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

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

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 −6.6% (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). 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 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.

Funding InterMune.

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. Disease progression is heterogeneous; however, the clinical course is ultimately deterioration, with an estimated median survival of 2–5 years. 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; and inhibit fibroblast proliferation and collagen synthesis and reduce cellular and histological markers of fibrosis in animal models of lung fibrosis. Clinical proof of concept was shown in a randomised, double-blind, placebo-controlled phase 2 study of 107 Japanese patients with idiopathic pulmonary fibrosis. 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.

Randomisation and masking

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

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).
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 usual interstitial pneumonia.

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, respectively, in study 006 (table 2).

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 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

Table 2: Secondary efficacy endpoints at week 72

<table>
<thead>
<tr>
<th>Study 004</th>
<th>Study 006</th>
<th>Pooled data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone 2403 mg/day (n=174)</td>
<td>Placebo (n=174)</td>
</tr>
<tr>
<td>Category</td>
<td>Categorical change in FVC ≥10%</td>
<td>-60.4 (4.4 to 1.4)</td>
</tr>
<tr>
<td>Progression-free survival time</td>
<td>-</td>
<td>0.64 (0.44 to 0.95)</td>
</tr>
<tr>
<td>Mean change in 6MWT distance (m)</td>
<td>-60.4</td>
<td>-76.8</td>
</tr>
<tr>
<td>Mean change in DLco (% predicted)</td>
<td>-7.9</td>
<td>-9.9</td>
</tr>
<tr>
<td>Mean change in dyspnoea score</td>
<td>12.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Mean change in worst SpO2 during 6MWT (%)</td>
<td>-1.5</td>
<td>-2.3</td>
</tr>
<tr>
<td>Time to worsening in idiopathic pulmonary fibrosis</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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.

FVC was forced vital capacity, 6MWT is 6-minute walk test, DLco is haemoglobin-corrected carbon monoxide diffusing capacity, SpO2 is peripheral oxygen saturation, HRCT is high-resolution CT, NA is 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.
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.
randomisation until 28 days after the last dose of study drug. ‡Assessed by the investigator, who remained masked to treatment assignment. §Defined as the time from
All-cause and idiopathic-pulmonary-fibrosis-related mortality in the pooled population

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

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone 2403 mg/day (n=345)</th>
<th>Placebo (n=347)</th>
<th>Hazard ratio* (95% CI)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>27 (8%)</td>
<td>34 (10%)</td>
<td>0.77 (0.47–1.28)</td>
<td>0.115</td>
</tr>
<tr>
<td>Idiopathic-pulmonary-fibrosis-related mortality</td>
<td>18 (5%)</td>
<td>28 (8%)</td>
<td>0.62 (0.35–1.13)</td>
<td>0.117</td>
</tr>
<tr>
<td>On-treatment§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>13 (6%)</td>
<td>29 (9%)</td>
<td>0.65 (0.36–1.16)</td>
<td>0.141</td>
</tr>
<tr>
<td>Idiopathic-pulmonary-fibrosis-related mortality</td>
<td>12 (3%)</td>
<td>25 (7%)</td>
<td>0.48 (0.24–0.95)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

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 4: Treatment-emergent adverse events

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone 2403 mg/day (n=345)</th>
<th>Placebo (n=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>125 (36%)</td>
<td>60 (17%)</td>
</tr>
<tr>
<td>Rash</td>
<td>111 (32%)</td>
<td>40 (12%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>66 (19%)</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>61 (18%)</td>
<td>35 (10%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47 (14%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>42 (12%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>37 (11%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>35 (10%)</td>
<td>24 (7%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>34 (10%)</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>33 (10%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30 (9%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>29 (8%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>28 (8%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (8%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>24 (7%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>24 (7%)</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>22 (6%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>18 (5%)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

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.

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 (one [1%] 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...
analyses of pooled FVC data provide evidence for a pirfenidone treatment effect in both studies. Third, change over all study timepoints showed a favourable repeated-measures analysis of percentage predicted FVC outcome, estimates in both studies favoured pirfenidone placebo-treated groups in a large trial of interferon-γ 1b,19 percentage predicted FVC at week 72 in the active and two placebo groups differed. Rates of decline in 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.

Panel: Research in context

Systematic review

We searched Medline from January, 1995, to December, 2010, for full reports of randomised, double-blind, placebo-controlled trials of pirfenidone in the treatment of patients with idiopathic pulmonary fibrosis. We identified Japanese phase 2 and phase 3 studies,13,14 and obtained further results from the sponsor (Shionogi, Osaka, Japan). We undertook comparative analyses and meta-analyses of the effect of pirfenidone on lung function by combining results from all four studies.

Interpretation

The patient populations and general characteristics in the Japanese phase 2 and phase 3 studies are quite similar to those in study 004 and study 006 despite being geographically different. More men (mean age –65 years) were enrolled in all four studies, with a diagnosis of idiopathic pulmonary fibrosis that met the standardised clinical and radiographic criteria, and mild-to-moderate impairment of lung function. The Japanese study populations had a greater proportion of current smokers and a lower mean bodyweight. In each study, the change from baseline in lung function was measured, represented as either forced vital capacity or vital capacity, and multiple other clinical, physiological, and functional variables.

Results from the two Japanese studies provide additional evidence that pirfenidone reduces decline in lung function and prolongs progression-free survival in patients with idiopathic progression-free survival. The meta-analysis of change in lung function that includes each study up to its point of completion shows a great consistency of treatment effect in all four studies, with the point estimate and 95% CIs at each assessment timepoint (ie, week 24 or 28, week 36 or 40, week 48 or 52, and week 72) clearly excluding no effect (webappendix p 11). The totality of the data from four randomised controlled trials (Japanese phase 2 and phase 3 trials, and studies 004 and 006) provides compelling evidence for the pirfenidone treatment effect on lung function. 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.15 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.16,17 An assessment of the proportion of patients with a 10% or more decrement—a threshold widely accepted as clinically meaningful and prognostic of death—16,17 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 evaluation of the effect of pirfenidone on lung function and mortality in patients with idiopathic pulmonary fibrosis.
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). 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.

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. 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.

Contributors
PWN and R MDB co-chaired the study steering committee. PWN, CA, WZB, UC, MKG, DK, TEK, LL, SAS, JS, DV, and RMDB participated in the design, conduct, analysis, and reporting the study. PWN, CA, UC, MKG, TEK, LL, SAS, DV, and RMDB were responsible for data implementation at the study sites. DK was responsible for data management and statistical analyses. All authors participated in the preparation, review, and critical revision of the report, which has been approved by each author.

CAPACITY Study Group
Study 006: C Agostini (Università degli Studi di Padova, Padova, Italy), J Allen (Ohio State University, Columbus, OH), C Andrews (Diagnostics Research Group, San Antonio, TX, USA), D Antin-Ozerik (Yale University School of Medicine, New Haven, CT, USA), R Baughman (University of Cincinnati, Cincinnati, OH, USA), S Burre (Birmingham Heartlands Hospital, Birmingham, UK), A Chan (UC Davis Medical Center, Sacramento, CA, USA), M Confalonieri (Azienda Ospedaliero Universitaria, Trieste, Italy), J Cordier (Hospital Louis Pradel, Bron, France), F Cordova (Temple University Hospital, Philadelphia, PA, USA), A Cuomo (Ospedale Maggiore di Parma, Parma, Italy), P Delaval (CHU Hospital Pontchaillou, Rennes, France), A Dhar (Windsor, ON, Canada), A Duarte (University of Texas, Galveston, TX, USA), K Dushay (Rhode Island Hospital, Providence, RI, USA), K Flaherty (University of Michigan, Ann Arbor, MI, USA), A Frost (Baylor College of Medicine, Houston, TX, USA), L Ginns (Massachusetts General Hospital, Boston, MA, USA), C Girod (Dallas, TX, USA), I Gaspole (The Alfred Hospital, Melbourne, VIC, Australia), J Golden (University of California, San Francisco, San Francisco, CA, USA), M Gottfried (Phoenix, AZ, USA), H Haller Jr (Louisville, KY, USA), S Haraz (Ospedale San Giuseppe, Milano, Italy), D Helmersen (Peter Lougheed Center, Calgary, AB, Canada), R Holder (Ottawa Hospital, Ottawa, ON, Canada), H Hollingsworth (Boston University School of Medicine, Boston, MA, USA), I Honik (Concordia Hospital, Winnipeg, MB, Canada), N Khalil (Vancouver General Hospital, Vancouver, BC, Canada), J Kus (Institut Grzulicy J Chorob Pleu, Warsaw, Poland), C Leonard (Wardhenshawe Hospital, Manchester, UK), M Malouf (St Vincent’s Hospital, Darlinghurst, NSW, Australia), S Mette (Maine Medical Center, Portland, ME, USA), K Meyer (University of Wisconsin, Madison, WI, USA), H Mezziane (CHU Hospital Arnaud de Villeneuve, Montpellier, France), S Nathan (Inova Transplant Center, Falls Church, VA, USA), M Padilla (Mount Sinai Medical Center, New York, NY, USA), R Panos (University of Cincinnati, Cincinnati, OH, USA), J Pantano (Elk Grove, IL, USA), N Patel (New York, NY, USA), V Pioletti (Azienda Sanitaria di Forlì, Forlì, Italy), W Ramesh (Fiduchildren, AB, Canada), M Salvagione Policlinico di Modena, Modena, Italy), J Rolf (Kolowna, BC, Canada), P Rottoli (Azienda Ospedaliera Universitaria Policlinico Le Scute, Siena, Italy), T Russell (Washington University School of Medicine, St Louis, MO, USA), C Saltini (Azienda Ospedaliera Universitaria Policlinico Tor Vergata, Rome, Italy), M Selman (Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico), H Shimizu (University of Southern California, Los Angeles, CA, USA), D Sinkowitz (Torrance, CA, USA), D Stollery (Grey Nuns Community Hospital, Edmonton, AB, Canada), M Sterk (University of Chicago, Chicago, IL, USA), G Tino (University of Pennsylvania, Philadelphia, PA, USA), B Wallart (Hospital Albert Calmette, Lille, France), A Wells (Royal Brompton Hospital, London, UK), T Whelan (University of Minnesota, Minneapolis, MN, USA), P Wilcox (St Paul’s Hospital, Vancouver, BC, Canada), J Zibrak (Beth Israel Deaconess Medical Center, Boston, MA, USA), D Ziora (Samodzielny Publiczny Szpital, Zabrze, Poland), D Zisman (University of California, Los Angeles, Los Angeles, CA, USA), J Kus (Institut Grzulicy J Chorob Pleu, Warsaw, Poland), C Leonard, J Lasky (Tulane University, New Orleans, LA, USA), J de Andrade (University of Alabama at Birmingham, Birmingham, AL, USA), D Doherty (University of Kentucky, Lexington, KY, USA), J Egan (Mater Misericordiae Hospital, Dublin, Ireland), N Ettinger (Chesterfield, MO, USA), P Fairman (Richmond, VA, USA), T Geiser (University Hospital of Bern, Bern, Switzerland), K Gibson (University of Pittsburgh, Pittsburgh, PA, USA), M Halib (VA Healthcare System, Tucson, AZ, USA), T Horiiuchi (Sarasota Memorial Healthcare System, Sarasota, FL, USA), T Ingrassia (OSF Saint Anthony Medical Center, Rockford, IL, USA), M Kallay (Highland Hospital, Rochester, NY, USA), J Landis (Baystate Medical Center, Springfield, MA, USA), J Lasky (Tulane University, New Orleans, LA, USA), D Lorch (Bradenton, FL, USA), H Magnusson (Pulmonary Research Institute, Grosshansdorf, Germany), F Morrell (Hospital Vall d’Hebron, Barcelona, Spain), I Morrison (Duke University Medical Center, Durham, NC, USA), M Musk (Royal Perth Hospital, Perth, WA, Australia), M Pfeifer (Krankenhaus Donaustauf, Donaustauf, Germany), J Roman (Emory University School of Medicine, Atlanta, GA, USA), G Rosen (Stanford University Medical Center, Palo Alto, CA, USA), H Sakkajia (University of Arkansas, Little Rock, AR, USA), T Schauberg (Oregon Clinic, Portland, OR, USA), M Scholand (University of Utah Health Sciences Center, Salt Lake City, UT, USA), G Serfilippi (Pulmonary and Critical Care Services, Albany, NY, USA), H Stabbergnyz (AZ Middelheim, Antwerpen, Belgium), R Sussman (Pulmonary and Allergy Associates, Summit, NJ, USA), J Swigris (National Jewish Medical and Research Center, Denver, CO, USA), M Thommer (University Hospital Gastrothurgis, Leuven, Belgium),
A Thompson (University of Nebraska, Omaha, NE, USA), G Vergheese (University of Virginia Medical Center, Charlottesville, VA, USA), M Wenzel (Chicita Clinic, Wichita, KS, USA), J Wirtz (University of Leipzig, Germany), J Wessellius (Mayo Clinic, Scottsdale, AZ, USA), H Worth (Klinikum Fürth, Fürth, Germany), A Xaubet (Barcelona, Spain), M Yagan (Midwest Pulmonary Consultants, Kansas City, MO, USA), G Yung (University of California, San Diego, CA, USA).

Conflicts of interest

PWN has served as a clinical investigator, study steering committee member, or consultant for Actelion, Boehringer Ingelheim, InterMune, and Novartis. CA has served as a study steering committee member and a consultant for InterMune. UC has served as a clinical investigator or consultant for Actelion, Boehringer Ingelheim, Centocor, Gilead, and InterMune; RMdB has served as a study steering committee co-chair or steering committee member for Actelion, Bayer, Boehringer Ingelheim, InterMune, and MondoBiotech. TEE has served as an advisory committee member or consultant for Actelion, Gilead, ImmuneWorks, and InterMune. SAS has served as a clinical investigator or steering committee member for Actelion, Arrosto, Celgene, Gilead, InterMune, and the National Institutes of Health Idiopathic Pulmonary Fibrosis Network. DV has served as a clinical investigator for Actelion and as a study steering committee member for InterMune. LL and MKG have no financial conflicts of interest to disclose. WZB, DK, and JS are employees of InterMune.

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References

18. du Bois RM, Albera C, Bradford WZ, et al. 6-minute walk test distance (6MWD) is a reliable, valid, and responsive outcome measure that predicts mortality in patients with IPF. Am J Respir Crit Care Med 2010; published online Dec 3. DOI:10.1164/rccm.201007-1179OC.