ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ($P<0.001$). Pirfenidone reduced the decline in the 6-minute walk distance ($P=0.04$) and improved progression-free survival ($P<0.001$). There was no significant between-group difference in dyspnea scores ($P=0.16$) or in rates of death from any cause ($P=0.10$) or from idiopathic pulmonary fibrosis ($P=0.23$). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause ($P=0.01$) and from idiopathic pulmonary fibrosis ($P=0.006$). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

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Idiopathic pulmonary fibrosis is a chronic, progressive, and fatal lung disease that is characterized by irreversible loss of lung function.[1] Although periods of transient clinical stability may be observed, continued progression of the disease is inevitable.[2] The prognosis is poor, with a 5-year survival rate that is similar to the rates for several cancers.[3-6]

Pirfenidone is an oral antifibrotic therapy that has been evaluated for the treatment of idiopathic pulmonary fibrosis in three phase 3, randomized, controlled trials. One of these trials was conducted in Japan and involved 275 patients. It was followed by two multinational studies, Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY studies 004 and 006), that were conducted in the United States, Europe, and Australia and involved 779 patients.[7,8] In the Japanese trial, pirfenidone reduced the decline in vital capacity at week 52 and improved progression-free survival. In the multinational trials, the primary end point of change from baseline to week 72 in the percentage of the predicted forced vital capacity (FVC) was met in study 004 but not in study 006, prompting U.S. regulatory authorities to request an additional trial to support the approval of pirfenidone.

In the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study, a randomized, double-blind, placebo-controlled trial, we aimed to confirm the effect of pirfenidone on disease progression in patients with idiopathic pulmonary fibrosis. Our design modifications with respect to the CAPACITY trial included the implementation of centralized procedures for diagnosis, spirometry, and adjudication of deaths; a minor modification of eligibility criteria to allow enrollment of patients with an increased risk of disease progression; and a standard 1-year study period.

METHODS

STUDY SITES AND PATIENTS

The study was conducted at 127 sites in 9 countries (11 sites in Australia, 6 in Brazil, 2 in Croatia, 5 in Israel, 5 in Mexico, 2 in New Zealand, 8 in Peru, 1 in Singapore, and 87 in the United States). Eligible patients were between the ages of 40 and 80 years and had received a centrally confirmed diagnosis of idiopathic pulmonary fibrosis. The diagnostic criteria, based on published consensus guidelines, were findings on high-resolution computed tomography (HRCT) that indicated either definite or possible usual interstitial pneumonia; the latter was confirmed on surgical lung biopsy.[1] Other criteria for enrollment included a range of 50 to 90% of the predicted FVC, a range of 30 to 90% of the predicted carbon monoxide diffusing capacity, a ratio of the forced expiratory volume in 1 second (FEV_1) to the FVC of 0.80 or more, and a 6-minute walk distance of 150 m or more. (A comprehensive list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) All patients provided written informed consent.

STUDY DESIGN AND ASSESSMENTS

Eligible patients were randomly assigned to receive oral pirfenidone (at a dose of 2403 mg per day) or placebo for 52 weeks. The study drug was administered with food in three equally divided doses, and the dose was gradually increased to the full dose over a 2-week period. Randomization codes were generated by computer with the use of a permuted-block design, and the study drug was assigned by means of an interactive voice-response system. Concomitant treatment with any investigational therapy was prohibited. Selected concomitant medications that are used for the treatment of idiopathic pulmonary fibrosis were permitted if they were used for another indication, provided that there was no clinically acceptable alternative.

Physical examination and clinical laboratory assessments were performed at baseline and at weeks 2, 4, 8, 13, 26, 39, and 52. Pulmonary function, exercise tolerance, and dyspnea were assessed at baseline and at weeks 13, 26, 39, and 52. Central reviewers at Biomedical Systems, who were unaware of study-group assignments, evaluated all FVC results for adequacy and repeatability, according to the criteria of the American Thoracic Society.[9] A data and safety monitoring committee reviewed safety and efficacy data throughout the trial.

The study protocol was approved by the institutional review board or ethics committee at each participating center. The protocol and statistical analysis plan are available at NEJM.org.

STUDY OVERSIGHT

The study sponsor (InterMune) and the steering committee cochairs were primarily responsible

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for the design of the study. All authors participated in the conduct of the study, analysis of data, and reporting of the results. A writing committee comprising the first and last authors, the study medical monitor, and a medical writer (who was paid by the study sponsor) prepared the first draft of the manuscript. All authors vouch for the accuracy and completeness of the report and for the fidelity of the report to the protocol; all the authors critically reviewed the manuscript and approved the final draft. All the authors had full access to data, and no limits were placed on the content of the report.

STATISTICAL ANALYSIS

The primary efficacy end point was the change from baseline to week 52 in the percentage of the predicted FVC in the intention-to-treat population. The test statistic for the primary efficacy analysis was a ranked analysis of covariance (ANCOVA), with the average standardized rank change in the percentage of the predicted FVC as the outcome variable and the standardized rank baseline value as a covariate. The primary efficacy analysis was tested with the use of a final two-tailed P value of 0.0498, which was adjusted for two planned interim analyses. The magnitude of the treatment effect was estimated by comparing the distribution of patients in the pirfenidone group with those in the placebo group across two thresholds of change at week 52: an absolute decline of 10 percentage points in the percentage of the predicted FVC or death, or no decline in the percentage of the predicted FVC. Supportive analyses to assess the robustness of the effect on FVC were also conducted.

Two key secondary end points and three additional secondary end points were prespecified. The key secondary end points, which were analyzed with the use of the Hochberg procedure for multiple comparisons,[10] were the change from baseline to week 52 in the 6-minute walk distance and progression-free survival. Progression-free survival was defined as the time to the first occurrence of any one of the following: a confirmed decrease of 10 percentage points or more in the percentage of the predicted FVC, a confirmed decrease of 50 m or more in the 6-minute walk distance, or death. Additional secondary end points included change in dyspnea, which was measured with the use of the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ), with scores ranging from 0 to 120 and higher scores indicating worse dyspnea (minimally important difference, 5 to 11 points) (Fig. S4 in the Supplementary Appendix); the rate of death from any cause; and the rate of death from idiopathic pulmonary fibrosis during the period from baseline to 28 days after the last dose of the study drug.

In accordance with the prespecified statistical analysis plan, rates of death from any cause and death from idiopathic pulmonary fibrosis were analyzed in the ASCEND study population and in the pooled population from the ASCEND trial and the two CAPACITY trials; the latter analysis was performed for the purpose of increasing the statistical power and deriving a more stable estimate of the treatment effect. For the pooled analysis, CAPACITY results were censored at day 365 so that the follow-up time would be the same for all three studies. The primary cause of death and its relation to idiopathic pulmonary fibrosis were assessed in a blinded fashion by an independent mortality assessment committee in the ASCEND trial and by the site investigators in the CAPACITY trials (Tables S1 and S2 in the Supplementary Appendix).

All efficacy analyses were conducted in the intention-to-treat population with the use of SAS software, version 9.2 (SAS Institute). For the ranked ANCOVA analyses, missing values owing to death were assigned the worst ranks, with early deaths ranked worse than later deaths. In analyses of mean change, missing values owing to death were assigned the worst possible outcome (e.g., FVC = 0). Missing values for reasons other than death were imputed as the average value for the three patients with the smallest sum of squared differences at each visit. For time-to-event analyses, pirfenidone was compared with placebo with the use of a log-rank test; hazard ratios were based on the Cox proportional-hazards model.

Adverse events were coded according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 11.0. Safety outcomes are reported as events that occurred in the period from baseline to 28 days after the last dose of the study drug.

RESULTS

STUDY PATIENTS

From July 2011 through January 2013, a total of 555 patients were enrolled; 278 were assigned to receive pirfenidone, and 277 were assigned to re-

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ceive placebo. Demographic and baseline characteristics are summarized in Table 1. There were no significant imbalances in clinically relevant baseline characteristics between the two study groups. The majority of patients were male (79.9% and 76.9% in the pirfenidone and placebo groups, respectively), white (91.7% and 90.6%, respectively), and 65 years of age or older (73.7% and 68.2%, respectively). The mean (±SD) baseline FVC was 67.8±11.2% of the predicted value in the pirfenidone group and 68.6±10.9% of the predicted value in the placebo group.

A total of 522 patients (94.1%) completed the study: 261 patients (93.9%) in the pirfenidone group and 261 patients (94.2%) in the placebo group (Fig. 1). Study treatment was discontinued prematurely in 55 patients (19.8%) in the pirfenidone group and in 39 patients (14.1%) in the placebo group. Adherence to the study treatment was high; 237 patients (85.3%) and 256 (92.4%) patients in the pirfenidone and placebo groups, respectively, received at least 80% of the prescribed doses of the assigned study drug.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pirfenidone (N=278)	Placebo (N=277)
Age — yr	68.4±6.7	67.8±7.3
Male sex — no. (%)	222 (79.9)	213 (76.9)
U.S. enrollment — no. (%)	187 (67.3)	184 (66.4)
Former smoker — no. (%)	184 (66.2)	169 (61.0)
Lung physiological features		
FVC — % of predicted value	67.8±11.2	68.6±10.9
FEV_1:FVC	0.84±0.03	0.84±0.04
Carbon monoxide diffusing capacity — % of predicted value	43.7±10.5	44.2±12.5
Dyspnea score†	34.0±21.9	36.6±21.7
Distance on 6-min walk test — m	415.0±98.5	420.7±98.1
Use of supplemental oxygen — no. (%)	78 (28.1)	76 (27.4)
Time since diagnosis — yr	1.7±1.1	1.7±1.1
Diagnostic finding on high-resolution computed tomography — no. (%)		
Definite pattern of usual interstitial pneumonia	266 (95.7)	262 (94.6)
Possible pattern of usual interstitial pneumonia‡	12 (4.3)	15 (5.4)
Surgical lung biopsy — no. (%)	86 (30.9)	79 (28.5)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any of the baseline characteristics shown. FEV_1 denotes forced expiratory volume in one second, and FVC forced vital capacity.

† Dyspnea was evaluated with the use of the University of California, San Diego, Shortness of Breath Questionnaire, scores on which range from 0 to 120, with higher scores indicating worse dyspnea; the minimally important difference is 5 to 11 points.

‡ The diagnosis was subsequently confirmed on surgical lung biopsy indicating a histologic pattern of usual interstitial pneumonia.

PRIMARY EFFICACY ANALYSIS

In the ranked ANCOVA analysis, treatment with pirfenidone resulted in a significant between-group difference in the primary end point, the change from baseline to week 52 in the percentage of the predicted FVC (P<0.001). At week 52, the proportion of patients who had a decline of 10 percentage points or more in the percentage of the predicted FVC or who had died was reduced by 47.9% in the pirfenidone group as compared with the placebo group (46 patients [16.5%] vs. 88 patients [31.8%]) (Fig. 2A), and the proportion of patients with no decline in the percentage of the predicted FVC was increased by 132.5% in the pirfenidone group (63 patients [22.7%] vs. 27 patients [9.7%]) (Fig. S1 in the Supplementary Appendix).

The treatment effect was evident by week 13 and increased throughout the duration of the trial. Supportive analyses of the primary end point yielded similar results. The mean decline from baseline in FVC was 235 ml in the pirfenidone group and 428 ml in the placebo group (absolute difference, 193 ml; relative difference, 45.1%; P<0.001) (Fig. 2B). The linear slope of decline in FVC at week 52 was –122 ml in the pirfenidone group and –262 ml in the placebo group (absolute difference, 140 ml; relative difference, 53.5%; P<0.001) (Fig. S2 in the Supplementary Appendix).

PRESPECIFIED SECONDARY EFFICACY ANALYSES

Pirfenidone resulted in a significant between-group difference in the change from baseline to week 52 in the 6-minute walk distance (P=0.04). At week 52, a decrease of 50 m or more in the 6-minute walk distance or death occurred in 72 patients (25.9%) in the pirfenidone group and in 99 patients (35.7%) in the placebo group, for a relative reduction of 27.5% in the pirfenidone group (Fig. 2C, and Fig. S3 in the Supplementary Appendix).

Pirfenidone, as compared with placebo, reduced the relative risk of death or disease progression by 43% (hazard ratio in the pirfenidone group, 0.57; 95% confidence interval [CI], 0.43 to 0.77; P<0.001) (Fig. 2D). For each component

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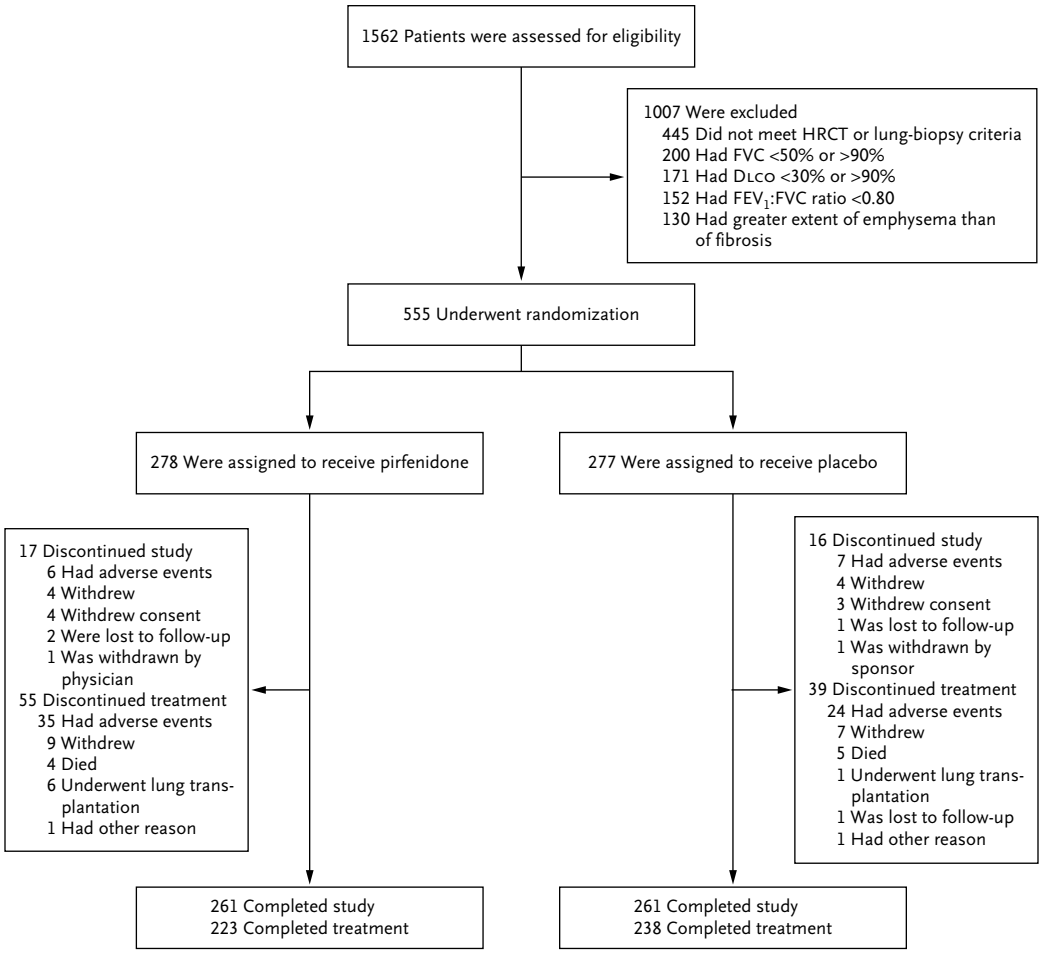

Figure 1. Enrollment and Outcomes.

The listed reasons for exclusion from the study were reported in at least 10% of the patients who underwent screening. Patients could have more than one reason for exclusion. The numbers of patients who withdrew from the study do not include patients who died or underwent lung transplantation. Patients who discontinued the study treatment were included in the analysis of data for patients who completed the study. DLCO denotes carbon monoxide diffusing capacity, FEV_1 forced expiratory volume in one second, FVC forced vital capacity, and HRCT high-resolution computed tomography.

of the composite end point, fewer patients in the pirfenidone group than in the placebo group had a qualifying event, including death (3.6% vs. 5.1%), a confirmed absolute decrease of 10 percentage points or more in the percentage of the predicted FVC (6.5% vs. 17.7%), and a confirmed decrease of 50 m or more in the 6-minute walk distance (16.5% vs. 19.5%).

Analysis of UCSD SOBQ scores showed no significant between-group difference in dyspnea at week 52. The end point of an increase of 20 points or more (indicating worsening) on the dyspnea score or death occurred in 81 patients (29.1%) in the pirfenidone group and in 100 patients (36.1%) in the placebo group (absolute difference, 7.0 percentage points; relative reduction, 19.3%; P=0.16) (Fig. S4 in the Supplementary Appendix).

MORTALITY OUTCOMES

Analysis of all-cause mortality showed fewer deaths in the pirfenidone group than in the placebo group, although the difference was not significant. Eleven patients (4.0%) in the pirfenidone group died during the study, as compared

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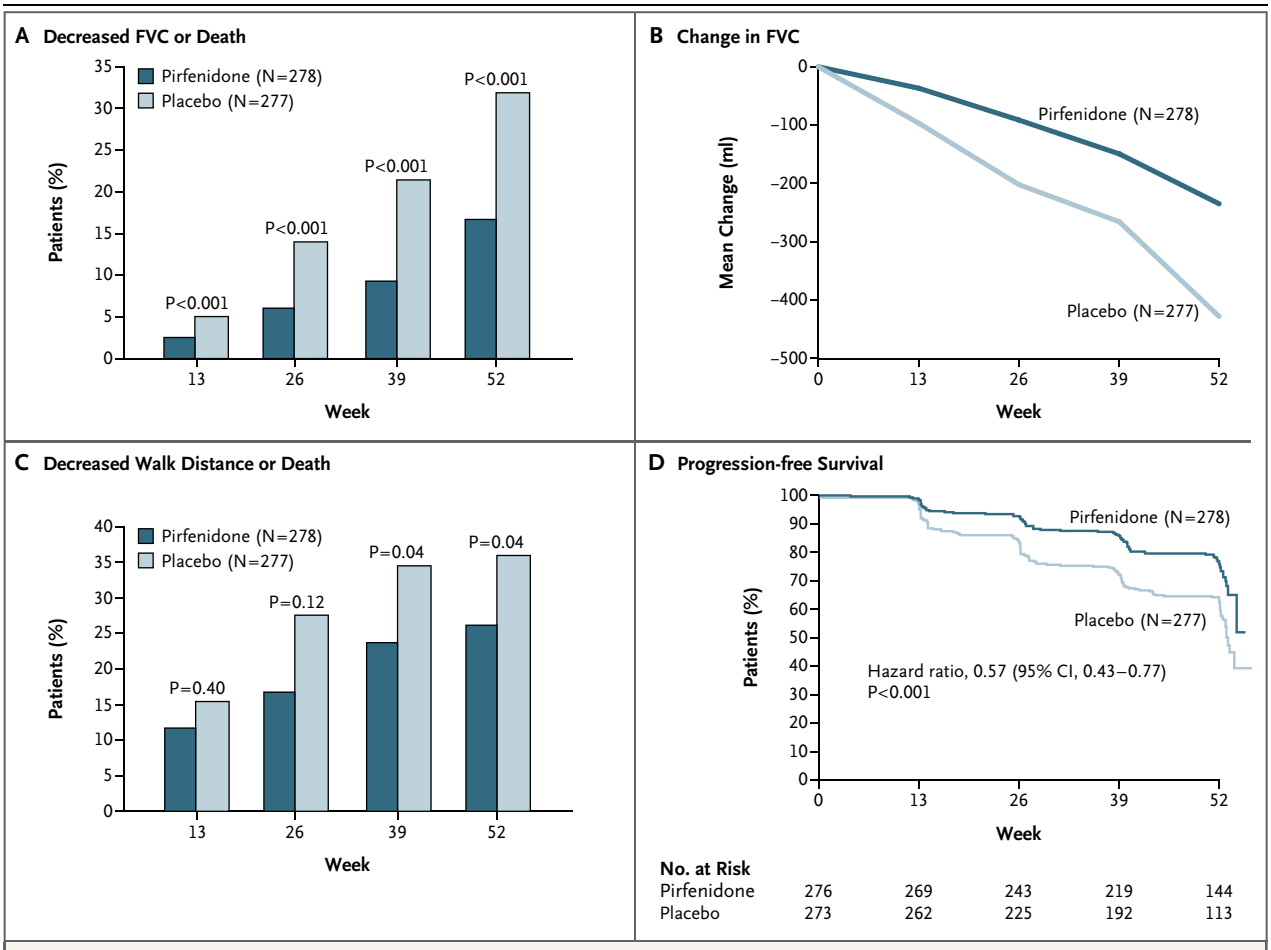

Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 m or more in the distance walked in 6 minutes) or who died. P values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan–Meier distribution for the probability of progression-free survival. The P value was calculated with the use of the log-rank test.

with 20 patients (7.2%) in the placebo group (hazard ratio, 0.55; 95% CI, 0.26 to 1.15; P=0.10). Deaths from idiopathic pulmonary fibrosis occurred in 3 patients (1.1%) and 7 patients (2.5%) in the pirfenidone and placebo groups, respectively (hazard ratio, 0.44; 95% CI, 0.11 to 1.72; P=0.23).

In the prespecified analysis of all-cause mortality in the pooled population of 1247 patients (555 from the ASCEND study and 692 from the CAPACITY studies), pirfenidone reduced the risk of death at 1 year by 48%, as compared with placebo (hazard ratio, 0.52; 95% CI, 0.31 to 0.87; P=0.01) (Table 2). In addition, in the pooled population, the risk of death from idiopathic pulmonary fibrosis at 1 year was reduced by 68% in the pirfenidone group, as compared with the placebo group (hazard ratio, 0.32; 95% CI, 0.14 to 0.76; P=0.006). (Additional mortality results are provided in Tables S3, S4, and S5 in the Supplementary Appendix.)

ADVERSE EVENTS

Adverse events that occurred during the study period are summarized in Table 3. Gastrointestinal and skin-related events were more common in the pirfenidone group than in the placebo group; these events were generally mild to moderate in severity, reversible, and without clinically signifi-

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Table 2. Mortality in the ASCEND and CAPACITY Trials.*

Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006

* Data from the two CAPACITY studies[8] were censored at 1 year to standardize the follow-up for the three studies.
† Hazard ratios are for the pirfenidone group, as compared with the placebo group, and were calculated with the use of the Cox proportional-hazards model.
‡ P values were calculated with the use of the log-rank test.
§ Death related to idiopathic pulmonary fibrosis was defined as death that occurred during the period from randomization to 28 days after the last dose of the study drug. This category was evaluated in a blinded fashion by an independent mortality-assessment committee in the ASCEND trial and by clinical investigators in the CAPACITY trials.

cant sequelae. Grade 3 gastrointestinal adverse events were reported in 15 patients (5.4%) in the pirfenidone group and 4 patients (1.4%) in the placebo group. Grade 3 skin-related adverse events were reported in 5 patients (1.8%) in the pirfenidone group and 1 patient (0.4%) in the placebo group. No patients in either group had a grade 4 gastrointestinal or skin-related event. Cough, worsening of idiopathic pulmonary fibrosis, and dyspnea occurred more frequently in the placebo group. There were fewer deaths in the pirfenidone group than in the placebo group (8 [2.9%] vs. 15 [5.4%] between baseline and 28 days after the last dose of a study drug).

The relative difference between treatment groups in the overall incidence of serious adverse events is less clear. If worsening of idiopathic pulmonary fibrosis is counted as an adverse event (as specified in the protocol), there were 55 patients (19.8%) in the pirfenidone group and 69 patients (24.9%) in the placebo group who had a serious adverse event. The most common serious adverse event was worsening of idiopathic pulmonary fibrosis, which was reported in 7 patients (2.5%) in the pirfenidone group and in 27 patients (9.7%) in the placebo group. However, since worsening of idiopathic pulmonary fibrosis is a study outcome, it is reasonable to exclude patients with worsening fibrosis in the analysis of serious adverse events. With such patients excluded, serious adverse events occurred in 52 patients (18.7%) in the pirfenidone group and 56 patients (20.2%) in the placebo group.

Elevations in the level of alanine or aspartate aminotransferase (values that were three or more times the upper limit of the normal range) occurred in eight patients (2.9%) in the pirfenidone group and two patients (0.7%) in the placebo group, including one patient in the pirfenidone group who had a concurrent elevation in the total bilirubin level that was more than two times the upper limit of the normal range. All aminotransferase elevations were reversible and without clinically significant consequences.

Adverse events led to discontinuation of study treatment in 40 patients (14.4%) in the pirfenidone group and 30 patients (10.8%) in the placebo group. The most common adverse event resulting in treatment discontinuation was a worsening of idiopathic pulmonary fibrosis in 3 patients (1.1%) in the pirfenidone group and in 15 patients (5.4%) in the placebo group. The only other adverse events leading to treatment discontinuation in at least 1% of the patients in the pirfenidone group were elevated hepatic en-

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Table 3. Adverse Events.*

Adverse Event	Pirfenidone (N=278)	Placebo (N=277)
	no. of patients (%)	
Cough	70 (25.2)	82 (29.6)
Nausea	100 (36.0)	37 (13.4)
Headache	72 (25.9)	64 (23.1)
Diarrhea	62 (22.3)	60 (21.7)
Upper respiratory tract infection	61 (21.9)	56 (20.2)
Fatigue	58 (20.9)	48 (17.3)
Rash	78 (28.1)	24 (8.7)
Dyspnea	41 (14.7)	49 (17.7)
Dizziness	49 (17.6)	36 (13.0)
Idiopathic pulmonary fibrosis†	26 (9.4)	50 (18.1)
Bronchitis	39 (14.0)	36 (13.0)
Constipation	32 (11.5)	38 (13.7)
Back pain	30 (10.8)	37 (13.4)
Dyspepsia	49 (17.6)	17 (6.1)
Nasopharyngitis	33 (11.9)	30 (10.8)
Anorexia	44 (15.8)	18 (6.5)
Vomiting	36 (12.9)	24 (8.7)
Decrease in weight	35 (12.6)	22 (7.9)
Gastroesophageal reflux	33 (11.9)	18 (6.5)
Insomnia	31 (11.2)	18 (6.5)

* Listed are all adverse events that were reported in at least 10% of patients in either study group. Preferred terms in the *Medical Dictionary for Regulatory Activities*, version 11.0, were used for documentation of adverse events.
† Since idiopathic pulmonary fibrosis was a criterion for enrollment, this category of adverse events refers to worsening of disease.

zyme levels, pneumonia, rash, and decreased weight in 3 patients (1.1%) each.

DISCUSSION

In this phase 3 study comparing pirfenidone with placebo in patients with idiopathic pulmonary fibrosis, treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by changes in FVC, the 6-minute walk distance, and progression-free survival. The treatment effect on FVC emerged early and increased during the course of the trial, resulting in an approximate halving in the rate of decline at 1 year. The highly significant finding with respect to the primary end point was supported by the favorable effect on rates of death from any cause and from idiopathic pulmonary fibrosis.

Treatment with pirfenidone was generally safe and had an acceptable side-effect profile, findings that are consistent with those in previous studies.[7,8,11,12] Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group; these events were generally mild to moderate in severity and led to treatment discontinuation in 2.2% and 2.9% of patients, respectively, in the pirfenidone group and 1.1% and 0.4% of those, respectively, in the placebo group. There were fewer serious adverse events and deaths in the pirfenidone group than in the placebo group. Clinically significant elevations in aminotransferase levels occurred more frequently in the pirfenidone group; however, these elevations occurred in less than 3% of patients, were reversible, and did not have clinically significant consequences.

The results of this study confirm and extend the findings of the two CAPACITY trials (studies 004 and 006),[8] each of which was smaller and of longer duration than the ASCEND trial. An important observation in the CAPACITY 006 trial was the attenuated rate of decline in FVC in the placebo group, as compared with that in the CAPACITY 004 study and another multinational trial.[13] In our study, we modified certain aspects of the CAPACITY study design, including increasing the sample size and requiring central confirmation of the diagnosis. We also modified selected eligibility criteria in order to enroll patients at higher risk for disease progression. Thus, we excluded patients with major airflow limitation (ratio of FEV_1 to FVC, <0.80) and reduced the minimum baseline carbon monoxide diffusing capacity from 35% to 30% of the predicted value. The latter modification meant that 22% of the patients in our study had a baseline carbon monoxide diffusing capacity of less than 35% of the predicted value. Despite these and other minor design modifications, the baseline characteristics of the patients in the ASCEND study were strikingly similar to those in the CAPACITY studies, and the magnitude of the treatment effect at 1 year was generally consistent in these three studies and the Japanese phase 3 trial.

Our findings are strengthened by the high rates of study completion and treatment adherence and the consistent magnitude of treatment

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effect across the primary and secondary end points. In addition, both FVC and 6-minute walk distance are reliable, valid, and responsive measures of disease status and independent predictors of the risk of death among patients with idiopathic pulmonary fibrosis.[14-24] Finally, the thresholds of change that were selected for the categorical analyses of FVC and 6-minute walk distance are well above the estimated minimal clinically important difference for each measure.[14,15,24-26]

The mortality analyses were prespecified to be conducted in both the ASCEND population and in the pooled population from the ASCEND and CAPACITY trials because of the low rate of death among patients who are typically enrolled in clinical trials of idiopathic pulmonary fibrosis and because of the need for a larger sample to obtain precise estimates of the treatment effect.[27] The magnitude of the treatment effect on mortality was large and internally consistent across analyses and populations — an important clinical finding. In addition, the effect size was generally consistent with the observed effect on measures of disease progression, providing further support for the use of these measures in subsequent clinical trials.

The results of our study should be interpreted in the context of certain limitations. First, we enrolled patients with mild-to-moderate physiological impairment; the degree to which our findings can be generalized to a population of patients with advanced disease is therefore uncertain. Second, we required central confirmation of the diagnosis of idiopathic pulmonary fibrosis on the basis of criteria from recent diagnostic guidelines.[1] However, the general similarity in outcomes at 1 year between our study and the CAPACITY studies — in which the site investigator determined the diagnosis — militates against any limitation that this requirement might impose on the generalizability of our results.

In conclusion, we found that pirfenidone as compared with placebo reduced disease progression in patients with idiopathic pulmonary fibrosis. Treatment was generally safe, had an acceptable side-effect profile, and was associated with fewer deaths.

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