Respiratory Medicine 153 (2019) 44–51

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment

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ARTICLE INFO

Keywords:
Idiopathic pulmonary fibrosis
Pirfenidone
Dyspnoea
Mortality

ABSTRACT

Background: Patients with idiopathic pulmonary fibrosis (IPF) demonstrate a range of lung function impairment. However, the efficacy of antifibrotics compared with placebo has not been assessed in patients with more advanced disease. This post-hoc analysis investigated the efficacy and safety of pirfenidone versus placebo in patients with IPF and more advanced lung function impairment, defined as percent predicted forced vital capacity (%FVC) < 50% and/or percent predicted carbon monoxide diffusing capacity < 35%.

Methods: Patients randomised to pirfenidone 2,403 mg/day or placebo in the ASCEND (NCT01366209) and CAPACITY (NCT00287716; NCT00287729) trials with more advanced baseline lung function impairment (pirfenidone, $n = 90$; placebo, $n = 80$) were included. Mortality, lung function, hospitalisation, exercise capacity and dyspnoea were investigated over 52 weeks.

Results: At Week 52 versus placebo, pirfenidone was associated with significantly lower risks of all-cause mortality (hazard ratio [HR] 0.28; 95% confidence interval [CI] 0.09–0.86; $p = 0.0180$), ≥10% absolute %FVC decline or all-cause mortality (HR 0.40; 95% CI 0.23–0.69; $p = 0.0006$) and ≥10% absolute %FVC decline or respiratory-related hospitalisation or all-cause mortality (HR 0.46; 95% CI 0.28–0.76; $p = 0.0018$). At Week 52, median treatment differences favouring pirfenidone were 36.7 m for 6-min walk distance and −8.0 points for the University of California—San Diego Shortness of Breath Questionnaire total score. Treatment-emergent adverse events (TEAEs) led to discontinuation in 14.4% and 21.3% of patients with pirfenidone and placebo, respectively.

Conclusion: Pirfenidone demonstrated clinically relevant benefits across multiple domains in patients with IPF and more advanced disease without an increased risk of discontinuation due to TEAEs.

Clinical trials registration: clinicaltrials. gov (ASCEND: NCT01366209; CAPACITY: NCT00287716; NCT00287729).

Abbreviations: 6MWD, 6-min walk distance; CI, confidence interval; %DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; GAP index, Gender Age and Physiology index; HR, hazard ratio; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NNT, number needed to treat; TEAE, treatment-emergent adverse event; UCSD SOBQ, University of California—San Diego Shortness of Breath Questionnaire; UIP, usual interstitial pneumonitis; URTI, upper respiratory tract infection

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https://doi.org/10.1016/j.rmed.2019.04.016
Received 2 November 2018; Received in revised form 5 March 2019; Accepted 18 April 2019
Available online 24 April 2019

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal and unpredictable fibrosing lung disease [1–4]. Two antifibrotics, pirfenidone and nintedanib, have been shown to significantly reduce lung function decline versus placebo over 52 weeks in patients with IPF [5–10].

Although the pivotal ASCEND and CAPACITY trials of pirfenidone provide valuable evidence supporting antifibrotic therapy in patients with IPF, these trials largely enrolled patients with less advanced lung function impairment, leaving unanswered the question of whether patients with more advanced disease can benefit from treatment. Patients with percent predicted forced vital capacity (%FVC) < 50% or carbon monoxide diffusing capacity (%DLco) < 30% at screening (in ASCEND), or %FVC < 50% at screening or Day 1 (pre-randomisation) and %DLco < 35% at screening (in CAPACITY), were excluded [11,12].

However, many patients with IPF experience delays in diagnosis, which means that some patients are diagnosed after their lung function has become significantly impaired [13]. A lack of knowledge surrounding antifibrotic treatment in more advanced disease is the main reason why treatment is not always reimbursed for these patients, disenfranchising patients from potentially effective treatment. Furthermore, most patients receiving antifibrotics will experience progression as part of the natural disease course and may develop more advanced disease. There are data demonstrating that continuing pirfenidone in patients who experience disease progression has a beneficial effect on outcomes [14], suggesting that patients with IPF and more advanced disease may benefit from pirfenidone. These observations support further research investigating the efficacy and tolerability of pirfenidone in patients with IPF and more advanced lung function impairment.

This post-hoc analysis used data from ASCEND and CAPACITY to investigate the efficacy and safety of pirfenidone versus placebo over 52 weeks in patients with IPF and more advanced lung function impairment, defined as %FVC < 50% and/or %DLco < 35%.

Some of the results of this study have been previously reported in an abstract [15].

2. Methods

2.1. Patients

This post-hoc analysis included all patients randomised to pirfenidone 2,403 mg/day or placebo in the ASCEND (NCT01366209) [11] and CAPACITY [12] (NCT00287716; NCT00287729) Phase III trials with baseline %FVC < 50% and/or baseline %DLco < 35%. Patients were aged 40–80 years with a confirmed diagnosis of IPF and had not previously received antifibrotics [11,12]. Although the inclusion criteria for ASCEND (%FVC ≥50% and %DLco ≥30% at screening) [11] and CAPACITY (%FVC ≥50% at screening and Day 1 and %DLco ≥35% at screening) [12] would suggest that patients with more advanced lung function impairment were not eligible for inclusion in these trials, this was not the case for several reasons. There were differences in eligibility criteria between the trials, and some inclusion criteria were assessed only at screening. Patients enrolled in ASCEND could be included in this analysis if they had %DLco ≥30% and < 35% at screening, or if they experienced a decline in %FVC to < 50% between screening and baseline (while %FVC was assessed again at baseline, these values were not used to determine eligibility; maximum permissible time between screening and randomisation was 8 weeks). In addition, there were differences between the definition of baseline used to determine eligibility and that used for statistical analysis purposes. For example, three separate measurements of %DLco were obtained at screening in CAPACITY. An investigator could use the maximum value to determine eligibility for the trial; however, the baseline value for a patient was calculated as the mean of the two closest values. Lastly, %FVC and %DLco were calculated centrally for this analysis, and the equations used at the investigative sites may have differed [16,17].

ASCEND and CAPACITY were conducted in accordance with the International Conference on Harmonisation Guidelines and the Declaration of Helsinki, as well as any relevant local legal and regulatory requirements. Written informed consent was obtained from all patients prior to any study procedure.

2.2. Disease-related outcomes

Outcomes investigated over 52 weeks included change from baseline in FVC volume, and the percentage of patients experiencing all-cause mortality, ≥10% absolute %FVC decline or hospitalisation (respiratory and non-respiratory). A number of composite outcomes were also analysed over 52 weeks: ≥10% absolute %FVC decline or all-cause mortality; respiratory hospitalisation or all-cause mortality; ≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality. Sensitivity analyses examined inclusion of ≥10% relative %FVC decline and all-cause hospitalisation in composite outcomes.

Changes from baseline in exercise capacity and dyspnoea were assessed at Week 52 using 6-min walk distance (6MWD) and the University of California—San Diego Shortness of Breath Questionnaire (UCSD SOBQ) total score, respectively. Composite outcomes analysed over 52 weeks were: 6MWD decline ≥50 m or all-cause mortality and increase in UCSD SOBQ total score of ≥20 points or all-cause mortality.

2.3. Treatment-emergent adverse events

Treatment-emergent adverse event (TEAE) data, including treatment-emergent serious AEs and TEAEs leading to discontinuation, were collected over 52 weeks in ASCEND and 72 weeks in CAPACITY. TEAE data in this analysis were limited to Week 52 of both trials.

2.4. Statistical analyses

The percentage of patients experiencing each individual or composite outcome over 52 weeks was summarised descriptively by treatment. TEAEs reported over 52 weeks were summarised descriptively by treatment.

Linear slope analysis of change from baseline to Week 52 in FVC volume was performed using a mixed model. Slopes were calculated based on observed data only and used actual observation times. Further details of this analysis are presented in the Appendix. For descriptive purposes, median (Q1, Q3) change from baseline to Week 52 in FVC volume and %FVC were provided for each treatment.

The percentages of patients experiencing the composite outcome of ≥10% absolute %FVC decline or all-cause mortality for pirfenidone versus placebo at Week 52 were compared using a rank analysis of covariance model that included treatment group, with ranked baseline %FVC as a covariate and study as a stratification factor. Details of how missing data were handled are presented in the Appendix.

Time-to-event outcomes were compared between pirfenidone and placebo using the log-rank test stratified by study. For composite outcomes where a patient could experience more than one event, the time to first event was used for analysis. A proportional hazards model, with treatment as a fixed effect and study as a stratification factor, was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). Kaplan-Meier curves were used to display event times and the numbers of patients at risk. Patients without an event were censored at or prior to 52 weeks, as appropriate for each outcome and 52-week completion status.

Treatment differences in changes from baseline in 6MWD and UCSD SOBQ total score for pirfenidone versus placebo were estimated using Hodges-Lehmann median difference (95% CI). For composite outcomes including 6MWD or UCSD SOBQ total score, *p*-values for pirfenidone versus placebo were calculated using ranked analysis of covariance adjusted for study and standardised ranked baseline value.

Details of number-needed-to-treat (NNT) and sample size calculations are presented in the Appendix.

3. Results

3.1. Patients

A total of 170 patients with more advanced lung function impairment were included in this analysis (pirfenidone, $n = 90$; placebo, $n = 80$), with 127 patients enrolled in ASCEND and 43 in CAPACITY. Five patients had both %FVC < 50% and %DLco < 35%, eight had %FVC < 50% only and 157 had %DLco < 35% only. Baseline characteristics were similar in the pirfenidone and placebo arms (Table 1).

The percentages of patients completing 52 weeks of treatment with pirfenidone and placebo were 82.2% and 76.3%, respectively.

3.2. Disease-related outcomes

A total of 16.7% (15/90) of patients with more advanced lung function impairment in the pirfenidone arm experienced ≥10% absolute %FVC decline over 52 weeks versus 35.0% (28/80) with placebo. NNT calculations suggested that for every six patients with IPF and more advanced disease treated with pirfenidone over 52 weeks, ≥10% absolute %FVC decline would be avoided in one patient. In the linear slope analysis, annual FVC decline was significantly lower with pirfenidone versus placebo (150 mL vs 278 mL; $p = 0.003$). Median (Q1, Q3) change from baseline to Month 12 in FVC volume was −187.5 mL (−335.0, −25.0) and −285.0 mL (−545.0, −90.0) for pirfenidone and placebo, respectively. Median (Q1, Q3) change from baseline to Month 12 in %FVC was −4.8% (−8.5, −0.6) and −7.6% (−14.3, −2.6) for pirfenidone and placebo, respectively.

The percentage of patients who died from any cause was 4.4% (4/90) in the pirfenidone arm compared with 15.0% (12/80) with placebo over 52 weeks. In time-to-event analyses, patients treated with pirfenidone had a significantly lower risk of all-cause mortality over 52 weeks versus placebo (HR 0.28; 95% CI 0.09–0.86; $p = 0.0180$) (Fig. 1). NNT calculations suggested that for every 10 patients with IPF and more advanced lung function impairment treated with pirfenidone over 52 weeks, death would be avoided in one patient.

The percentage of patients with ≥10% absolute %FVC decline or all-cause mortality at Week 52 was significantly lower in the pirfenidone arm versus placebo (18.9% [17/90] vs 42.5% [34/80]; $p = 0.0038$) (Fig. 2). In time-to-event analyses, patients with more advanced lung function impairment treated with pirfenidone had a significantly lower risk versus placebo for ≥10% absolute %FVC decline or all-cause mortality (HR 0.40; 95% CI 0.23–0.69; $p = 0.0006$) (Table 2).

Up to 52 weeks, the percentages of patients who experienced at least one respiratory hospitalisation in the pirfenidone and placebo arms were 11.1% (10/90) and 25.0% (20/80), respectively, and the percentages of patients who experienced at least one non-respiratory hospitalisation were 13.3% (12/90) and 13.8% (11/80), respectively. The most frequent reason for respiratory hospitalisation was IPF.

Patients with more advanced lung function impairment treated with pirfenidone had a significantly lower risk versus placebo for respiratory hospitalisation or all-cause mortality (HR 0.45; 95% CI 0.22–0.91; $p = 0.0219$) and ≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality (HR 0.46; 95% CI 0.28–0.76; $p = 0.0018$) (Table 2).

Results were similar in sensitivity analyses, which included the individual outcomes of ≥10% relative %FVC decline and all-cause hospitalisation in composite outcomes, with the exception that the comparison between treatments was not significant for the composite outcome of all-cause hospitalisation or all-cause mortality over 52 weeks (Supplementary Table 1). The limitations of performing multiple analyses in this small subgroup of patients should be acknowledged.

Table 1
Demographics and baseline clinical characteristics.

Characteristic	Patients with more advanced lung function impairment[a] $N = 170$	
	Pirfenidone $n = 90$	Placebo $n = 80$
Age, years[b]	70 (46–80)	69 (40–80)
Male, *n (%)*	74 (82.2)	59 (73.8)
White, *n (%)*	84 (93.3)	76 (95.0)
Supplemental oxygen use, *n (%)*	38 (42.2)	32 (40.0)
HRCT diagnosis, *n (%)*		
Definite UIP	87 (96.7)	78 (97.5)
Probable/possible UIP	3 (3.3)	2 (2.5)
Time since diagnosis to randomisation, years[b]	1.42 (0.1–4.0)	1.30 (0.2–4.1)
%FVC, %	59.2 (53.8, 67.9)	64.2 (56.4, 75.8)
< 50%, *n (%)*	9 (10.0)	4 (5.0)
%DLco, %[c]	32.5 (30.8, 34.5)	32.1 (30.9, 33.8)
< 30%, *n (%)*	16 (17.8)	12 (15.0)
30% to < 35%, *n (%)*	67 (74.4)	67 (83.8)
6MWD, m	385.5 (320.0, 435.0)	375.5 (322.5, 426.0)[d]
UCSD SOBQ total score	42.0 (28.0, 55.0)[e]	43.8 (29.9, 64.8)
GAP index, *n (%)*		
I	8 (8.9)	3 (3.8)
II	39 (43.3)	51 (63.8)
III	43 (47.8)	26 (32.5)

6MWD, 6-min walk distance; %DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; GAP index, Gender, Age and Physiology index; HRCT, high-resolution computed tomography; UCSD SOBQ, University of California—San Diego Shortness of Breath Questionnaire; UIP, usual interstitial pneumonitis.
Data are presented as median (Q1, Q3) unless otherwise specified.
[a] Patients with %FVC < 50% and/or %DLco < 35%. Inclusion criteria for ASCEND were %FVC ≥50% and %DLco ≥30% at screening. Inclusion criteria for CAPACITY were %FVC ≥50% at screening and Day 1, and %DLco ≥35% at screening.
[b] Median (range).
[c] Corrected for haemoglobin.
[d] $n = 78$.
[e] $n = 89$.

At Week 52, median (Q1, Q3) changes from baseline in 6MWD were −34.0 m (−107.0, 5.5) and −81.5 m (−187.0, 2.5) for pirfenidone and placebo, respectively (Hodges-Lehmann median difference 36.7 m; 95% CI 3.0–71.5). The percentage of patients with 6MWD decline ≥50 m or all-cause mortality at Week 52 was significantly lower in the pirfenidone arm versus placebo (43.3% [39/90] vs 61.5% [48/78]; $p = 0.0279$). Median (Q1, Q3) changes from baseline for the UCSD SOBQ total score were 17.0 (4.5, 29.0) and 21.5 (7.6, 42.1) for pirfenidone and placebo, respectively (Hodges-Lehmann median difference: 8.0; 95% CI –15.5 to −0.5). The percentage of patients with an increase in UCSD SOBQ total score of ≥20 points or all-cause mortality at Week 52 was significantly lower in the pirfenidone arm versus placebo (43.8% [39/89] vs 57.5% [46/80]; $p = 0.0081$).

In sample size calculations for theoretical placebo-controlled trials that included varying percentages of patients with more advanced IPF, the number of patients needed to adequately power a trial consistently decreased with increasing percentages of patients with more advanced lung function impairment (Table 3).

3.3. TEAEs

Ninety patients (100.0%) in the pirfenidone arm and 77 (96.3%) patients in the placebo arm reported at least one TEAE. TEAEs occurring in ≥10% of patients with more advanced disease in either treatment arm are presented in Table 4. A total of 25/90 (27.8%) patients in the pirfenidone arm and 32/80 (40.0%) patients in the placebo arm reported at least one treatment-emergent serious AE. Treatment-

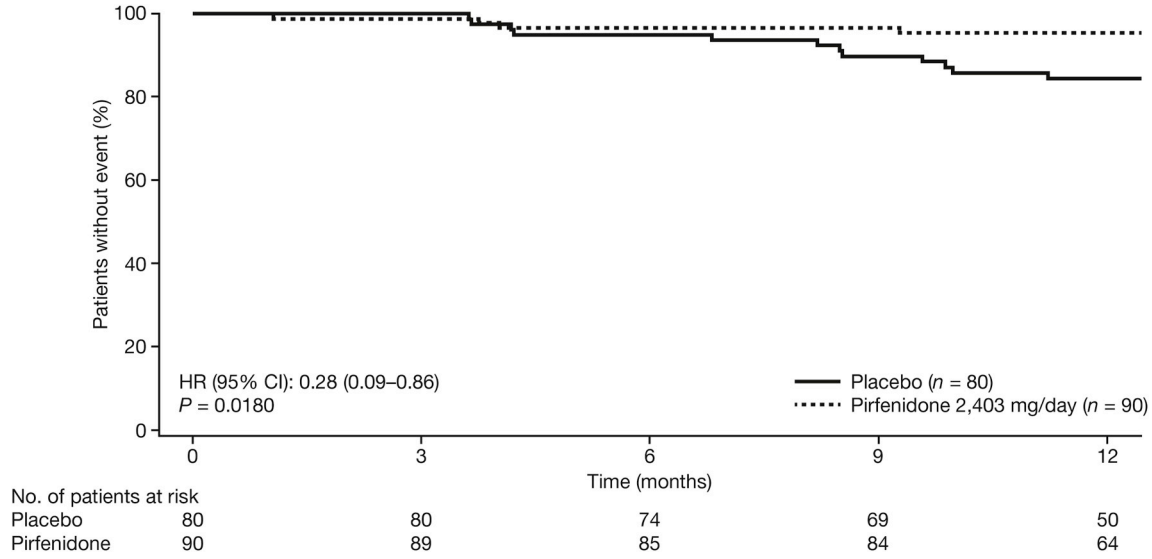

Fig. 1. Time-to-event analysis of all-cause mortality over 52 weeks in patients with more advanced lung function impairment. HR (95% CI) estimated in the context of a proportional hazards model with treatment as a fixed effect and study as a stratification factor. *P*-value is from a log rank test stratified by study. CI, confidence interval; HR, hazard ratio.

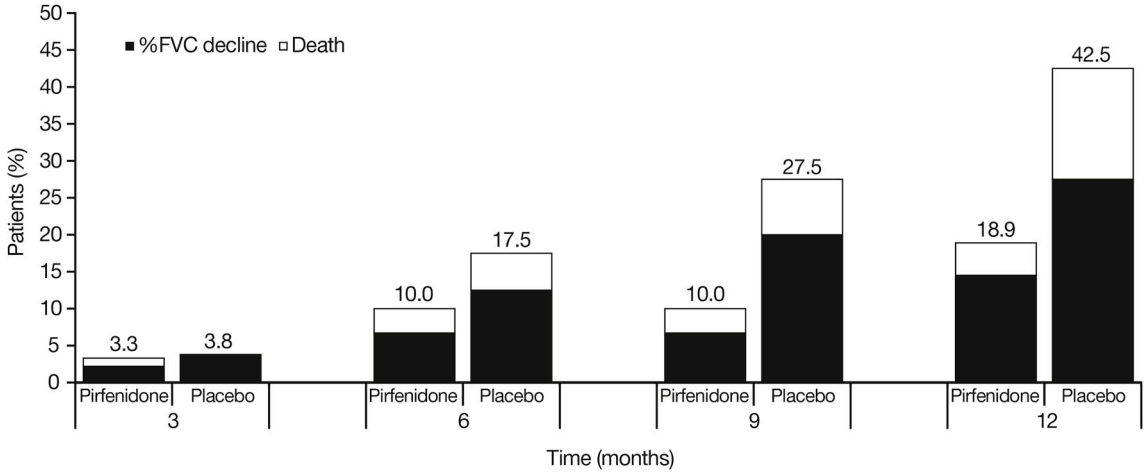

Fig. 2. Percentage of patients with more advanced lung function impairment who experienced ≥10% absolute %FVC decline or all-cause mortality over time. %FVC, percent predicted forced vital capacity.

emergent serious AEs reported by two or more patients in a treatment arm were angina pectoris (pirfenidone, $n = 4$; placebo, $n = 0$), viral gastroenteritis (pirfenidone, $n = 0$; placebo, $n = 2$), pneumonia (pirfenidone, $n = 4$; placebo, $n = 2$), dyspnoea (pirfenidone, $n = 0$; placebo, $n = 2$), IPF (pirfenidone, $n = 3$; placebo, $n = 15$) and respiratory failure (pirfenidone, $n = 0$; placebo, $n = 2$).

A total of 13/90 (14.4%) patients in the pirfenidone arm and 17/80 (21.3%) patients in the placebo arm discontinued treatment due to a

Table 2
Time-to-event analyses and NNT calculations for pirfenidone versus placebo for all-cause mortality and composite outcomes over 52 weeks in patients with more advanced lung function impairment who received pirfenidone 2,403 mg/day or placebo in ASCEND and CAPACITY.

Outcome, *n (%)*	Patients with more advanced lung function impairment[a] $N = 170$			
	Pirfenidone $n = 90$	Placebo $n = 80$	HR (95% CI)	NNT
All-cause mortality	4 (4.4)	12 (15.0)	0.28 (0.09–0.86) $p = 0.0180$[b]	10
≥10% absolute %FVC decline or all-cause mortality	19 (21.1)	35 (43.8)	0.40 (0.23–0.69) $p = 0.0006$[b]	5
Respiratory hospitalisation or all-cause mortality	12 (13.3)	22 (27.5)	0.45 (0.22–0.91) $p = 0.0219$[b]	8
≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality	25 (27.8)	40 (50.0)	0.46 (0.28–0.76) $p = 0.0018$[b]	5

CI, confidence interval; %DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; HR, hazard ratio; NNT, number-needed-to-treat.

[a] %FVC < 50% and/or %DLco < 35%.

[b] *P*-value is from a log-rank test stratified by study.

Table 3
Sample size calculations for clinical trials in patients with IPF enrolling different percentages of patients with more advanced lung function impairment.

	Percentage of study population with more advanced lung function impairment (%)[a,b]		
	100.0	30.0	13.6
All-cause mortality			
Total sample size 80% power, *N*	244	806	1,482
Total sample size 90% power, *N*	324	1,078	1,984
Proportion of patients in the pirfenidone arm	0.044	0.037	0.035
Proportion of patients in the placebo arm	0.150	0.084	0.067
≥10% absolute %FVC decline or all-cause mortality			
Total sample size 80% power, *N*	132	312	430
Total sample size 90% power, *N*	176	418	574
Proportion of patients in the pirfenidone arm	0.211	0.187	0.181
Proportion of patients in the placebo arm	0.438	0.325	0.296
Respiratory hospitalisation or all-cause mortality			
Total sample size 80% power, *N*	252	746	1,300
Total sample size 90% power, *N*	336	998	1,740
Proportion of patients in the pirfenidone arm	0.133	0.092	0.083
Proportion of patients in the placebo arm	0.275	0.160	0.131
≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality			
Total sample size 80% power, *N*	150	306	392
Total sample size 90% power, *N*	200	408	522
Proportion of patients in the pirfenidone arm	0.278	0.217	0.204
Proportion of patients in the placebo arm	0.500	0.362	0.329

%DLco, percent predicted carbon monoxide diffusing capacity; %FVC, percent predicted forced vital capacity; IPF, idiopathic pulmonary fibrosis.
[a] %FVC < 50% and/or %DLco < 35%.
[b] Sample size estimates were obtained on the assumption that a future clinical trial population would include a percentage of patients with more advanced lung function impairment between the values observed in the current randomised patient population (13.6%) and the current more advanced lung function impairment subgroup (100.0%), and a value of 30% was selected. Sample size calculations assume two-sided, two-group chi-squared test of equal proportions with a 0.05 level of significance.

TEAE. The most frequent reason for discontinuation due to a TEAE was IPF (pirfenidone, $n = 0$; placebo, $n = 10$). All other TEAEs leading to discontinuation occurred in only one patient in the pirfenidone and/or placebo arms, with the exception of weight decrease, which led to discontinuation of pirfenidone in two patients. By system organ class, gastrointestinal-related TEAEs led to discontinuation in three (3.3%) patients in the pirfenidone arm and one (1.3%) patient in the placebo arm. One patient discontinued pirfenidone due to a skin and subcutaneous tissue disorder event (rash).

Table 4
TEAEs over 52 weeks reported by ≥ 10% of patients with more advanced lung function impairment in either treatment arm.

TEAE *n (%)*	Patients with more advanced lung function impairment[a] *N* = 170	
	Pirfenidone 2,403 mg/day *n* = 90	Placebo *n* = 80
Dyspnoea	20 (22.2)	27 (33.8)
Nausea	29 (32.2)	14 (17.5)
Cough	20 (22.2)	23 (28.8)
IPF	10 (11.1)	29 (36.3)
Fatigue	22 (24.4)	15 (18.8)
Headache	26 (28.9)	11 (13.8)
Rash	26 (28.9)	7 (8.8)
Diarrhoea	18 (20.0)	15 (18.8)
Weight decrease	19 (21.1)	13 (16.3)
Dizziness	16 (17.8)	14 (17.5)
Bronchitis	18 (20.0)	11 (13.8)
URTI	12 (13.3)	15 (18.8)
Constipation	9 (10.0)	14 (17.5)
Dyspepsia	18 (20.0)	5 (6.3)
Anorexia	14 (15.6)	7 (8.8)
Nasopharyngitis	11 (12.2)	7 (8.8)
Decreased appetite	12 (13.3)	6 (7.5)
Insomnia	11 (12.2)	6 (7.5)
Back pain	9 (10.0)	6 (7.5)
Pneumonia	10 (11.1)	5 (6.3)
Peripheral oedema	6 (6.7)	8 (10.0)
Stomach discomfort	12 (13.3)	1 (1.3)

IPF, idiopathic pulmonary fibrosis; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.
[a] %FVC < 50% and/or %DLco < 35%.

4. Discussion

The results of this analysis suggest that pirfenidone is associated with improved outcomes over 52 weeks versus placebo in patients with IPF and more advanced lung function impairment, defined as %FVC < 50% and/or %DLco < 35%. Compared with placebo, patients treated with pirfenidone had significantly reduced risks of all-cause mortality and significantly less deterioration in lung function, exercise capacity and dyspnoea. Pirfenidone also demonstrated significant benefits versus placebo for multiple composite outcomes: ≥10% absolute %FVC decline or all-cause mortality, respiratory hospitalisation or all-cause mortality, ≥10% absolute %FVC decline or respiratory hospitalisation or all-cause mortality, 6MWD decline ≥50 m or all-cause mortality and increase in UCSD SOBQ total score of ≥20 points or all-cause mortality. The consistency of the effects of treatment with pirfenidone across these different parameters indicates the robustness of these findings.

Baseline characteristics other than FVC and DLco confirmed that patients in this analysis had more advanced disease versus the pooled randomised ASCEND and CAPACITY population, with a greater percentage of patients receiving supplemental oxygen, and greater impairment assessed by the 6-min walk test and UCSD SOBQ [9]. This analysis found that the treatment benefits of pirfenidone in more advanced disease were generally consistent with those observed in the overall pooled population, which included patients with a broader range of lung function impairment [18]. Of note, the treatment effect of pirfenidone versus placebo was greater in patients with more advanced disease versus the overall pooled population for a number of outcomes, a finding that is largely driven by the higher event rate in placebo patients with more advanced disease. For example, the mortality event rate over 52 weeks in patients treated with placebo was higher in patients with more advanced disease versus the pooled randomised population (15.0% vs 6.7%) [19]. In this analysis, pirfenidone

significantly reduced the risk of all-cause mortality by 72% in patients with more advanced disease versus 48% in the pooled population [19]. Furthermore, NNT calculations suggested that one death could be avoided for every 10 patients with IPF and more advanced disease treated with pirfenidone over 52 weeks.

Other clinically relevant outcomes investigated in this analysis included respiratory hospitalisation, exercise capacity and dyspnoea. As might be expected, respiratory hospitalisation in patients receiving placebo was more frequent in patients with more advanced disease versus the pooled randomised population (25.0% vs 11.9%) [20]. Respiratory hospitalisation is a key outcome in IPF and an important predictor of mortality [20]. The finding that pirfenidone can reduce the incidence of this clinically relevant outcome in a subgroup of patients at heightened risk is arguably critical to informing the management of these patients. In addition, pirfenidone was associated with significant benefits in median change from baseline in 6MWD and UCSD SOBQ total score, with median treatment differences versus placebo of 36.7 m and −8.0 points, respectively. Overall, our results suggest that patients with IPF can benefit from pirfenidone across a broad range of disease severities, including more advanced disease.

The results of this analysis are of particular interest because clinical trials in more advanced IPF have been limited. For example, the pivotal Phase III trials of pirfenidone excluded patients with %FVC < 50% or %DLco < 30% at screening (ASCEND) or %FVC < 50% at screening or Day 1 and %DLco < 35% at screening (CAPACITY) [11,12]. Similarly, the INPULSIS trials of nintedanib excluded patients with %FVC < 50% or %DLco < 30% [10]. Possible reasons for excluding patients with more advanced disease include concerns that fibrotic lung damage might be too extensive to allow documentation of a treatment benefit, that follow-up might not be feasible, that AEs might be more pronounced versus less advanced disease or that ascertaining efficacy might be complicated by the higher mortality expected among patients with more advanced disease. Although some studies have included patients with more advanced disease, those data are limited due to factors including retrospective study design, low patient numbers, different methods of measuring disease severity and doses of pirfenidone ≤1,800 mg/day [21,22]. Our results show that approximately 80% of patients with more advanced disease treated with pirfenidone completed 52 weeks of treatment, indirectly suggesting that patients were able to attend follow-up visits. Furthermore, this analysis suggests that pirfenidone has higher comparative efficacy in patients with more advanced disease versus the overall pooled population, with a similar occurrence of common TEAEs and discontinuation due to TEAEs compared with the pooled population.

It should be recognised that delayed diagnosis and inevitable disease progression mean that many patients with IPF in clinical practice present with, or develop, more advanced lung function impairment. Post-hoc evidence has suggested that patients with varying levels of lung function impairment can benefit from initiating treatment. For example, in a subgroup analysis of ASCEND and CAPACITY, pirfenidone significantly reduced the rate of lung function decline versus placebo in patients with %FVC < 65% and %DLco < 40% [9]. Furthermore, in the open-label RECAP extension study of ASCEND and CAPACITY, patients with %FVC < 50% and ≥50% at the baseline visit of RECAP experienced similar annual FVC decline over 180 weeks with pirfenidone, regardless of prior treatment group [23]. Similar findings have been reported with nintedanib; for example, in a post-hoc analysis of the open-label INPULSIS-ON extension study, comparable FVC decline over 48 weeks was reported in patients with %FVC ≤50% and > 50% [24].

The frequency of TEAEs in patients receiving pirfenidone was similar in patients with more advanced lung function impairment versus the pooled population for a number of common AEs, including nausea (32.2% vs 35.5%, respectively), rash (28.9% vs 29.2%) and fatigue (24.4% vs 23.0%) [9]. Overall, these results suggest that the tolerability of pirfenidone in patients with more advanced disease is comparable with the known safety profile of pirfenidone [9,25]. These results are supported by real-world data from an analysis of 1,009 patients with IPF in the PASSPORT registry, which indicated that the incidence of adverse drug reactions after 6 months of pirfenidone treatment was comparable in patients with %FVC < 50% versus ≥50%, with the exception of nausea and decreased appetite, which were more frequent in patients with %FVC < 50%, and rash, which was more frequent in patients with %FVC ≥50% [26]. Further to the observation that the TEAE profile of pirfenidone in patients with more advanced disease was similar to that found in the pooled population, the percentage of patients discontinuing pirfenidone due to a TEAE was also comparable between the populations [9]. This finding is aligned with that of a Japanese post-marketing surveillance study of 1,371 patients treated with pirfenidone, two-thirds of whom had more advanced disease. In the surveillance study, similar rates of discontinuation due to an adverse drug reaction were reported across the disease severity spectrum. However, it should be noted that in this study, the dose of pirfenidone was 1,800 mg/day and disease severity was classified according to arterial partial pressure of oxygen at rest [21].

Prescribing and/or reimbursement restrictions are institutionalised in Europe, where pirfenidone is not approved for the treatment of 'severe' IPF [5], unlike in the USA where pirfenidone is approved regardless of disease severity [7]. This is largely due to the lack of an evidence base characterising the risk-benefit profile of antifibrotics versus placebo in more advanced disease. Although this analysis addresses some of the gaps in the literature regarding antifibrotic treatment in patients with more advanced lung function impairment, prospective clinical trials would ideally investigate this topic further. As a theoretical exercise, we used our results to calculate the sample size required in a placebo-controlled trial to detect a significant difference in all-cause mortality over 52 weeks between treatments with 80% and 90% power. For a trial with a population similar to the pooled ASCEND and CAPACITY population, where 13.6% of patients had more advanced lung function impairment, a sample size of 1,984 patients would be required for 90% power [9]. In contrast, if 30% of enrolled patients had more advanced lung function impairment, the required sample size would be reduced to 1,078. The use of a composite outcome further reduced the required sample sizes. Finding ways to reduce sample size is important because IPF is a rare disease [27], and recruiting sufficient numbers of patients for trials can be challenging. These results suggest that use of composite outcomes and increased enrolment of patients with more advanced disease are effective methods to reduce the required sample size in future IPF trials. Indeed, patients with more advanced disease appear to be an ideal target group for enrolment in future trials because of the high event rates of outcomes such as hospitalisation and mortality, which were apparent in this analysis. Increasing the trial duration might also be expected to increase event rates of important outcomes; however, this was not considered in our calculations because results were limited to those occurring over 52 weeks.

Overall, our observations support the inclusion of patients with more advanced lung function impairment in future IPF trials investigating novel therapies, as well as combination antifibrotic therapy [28,29]. Whether patients with even greater lung function impairment than those included in this analysis should be included in future clinical trials is open to speculation, but it is certainly a concept for further investigation.

It should be acknowledged that the results of this analysis are limited by its post-hoc nature and the relatively small number of patients in the pivotal Phase III trials of pirfenidone with more advanced disease. Although the NNT calculations in this analysis are helpful for putting effect sizes into perspective, the relatively small sample size should be considered when interpreting these data. The majority of patients included in this analysis were eligible on the basis of their %DLco values, with only a small number of patients meeting the %FVC inclusion criteria. Differences in study design between ASCEND and CAPACITY may

also have affected results obtained from pooling data [11,12]; 74.7% of patients included in this analysis were enrolled in ASCEND. It should also be noted that ASCEND and CAPACITY excluded patients with certain comorbidities including recent unstable cardiac or pulmonary disease, cancer, asthma and chronic obstructive pulmonary disease [11,12]. It is possible that these aspects of study design may affect the generalisability of our results to real-world populations of patients who are likely to have multiple comorbidities.

5. Conclusion

The results of this study suggest that pirfenidone is effective in patients with IPF and more advanced lung function impairment across multiple important disease domains. In addition, these consistent salutary effects were not accompanied by any discernable increased risk of TEAEs compared with the known safety profile of pirfenidone. Further research is needed to increase the evidence base supporting the treatment of patients with more advanced disease. While previous studies have focused on patients with limited-to-moderate lung function impairment, patients with more advanced disease should be considered for inclusion in future IPF clinical trials.

Funding

This analysis was supported by Genentech. and F. Hoffmann-La Roche. This analysis used data from studies sponsored by F. Hoffmann-La Roche, Ltd., Basel, Switzerland, which was involved in study design and in the collection, analysis and interpretation of the data. The analysis presented here was designed and conducted by F. Hoffmann-La Roche, Ltd. in collaboration with the academic authors. The authors made the decision to submit the article for publication.

Competing interests

SDN is a consultant and is on the speakers' bureau for F. Hoffmann-La Roche, Ltd. and Boehringer Ingelheim. His institution has received research funding from both companies.

UC has served as a member of a study adjudication committee for Gilead, and has served as a consultant and speaker for Bayer, Boehringer Ingelheim, F. Hoffmann-La Roche, Ltd. and InterMune, a wholly owned subsidiary of F. Hoffmann-La Roche, Ltd. since 2014. He has received grants from Boehringer Ingelheim and InterMune, a wholly owned subsidiary of F. Hoffmann-La Roche, Ltd. since 2014, and has served as a consultant for Biogen, Centocor, FibroGen, Gilead, GlaxoSmithKline, Global Blood Therapeutics and UCB Celltech.

CA has received personal fees for lectures and consulting services from Bayer, Boehringer Ingelheim, F. Hoffmann-La Roche, Ltd., GlaxoSmithKline, InterMune, a wholly owned subsidiary of F. Hoffmann-La Roche, Ltd. since 2014, and MSD. He has received grants from Boehringer Ingelheim.

JB has received personal fees for lectures and consulting services from Actelion, Bayer, Biogen, Boehringer Ingelheim, F. Hoffmann-La Roche, Ltd. and Galapagos. He is a member of national and international guideline committees for IPF.

WAW has received grants paid to his institution from F. Hoffmann-La Roche, Ltd. and Boehringer Ingelheim.

K-UK, JLS, EM, WC[1] and SLL are employees of F. Hoffmann-La Roche, Ltd./Genentech, Inc.

[1]Now based at FibroGen, Inc., San Francisco, CA, USA.

PWN was a member of the ASCEND and CAPACITY study steering committees, and was a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, F. Hoffmann-La Roche, Ltd./Genentech, Inc., InterMune, a wholly owned subsidiary of F. Hoffmann-La Roche, Ltd. since 2014, Moerae Matrix and Takeda.

Data-sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). 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.html).

Patient consent

Obtained.

Ethics approval

ASCEND and CAPACITY were conducted in accordance with the International Conference on Harmonisation Guidelines and the Declaration of Helsinki, as well as any relevant local legal and regulatory requirements.

Acknowledgements

The authors would like to thank Benjamin Trzaskoma and Chin-Yu Lin, employees of Genentech, Inc., for their work on the statistical analyses presented in this manuscript. Medical writing support was provided by Catherine Stanton of CMC AFFINITY, a division of McCann Health Medical Communications, Ltd., Glasgow, UK, funded by Genentech, Inc. and F. Hoffmann-La Roche, Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.04.016.

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