Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

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Summary

Background Idiopathic pulmonary fibrosis is a progressive and fatal lung disease with inevitable loss of lung function. The CAPACITY programme (studies 004 and 006) was designed to confirm the results of a phase 2 study that suggested that pirfenidone, a novel antifibrotic and anti-inflammatory drug, reduces deterioration in lung function in patients with idiopathic pulmonary fibrosis.

Methods In two concurrent trials (004 and 006), patients (aged 40–80 years) with idiopathic pulmonary fibrosis were randomly assigned to oral pirfenidone or placebo for a minimum of 72 weeks in 110 centres in Australia, Europe, and North America. In study 004, patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo; in study 006, patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The randomisation code (permuted block design) was computer generated and stratified by region. All study personnel were masked to treatment group assignment until after final database lock. Treatments were administered orally, 801 mg or 399 mg three times a day. The primary endpoint was change in percentage predicted forced vital capacity (FVC) at week 72. Analysis was by intention to treat. The studies are registered with ClinicalTrials.gov, numbers NCT00287729 and NCT00287716.

Findings In study 004, 174 of 435 patients were assigned to pirfenidone 2403 mg/day, 87 to pirfenidone 1197 mg/day, and 174 to placebo. In study 006, 171 of 344 patients were assigned to pirfenidone 2403 mg/day, and 173 to placebo. All patients in both studies were analysed. In study 004, pirfenidone reduced decline in FVC (p=0·001). Mean FVC change at week 72 was –8·0% (SD 16·5) in the pirfenidone 2403 mg/day group and –12·4% (18·5) in the placebo group (difference 4·4%, 95% CI 0·7 to 9·1); 35 (20%) of 174 versus 60 (35%) of 174 patients, respectively, had a decline of at least 10%. A significant treatment effect was noted at all timepoints from week 24 and in an analysis over all study timepoints (p=0·0007). Mean change in percentage FVC in the pirfenidone 1197 mg/day group was intermediate to that in the pirfenidone 2403 mg/day and placebo groups. In study 006, the difference between groups in FVC change at week 72 was not significant (p=0·501). Mean change in FVC at week 72 was –9·0% (SD 19·6) in the pirfenidone group and –9·6% (19·1) in the placebo group, and the difference between groups in predicted FVC change at week 72 was not significant (0·6%, –3·5 to 4·7); however, a consistent pirfenidone effect was apparent until week 48 (p=0·005) and in an analysis of all study timepoints (p=0·007). Patients in the pirfenidone 2403 mg/day group had higher incidences of nausea (125 [36%] of 345 vs 60 [17%] of 347), dyspepsia (66 [19%] vs 26 [7%]), vomiting (47 [14%] vs 15 [4%]), anorexia (37 [11%] vs 13 [4%]), photosensitivity (42 [12%] vs 6 [2%]), rash (111 [32%] vs 40 [12%]), and dizziness (63 [18%] vs 35 [10%]) than did those in the placebo group. Fewer overall deaths (19 [6%] vs 29 [8%]) and fewer deaths related to idiopathic pulmonary fibrosis (12 [3%] vs 25 [7%]) occurred in the pirfenidone 2403 mg/day groups than in the placebo groups.

Interpretation The data show pirfenidone has a favourable benefit risk profile and represents an appropriate treatment option for patients with idiopathic pulmonary fibrosis.

Introduction

Idiopathic pulmonary fibrosis is a chronic, progressive, and fatal lung disease with no known cause or cure. It is characterised by progressive dyspnoea and irreversible loss of lung function.[1] Disease progression is heterogeneous; however, the clinical course is ultimately deterioration, with an estimated median survival of 2–5 years.[2–4] The uniformly poor prognosis, with paucity of treatments, provides a strong rationale for the development of novel drugs that target the underlying fibroproliferative process and attenuate decline in pulmonary function.

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally bioavailable synthetic molecule. It was shown to regulate the activity of transforming growth factor (TGF) β and tumour necrosis factor (TNF) α in vitro;[5–9] and inhibit fibroblast proliferation and collagen synthesis and reduce cellular and histological markers of fibrosis in animal models of lung fibrosis.[6,9–12]

Clinical proof of concept was shown in a randomised, double-blind, placebo-controlled phase 2 study of 107 Japanese patients with idiopathic pulmonary fibrosis.[13] This study was stopped early because an

interim analysis showed favourable efficacy; final analysis at 9 months showed a reduced decline in the mean change in vital capacity in pirfenidone-treated patients (p=0·037).[13] These findings led to three phase 3 studies with primary endpoints of change in lung function—one in Japan and two across North America and Europe. In the Japanese phase 3, randomised, double-blind, placebo-controlled study of 275 patients with idiopathic pulmonary fibrosis, pirfenidone reduced mean change in vital capacity at week 52 (absolute difference 70 mL; relative difference 44%; p=0·042), and improved progression-free survival time (p=0·028).[14] These data, with the results of the phase 2 study, led to regulatory approval of pirfenidone in Japan for the treatment of idiopathic pulmonary fibrosis.

The CAPACITY (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes) programme included two similar multinational trials (studies 004 and 006) designed to confirm the effect of pirfenidone on reduction of decline in lung function.

Methods

Patients

The studies were done at 110 centres in 13 countries (Australia [n=3], Belgium [n=2], Canada [n=9], France [n=5], Germany [n=6], Ireland [n=1], Italy [n=9], Mexico [n=1], Poland [n=2], Spain [n=4], Switzerland [n=1],

UK [n=3], and USA [n=64]). All methods apply to both studies 004 and 006, unless otherwise noted. Eligible patients were aged 40–80 years with a diagnosis of idiopathic pulmonary fibrosis in the previous 48 months and no evidence of improvement in measures of disease severity over the preceding year. Inclusion criteria included predicted FVC of at least 50%, predicted carbon monoxide diffusing capacity (DLco) of at least 35%, either predicted FVC or predicted DLco of 90% or less, and 6-min walk test (6MWT) distance of at least 150 m. Patients younger than 50 years and those not meeting protocol criteria for definite idiopathic pulmonary fibrosis by use of high-resolution CT (HRCT) were required to have a lung biopsy sample showing usual interstitial pneumonia (webappendix pp 1–3). Independent expert adjudication was obtained for interpretation of HRCT or surgical biopsy sample in instances of uncertainty. Exclusion criteria included obstructive airway disease, connective tissue disease, alternative explanation for interstitial lung disease, and being on a waiting list for a lung transplant.

All patients provided written informed consent, and the protocol was approved by the institutional review board or ethics committee at each centre.
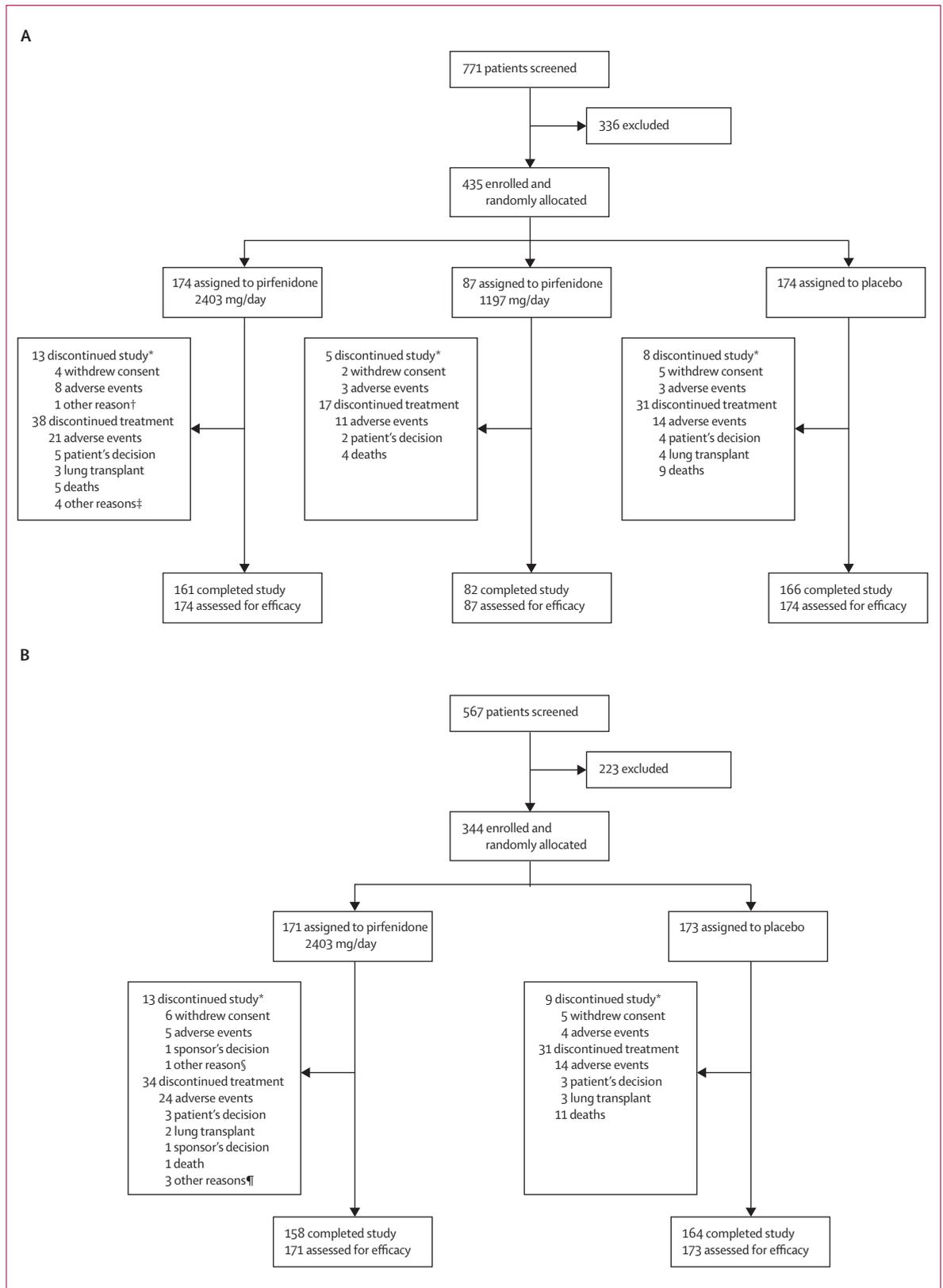
See **Online** for webappendix

Randomisation and masking

Patients were randomly assigned to oral pirfenidone or placebo for 72 weeks from the date the last patient was

	Study 004			Study 006	
	Pirfenidone 1197 mg/day (n=87)	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)
Age (years)	68·0 (7·6)	65·7 (8·2)	66·3 (7·5)	66·8 (7·9)	67·0 (7·8)
Men	65 (75%)	118 (68%)	128 (74%)	123 (72%)	124 (72%)
White	83 (95%)	168 (97%)	168 (97%)	169 (99%)	171 (99%)
Weight (kg)					
Men	88·4 (13·5)	91·3 (15·9)	88·9 (16·1)	95·4 (17·4)	93·2 (15·1)
Women	72·8 (13·0)	77·0 (13·2)	77·0 (13·6)	76·6 (14·0)	77·5 (14·8)
Non-US enrolment	29 (33%)	60 (34%)	60 (34%)	23 (13%)	23 (13%)
Smoking status					
Never	27 (31%)	56 (32%)	51 (29%)	59 (35%)	64 (37%)
Former	57 (66%)	110 (63%)	114 (66%)	112 (65%)	101 (58%)
Current	3 (3%)	8 (5%)	9 (5%)	0	8 (5%)
Definite idiopathic pulmonary fibrosis (HRCT)	83 (95%)	159 (91%)	164 (94%)	149 (87%)	158 (91%)
Surgical lung biopsy	32 (37%)	86 (49%)	85 (49%)	94 (55%)	94 (54%)
Diagnosis (≤1 year) of idiopathic pulmonary fibrosis	46 (53%)	83 (48%)	81 (47%)	100 (58%)	107 (62%)
Predicted FVC (%)	76·4 (14·4)	74·5 (14·5)	76·2 (15·5)	74·9 (13·2)	73·1 (14·2)
DLco (% predicted)	47·2 (8·2)	46·4 (9·5)	46·1 (10·2)	47·8 (9·8)	47·4 (9·2)
A-a gradient (mm Hg)	15·5 (10·4)	17·7 (10·6)	18·9 (14·7)	18·3 (11·1)	17·0 (10·4)
6MWT distance (m)	417·5 (112·8)	411·1 (91·8)	410·0 (90·9)	378·0 (82·2)	399·1 (89·7)
Use of supplemental oxygen	15 (17%)	29 (17%)	25 (14%)	48 (28%)	49 (28%)

Data are number (%) or mean (SD). HRCT=high-resolution CT. FVC=forced vital capacity. DLco=haemoglobin-corrected carbon monoxide diffusing capacity. A-a gradient=alveolar-arterial oxygen gradient. 6MWT=6-minute walk test.

Table 1: Baseline characteristics of patients

A

771 patients screened

336 excluded

435 enrolled and
randomly allocated

174 assigned to pirfenidone
2403 mg/day

87 assigned to pirfenidone
1197 mg/day

174 assigned to placebo

13 discontinued study*
  4 withdrew consent
  8 adverse events
  1 other reason†
38 discontinued treatment
  21 adverse events
  5 patient's decision
  3 lung transplant
  5 deaths
  4 other reasons‡

5 discontinued study*
  2 withdrew consent
  3 adverse events
17 discontinued treatment
  11 adverse events
  2 patient's decision
  4 deaths

8 discontinued study*
  5 withdrew consent
  3 adverse events
31 discontinued treatment
  14 adverse events
  4 patient's decision
  4 lung transplant
  9 deaths

161 completed study
174 assessed for efficacy

82 completed study
87 assessed for efficacy

166 completed study
174 assessed for efficacy

B

567 patients screened

223 excluded

344 enrolled and
randomly allocated

171 assigned to pirfenidone
2403 mg/day

173 assigned to placebo

13 discontinued study*
  6 withdrew consent
  5 adverse events
  1 sponsor's decision
  1 other reason§
34 discontinued treatment
  24 adverse events
  3 patient's decision
  2 lung transplant
  1 sponsor's decision
  1 death
  3 other reasons¶

9 discontinued study*
  5 withdrew consent
  4 adverse events
31 discontinued treatment
  14 adverse events
  3 patient's decision
  3 lung transplant
  11 deaths

158 completed study
171 assessed for efficacy

164 completed study
173 assessed for efficacy

Figure 1: **Trial profile**
(A) Study 004. (B) Study 006.
*Does not include death or
lung transplantation.
†Discontinued study because
of deportation. ‡Includes
unknown interaction with
chemotherapy (n=1),
deportation (n=1),
non-adherence to assigned
treatment regimen (n=1), and
spontaneous discontinuation
of study drug (n=1).
§Discontinued study due to
placement on lung
transplantation schedule.
¶Includes placement on lung
transplantation schedule (n=1),
prolonged QTc interval that
was subsequently ascertained
to be present at baseline (n=1),
and unknown (n=1).

enrolled. In study 004, patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo; in study 006, patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The 2403 mg/day dose was derived by normalisation of the 1800 mg/day dose used in the Japanese studies to the predicted bodyweights of the predominantly US-based study population. The randomisation code (permuted block design with five patients per block in study 004 and four per block in study 006) was computer generated, stratified by region, by an independent statistician. Study centres, using an interactive voice response system, assigned study drug bottles to patients. The independent statistician had no role other than assignation of the randomisation code and study drug bottle numbers. All personnel involved in the study were masked to treatment group assignment until after final database lock.

Study drug was administered with food in three daily doses (pirfenidone 801 mg or 399 mg) and increased to full dose over 2 weeks. Dose modification guidelines were provided for expected adverse events, including fatigue, gastrointestinal symptoms, skin reactions, and liver function test abnormalities. Concomitant treatments for idiopathic pulmonary fibrosis were prohibited, with exceptions for short courses of azathioprine, cyclophosphamide, corticosteroids, or acetylcysteine for protocol-defined acute exacerbation of idiopathic pulmonary fibrosis, acute respiratory decompensation, or progression of disease (webappendix p 4).

Physical examination and clinical laboratory assessments were done at weeks 2, 4, 6, and 12, and every 12 weeks thereafter. Pulmonary function, exercise tolerance, and dyspnoea were assessed every 12 weeks. Patients were to continue assessments until study completion, even after permanent treatment discontinuation, and all such assessments were included in the intention-to-treat (ITT) analyses.

Statistical analysis

The primary endpoint was change in percentage of predicted FVC from baseline to week 72. The primary efficacy analysis was by use of a rank analysis of covariance (ANCOVA) model, stratified by region, with standardised rank change in FVC as the outcome and standardised rank baseline percentage predicted FVC as a covariate, evaluated against a final adjusted two-tailed p value of 0·0498. Magnitude of treatment effect was estimated by use of differences in treatment group means and categorical change in FVC. To assess treatment effect over the full study, a repeated-measures analysis with averaging of percentage predicted FVC change over all assessment timepoints was prespecified.

Secondary efficacy endpoints were categorical FVC (5-level scale), progression-free survival (time to confirmed ≥10% decline in percentage predicted FVC, ≥15% decline in percentage predicted DLco or death), worsening idiopathic pulmonary fibrosis (time to acute exacerbation, death, lung transplantation, or admission to hospital for respiratory problems), dyspnoea (University of California San Diego Shortness of Breath Questionnaire),[15] 6MWT distance, worst peripheral oxygen saturation (SpO2) during the 6MWT, percentage predicted DLco, and fibrosis by use of HRCT (study 006 only). Mortality was prespecified as an exploratory endpoint, and death related to idiopathic pulmonary fibrosis was assigned by investigators masked to assignment.

In the efficacy analyses, pirfenidone 2403 mg/day was compared with placebo in the ITT population by use of SAS (version 9.1.3). The group assigned to pirfenidone 1197 mg/day in study 004 was summarised descriptively.
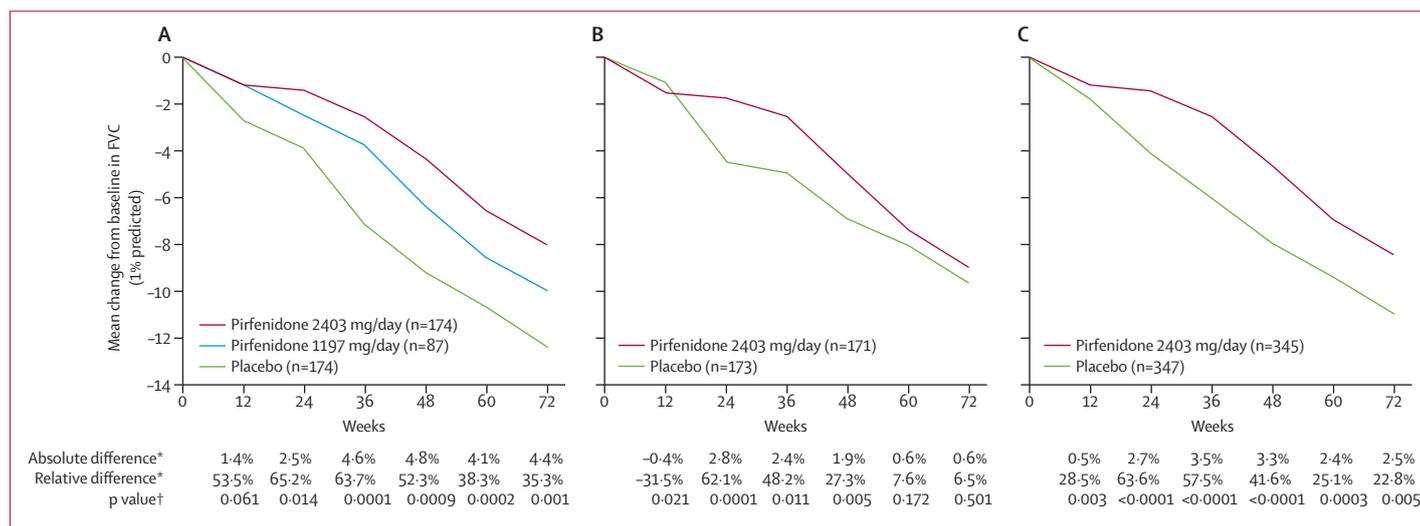

Figure 2: Mean change from baseline in percentage predicted FVC in study 004 (A), study 006 (B), and the pooled population (C)

FVC=forced vital capacity. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day *vs* placebo). 95% CIs were only calculated for absolute differences for the week 72 timepoint in study 004 (0·7 to 9·1) and study 006 (−3·5 to 4·7).

	Study 004				Study 006				Pooled data			
	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Absolute difference (95% CI)	p value*
Categorical change in FVC ≥10%	35 (20%)	60 (35%)	14·4 (7·4 to 21·3)	0·001†	39 (23%)	46 (27%)	3·8 (−2·7 to 10·2)	0·440†	74 (21%)	106 (31%)	9·1 (4·3 to 13·9)	0·003†
Progression-free survival time‡	..	..	0·64 (0·44 to 0·95)	0·023§	..	..	0·84 (0·58 to 1·22)	0·355§	..	..	0·74 (0·57 to 0·96)	0·025§
Mean change in 6MWT distance (m)	−60·4	−76·8	16·4 (−10·9 to 43·7)	0·171	−45·1	−76·9	31·8 (3·2 to 60·4)	0·0009	−52·8	−76·8	24·0 (4·3 to 43·7)	0·0009
Mean change in DLco (% predicted)	−7·9	−9·9	2·0 (−0·4 to 4·4)	0·145	−9·8	−9·2	−0·5 (−3·2 to 2·2)	0·996	−8·8	−9·6	0·7 (−1·1 to 2·5)	0·301
Mean change in dyspnoea score¶	12·1	15·2	−3·1 (−8·5 to 2·3)	0·509	11·9	13·9	−2·0 (−7·6 to 3·6)	0·604	12·0	14·5	−2·5 (−6·4 to 1·4)	0·405
Mean change in worst SpO₂ during 6MWT (%)	−1·5	−2·3	0·8 (−0·2 to 1·8)	0·087	−1·9	−1·3	−0·5 (−1·7 to 0·7)	0·893	−1·7	−1·8	0·1 (−0·7 to 0·9)	0·261
Time to worsening in idiopathic pulmonary fibrosis	..	..	0·84 (0·50 to 1·42)‡	0·515§	..	..	0·73 (0·43 to 1·24)‡	0·248§	..	..	0·78 (0·54 to 1·14)‡	0·201§
Categorical change in HRCT-diagnosed fibrosis‖	NA	NA	NA	NA	NA	NA	NA	0·894	NA	NA	NA	NA

FVC=forced vital capacity. 6MWT=6-minute walk test. DLco=haemoglobin-corrected carbon monoxide diffusing capacity. SpO₂=peripheral oxygen saturation. HRCT=high-resolution CT. NA=not applicable. *Rank ANCOVA (pirfenidone 2403 mg/day vs placebo), unless otherwise indicated. †Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day vs placebo) based on five categories (severe decline, ≥20%; moderate decline, <20% but ≥10%; mild decline; <10% but ≥0; mild improvement, >0 but <10%; and moderate improvement, ≥10%). ‡Hazard ratio (95% CI) based on the Cox proportional hazard model with geographic region (USA vs non-USA) as a stratum. §Log-rank test (pirfenidone 2403 mg/day vs placebo). ¶Based on the University of California San Diego Shortness of Breath Questionnaire: total score ranges from 0 to 120, with larger scores indicating greater shortness of breath. ‖Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day vs placebo) based on five categories (much better, better, same, worse, or much worse); assessed in study 006 only.

Table 2: Secondary efficacy endpoints at week 72

Analyses of pooled data were prespecified to derive precise estimates of magnitude of treatment effect. Missing values as a result of death were assigned the worst rank in ANCOVA analyses, and worst possible outcome in mean change analyses (eg, FVC=0) and categorical analyses (webappendix p 5). Other missing data were imputed with the average value from three patients with the smallest sum of squared differences at each visit with data that were not missing. A data monitoring committee reviewed safety and efficacy data and undertook two interim analyses of all-cause mortality in the pooled dataset against a conservative stopping boundary of p=0·0001.

The studies are registered with ClinicalTrials.gov, numbers NCT00287729 and NCT00287716.

Role of the funding source

The sponsor participated in the study design, data collection, data analysis, and writing the report. After study completion, the sponsor analysed and maintained the data. Authors participated in design, conduct, analysis, and reporting; had full access to data; and no limits were placed on the content of the report.

Results

Between April, 2006, and November, 2008, 435 patients were enrolled in study 004, and 344 in study 006. Table 1 shows that there were no pronounced baseline imbalances between treatment groups within each study. The percentages of patients with diagnoses of idiopathic pulmonary fibrosis within 1 year, on supplemental oxygen, and enrolment at US sites were higher in study 006 than in study 004 (table 1). 713 (92%) of 779 patients met criteria for definite idiopathic pulmonary fibrosis with HRCT; 391 (50%) underwent surgical lung biopsy, with 372 (95%) having definite usual interstitial pneumonia.

Figure 1 shows that 409 (94%) of 435 patients in study 004 and 322 (94%) of 344 in study 006 completed the study. 109 patients (14%) discontinued treatment prematurely: 13 (15%), 30 (17%), and 18 (10%) in the pirfenidone 1197 mg/day, pirfenidone 2403 mg/day, and placebo groups, respectively in study 004; and 31 (18%) and 17 (10%) in the pirfenidone and placebo groups, respectively, in study 006 (figure 1). Treatment compliance was high: 380 (88%) of 432 patients in the pirfenidone groups and 323 (93%) of 347 in the placebo groups adhered to treatment (ie, received ≥80% of scheduled doses).

In study 004, at week 72, pirfenidone 2403 mg/day significantly reduced mean decline in percentage predicted FVC compared with placebo (−8·0% [SD 16·5] vs −12·4% [18·5], respectively; figure 2A), and the proportion of patients with FVC decline of 10% or more (table 2). Treatment effect was evident by week 24 and

persisted until week 72 (figure 2). Repeated-measures analysis of percentage predicted FVC change across all assessment timepoints also showed a pirfenidone effect (p=0·0007; webappendix p 6). Outcomes in the pirfenidone 1197 mg/day group were intermediate to the pirfenidone 2403 mg/day and placebo groups.

In study 006, no significant difference was noted between the pirfenidone and placebo groups in percentage predicted FVC change at week 72 (figure 2B): mean change was –9·0% (SD 19·6) in patients in the pirfenidone 2403 mg/day group and –9·6% (19·1) in patients in the placebo group, respectively. The proportions of patients with a decline in FVC of 10% or more were not significantly different (table 2). However, a significant treatment effect was evident at every timepoint from week 12 until week 48 (figure 2B), and in the repeated-measures analysis of percentage predicted FVC change over all assessment timepoints (p=0·007; webappendix p 6).

The primary endpoint analysis of the pooled population also showed a pirfenidone treatment effect on percentage predicted FVC at week 72 (p=0·005; figure 2C): mean change was –8·5% in the patients in the pirfenidone 2403 mg/day group and –11·0% in those in the placebo group, and a smaller proportion of patients had a decline in FVC of 10% or more in the pooled pirfenidone group (table 2).

Pirfenidone 2403 mg/day prolonged progression-free survival in study 004, with a 36% reduction in risk of death or disease progression (table 2). In study 006, no significant effect was noted on progression-free survival (table 2). In the pooled analysis, pirfenidone prolonged progression-free survival by 26% compared with placebo (table 2; figure 3C).

Pirfenidone 2403 mg/day significantly reduced decline in 6MWT distance at week 72 in study 006 but not study 004 (table 2). In the pooled population, a 31% relative difference was noted between treatment groups at week 72 (figure 4). The minimum clinically important difference in 6MWT distance in patients with idiopathic pulmonary fibrosis has been reported as 24–45 m.[16–18] In a post-hoc analysis, 62 (36%) of 170 patients in the pirfenidone group and 80 (47%) of 170 in the placebo group had a 50 m or more decrement in 6MWT distance in study 004 (p=0·049), and 56 (33%) of 169 and 79 (47%) of 168, respectively in study 006 (p=0·010). The Mantel-Haenszel relative risk was 0·74 (95% CI 0·62–0·89) for overall relative risk in the post-hoc analysis in the pooled population.

No significant treatment group differences were noted in either study in percentage predicted DLco, dyspnoea, worst SpO2 during the 6MWT, time to worsening idiopathic pulmonary fibrosis, or fibrosis diagnosed by use of HRCT (table 2).

In the analyses of the pooled population, the hazard ratios for overall all-cause mortality and mortality related to idiopathic pulmonary fibrosis at any time during the study favoured pirfenidone (table 3). Hazard ratios for
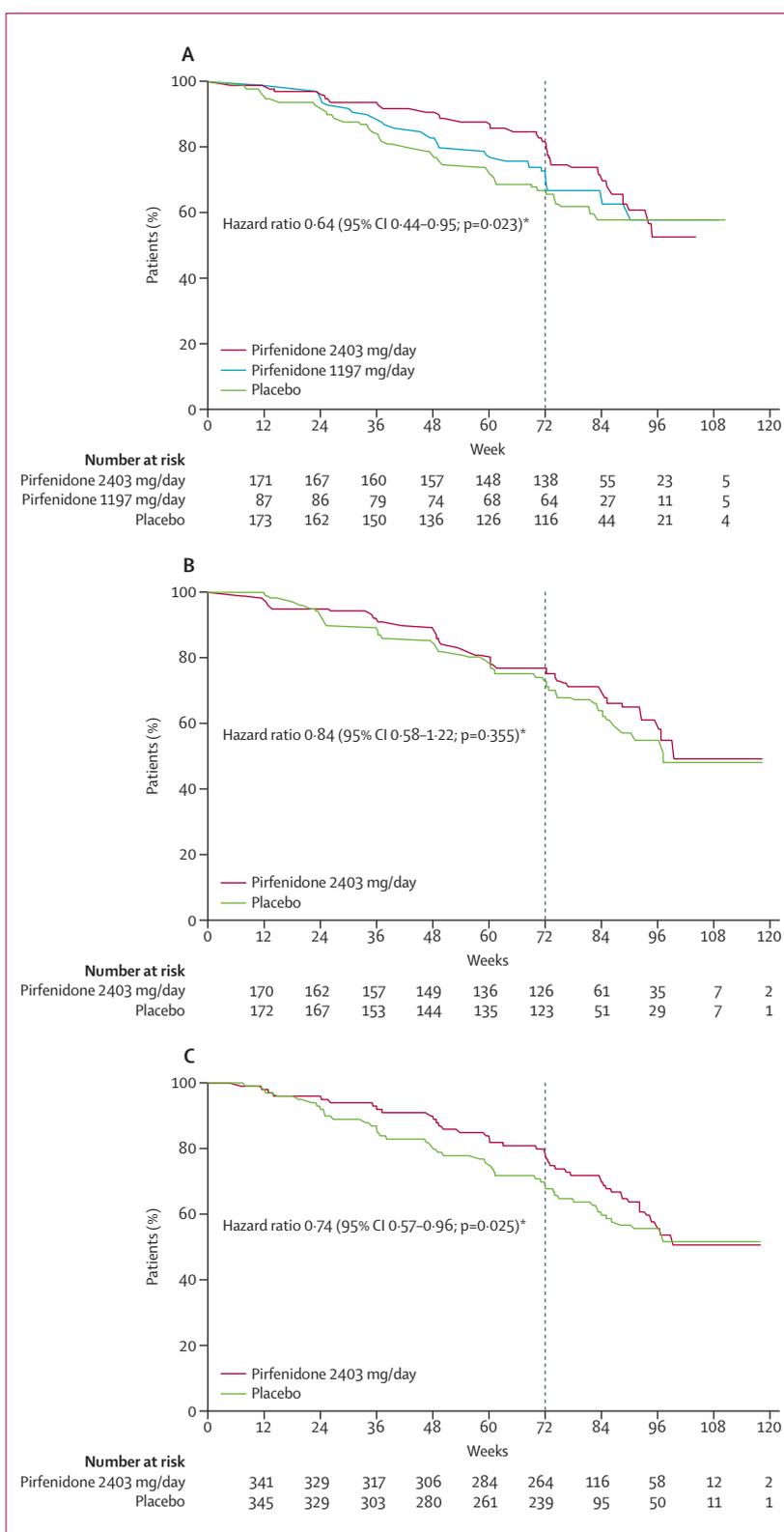

Figure 3: Kaplan-Meier distribution of progression-free survival time in study 004 (A), Study 006 (B), and the pooled population (C)
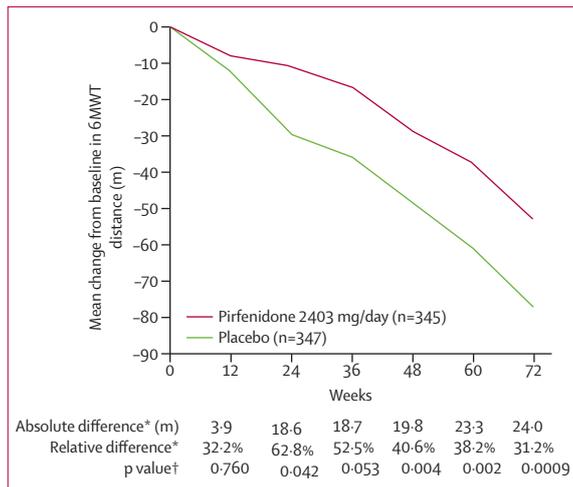*Pirfenidone 2403 mg/day versus placebo.

Figure 4: **Mean change from baseline in 6-min walk test distance in the pooled patient population (studies 004 and 006)**
6MWT=6-min walk test. *Pirfenidone 2403 mg/day versus placebo. †Rank ANCOVA (pirfenidone 2403 mg/day *vs* placebo).

	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Hazard ratio* (95% CI)	p value†
Overall				
All-cause mortality	27 (8%)	34 (10%)	0·77 (0·47–1·28)	0·315
Idiopathic-pulmonary-fibrosis-related mortality‡	18 (5%)	28 (8%)	0·62 (0·35–1·13)	0·117
On-treatment§				
All-cause mortality	19 (6%)	29 (8%)	0·65 (0·36–1·16)	0·141
Idiopathic-pulmonary-fibrosis-related mortality‡	12 (3%)	25 (7%)	0·48 (0·24–0·95)	0·030

Data are number (%). *Based on the Cox-proportional hazard model. †Log-rank test (pirfenidone 2403 mg/day *vs* placebo). ‡Assessed by the investigator, who remained masked to treatment assignment. §Defined as the time from randomisation until 28 days after the last dose of study drug.

Table 3: **All-cause and idiopathic-pulmonary-fibrosis-related mortality in the pooled population**

	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)
Nausea	125 (36%)	60 (17%)
Rash	111 (32%)	40 (12%)
Dyspepsia	66 (19%)	26 (7%)
Dizziness	63 (18%)	35 (10%)
Vomiting	47 (14%)	15 (4%)
Photosensitivity reaction	42 (12%)	6 (2%)
Anorexia	37 (11%)	13 (4%)
Arthralgia	36 (10%)	24 (7%)
Insomnia	34 (10%)	23 (7%)
Abdominal distension	33 (10%)	20 (6%)
Decreased appetite	30 (9%)	10 (3%)
Stomach discomfort	29 (8%)	6 (2%)
Weight reduction	28 (8%)	12 (3%)
Abdominal pain	26 (8%)	12 (3%)
Asthenia	24 (7%)	13 (4%)
Pharyngolaryngeal pain	24 (7%)	16 (5%)
Pruritus	22 (6%)	14 (4%)
Hot flush	18 (5%)	4 (1%)

Data are number of patients (%). *Occurring in 5% or more of patients given pirfenidone 2403 mg/day in study 004 and study 006, and with an incidence 1·5 times greater than that in patients given placebo.

Table 4: **Treatment-emergent adverse events***

on-treatment effect also favoured pirfenidone for all-cause and disease-related mortality (table 3).

Almost all patients in both studies (765 [98%] of 779) reported at least one treatment-emergent adverse event (table 4; webappendix p 6). The most commonly reported adverse events in the pooled pirfenidone 2403 mg/day group, with at least a 1·5-times increased incidence relative to placebo, were gastrointestinal events (nausea, dyspepsia, vomiting, and anorexia), skin disorders (rash, photosensitivity), and dizziness; a dose-response in frequency was noted (webappendix p 7). These events were generally mild or moderate in severity and without any clinically significant consequences. Stevens-Johnson syndrome or toxic epidermal necrolysis were not reported. Treatment-emergent serious adverse events occurred in 113 (33%) of 345 patients in the pooled pirfenidone group and 109 (31%) of 347 patients in the pooled placebo group (webappendix pp 8–9).

Study treatment was discontinued because of adverse events in 51 (15%) of 345 patients in the pooled pirfenidone group and 30 (9%) of 347 patients in the pooled placebo group; the most common event in both groups was idiopathic pulmonary fibrosis (ten [3%] *vs* nine [3%]). The only other adverse events leading to treatment discontinuation in more than 1% of patients in the pooled pirfenidone groups were rash (five [1%]) and nausea (five [1%]).

Substantial laboratory abnormalities (grade 4 or a shift of 3 grades—ie, from 0 to 3) occurring more frequently in the patients in the pooled pirfenidone group were hyperglycaemia (four [1%] of 345 *vs* three [<1%] of 347), hyponatraemia (five [1%] *vs* 0), hypophosphataemia (six [2%] *vs* three [<1%]), and lymphopenia (five [1%] *vs* 0); none were associated with clinical sequelae. More patients in the pooled pirfenidone group than in the pooled placebo group had elevations in alanine aminotransferase and aspartate aminotransferase of more than three times the upper limit of normal (14 [4%] *vs* two [<1%]); however, all were reversible and without clinical sequelae, and there was no imbalance between groups in increases of more than ten times the upper limit of normal (one [<1%] and two [<1%] in the pirfenidone 2403 mg/day and placebo groups, respectively).

Discussion
The results of study 004 showed a pirfenidone treatment effect on the change in percentage predicted FVC at week 72. Significant treatment effect was also noted at earlier timepoints, in the repeated-measures analysis

over all study timepoints, and on progression-free survival and categorical FVC change. An efficacy dose-response relation was noted. In study 006, no significant difference was noted between the pirfenidone and placebo groups on percentage predicted FVC change at week 72. However, a significant pirfenidone treatment effect was noted on percentage predicted FVC at all timepoints during the first year and in the repeated-measures analysis over all study timepoints. Analyses of pooled data for the two studies supported a pirfenidone treatment effect on percentage predicted FVC, progression-free survival, and 6MWT distance.

Pirfenidone was safe and generally well tolerated. Adherence to treatment was high despite a dosing schedule of three times a day. The type and frequency of adverse events were consistent with the known safety profile of pirfenidone, including gastrointestinal events, photosensitivity, and rash. Adverse events were typically mild or moderate in severity, and few led to treatment discontinuation. Fewer overall deaths and significantly fewer on-treatment deaths related to idiopathic pulmonary fibrosis occurred in the pirfenidone group than in the placebo group. The difference in FVC outcomes in the two studies might be partly attributable to a lower than expected rate of FVC decline in study 006 after 1 year. Although the magnitude of decline over time was similar in the two pirfenidone groups, those in the two placebo groups differed. Rates of decline in percentage predicted FVC at week 72 in the active and placebo-treated groups in a large trial of interferon-γ 1b,[19] in which no evidence of treatment effect was noted, were very similar to the placebo group in study 004 (webappendix p 6), further strengthening the hypothesis of attenuated FVC decline in the placebo group in study 006. An assessment of baseline characteristics in studies 004 and 006 showed that study 006 had a greater proportion of patients with a recent diagnosis of idiopathic pulmonary fibrosis, and the placebo group in study 006 had a greater proportion of patients with obstructive airway disease, characteristics associated with reduced FVC decline. These baseline imbalances, with the intrinsic variability in rates of FVC decline in patients with idiopathic pulmonary fibrosis, could partly account for the attenuated rate of FVC decline in the placebo group in study 006.

The collective data provide evidence that pirfenidone reduces decline in lung function in patients with idiopathic pulmonary fibrosis. First, in the primary analyses of both studies, the magnitude of treatment effect was similar at all assessment timepoints during 1 year. At week 72, despite significant differences in outcome, estimates in both studies favoured pirfenidone and confidence intervals overlapped. Second, the repeated-measures analysis of percentage predicted FVC change over all study timepoints showed a favourable pirfenidone treatment effect in both studies. Third, analyses of pooled FVC data provide evidence for a

pirfenidone treatment effect. Fourth, an efficacy dose-response relation was noted in study 004.

The clinical relevance of the treatment effect is an important issue. Change in FVC was selected as the primary endpoint because of its widespread clinical use and the clinical relevance of irreversible loss of lung function.[13] FVC was selected as the primary endpoint because it is a reliable, valid, and responsive measurement of irreversible morbidity in idiopathic pulmonary fibrosis, and is highly predictive of survival.[1,20–25] An assessment of the proportion of patients with a 10% or more decrement —a threshold widely accepted as clinically meaningful and prognostic of death—[1,20–25] is more directly clinically meaningful than is the assessment of differences in treatment group means. In the pooled analysis of categorical FVC change, pirfenidone reduced the proportion of patients with a 10% or more decrement by 30% compared with placebo. Moreover, pirfenidone was associated with a 26% reduction in the risk of death or disease progression in analyses of progression-free survival, a 31% reduced mean decline in 6MWT at week 72, and a consistently favourable direction of effect on mortality, despite the trials not being powered to assess mortality.

These findings are supported by their consistency with those of a third independently sponsored phase 3

study of pirfenidone in patients with idiopathic pulmonary fibrosis, in which the decline in vital capacity was significantly reduced at week 52 with a similar magnitude of effect to that at week 48 in studies 004 and 006 (panel).[14] Additionally, an independent Cochrane meta-analysis of all three phase 3 trials of pirfenidone in patients with idiopathic pulmonary fibrosis (n=1046) showed significant improvement in progression-free survival (hazard ratio 0·70, 95% CI 0·56–0·88; p=0·002), an endpoint predominantly driven by large reductions in lung function.[26]

Our studies have several limitations. Since we enrolled patients with mild to moderate idiopathic pulmonary fibrosis and few comorbidities, our results cannot necessarily be generalised to the broader population of patients. Because concomitant administration of other treatments for idiopathic pulmonary fibrosis was generally prohibited, the effect of these therapies in patients given pirfenidone is not known. Also, the lack of adjustment for multiple statistical testing has the potential for overinterpretation of the results. Although the results of these studies and ongoing open-label extension studies suggest that long-term pirfenidone is safe and generally well tolerated, the effect of treatment for longer than 72 weeks on pulmonary function and disease status is not known.

Idiopathic pulmonary fibrosis remains a progressive and fatal disorder, and no treatment so far has been shown to be efficacious, despite several clinical trials in the past decade.[19,27–30] The orphan status of idiopathic pulmonary fibrosis, heterogeneity in rates of disease progression, and lack of a precedent for regulatory approval complicate efforts to develop novel treatments. The data from these two multinational, double-blind, placebo-controlled phase 3 studies show the clinically meaningful benefit and favourable safety profile of pirfenidone in patients with idiopathic pulmonary fibrosis. In conclusion, pirfenidone has a favourable benefit-risk profile and represents a suitable treatment option for patients with idiopathic pulmonary fibrosis.

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