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An Open-Label Study of the Long-Term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (RECAP)

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Keywords
Idiopathic pulmonary fibrosis · Pirfenidone · Long-term safety

Abstract
Background: RECAP (NCT00662038) was an open-label extension study in patients with idiopathic pulmonary fibrosis (IPF) who completed either the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) 016 phase 3 trial or the Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) 004/006 phase 3 trials. ***Objective:*** To obtain long-term safety data for pirfenidone in patients with IPF in RECAP. ***Methods:*** Of the 1,334 patients who participated in the phase 3 trials, 1,058 entered RECAP. The final analysis from enrollment (September 2008) to June 2015 is presented. ***Results:*** Mean (SD) and median (range) pirfenidone exposures in RECAP were 122 (98) weeks and 88 (>0 to 349) weeks, respectively, with a mean daily dose of 2,091.1 mg. Cumulative total exposure was 2,482 patient exposure years (PEY). The treatment-emergent adverse event (TEAE) rate was 701.9 per 100 PEY. The serious TEAE rate was 53.5 per 100 PEY, with the most common serious TEAE being IPF (11.1 per 100 PEY). Of the 231 deaths (9.3 per 100 PEY), the most common cause was IPF (5.4 per 100 PEY). The treatment discontinuation rate due to a TEAE was 17.9 per 100 PEY; discontinuations were due to IPF (7.2 per 100 PEY), pneumonia, respiratory failure, acute respiratory failure, rash (0.5 per 100 PEY each), and nausea (0.4 per 100 PEY). For patients from CAPACITY 004/006 who entered RECAP, the mean change in percent predicted forced vital capacity from RECAP baseline at 180 weeks was –9.6%. Median on-treatment survival from the first pirfenidone dose in RECAP was 77.2 months. ***Conclusions:*** RECAP provides long-term follow-up and safety data for pirfenidone that were consistent with the known profile, with no new safety signals observed.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a serious, devastating, progressive, and often fatal fibrosing lung disease. Pirfenidone is an oral antifibrotic agent with anti-inflammatory properties that was approved for the treatment of IPF in the European Union in 2011 and in the United States in 2014. In the 2015 update of the American Thoracic Society, European Respiratory Society, Japanese

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Respiratory Society, and Latin American Thoracic Association treatment guidelines for IPF, pirfenidone is conditionally recommended for the treatment of IPF [1].

In clinical trials, pirfenidone has slowed disease progression and decreased mortality compared with placebo, and observations of attenuated decline in lung function (forced vital capacity, FVC) from real-world data are consistent with findings from clinical trials [2–8]. Pirfenidone slowed disease progression as measured by changes in FVC [9, 10] and reduced the risk of death from any cause by 48% at 1 year [3, 11]. In addition, a treatment benefit for pirfenidone was observed for other outcomes, including 6-min walking distance and progression-free survival [2, 11].

Pirfenidone has a favorable benefit-risk profile, with well-characterized long-term safety and tolerability data as well as manageable side effects [12, 13]. Gastrointestinal- and skin-related events, the most commonly reported side effects from pirfenidone, are often manageable with appropriate mitigation strategies and education [14, 15].

RECAP was an open-label extension study evaluating the long-term safety of pirfenidone in patients with IPF who completed the Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) 006 (PIPF-006; NCT00287729), CAPACITY 004 (PIPF-004; NCT00287716), or the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND; PIPF-016; NCT01366209) trial [16]. Here we present the primary analysis of the RECAP study.

Methods

Patients

To be eligible for RECAP, patients had to have completed the final visit and not have permanently discontinued pirfenidone in a previous, qualifying phase 3 clinical trial (CAPACITY 004/006 or ASCEND 016). Patients were to be enrolled in RECAP within 10 days of completing the final visit in their qualifying trial. Enrollment of CAPACITY 004/006 patients into RECAP was initiated nearly 4 years before the patients from ASCEND first entered RECAP.

Study Design

RECAP (PIPF-012) was an open-label, multicenter, single-arm, rollover study for patients with IPF who completed CAPACITY 004/006 or ASCEND. The primary objective was to obtain additional safety data for pirfenidone 2,403 mg/day. Patients entering this study from any of the parent studies transitioned from one of three treatment arms: pirfenidone 1,197 mg/day (CAPACITY 004 only), pirfenidone 2,403 mg/day, or placebo. All patients were treated as if they had been receiving placebo during the phase 3 trials due to patients entering RECAP before the unblinding in the parent study.

Table 1. Patient demographics and baseline characteristics (n = 1,058)

Age, years	68.5 (7.47)
Age ≥65 years	745 (70.4%)
Male	790 (74.7%)
White	1,007 (95.2%)
Not Hispanic or Latino ethnicity	947 (89.5%)
Male weight, kg	88.3 (15.7)
Female weight, kg	73.6 (14.6)
Years since IPF diagnosis	
<2	309 (29.2%)
2 to <4	572 (54.1%)
≥4	176 (16.7%)
For CAPACITY 004/006 patients only	
FVC, % predicted	70.9 (16.68)
DL_{CO}, % predicted[1]	41.2 (12.41)

Values are presented as mean (SD) or n (%). Note that the collection of baseline assessments varied by parent study, but in general, baseline was defined as the last assessment before first dose. CAPACITY, Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes; DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis. [1] Corrected for hematocrit.

Patients received pirfenidone 2,403 mg/day in equally divided doses three times per day with food [17]. The pirfenidone dose was titrated from 801 mg/day over the first 15 days in RECAP to the maintenance dose of 2,403 mg/day or as high as was tolerated (≤2,403 mg/day), depending on investigator judgment. The duration of treatment for each patient continued until pirfenidone became commercially or otherwise available. Written informed consent was required from all patients, and the study protocol was approved by the institutional review board or ethics committee at each center.

Study Assessments

Patients were assessed via telephone at week 1. Physical examination and clinical laboratory assessments were performed at baseline and at weeks 2, 4, 6, and 12 and at 12-week intervals thereafter. A directed history, including a review of adverse events (AEs), serious AEs, concomitant medications, and treatment adherence, was recorded at each visit. FVC, forced expiratory volume in 1 s, and diffusing capacity for carbon monoxide were measured at baseline and at week 12, then every 24 weeks. Week 8, 16, and 20 visits were added for clinical lab assessments of liver chemistries when the patients from ASCEND entered the study.

The analysis population consisted of all patients who were enrolled and received ≥1 dose of pirfenidone. The primary analysis was based on data collected as of June 30, 2015, with 5 of the 1,058 patients still ongoing. Assessments at each time point and their changes from baseline were summarized with descriptive statistics from all study visits, using all available data. Kaplan-

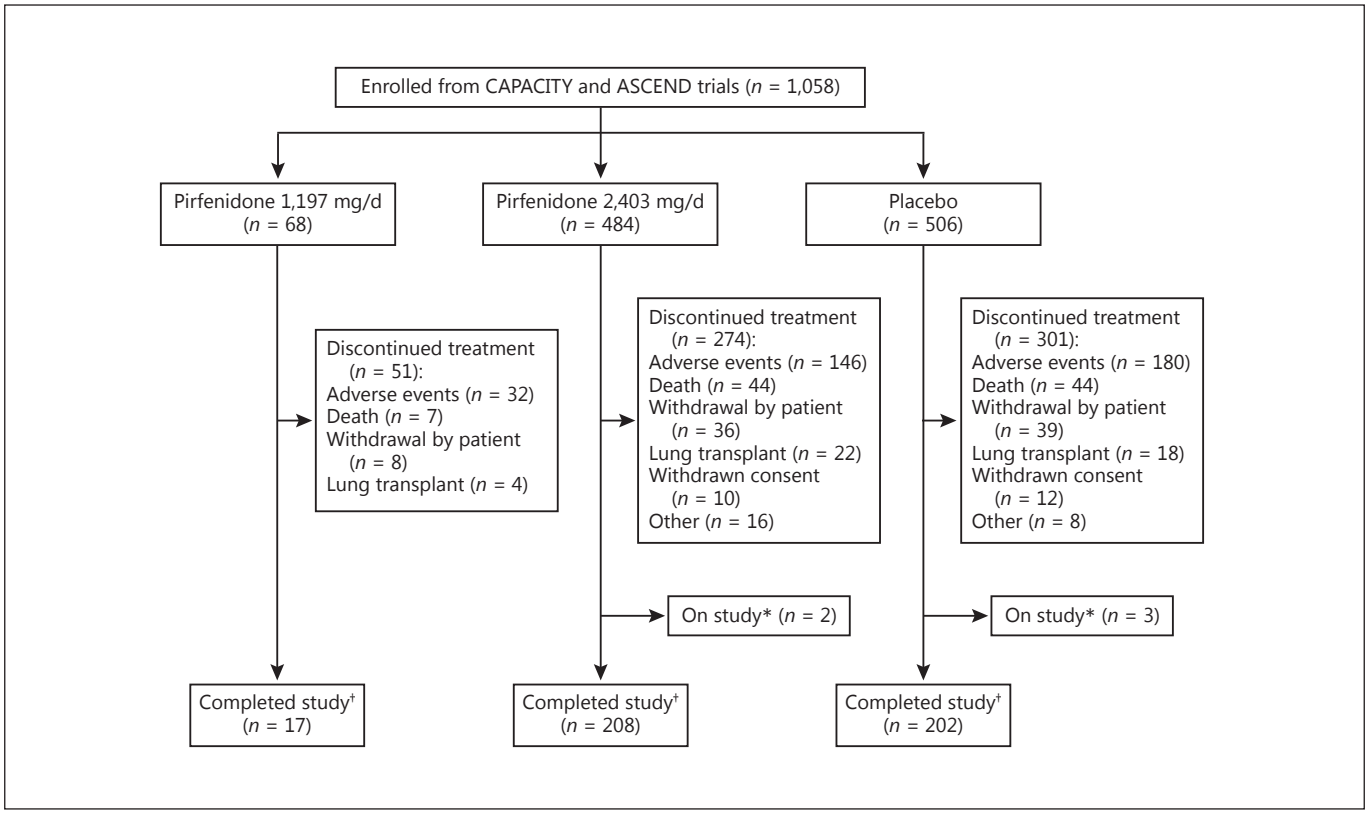

Fig. 1. Patient disposition in RECAP. Patients who had received prior pirfenidone 1,197 mg/day, pirfenidone 2,403 mg/day, or placebo were enrolled into RECAP. ASCEND, Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; CAPACITY, Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes. * Patients were considered to have been on study if they were still in the study at the time the study was terminated. † Patients were considered to have completed the study if they were active at the time their study site was closed due to availability of commercial pirfenidone or a posttrial access program.

Meier estimates were used to summarize time to early discontinuation of pirfenidone. Efficacy data were collected on rollover patients from CAPACITY 004/006 through May 2012, when patients from ASCEND entered the study. No efficacy data were collected after that time because these data would not be comparable due to differences in the study design between the ASCEND and CAPACITY 004/006 trials. Kaplan-Meier estimates were used to summarize survival time, as measured by time from the first dose of pirfenidone in RECAP to death (all-cause mortality). The annualized rate of decline in FVC volume was estimated using a random coefficient regression model (with random slopes and intercepts) that included sex, age, and height as covariates. The decrease in FVC was assumed to be linear within each patient. The intercepts and slopes were assumed to be normally distributed with an unstructured covariance matrix. The within-patient error was assumed to be independent and normally distributed with mean zero and a common variance. All observed FVC volumes from baseline were included in the model. Missing data were imputed implicitly by the model assuming missing at random.

The primary survival analysis was a treatment-emergent analysis, in which all deaths occurring within 28 days after the last dose were included as events. Deaths occurring after the lung transplantation date (if applicable) were excluded. Patients without events were censored at their lung transplantation date (if applicable), their last known alive date, or their last dose date plus 28 days, whichever was earlier.

Safety data collected throughout the study included treatment-emergent adverse events (TEAEs) and laboratory results. TEAEs were events occurring from the first dose in RECAP through 28 days after the last dose in RECAP. A dose interruption was defined as a dosing gap of ≥1 day, excluding the initial dose escalation period. A drug holiday was defined as an interruption of ≥14 days when the patient was not permanently discontinued from pirfenidone. Adverse drug reactions (ADRs) were AEs judged by the investigator as possibly or probably related to pirfenidone. AEs were summarized using patient incidence (defined as the number of patients with an event divided by total number of patients) and adjusted event rate per 100 patient exposure years (PEY) (defined as the number of events divided by the total PEY times 100).

All authors participated in the design, conduct, and analysis of the study. The authors had full access to data, and no limits were placed on reporting of the results by the study sponsor.

Results

Baseline Characteristics, Patient Disposition, and Pirfenidone Exposure

From the CAPACITY 004/006 and ASCEND trials, 1,089 of 1,334 patients (81.6%) with IPF completed the study treatment. Between September 2008 and January 2014, 1,058 of the 1,334 patients (79.3%) entered into RECAP (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000479976).

Patients in RECAP were mostly white (95.2%) and male (74.7%) and had an IPF disease duration between 2 and 4 years (54.1%; Table 1). For patients from the CAPACITY 004/006 trials at the start of RECAP, the baseline mean (SD) values for percent predicted FVC and percent predicted diffusing capacity for carbon monoxide were 70.9% (16.68%) and 41.2% (12.41%), respectively.

Of the 1,058 patients who entered RECAP, 427 patients (40.4%) had completed the study, 626 patients (59.2%) had discontinued it, and 5 patients in Mexico were still ongoing at the time of this analysis (Fig. 1; June 30, 2015). The 5 Mexican patients were all transferred to an alternative source of pirfenidone and discontinued from the study in February 2016. The median (95% CI) time to study discontinuation was 150 (132–166) weeks (online suppl. Fig. 1A).

The mean (SD) and median (range) of pirfenidone exposure in RECAP was 122 (98) weeks and 88 (>0 to 349) weeks, respectively, with a mean (SD) dose of 2,091.1 (507.5) mg/day. The majority of patients (68.5%) received a mean daily dose of pirfenidone ranging from 2,200 to 2,403 mg/day. The cumulative total exposure to pirfenidone was 2,482 PEY. Overall, 557 patients (52.6%) had a dose interruption, and 202 patients (19.1%) had ≥3 dose interruptions. The median (range) duration of dose interruptions was 13 (1–320) days.

Safety

The majority of patients (98.0%) reported ≥1 TEAE. The most frequent TEAEs based on incidence were IPF (33.6%), cough (31.3%), and dyspnea (30.9%) (Table 2). When adjusted for exposure, the most frequent TEAEs were IPF (22.0 per 100 PEY), upper respiratory infection (21.1 per 100 PEY), and bronchitis (19.5 per 100 PEY). TEAEs resulting in pirfenidone withdrawal occurred in 444 patients (42.0%; 17.9 per 100 PEY; Table 3) and included 95 patients who died. The most frequent TEAE leading to pirfenidone withdrawal was IPF (16.8%; 7.2 per 100 PEY). However, of the patients who discontinued the study due to an AE (n = 358), 243 (67.9%) discontinued due to an AE unrelated to IPF progression (online suppl. Fig. 1B). These discontinuations resulting in study withdrawal due to AEs other than IPF most often occurred during the first year of treatment (online suppl. Fig. 1B).

Table 2. Summary of TEAEs (n = 1,058)

TEAEs	n (%)	Adjusted rate[1]	
		events, n	rate per 100 PEY[2]
TEAEs with incidence in ≥15% of patients			
Total	1,037 (98.0)	17,422	701.9
IPF	355 (33.6)	547	22.0
Upper RTI	295 (27.9)	523	21.1
Bronchitis	260 (24.6)	485	19.5
Cough	331 (31.3)	436	17.6
Nausea	305 (28.8)	433	17.4
Dyspnea	327 (30.9)	420	16.9
Nasopharyngitis	202 (19.1)	359	14.5
Diarrhea	242 (22.9)	357	14.4
Fatigue	210 (19.8)	251	10.1
Dizziness	176 (16.6)	226	9.1
Serious TEAEs with incidence in ≥2% of patients			
Total	571 (54)	1,329	53.5
IPF	230 (21.7)	276	11.1
Pneumonia	90 (8.5)	104	4.2
Bronchitis	32 (3.0)	38	1.5
Atrial fibrillation	26 (2.5)	32	1.3
Acute respiratory failure	30 (2.8)	30	1.2
Respiratory failure	29 (2.7)	29	1.2

IPF, idiopathic pulmonary fibrosis; PEY, patient exposure years; RTI, respiratory tract infection; TEAEs, treatment-emergent adverse events. [1] Adjusted rate per 100 PEY = (total number of events/total years of exposure) × 100. [2] Cumulative total exposure: 2,482 PEY.

ADRs occurred in 786 patients (74.3%). The most frequent ADRs were nausea (21.6%; 11.6 per 100 PEY), diarrhea (12.3%; 6.9 per 100 PEY), and rash (11.6%; 7.2 per 100 PEY), which were also observed in the phase 3 clinical trials (online suppl. Table 2). Discontinuation of pirfenidone due to an ADR occurred in 120 patients (11.3%; 4.8 per 100 PEY) (online suppl. Table 3). The most frequent ADRs leading to discontinuation were rash (1.1%; 0.5 per 100 PEY) and nausea (1.0%; 0.4 per 100 PEY).

Severe or life-threatening TEAEs were reported in 597 patients (56.4%), and the most frequent ones were IPF (23.0%), pneumonia (6.3%), and dyspnea (5.1%). Serious TEAEs were reported in 571 patients (54.0%), and the most frequent serious TEAEs were IPF (21.7%) and pneumonia (8.5%) (Table 2).

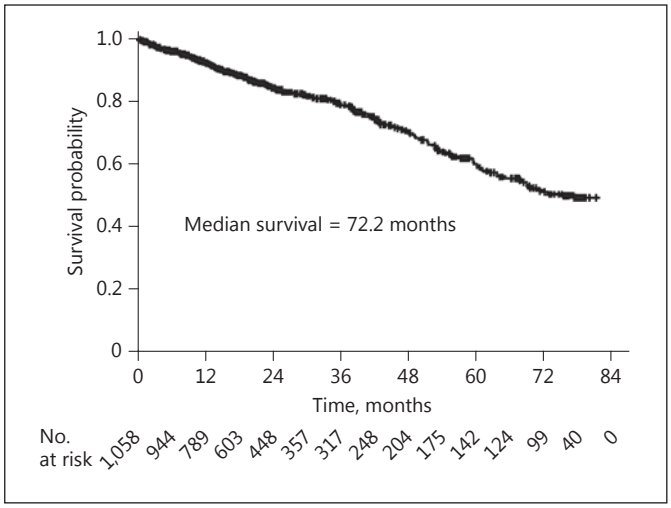

Fig. 2. On-treatment survival from the first dose of pirfenidone in RECAP (assume 1 month = 30.4375 days).

Table 3. Summary of TEAEs resulting in pirfenidone withdrawal with incidence in ≥1% of patients (n = 1,058)

TEAEs	n (%)	Adjusted rate[1]	
		events, n	rate per 100 PEY[2]
Total	444 (42.0)	444	17.9
IPF	178 (16.8)	178	7.2
Pneumonia	13 (1.2)	13	0.5
Respiratory failure	13 (1.2)	13	0.5
Acute respiratory failure	12 (1.1)	12	0.5
Rash	12 (1.1)	12	0.5
Nausea	11 (1.0)	11	0.4

IPF, idiopathic pulmonary fibrosis; PEY, patient exposure years; TEAEs, treatment-emergent adverse events. [1] Adjusted rate per 100 PEY = (total number of events/total years of exposure) × 100. [2] Cumulative total exposure: 2,482 PEY.

Death as the outcome of a TEAE was reported in 231 patients (21.8%; 9.3 per 100 PEY) (online suppl. Table 4). The most frequent TEAEs that resulted in death were IPF (12.6%), respiratory failure (1.7%), and acute respiratory failure (1.0%). Deaths due to an ADR deemed as possibly related by investigators were reported in 13 patients (1.2%; 0.5 per 100 PEY) (online suppl. Table 5).

Efficacy

In CAPACITY 004/006 patients entering RECAP with FVC data, the annualized rate (SD) of FVC decline was 144.3 (6.0) mL using a linear mixed-effects model, which showed a slow decrease in FVC over the 180-week period (online suppl. Fig. 2). The median on-treatment survival from the first dose of 2,403 mg/day pirfenidone in RECAP was 77.2 months (Fig. 2).

Discussion

This study evaluated safety outcomes in a large cohort of patients treated with pirfenidone 2,403 mg/day who had completed a previous phase 3 trial. RECAP provides long-term safety follow-up data for pirfenidone, with a cumulative total exposure of 2,482 PEY. At the time that patients from RECAP transitioned to commercially available pirfenidone or a posttrial access program, 40% were still receiving pirfenidone, after a median treatment duration in RECAP of 88 weeks (range >0 to 349 weeks).

In contrast to the phase 3 clinical trials, the frequency and adjusted rate of ADRs were lower in RECAP (74.3%; 133.7 per 100 PEY vs. 89.2%; 418.8 per 100 PEY). These results may be attributable to positive selection bias introduced by extending observations in patients with prior chronic trial exposure to pirfenidone, which is a common issue in long-term extension studies. However, the most common ADRs observed in RECAP (nausea and rash) were consistent with those seen in the phase 3 clinical trials and led to similar rates of discontinuation (1.0 vs. 1.1% and 1.1 vs. 1.4%, respectively) [12]. Only 13 patients experienced an ADR that resulted in death, the most common ones being acute respiratory failure and IPF (2 each), which are indicative of the progressive nature of the disease. Overall, these data demonstrate that prolonged exposure to pirfenidone does not increase the risk of ADRs, consistent with the known safety profile of pirfenidone.

A total of 33.8% of patients discontinued RECAP due to AEs over the entire course (≥5 years) of the study. Most discontinuations (23.0%; online suppl. Fig. 1B) were due to AEs that were unrelated to IPF progression. These events occurred most frequently during the first year of treatment and in patients who were newly initiating pirfenidone (data not shown), suggesting that patients must be carefully monitored during this early treatment period to reduce the risk of discontinuation. Patient support programs have shown that early and careful management reduces the rate of discontinuations [18]. While the overall discontinuation rate is higher than in the shorter phase 3 trials, RECAP was a study conducted over several years, and IPF worsening did not appear to be the main driver for treatment discontinuations.

The annual rate of FVC decline was 144.3 mL for patients who entered RECAP from CAPACITY 004/006 (no efficacy measurements were acquired in the post-ASCEND phase of the study), which was comparable to the 164-mL/year slope observed in the pirfenidone-treated patients in ASCEND and using a similar mixed-effects model for the calculation [2]. In addition, the annual rate of FVC decline (mL) was similar for both prior pirfenidone-treated and prior placebo-treated patients from CAPACITY 004/006 who were treated with pirfenidone in RECAP, indicating that prior treatment did not appear to influence the annual rate of decline observed in RECAP (data not shown). The median on-treatment survival from the first dose of pirfenidone 2,403 mg/day in RECAP was 77.2 months. These data reinforce/support the long-term efficacy of pirfenidone and suggest that the treatment benefit of pirfenidone was maintained in patients who continued receiving therapy.

These results of this study should be interpreted in the context of some limitations because of its open-label, uncontrolled design with no applicable sample size and power calculations, as well as the inherent biases in the study, including the survival bias for patients in RECAP who did not die in the previous phase 3 studies; in addition, the vital status of patients who discontinued RECAP was not captured at the end of RECAP as was done in ASCEND/CAPACITY 004/006. Patients who did not tolerate pirfenidone were not eligible for RECAP because patients were required to have completed their previous phase 3 study and were generally compliant with study treatment. Although reasons for not rolling over into RECAP were also not collected, the majority of patients (1,058 of 1,089; 97.2%) who completed ASCEND/CAPACITY 004/006 while on treatment enrolled into RECAP.

The long-term safety results from this study are consistent with the known safety profile of pirfenidone, with no new safety signals observed. These findings support the clinical use of pirfenidone in patients with IPF.

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U. Costabel was an advisor to InterMune (wholly owned Roche subsidiary since 2014), Boehringer Ingelheim, Bayer, Roche, and Gilead on IPF trials and has received lecture fees from InterMune, Bayer, and Boehringer Ingelheim. C. Albera was a member of the steering committee at InterMune as well as a consultant and investigator in the clinical trials. L.H. Lancaster was a consultant for InterMune and Boehringer Ingelheim. H.N. Hulter was a consultant for Genentech, Inc. P. Hormel and C.-Y. Lin are employees of Genentech, Inc. P.W. Noble was a consultant for InterMune, Boehringer Ingelheim, Genentech, Inc., GlaxoSmithKline, and Moerae Matrix.

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Author Contributions

U. Costabel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. H.N. Hulter, P. Hormel, and C.-Y. Lin (Genentech, Inc.) conducted and are responsible for the data analysis. All authors had access to the data and interpreted them as well as contributed to the preparation, review, and approval of the manuscript. U. Costabel had the final full responsibility for the decision to submit the manuscript for publication.

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