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ORIGINAL ARTICLE

Comprehensive assessment of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Background and objective: **Pirfenidone is an oral antifibrotic agent that is approved in several countries for the treatment of idiopathic pulmonary fibrosis (IPF). We performed a comprehensive analysis of safety across four clinical trials evaluating pirfenidone in patients with IPF.**

Methods: **All patients receiving pirfenidone 2403 mg/day in the Phase 3 CAPACITY studies (Studies 004 and 006) and all patients receiving at least one dose of pirfenidone in one of two ongoing open-label studies in patients with IPF (Studies 002 and 012) were selected for inclusion. Safety outcomes were evaluated from baseline until 28 days after the last dose of study drug.**

Results: **A total of 789 patients were included in the analysis. The median duration of exposure to pirfenidone was 2.6 years (range, 1 week–7.7 years), and the cumulative total exposure was 2059 person exposure years (PEY). Gastrointestinal and skin-related events were the most commonly reported adverse events; these were almost always mild to moderate in severity, and rarely led to treatment discontinuation. Elevations (>3× upper limit of normal) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurred in 21/789 (2.7%) patients; the adjusted incidence of AST/ALT elevations was 1.7 per 100 PEY.**

Conclusions: **This comprehensive analysis of safety in a large cohort of IPF patients receiving pirfenidone for a total of 2059 PEY demonstrates that long-term treatment with pirfenidone is safe and generally well tolerated.**

SUMMARY AT A GLANCE

Comprehensive analysis of safety outcomes in a large cohort of patients with IPF demonstrated that treatment with pirfenidone for up to 7.7 years (median, 2.6 years; range, 1 week–7.7 years) was safe and generally well tolerated.

Key words: adverse event, idiopathic pulmonary fibrosis, pirfenidone, safety, treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DL_{CO}, carbon monoxide diffusing capacity; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PEY, person exposure years; TE SAE, treatment-emergent serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

INTRODUCTION

Pirfenidone is a novel antifibrotic agent that has been approved in Europe, North America, Asia and Latin America for the treatment of idiopathic pulmonary fibrosis (IPF)—a chronic, irreversible and ultimately fatal lung disease characterized by variable but inevitable decline in lung function and exercise capacity.[1,2]

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Preclinical studies demonstrate that pirfenidone exhibits antifibrotic and anti-inflammatory activity in a variety of *in vitro* and animal models.[3–7] In models of pulmonary fibrosis, pirfenidone inhibits fibroblast proliferation and collagen synthesis,[7–10] reduces cellular and histologic markers of fibrosis,[8–10] and attenuates the decline in lung function.[11] In an open-label, compassionate use trial evaluating the safety of pirfenidone in 54 terminally ill patients with IPF who experienced deterioration despite conventional therapy, treatment with pirfenidone 40 mg/kg/day (maximum of 3600 mg/day) for up to 2 years was generally well tolerated.[12] Gastrointestinal and skin-related adverse events were common but rarely led to treatment discontinuation.

The clinical efficacy and safety of pirfenidone has been demonstrated in four randomized, 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 (CAPACITY).[13–15] In an independent meta-analysis of data from the three Phase 3 trials, Spagnolo *et al.*[16] reported an improvement in progression-free survival time among patients treated with pirfenidone.

Administration of pirfenidone was safe and generally well tolerated in the Phase 3 studies.[14,15] In the CAPACITY trials, gastrointestinal and skin-related events were the most common treatment-emergent adverse events (TEAE); these were almost exclusively mild to moderate in severity and rarely resulted in treatment discontinuation. Grade 3/4 elevations in liver enzymes, which occurred in 14 (4%) and 2 (<1%) patients, respectively, in the pirfenidone and placebo groups, were generally transient, reversible and without significant clinical sequelae.[15]

The long-term clinical safety of pirfenidone is currently being evaluated in two open-label trials, including one study in the United States (Study 002) and a multinational open-label extension study (Study 012 (RECAP)) in patients who completed either of the Phase 3 CAPACITY studies or the ongoing ASCEND study. The aim of the present study was to conduct a comprehensive analysis of safety in the integrated population from four clinical studies evaluating pirfenidone in patients with IPF.

METHODS

Study subjects

All patients who were randomized to treatment with pirfenidone and received at least one dose of study drug in the Phase 3 CAPACITY studies and all patients who received at least one dose of pirfenidone in one of two ongoing open-label studies were included in the analysis (Fig. 1). The CAPACITY studies (Study 004 and Study 006) were randomized, double-blind, placebo-controlled studies evaluating pirfenidone in patients with IPF. The open-label studies included Study 002, a compassionate-use study in patients with either IPF or secondary pulmonary fibrosis, and Study 012 (RECAP), an open-label extension study in patients who completed either of the two CAPACITY studies or the ongoing ASCEND study (patients who completed the ASCEND study enrolled in Study 012 after the interim data cut-off date and were therefore not included in the analysis).

Eligibility criteria for the CAPACITY studies have been previously described.[15] Briefly, eligible patients were between 40 and 80 years of age, with a confident diagnosis of IPF in the previous 48 months and no evidence of improvement in disease severity during the preceding year. Physiological criteria for enrolment included percent predicted forced vital capacity (FVC) ≥ 50%, carbon monoxide diffusing capacity

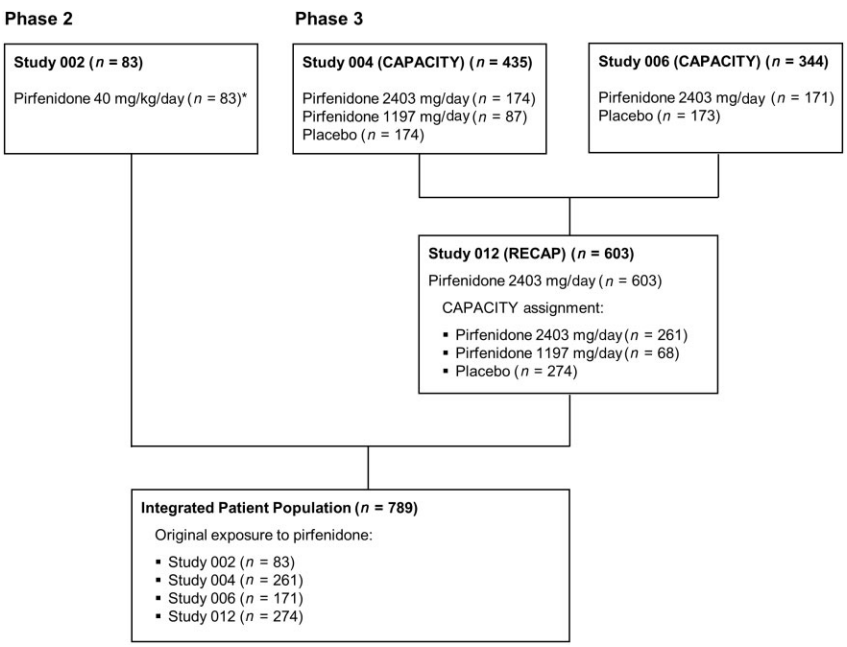

Figure 1 Study profile. *Patients who enrolled after Protocol Amendment 2 (15 September 2005) were treated with a target maintenance dose of 2403 mg/day, adminstered with food three times daily following a 2-week dose escalation period.

(DL_{CO}) ≥ 35%, either percent predicted FVC or DL_{CO} ≤ 90%, and 6-min walk test distance ≥150 m. Patients who completed the final study visit and received ≥80% of the assigned study drug doses in the CAPACITY studies were eligible for enrolment in Study 012. In Study 002, original eligibility criteria included a diagnosis of either IPF or secondary pulmonary fibrosis; secondary pulmonary fibrosis was subsequently eliminated as an inclusion criterion following Protocol Amendment 1 (15 December 2003).

Study design

Patients who met the criteria for enrolment in CAPACITY were randomized to treatment with pirfenidone or placebo for a minimum of 72 weeks. In Study 004, patients were randomly assigned (2:1:2) to one of three arms: pirfenidone 2403 mg/day, pirfenidone 1197 mg/day or placebo. In Study 006, patients were randomly assigned (1:1) to treatment with pirfenidone 2403 mg/day or placebo. Study drug was administered orally with food in three equally divided doses and escalated to the full dose over a 2-week period. In Study 012, eligible patients were treated with pirfenidone 2403 mg/day administered according to the same schedule as the CAPACITY studies. In Study 002, patients who enrolled prior to protocol amendment 2 (15 September 2005) received pirfenidone 40 mg/kg/day (maximum of 3600 mg/day) administered orally in three equally divided daily doses following a 2-week dose escalation period. Patients who enrolled after Protocol Amendment 2 were treated with a target maintenance dose of 2403 mg/day.

Physical examination and clinical laboratory tests were performed at prespecified intervals in each study. A directed history, including a review of adverse events, concomitant medications, hospitalizations and compliance, was conducted at each study visit in all four studies.

Written informed consent was required from all patients, and all study protocols were approved by the institutional review board or ethics committee at each centre. All trials in this report are registered at http://www.clinicaltrials.gov (NCT00287729, NCT00287716 and NCT00662038).

Statistical analysis

Data from the ongoing open-label studies are based on the interim data cut-off date of 29 April 2011. Demographic and baseline characteristics were summarized using descriptive statistics for continuous variables, and number and percentage counts of patients for categorical variables. The total duration of study drug exposure, total person exposure years (PEY) and mean daily dose of study treatment were summarized for the integrated pirfenidone population. The total duration of exposure is defined as the time between the first dose and the last dose of study drug.

TEAE are defined as adverse events with an onset or worsening between the first and 28 days after the last dose of study drug. TEAE rates were computed for the integrated pirfenidone population as well as the CAPACITY studies.

The crude and adjusted incidence of all-cause and IPF-related death was also summarized for the integrated population and by treatment assignment in the CAPACITY studies. Crude incidence was corrected for differences in duration of exposure by using person-time in the denominator. The adjusted incidence of mortality is reported as deaths per 100 PEY, calculated as the number of deaths divided by the total PEY for the group, multiplied by 100.

Assessment of crude and adjusted incidence rates of liver-related laboratory outcomes was performed for patients with at least 4 weeks of exposure to study drug. The crude incidence rate was computed as the number of events divided by the total number of patients exposed to study drug by treatment group. Adjusted incidence rate of events was defined as the number of events divided by the total number of patient-years of exposure for each treatment group.

RESULTS

A total of 789 patients were included in the analysis; of these, 432 were newly treated with pirfenidone in the CAPACITY trials (345 and 87 patients, respectively, were randomized to treatment with pirfenidone 2403 mg/day and pirfenidone 1197 mg/day), 274 were newly treated with pirfenidone in Study 012 and 83 received pirfenidone in Study 002. Demographics and baseline characteristics for the integrated patient population are summarized in Table 1. Forty-two (5.4%) and 159 (20.4%) patients, respectively, had baseline values for FVC and DL_{CO} that were below the minimum criteria for enrolment in the CAPACITY

Table 1 Demographics and baseline characteristics

Characteristic[†]	Integrated pirfenidone population (*n* = 789)
Age, years	68.0 (42, 88)
Male, *n* (%)	566 (71.7)
Caucasian, *n* (%)	761 (96.5)
FVC (% predicted)	71.6 (22, 127)
<50% predicted, *n* (%)	42 (5.4)
DL_{CO} (% predicted)	43.9 (10, 108)
<35% predicted, *n* (%)	159 (20.4)
Supplemental oxygen use, *n* (%)	149 (18.9)
Diagnosis, *n* (%)	
Idiopathic pulmonary fibrosis	787 (99.7)
Secondary pulmonary fibrosis	2 (0.3)
Time since IPF diagnosis, years[‡]	1.9 (>0, 10)

[†] Values are expressed as the median (range) unless otherwise indicated.

[‡] Measured at the time of first dose of study drug.

DL_{CO}, haemoglobin-corrected carbon monoxide diffusing capacity; FVC, orced vital capacity; IPF, idiopathic pulmonary fibrosis.

studies. Two patients (0.3%) who enrolled in Study 002 had secondary pulmonary fibrosis; all other patients in the integrated population had IPF.

Overall exposure to pirfenidone is summarized in Table 2. The cumulative total exposure in the integrated patient population was 2059 PEY. The median duration of exposure to pirfenidone was 2.6 years (range, 1 week–7.7 years), and the median daily dose was 2257 mg (range, 25–3600 mg). The majority of patients (54.6%) received an average daily dose of pirfenidone between 2200 and 2600 mg. A total of 293 (37.1%) patients had received treatment with pirfenidone for ≥3 years and 175 (22.2%) patients had received treatment for ≥4 years.

Consistent with observations in both the pirfenidone and placebo groups in the Phase 3 trials, nearly all patients in the integrated population reported at least one TEAE (Table 3). Treatment was discontinued because of adverse events in 277 (35.1%) patients in the integrated population compared with 51 (14.8%) patients in the pirfenidone 2403 mg/day group and 30 (8.6%) patients in the placebo group in the 72-week CAPACITY studies. Worsening IPF (8.7%) was the most common event leading to treatment discontinuation in the integrated population; the only other adverse events that resulted in treatment discontinuation in >1% of patients in the integrated population were nausea (2.3%), rash (1.6%) and respiratory failure (1.3%).

Gastrointestinal and skin-related events were the most commonly reported TEAE (Table 4); these included nausea (40%), dyspepsia (21%), vomiting (18%) and rash (26%). The incidence of such events was consistent with the observed incidence among patients treated with pirfenidone in the CAPACITY trials—despite the longer median duration of exposure in the integrated population. These events were almost always mild to moderate in severity and rarely led to treatment discontinuation (Table 5). Analysis of new-onset adverse events by 6-month intervals demonstrated that gastrointestinal and skin-related adverse events tended to occur early in the course of treatment (Fig. 2). The incidence of new-onset gastrointestinal and skin-related events declined markedly after the first 6 months and remained low during subsequent intervals; the slight increase in the incidence of gastrointestinal events during the intervals beginning at 18 and 24 months corresponded with the period during which patients who completed the CAPACITY studies were reinitiating pirfenidone upon enrolment in Study 012. Dizziness and insomnia also occurred with a higher frequency in the integrated population compared with pirfenidone treated patients in CAPACITY (Table 4); however, no patient experienced a treatment-emergent serious adverse event (TE SAE) related to dizziness or insomnia, and neither event led to discontinuation of therapy.

TE SAE occurred in 418 (53.0%) patients in the integrated population compared with 113 (32.8%) and 109 (31.4%) patients, respectively, in the pirfenidone and placebo groups in CAPACITY (Table 3). The adjusted incidence of TE SAE was 47.6 per 100 PEY in the integrated population compared with 42.7 in the CAPACITY pirfenidone group and 44.4 per 100 PEY in the CAPACITY placebo group. Consistent with prior observations, the most commonly reported TE SAE was worsening IPF (adjusted incidence, 7.7

Table 2 Extent of exposure to pirfenidone

	Integrated pirfenidone population (*n* = 789)
Duration of treatment, weeks	
Mean (SD)	135.7 (74.3)
Median (range)	133.4 (1, 400)
>0 to <18	6.5%
18 to <54	11.4%
54 to <150	43.6%
≥150	38.5%
Person exposure years†	2059
Mean daily dose‡	
Mean (SD)	2015 (527)
Median (range)	2257 (25, 3600)
>0 to ≤1400 mg	15.1%
>1400 to ≤2200 mg	27.9%
>2200 to ≤2600 mg	54.6%
>2600 mg	2.3%

† One person exposure year (PEY) is the equivalent of one patient exposed to study drug for one year. Total PEY is the sum of the person exposure years of each patient.

‡ Calculated over the total duration of use, excluding the 2-week titration period.

SD, standard deviation.

Table 3 Summary of treatment-emergent adverse events†

		CAPACITY	
	Integrated population (*n* = 789)	Pirfenidone 2403 mg/day (*n* = 345)	Placebo (*n* = 347)
Median duration of exposure, years	2.6	1.4	1.4
Any TEAE (%)	99.7	98.6	97.7
Any TE SAE (%)	53.0	32.8	31.4
Any TEAE leading to tx discontinuation (%)	35.1	14.8	8.6

† Occurring after the first dose and within 28 days of the last dose of study treatment.

TEAE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse event.

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Table 4 Treatment-emergent adverse events[†]

Patients (%)	Integrated population (n = 789)	CAPACITY pirfenidone 2403 mg/day (n = 345)	CAPACITY placebo (n = 347)
Median duration of exposure, years	2.6	1.4	1.4
TEAEs with a greater frequency in the CAPACITY pooled pirfenidone 2403 mg/day group than the CAPACITY pooled placebo group[‡]			
Nausea	40	36	17
Rash	26	32	12
Dizziness	23	18	10
Dyspepsia	21	19	7
Vomiting	18	14	4
Insomnia	17	10	7
TEAEs occurring with a frequency <1.5× placebo in the pooled pirfenidone 2403 mg/day group in CAPACITY			
Cough	37	30	29
Upper respiratory tract infection	35	31	29
Fatigue	34	30	21
Dyspnoea	32	19	22
Diarrhoea	29	29	19
Idiopathic pulmonary fibrosis	29	16	21
Nasopharyngitis	27	21	24
Bronchitis	26	14	17
Headache	22	19	16
Back pain	17	10	8
Sinusitis	16	14	12

[†] Occurring in ≥15% of patients in the cumulative clinical database.
[‡] Occurring in the pooled pirfenidone 2403 mg/day group with a frequency ≥1.5× placebo.
TEAE, treatment-emergent adverse event.

Table 5 Gastrointestinal and skin-related adverse events of interest

Patients (%)	Integrated population (n = 789)[†]	CAPACITY pirfenidone 2403 mg/day (n = 345)[‡]	CAPACITY placebo (n = 347)[‡]
Nausea	39.9	36.2	17.3
Grade 3 or 4 TEAE	2.0	1.7	0.6
TE SAE	0.1	0	0
Treatment discontinuation	2.3	1.4	0
Diarrhoea	29.3	28.7	19.3
Grade 3 or 4 TEAE	1.0	0.6	0
TE SAE	0	0	0
Treatment discontinuation	0.4	0	0.6
Dyspepsia	20.8	19.1	7.5
Grade 3 or 4 TEAE	0.4	0.3	0.6
TE SAE	0	0	0
Treatment discontinuation	0.1	0	0
Vomiting	17.9	13.6	4.3
Grade 3 or 4 TEAE	0.6	0.3	0
TE SAE	0	0	0
Treatment discontinuation	0.4	0.3	0
Photosensitivity reaction	12.9	12.2	1.7
Grade 3 or 4 TEAE	0.5	0.9	0.3
Treatment-emergent SAE	0.3	0.3	0
Treatment discontinuation	0.6	0.9	0.3
Rash	26.4	32.2	11.5
Grade 3 or 4 TEAE	0.5	0.6	0
TE SAE	0.1	0.3	0
Treatment discontinuation	1.6	1.4	0

[†] Median duration of exposure = 2.6 years.
[‡] Median duration of exposure = 1.4 years.
TEAE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse event.

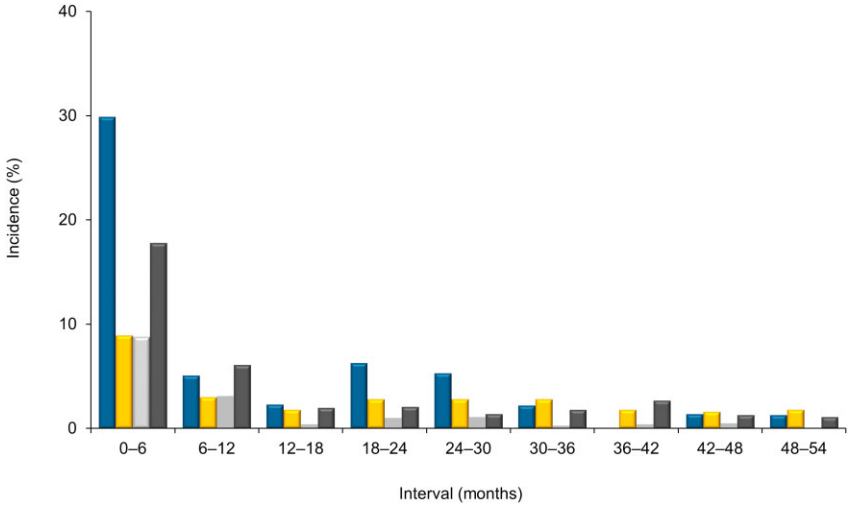

Figure 2 Incidence of new-onset treatment-emergent gastrointestinal and skin-related adverse events by 6-month intervals in the integrated patient population. (■) Nausea, (■) vomiting, (■) photosensitivity, (■) rash.

Table 6 Liver-related outcomes

	Integrated population (n = 789)[†]	CAPACITY pirfenidone 2403 mg/day (n = 345)[‡]	CAPACITY placebo (n = 347)[‡]
ALT or AST increased			
3× ULN	2.7%	4.1%	0.6%
10× ULN	0.1%	0.3%	0.3%
20× ULN	0	0	0.3%
Total serum bilirubin >2× ULN	0.3%	0	0
Study treatment discontinuation[§]	1.0%	0.9%	0.6%
Liver-related TE SAE[§]	0.6%	0.9%	0.3%
Death[§]	0	0	0
Hy's law[¶]	0	0	0

[†] Median duration of exposure = 2.6 years.
[‡] Median duration of exposure = 1.4 years.
[§] Due to any liver-related abnormality, including those without aminotransferase elevation.
[¶] ALT or AST > 3× ULN and total serum bilirubin >2× ULN based on the same blood sample and no other cause can be found to explain the combination of increased ALT/AST and total serum bilirubin (modified from Temple[17]).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TE SAE, treatment-emergent serious adverse event; ULN, upper limit of normal.

per 100 PEY compared with 5.6 and 7.6 per 100 PEY in the CAPACITY pirfenidone and placebo groups, respectively).

The incidence of clinically significant elevations in liver aminotransferases is summarized in Table 6. Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of more than three times the upper limit of normal (3× ULN) occurred in 2.7% of patients in the integrated population compared with 4.1% of patients in the CAPACITY pirfenidone 2403 mg/day treatment group and <1% of patients in the CAPACITY placebo group. All elevations in liver aminotransferase(s) were reversible and without clinical sequelae. Additionally, there were no deaths due to liver-related abnormalities, and no patient met the modified criteria for Hy's Law, defined as AST or ALT > 3× ULN and total bilirubin >2× ULN from the same blood sample and with no other cause that would explain the abnormality. The incidence of treatment discontinuation and treatment-related serious adverse events due to liver-related abnormalities—including those without elevations in aminotransferase(s)—was similar between the integrated population and the CAPACITY pirfenidone 2403 mg/day treatment group.

A total of 148 (18.8%) patients in the integrated population died during the period of observation. Treatment-emergent deaths, defined as deaths occurring after the first dose and within 28 days of the last dose of study drug, occurred in 123 (15.6%) patients; of these, 88 (11.2%) were assessed by the investigator as IPF related. The adjusted incidence of treatment-emergent death, defined as treatment-emergent deaths per 100 PEY, was 6.0 for all-cause death and 4.3 for IPF-related death. In CAPACITY, the adjusted incidence of treatment-emergent all-cause death was 3.9 in the pirfenidone group and 6.0 in the placebo group; the adjusted incidence of treatment-emergent IPF-related death was 2.5 in the pirfenidone group and 5.1 in the placebo group.

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DISCUSSION

IPF is a chronic progressive lung disease that requires long-term clinical management. Accordingly, a thorough understanding of the long-term safety and tolerability of novel therapeutic agents is necessary to ensure safe and appropriate treatment. In the present analysis, we examined the safety and tolerability of pirfenidone in a large cohort of patients with IPF who received treatment for up to 7.7 years (median, 2.6 years; interquartile range, 1.5–4.0 years) and had a cumulative total exposure of 2059 PEY.

Our results show that long-term treatment with pirfenidone (median duration, 2.6 years) was safe and generally well tolerated. Gastrointestinal and skin-related events were the most commonly reported adverse events; these were generally mild to moderate in severity and rarely led to treatment discontinuation. Additionally, the incidence of new-onset gastrointestinal and skin-related events declined markedly following the first 6 months of treatment and remained low during the subsequent period of observation. This finding, coupled with the low rate of discontinuation due to gastrointestinal and skin-related events, suggests that such events tend to occur early in the course of treatment and can be effectively managed through dose adjustment and adverse event mitigation strategies. Of note, patients in these studies were instructed to take pirfenidone with food and advised to avoid direct sun exposure and apply sun block to exposed areas of the skin. Additionally, protocol-defined dose modification strategies for specific gastrointestinal and skin-related adverse events were employed in the CAPACITY and RECAP studies. The relatively low incidence of discontinuation due to such events supports these recommendations, which are summarized in the approved product label.[18]

TE SAE were reported by approximately half of the patients in the integrated population compared with one-third of patients in both the pirfenidone and placebo groups in the CAPACITY trials. When adjusted for duration of exposure, the rate of TE SAE in the integrated population was similar to the observed rates in the CAPACITY trials. The difference in the crude incidence of TE SAE between the integrated population and the CAPACITY trials was driven largely by a higher incidence of IPF (16.2% vs 7.5%), a finding that is consistent with the longer median duration of follow up and the progressive nature of the disease.

Clinically significant elevations in liver enzymes were observed in approximately 3% of patients in the integrated population compared with 4% of patients in the pirfenidone group in CAPACITY. Analysis of serial laboratory results demonstrated that these elevations were generally transient, reversible and without significant clinical consequence. Collectively, these data provide no evidence of an increased risk of clinically significant elevations in liver enzymes with long-term exposure to pirfenidone. The current recommendation in the European and Canadian pirfenidone product labels to conduct liver function tests at monthly intervals for the first 6 months after initiating therapy and at 3-month intervals thereafter is also supported by these results.

The findings of the present analysis are strengthened by the large size of the study population and the overall duration of exposure to the study drug, both of which are unique for novel agents for orphan diseases. Moreover, the rigorous, prospective collection of longitudinal data in a well-defined cohort of patients with a broad range of physiologic impairment (including those with baseline FVC and DL_{CO} values that may be characterized as severe physiologic impairment) that were enrolled in studies with different eligibility criteria enhances the generalizability of the results. However, our analysis does have certain limitations, including the open-label study design and the lack of a control arm in two of the four studies that were included in the analysis. Additionally, while the generalizability of the results is enhanced by the inclusion of patients with a broad range of physiologic impairment, it should be noted that all patients in our cohort were enrolled in clinical trials that excluded patients with common comorbidities as well as those receiving treatment with selected therapies. Therefore, the degree to which our findings can be generalized to the broader population of IPF patients with selected comorbidities or those receiving concomitant therapies is unknown. Finally, a subset of patients in Study 002 received a dose of pirfenidone (40 mg/kg/day) that was different from the dose that was administered in the subsequent Phase 3 studies and higher than the recommended dose in the product label in countries in which pirfenidone is currently approved. Our results should therefore be interpreted in the context of prior research demonstrating evidence of a dose response for TEAE.[14,15]

In conclusion, this comprehensive analysis of safety data from four clinical trials evaluating pirfenidone in patients with IPF demonstrated that treatment with pirfenidone for up to 7.7 years was safe and generally well tolerated. These data provide further evidence to support the long-term clinical use of pirfenidone in patients with IPF.

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