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Analysis of lung function and survival in RECAP: An open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis

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Abstract. *Background:* RECAP is an open-label extension study evaluating pirfenidone in patients with idiopathic pulmonary fibrosis (IPF) who completed the Phase 3 CAPACITY program. *Objective:* We examined the effect of pirfenidone on lung function and survival in patients who were previously randomised to the placebo group in one of the two CAPACITY studies and received pirfenidone for the first time in RECAP. *Methods:* Eligible patients received oral pirfenidone 2403 mg/day. Forced vital capacity (FVC) was measured at baseline and at weeks 12, 36, and 60. To facilitate comparison with CAPACITY outcomes, analyses were based on patients newly treated with pirfenidone in RECAP who had baseline FVC and carbon monoxide diffusing capacity (DLCO) values that met CAPACITY entry criteria. *Results:* A total of 178 patients were included in the analysis. Among these, 16.3% experienced an FVC decline ≥10% at week 60, compared with 16.8% and 24.8%, respectively, in the CAPACITY pirfenidone (n=345) and placebo (n=347) groups. The mean change from baseline to week 60 in %FVC was −5.9%, compared with −7.0% and −9.4% in the CAPACITY pirfenidone and placebo groups. Overall survival was similar to that of pirfenidone treated patients in CAPACITY. Treatment was safe and generally well tolerated; the type and frequency of adverse events were consistent with previous clinical experience. *Conclusion:* FVC and survival outcomes in IPF patients newly treated with pirfenidone in RECAP were similar to those in the CAPACITY pirfenidone group. These data provide further evidence to support the use of pirfenidone in patients with IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 198-205)*

Key words: IPF, Treatment, Pirfenidone, FVC, Survival

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Abbreviations

ANCOVA - analysis of covariance
DL_{CO} - hemoglobin-corrected carbon monoxide diffusing capacity
FEV^1 - forced expiratory volume in 1 second
FVC - forced vital capacity
IPF - idiopathic pulmonary fibrosis
VC - vital capacity

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal interstitial lung disease characterised by a relentless and irreversible loss of lung function that limits and eventually precludes routine physical activity. The prognosis for patients with IPF is poor; the estimated median survival is only 2 to 5 years after diagnosis (1-3) and the 5-year survival rate is comparable to that of non-small cell lung cancer (1,4).

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally bioavailable molecule with antifibrotic and anti-inflammatory properties (5-10) that has recently been approved in multiple countries in Europe, Asia, North America and South America for the treatment of patients with IPF. Evidence of the clinical efficacy and safety of pirfenidone in patients with IPF was demonstrated in four randomised, double-blind, placebo controlled trials, including one Phase 2 and one Phase 3 trial conducted in Japan and two multinational Phase 3 trials conducted in North America, Europe, and Australia (11-13).

The CAPACITY program included two nearly-identical, concurrent, randomised, double-blind, placebo controlled, multinational trials (Study 004 and Study 006) designed to confirm the effect of treatment with pirfenidone on the decline in lung function observed in the Japanese clinical trials (13). Patients were randomised to treatment with pirfenidone 2403 mg/day or matched placebo for 72 weeks. In Study 004 (N=435), treatment with pirfenidone reduced the mean decline in percent predicted forced vital capacity (FVC) at week 72 compared to placebo (-8.0% vs. -12.4%; rank ANCOVA p value=0.001) and improved progression-free survival time (HR 0.64; 95% CI 0.44, 0.95; p=0.023). Additionally, fewer patients in the pirfenidone group experienced a ≥10% decline in percent predicted FVC (20% vs. 35%; p<0.001). In Study 006 (N=344), there was no significant difference between groups in the mean change in percent predicted FVC at week 72 (-9.0% vs. -9.6%; rank ANCOVA p value=0.503); however, a consistent treatment effect was evident through week 48 (p=0.005). Pooled analyses of survival showed that there were fewer overall deaths (6% vs. 8%) and fewer IPF-related deaths (3% vs. 7%) among patients treated with pirfenidone.

In light of the chronic nature of IPF and the corresponding need for long-term therapeutic management, patients who completed either study in the CAPACITY program were offered the opportunity to enrol in RECAP, an open-label extension study evaluating the effect of long-term treatment with pirfenidone. The primary objective of the RECAP study was to evaluate the long-term safety and tolerability of pirfenidone in patients with IPF; the secondary objective was to obtain additional efficacy data for pirfenidone 2403 mg/day. A comprehensive analysis of long-term safety data from the RECAP study is the subject of a separate report. In the present analysis, we examined change in lung function and overall survival in patients who were originally randomised to the placebo group in the CAPACITY trials and were newly initiating treatment with pirfenidone in RECAP. The results were compared with outcomes over the same duration of treatment in the CAPACITY studies. The primary objective of the analysis was to examine the change in lung function and overall survival in a fourth large, well-defined, cohort of IPF patients treated with pirfenidone and followed prospectively for a period of at least one year. This work has been presented in part at the 2012 Annual Congress of the European Respiratory Society (14).

Methods

Study Subjects

Patients were recruited for enrolment in RECAP at 88 sites in North America, Europe and Australia. Eligible patients were those who completed the final follow-up visit and received ≥80% of the assigned study treatment in either of the Phase 3 CAPACITY studies. In order to facilitate comparison with CAPACITY outcomes, patients were selected for inclusion in the present analysis if they were newly initiating treatment with pirfenidone and had baseline percent predicted FVC and percent predicted carbon monoxide diffusing capacity (DL_{CO}) values that met the original criteria for enrollment in CAPACITY (percent predicted FVC ≥50%, percent predicted DL_{CO}≥35%, and either percent predicted FVC or percent predicted DL_{CO}≤90%). For patients with missing baseline values for percent predicted

FVC or percent predicted DL_{CO}, the last observed value from CAPACITY was used.

Patients were excluded from enrolment in RECAP if their medical status had declined significantly during the previous trial and, in the opinion of the investigator, the patient was no longer a suitable candidate for participation in the study. Additionally, patients who permanently discontinued study drug for any reason during CAPACITY were excluded from enrolment. Patients were not permitted to participate in another interventional clinical trial between the time of completion of the CAPACITY trials and the time of enrolment in RECAP.

Study Design

Pirfenidone was administered orally with food in three equally divided daily doses and increased to the full dose of 2403 mg/day following a two-week dose titration period. Concomitant therapy with corticosteroids, azathioprine, cyclophosphamide, and/or N-acetylcysteine (NAC) was permitted if judged by the investigator to be clinically appropriate.

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, serious adverse events, concomitant medications, and treatment compliance was performed at each visit. FVC, forced expiratory volume in 1 second (FEV_1), and DL_{CO} were measured at baseline and at weeks 12, 36, and 60.

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.

Statistical Analysis

The population used for all analyses included all patients who were newly initiating treatment with pirfenidone 2403 mg/day in RECAP and had baseline percent predicted FVC and percent predicted DL_{CO} values that met the original criteria for enrollment in CAPACITY. All analyses are based on final data from the RECAP April 14, 2010 interim data cut.

In light of the open-label study design, no formal tests of inferential statistics were performed for comparisons between the study population and the pooled treatment groups in the CAPACITY studies. Categorical decline in percent predicted FVC, defined as an absolute decline ≥10%, is summarised descriptively and presented with the observed categorical decline in the pooled pirfenidone 2403 mg/day and placebo groups in the CAPACITY studies. The change from baseline in percent predicted FVC at each assessment interval is also summarised descriptively and presented with the observed change during the corresponding interval in the pooled pirfenidone 2403 mg/day and placebo groups in the CAPACITY studies. For percent predicted FVC, missing values due to death were assigned the worst possible value (FVC=0). Missing values for reasons other than death were imputed with the average value for that visit of the 3 patients with the smallest sum of squared differences at each visit with data that were not missing. Kaplan-Meier estimates were used to summarise overall survival time, defined as the time from the first dose of study drug in the respective study to death due to any cause. The incidence of treatment emergent deaths, defined as deaths occurring between baseline and week 60 and within 28 days after the last dose of study drug, was also evaluated. Treatment emergent deaths were further classified as either IPF-related or unrelated to IPF based on the assessment of the clinical investigator.

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

Results

Between September 2, 2008 and November 10, 2008, a total of 603 patients enrolled in RECAP; of these, 178 were newly initiating treatment with pirfenidone and had baseline percent predicted FVC and DL_{CO} values that met the original criteria for enrolment in CAPACITY (Figure 1). Demographics and baseline characteristics for this population are summarised in Table 1. With the exception of time since IPF diagnosis, baseline characteristics were similar to those in the pooled population from the

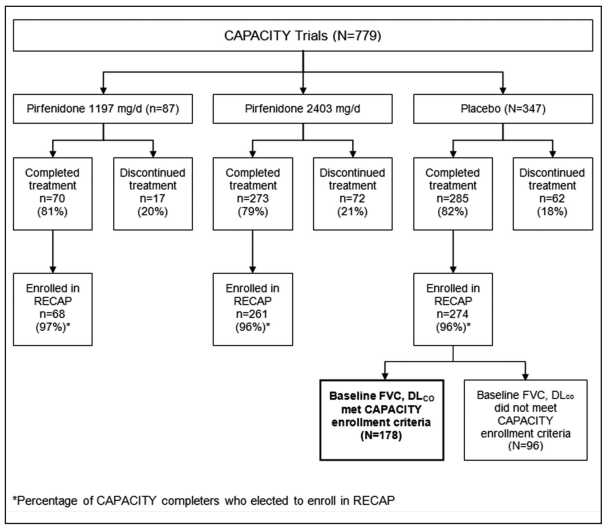

Fig. 1. Trial profile.

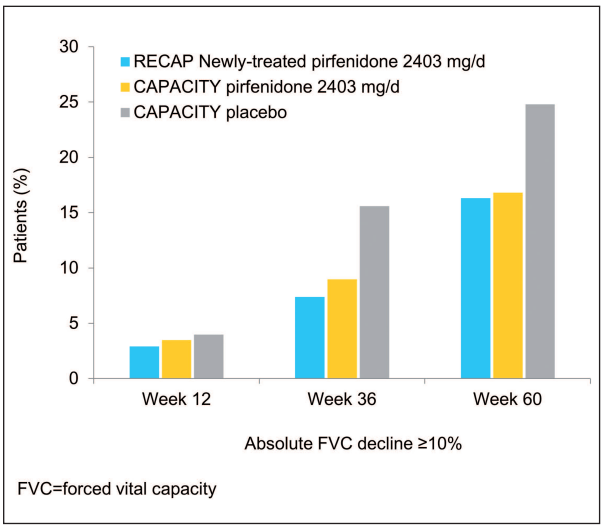

Fig. 2. Categorical analysis of change in percent predicted FVC.

CAPACITY studies. The majority of patients were Caucasian (97%) and male (71%). The median values for percent predicted FVC and percent predicted DL_{CO} were 73.4 and 46.1, respectively.

At week 60, 16.9% of patients who newly initiated pirfenidone in RECAP had discontinued treatment, compared with 14.5% and 13.5%, respectively, in the pirfenidone 2403 mg/day and placebo groups in CAPACITY.

The percentage of patients with an FVC decline ≥10% at each assessment interval is summarised in Figure 2. At week 60, 16.3% of newly treated patients in RECAP experienced an absolute decline in FVC ≥10%, compared with 16.8% and 24.8%, respectively, in the pirfenidone and placebo groups in CAPACITY. The magnitude of the treatment effect was consistent with the 32% relative reduction in the proportion of patients with a ≥10% decline in FVC observed in the pirfenidone 2403 mg/day group at week 60 in CAPACITY. Outcomes at earlier time points were also similar to those in pirfenidone treated patients in CAPACITY; 2.8% and 3.5% of patients newly initiating pirfenidone in RECAP and CAPACITY, respectively, experienced an FVC decline ≥10% at week 12, and 7.3% and 9.0%, respectively, experienced a ≥10% decline at week 36. In the CAPACITY placebo group, 4.0% of patients at week 12 and 15.6% of patients at week 36 experienced an FVC decline of at least 10%.

Table 1. Demographics and baseline characteristics.

Characteristic*	RECAP	CAPACITY	
	Pirfenidone 2403 mg/d (N=178)†	Pirfenidone 2403 mg/d (N=345)	Placebo (N=347)
Age, y	69.0 (42, 83)	67.0 (45, 80)	68.0 (40, 80)
Male, n (%)	127 (71.3)	241 (69.9)	252 (72.6)
Caucasian, n (%)	172 (96.6)	337 (97.7)	339 (97.7)
FVC (% predicted)	73.4 (51.1, 122.3)	73.7 (50.3, 123.9)	72.2 (48.0, 135.5)
DLco (% predicted)	46.1 (35.1, 81.0)	45.6 (30.3, 81.2)	45.4 (29.9, 90.1)
Time since IPF diagnosis, y	2.52 (1.5, 5.7)	0.82 (0.0, 4.1)	0.90 (0.0, 4.1)

FVC=forced vital capacity; DLCO=hemoglobin-corrected carbon monoxide diffusing capacity
** Values are expressed as the median (range) unless otherwise indicated*
† Newly treated with pirfenidone 2403 mg/day and had FVC and DLCO values that met CAPACITY enrolment criteria

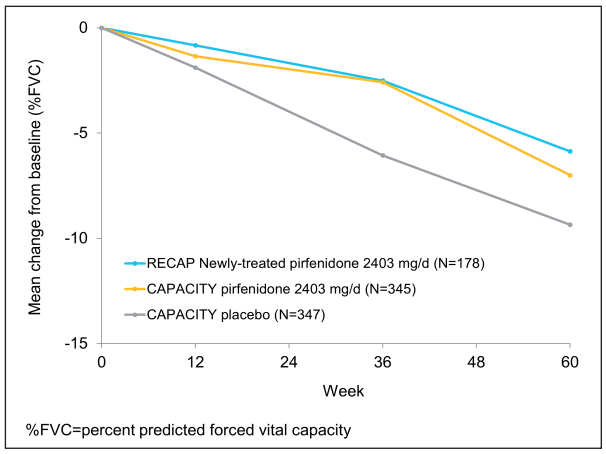

Fig. 3. Mean change from baseline in percent predicted FVC.

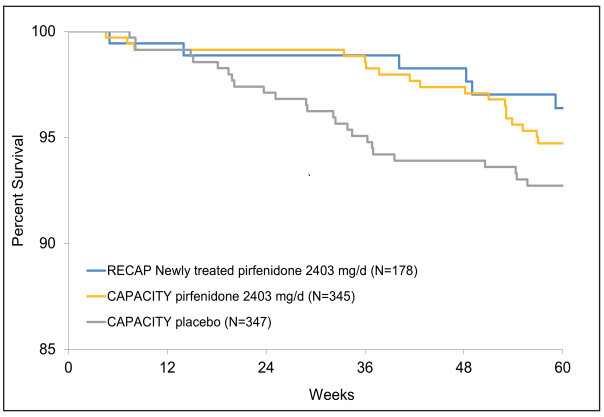

Fig. 4. Kaplan-Meier estimates of overall survival.

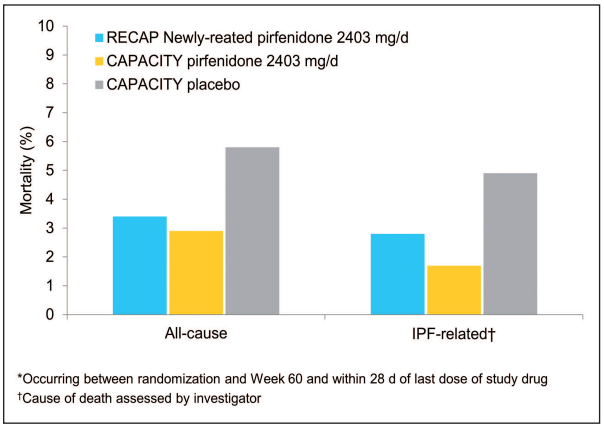

Fig. 5. Treatment emergent deaths.*

Figure 3 summarises the mean change from baseline in percent predicted FVC. At week 60, the mean change in percent predicted FVC in patients who were newly initiating treatment with pirfenidone in RECAP was −5.9%; mean change over the corresponding period in CAPACITY was −7.0% in the pirfenidone 2403 mg/day group and −9.4% in the placebo group. Analysis of outcomes at earlier time points showed a similar magnitude of change between patients who were newly initiating treatment with pirfenidone in RECAP and those who were newly treated in CAPACITY. At week 36, the mean change in percent predicted FVC was −2.5% in patients newly initiating treatment in RECAP and −2.6% in those who were newly treated in CAPACITY, compared with −6.1% in the CAPACITY placebo group.

Overall survival in patients newly treated with pirfenidone in RECAP was similar to that of pirfenidone treated patients in CAPACITY (Figure 4). A total of 6 (3.4%) newly treated patients died between baseline and week 60 in RECAP, compared with 18 (5.2%) and 25 (7.2%) patients in the pirfenidone 2403 mg/day and placebo groups, respectively, in CAPACITY. Treatment emergent deaths, defined as deaths occurring between baseline and week 60 and within 28 days after the last dose of study drug, occurred in 6 (3.4%) patients who initiated therapy in RECAP; of these, 5 (2.8%) were assessed by the investigator as IPF-related (Figure 5). In CAPACITY, treatment emergent deaths occurred in 10 (2.9%) patients in the pirfenidone 2403 mg/day group, compared with 20 (5.8%) patients in the placebo group. Death was assessed by the investigator as IPF-related in 6 (1.7%) patients in the CAPACITY pirfenidone 2403 mg/day group and 17 (4.9%) patients in the CAPACITY placebo group.

Consistent with observations in both the pirfenidone and placebo groups in the CAPACITY studies, nearly all patients newly initiating therapy with pirfenidone in RECAP experienced at least one treatment emergent adverse event (Table 2). The type and frequency of adverse events were generally consistent with prior observations. Gastrointestinal (nausea, dyspepsia, diarrhea) and skin-related events (rash, photosensitivity reaction) were among the most commonly reported adverse events; these were generally mild to moderate in severity and rarely resulted in early discontinuation of therapy.

Table 2. Demographics and baseline characteristics.

Treatment-emergent adverse events*

Patients (%)	RECAP	CAPACITY	
	Pirfenidone 2403 mg/d (N=178)	Pirfenidone 2403 mg/d (N=345)	Placebo (N=347)
Nausea	32.0	35.4	17.0
Dyspepsia	19.7	18.3	7.2
Upper respiratory tract infection	19.1	25.8	22.8
Nasopharyngitis	18.5	18.0	20.5
Dizziness	18.0	16.5	7.8
Rash	18.0	31.0	10.1
Diarrhea	16.9	27.0	16.7
Fatigue	15.7	26.1	17.0
Dyspnea	14.0	14.2	16.7
Headache	12.9	17.7	14.4
Bronchitis	12.4	10.4	14.7
Cough	12.4	23.2	22.2
Photosensitivity reaction	11.8	11.9	1.7
Gastroesophageal reflux disease	10.7	9.3	6.1
Vomiting	10.1	13.3	4.3
Sinusitis	6.7	11.9	8.4
Anorexia	3.9	10.4	2.9

**Occurring in at least 10% of patients in either pirfenidone 2403 mg/day group*

Discussion

The clinical efficacy and safety of pirfenidone have been evaluated in three randomised, double-blind, placebo controlled, Phase 3 trials in patients with IPF (12,13). Analysis of outcomes at one year demonstrated a significant treatment effect on the change in lung volume in all three studies. In addition, fewer overall deaths and significantly fewer on-treatment deaths related to IPF occurred in the pirfenidone 2403 mg/day group compared to placebo in the pooled analysis of data from the CAPACITY studies (13). In the present analysis, we examined FVC change and overall survival in patients who were newly treated with pirfenidone in RECAP, an open-label extension study evaluating pirfenidone in patients who completed either of the two Phase 3 CAPACITY trials.

Our findings demonstrate that FVC and survival outcomes in IPF patients newly treated with pirfenidone in RECAP were highly consistent with those in pirfenidone treated patients in the CAPACITY studies. The mean change from baseline to week 60 in percent predicted FVC among newly treated patients in RECAP was comparable to that in the pirfenidone 2403 mg/day group and lower than the placebo group in the pooled analysis of data from the CAPACITY studies. Similar results were observed at week 36. Additionally, the proportion of patients who experienced an FVC decline ≥10% at week 60 was nearly identical in newly treated patients in RECAP and CAPACITY, and the proportion was lower in both groups than in the CAPACITY placebo group. Of note, the magnitude of the observed treatment effect on categorical FVC decline at week 60 in the CAPACITY studies was also consistent with the magnitude of effect on the categorical change in vital capacity (VC) in the Japanese Phase 3 trial. Treatment with pirfenidone resulted in a 32% relative reduction in the proportion of patients with an FVC decline ≥10% at week 60 in CAPACITY and a 34% reduction in the proportion

of patients with a ≥10% decline in VC at one year in the Japanese trial (12,13). Importantly, several studies have demonstrated that an FVC decrement ≥10% is both clinically meaningful and prognostic of near term mortality in patients with IPF (15-20). The similar outcomes at week 60 between newly treated patients in RECAP and CAPACITY, coupled with the consistent magnitude of treatment effect on categorical change in FVC/VC in the Phase 3 trials provides compelling evidence of a consistent and clinically meaningful pirfenidone treatment benefit in patients with IPF.

Analysis of overall survival provided further evidence to support a meaningful treatment benefit. While the CAPACITY studies were not powered to assess survival, Kaplan-Meier estimates showed similar overall survival between patients newly treated with pirfenidone in RECAP and CAPACITY and reflect a survival rate greater than that in the CAPACITY placebo group. Treatment emergent deaths and deaths related to IPF also occurred with a similar frequency in pirfenidone treated patients in RECAP and CAPACITY, and the incidence of both treatment emergent and IPF-related deaths was lower in both pirfenidone groups than in the CAPACITY placebo group.

The findings of our study provide supplemental evidence to support the clinical efficacy of pirfenidone in patients with IPF; however, these findings should be interpreted in the context of several important limitations. First, the open-label study design and the lack of a concurrent control group limit the degree to which meaningful inferences may be made on the basis of the observed results. Additionally, neither the cause of death nor the relation of death to IPF was formally adjudicated and assessments in RECAP were performed by investigators who were not blinded to treatment assignment. Third, eligible patients were required to have baseline physiologic measures that met the original entry criteria for the CAPACITY trials despite receiving no active treatment during the preceding 72 weeks; therefore, the possibility that the population in the present analysis reflects a more clinically stable phenotype relative to the overall population in the CAPACITY studies cannot be excluded. Finally, only limited efficacy data were collected during RECAP; observations regarding the effect of treatment on percent predicted FVC therefore cannot be corroborated by findings on other potentially relevant measures like dyspnea and 6-minute walk test distance. We note, however, that both percent predicted FVC and overall survival outcomes were highly consistent with observations from previous randomised controlled trials evaluating pirfenidone in patients with IPF.

In conclusion, the patients included in this analysis represent the fourth large, well-defined cohort of IPF patients to be treated with pirfenidone and followed prospectively for a period of at least one year. FVC and survival outcomes at week 60 were strikingly similar to those in patients randomised to treatment with pirfenidone in three previous Phase 3 clinical trials. The current findings, coupled with prior evidence of a treatment benefit on clinically meaningful outcomes like progression-free survival and 6-minute walk test distance provide further evidence to support the use of pirfenidone in patients with IPF.

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