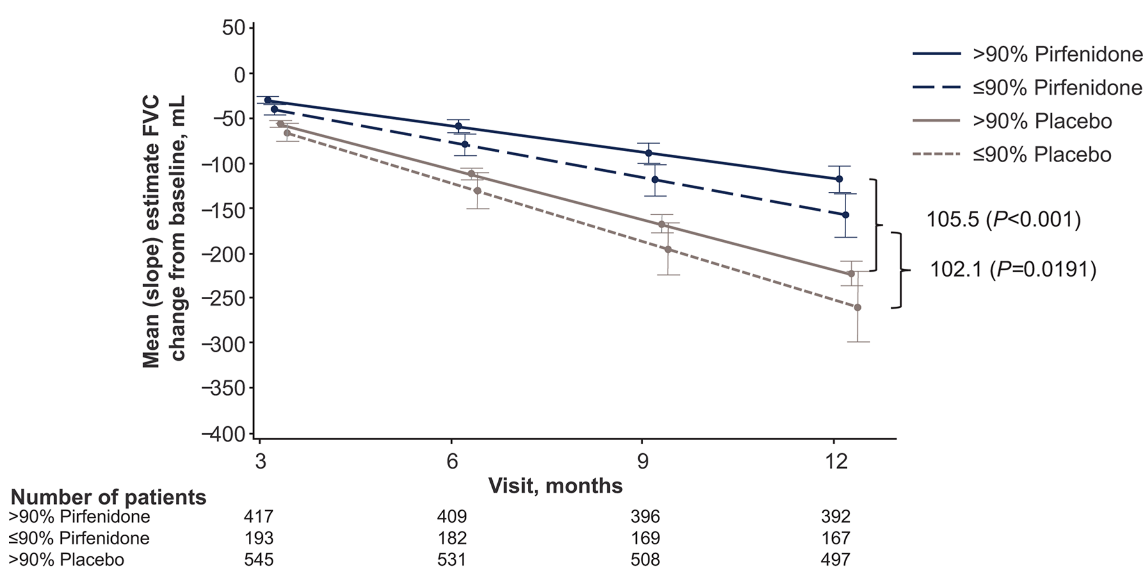

Figure 5 Modelled mean (SEM) observed forced vital capacity (FVC) volume change from baseline (mL) over time by dose intensity (>90%, ≤90%), based on actual dose (modified intention-to-treat population). No imputation for missing values and deaths. Months 3, 6, 9 and 12 correspond to weeks 12, 24, 36 and 48 for CAPACITY (004 and 006) studies and weeks 13, 26, 39 and 52 for ASCEND (016), respectively. The annual rate of decline was estimated from the linear mixed-effects model comparing pirfenidone with placebo for each of the dose intensity groups (>90%, ≤90%), with change from baseline as the outcome variable. Study (CAPACITY 004 and 006 and ASCEND 016), treatment, sex, age and height were evaluated as fixed effects, and patient and assessment time were evaluated as random effects in an unstructured variance–covariance matrix.

Table 3 Analysis of %FVC and 6MWD at month 12 (with imputation by the sum of squared differences) by dose intensity (based on actual dose)

Change from baseline category, n (%)	DI>90%				DI≤90%			
	Pirfenidone (n=424)	Placebo (n=559)	Relative difference, %	P values*	Pirfenidone (n=199)	Placebo (n=65)	Relative difference, %	P values*
Decline ≥10% in %FVC or death	49 (11.6)	143 (25.6)	−54.8	<0.0001	43 (21.6)	21 (32.3)	−33.1	0.0805
Decline ≥50 m in 6MWD or death	103 (24.4)	184 (33.4)	−26.9	0.0023	50 (25.6)	30 (46.9)	−45.3	0.0014

Relative difference=100 × (% pirfenidone − % placebo)/%placebo.
*For χ^2 test, the categories 'No decline and decline <10% to 0%' and 'No decline and decline <50 m to 0 m', respectively, were combined.
6MWD, 6 min walk distance; %FVC, per cent predicted forced vital capacity; DI, dose intensity.

pirfenidone group (41.7% of patients at ≤90% pirfenidone dose intensity vs 33.0% of patients at >90% dose intensity). To assess whether body size was associated with dose intensity differences in TEAE occurrence, safety data were stratified according to body size: BMI, BSA and weight (online supplementary table 3). There was no clear relationship of key pirfenidone TEAEs of interest with body size. The potential influence of other demographic characteristics, such as age or sex, in combination with body size on TEAEs was not assessed due to the relatively limited size of such subgroups.

DISCUSSION

Pirfenidone is approved for the treatment of IPF and reduces the decline in lung function seen in patients while also improving progression-free survival.[9 10 12] Although long-term treatment with pirfenidone is generally well tolerated, dose modification is a recognised management tool used to decrease the occurrence and/or severity of adverse events and to maintain adherence.[16 17]

The results from this post-hoc analysis support such an approach, with a treatment benefit with pirfenidone over placebo at different dose intensities: the annual rate of decline in FVC and the proportion of patients who experienced a decline of ≥50 m in 6MWD or death at month 12 were lower in the pirfenidone group than in the placebo group at either >90% dose intensity or when the dose was reduced to ≤90% dose intensity. However, we did observe a dose–response relationship for pirfenidone. The relative difference of patients who experienced a decline of ≥10% in % predicted FVC or death who were randomised to receive placebo or pirfenidone was −33.1% in the ≤90% dose intensity group and −54.8% in the >90% dose intensity group, with a greater difference observed in the >90% dose intensity group. Several preclinical and clinical studies have indicated that pirfenidone acts in a dose-dependent manner.[18 19] CAPACITY (Study 004) showed that FVC decline in patients receiving pirfenidone 1197 mg/day (≈50% standard dose) was intermediate to pirfenidone 2403 mg/day and placebo at month 12, illustrating a dose-dependent effect; however, this study was not powered to detect any significant differences between the 1197 mg/day dose and placebo.[9] Previously published data suggest adverse events may also occur in a dose-dependent manner. Pirfenidone-related adverse events have been associated with postdose, peak plasma concentrations.[20 21] A recently published post-hoc analysis from the pirfenidone phase III trials using prescribed doses found that the median time to the first adverse event of interest that led to dose modification was 62.0 days (IQR, 26.0–122.0 days).[22] Mason *et al*[22] also reported that 67.6% of patients with adverse events who required dose reductions reached their initial doses after retitration without discontinuation. Similarly, almost half of the patients in the US Expanded Access Program (NCT02141087) who reached the full daily dose and then had dose modifications or interruptions (and did not discontinue due to

Table 4 Patients with TEAEs of interest by dose intensity (based on actual dose), modified intention-to-treat population

TEAEs (all-grade, grouped), n (%)	Pirfenidone (n=623)		Placebo (n=624)	
	DI≤90% (n=199)	DI>90% (n=424)	DI≤90% (n=65)	DI>90% (n=559)
Any TEAE, n (%)	166 (83.4)	275 (64.9)	37 (56.9)	219 (39.2)
Nausea	97 (48.7)	128 (30.2)	19 (29.2)	79 (14.1)
Rash	83 (41.7)	140 (33.0)	13 (20.0)	72 (12.9)
Diarrhoea	49 (24.6)	112 (26.4)	18 (27.7)	109 (19.5)
Vomiting	39 (19.6)	45 (10.6)	7 (10.8)	33 (5.9)
Photosensitivity	21 (10.6)	37 (8.7)	2 (3.1)	5 (0.9)

DI, dose intensity; TEAE, treatment-emergent adverse event.

an adverse drug reaction) returned to the full dose by the end of the study period.[17] Recently published long-term real-world data from the UK suggest the same: many patients on pirfenidone who require dose modifications can remain on drug, either at a reduced dose (16%) or after a temporary dose interruption (9%). An interim analysis from the PASSPORT study (a safety registry study initiated in Europe in 2011) revealed that the rate of discontinuation due to adverse drug reactions was lower in patients who had a dose adjustment compared with those who did not (20% vs 33%).[23]

Although dose modification is now a recognised management tool to help reduce the risk of treatment discontinuation, limited research has been done on factors determining the extent and period of dose modification that a patient may require. It is also unknown if a minimum dose may be needed to maintain the efficacy of pirfenidone through a modification period; further division into dose subgroups (eg, <80% or <70% dose) was not possible in this analysis due to small sample sizes. A recent report from a retrospective analysis of Japanese patients with IPF suggested that pirfenidone dose adjustment by BSA could be adequate to prevent TEAEs and still achieve effective treatment in that cohort.[24] Body size may therefore influence relative drug exposure and act as an indicator of more generalised frailty. However, no clear relationship between body weight, BMI or BSA with TEAEs was identified in this analysis. Therefore, these results do not support presumptive weight-based dosing with pirfenidone for safety and tolerability reasons, although the limited number of patients with low body size restricted the ability to explore potential relationships more fully. Another finding from our study was that a higher proportion of men remained on >90% dose intensity than did women. Whether such a sex imbalance exists in the real world is unknown, and what might explain the findings in this study is uncertain.

This post-hoc study has some limitations. Imputed data were used to compare the proportion of patients experiencing a decline of ≥10% in % predicted FVC, or ≥50 m in 6MWD or death, combined with observed data for longitudinal change in FVC. The method for handling missing data has been shown to have a significant influence on the size of FVC change and associated effect sizes in clinical trials with IPF.[25] The analytical methodology could therefore have impacted the results presented here. However, the magnitude of the treatment effect using different methodology, in the context of a sensitivity analysis of the ASCEND data, was consistent.[25] An added limitation of this study was the lack of information available on actual adherence. In addition, some groups had small and asymmetric numbers of patients. This included too few patients on ≤90% dose intensity, or with true low body weight, to enable a stratification of analyses into subgroups.

The population from the pooled pirfenidone phase III clinical trials may not accurately reflect the general population because the trials required patients to fall within a defined range of physiological impairment and patients were followed longitudinally for a limited period of time. In a recent postauthorisation study, older age, female sex and prior steroid use were associated with greater odds of pirfenidone discontinuation due to adverse drug reactions.[26] Future studies should therefore focus on specific subgroups of patients to further elucidate which patients may benefit from a dose modification strategy.

Dose modifications are increasingly supported as a management strategy to enable continuation of pirfenidone treatment for IPF when TEAEs are present. Despite the limitations presented, with small sample sizes of patients stratified into lower dose subgroups, this study supports this approach, with the finding that the treatment effect of pirfenidone compared with placebo in patients at a dose intensity of <90% is similar to the effect in patients at a dose intensity of ≥90%. The possible dose-dependent effect observed in this study warrants further investigation, and larger meta-analyses of small subgroups of patients for whom dose adjustment may be of particular interest would be useful. We conclude that dose modifications are an appropriate strategy to manage adverse events and to help ensure long-term persistence with pirfenidone treatment.

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F. Hoffmann-La Roche, Ltd., and K-UK is a shareholder. SLL is an employee of Genentech.

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REFERENCES

1. Raghu G, Collard HR, Egan JJ, *et al*. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
2. Fernández Pérez ER, Daniels CE, Schroeder DR, *et al*. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest* 2010;137:129–37.
3. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431–40.
4. Nathan SD, Shlobin OA, Weir N, *et al*. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. *Chest* 2011;140:221–9.
5. Raghu G, Rochwerg B, Zhang Y, *et al*. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19.
6. Hutchinson J, Fogarty A, Hubbard R, *et al*. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015;46:795–806.
7. Nalysnyk L, Cid-Ruzafa J, Rotella P, *et al*. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev* 2012;21:355–61.
8. King TE Jr, Bradford WZ, Castro-Bernardini S, *et al*. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–92.
9. Noble PW, Albera C, Bradford WZ, *et al*. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377:1760–9.
10. Noble PW, Albera C, Bradford WZ, *et al*. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J* 2016;47:243–53.
11. Paterniti MO, Bi Y, Rekić D, *et al*. Acute exacerbation and decline in forced vital capacity Are associated with increased mortality in idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2017;14:1395–402.
12. Nathan SD, Albera C, Bradford WZ, *et al*. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017;5:33–41.
13. Nathan SD, Albera C, Bradford WZ, *et al*. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. *Thorax* 2016;71:429–35.
14. Lancaster L, Albera C, Bradford WZ, *et al*. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. *BMJ Open Respir Res* 2016;3:e000105.
15. Corte T, Bonella F, Crestani B, *et al*. Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. *Respir Res* 2015;16:116–015.
16. Costabel U, Bendstrup E, Cottin V, *et al*. Pirfenidone in idiopathic pulmonary fibrosis: expert panel discussion on the management of drug-related adverse events. *Adv Ther* 2014;31:375–91.
17. Lancaster L, Morrison L, Auais A, *et al*. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: experience from 92 sites in an open-label US expanded access program. *Pulm Ther* 2017;3:317–25.
18. Myllärniemi M, Kaarteenaho R. Pharmacological treatment of idiopathic pulmonary fibrosis - preclinical and clinical studies of pirfenidone, nintedanib, and N-acetylcysteine. *Eur Clin Respir J* 2015;2:26385.
19. Spond J, Case N, Chapman RW, *et al*. Inhibition of experimental acute pulmonary inflammation by pirfenidone. *Pulm Pharmacol Ther* 2003;16:207–14.
20. Rubino CM, Bhavnani SM, Ambrose PG, *et al*. Effect of food and antacids on the pharmacokinetics of pirfenidone in older healthy adults. *Pulm Pharmacol Ther* 2009;22:279–85.
21. Shi S, Wu J, Chen H, *et al*. Single- and multiple-dose pharmacokinetics of pirfenidone, an antifibrotic agent, in healthy Chinese volunteers. *J Clin Pharmacol* 2007;47:1268–76.
22. Mason WR, Nathan SD, Zibrak JD, *et al*. Time-to-event analysis of common adverse events with pirfenidone in patients with IPF—a pooled analysis of three phase III clinical trials. *Am J Respir Crit Care Med* 2017;195:A6798.
23. Cottin V, Maher TM, Azuma A, *et al*. Pirfenidone post-authorization safety registry (PASSPORT) update. *Eur Respir J* 2015;46:OA4500.
24. Uehara M, Enomoto N, Karayma M. Evaluation of pirfenidone dose adjusted by body weight or body surface area in the treatment for Japanese patients with interstitial pneumonia. *Am J Respir Crit Care Med* 2017;19S:AS401.
25. Lederer DJ, Bradford WZ, Fagan EA, *et al*. Sensitivity analyses of the change in FVC in a phase 3 trial of pirfenidone for idiopathic pulmonary fibrosis. *Chest* 2015;148:196–201.
26. Cottin V, Guenther A, Albera C. Risk factors associated with pirfenidone discontinuation in patients with idiopathic pulmonary fibrosis in a real-world setting. *Am J Respir Crit Care Med* 2017;195:A5392.