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Pirfenidone in real life: A retrospective observational multicentre study in Italian patients with idiopathic pulmonary fibrosis

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ABSTRACT

Rationale: Real-world data on pirfenidone treatment of patients with idiopathic pulmonary fibrosis (IPF) are limited. This study assessed the effectiveness of pirfenidone in a large real-life Italian IPF cohort.
Methods: IRENE was an observational, retrospective study of patients with IPF treated with pirfenidone in routine clinical practice (18 centres). At Month 6, a mandatory re-evaluation of forced vital capacity (FVC) decline (absolute change < 10%) was required to continue pirfenidone. The primary effectiveness outcomes were absolute change from baseline in FVC and the percentage of patients with ≥ 10% absolute decline in % predicted FVC at Month 12. Safety was described by adverse event (AE) occurrence. Prespecified subgroups included sex, age, presence/absence of emphysema, usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography, and baseline lung function.
Results: The study included 379 patients (mean age, 67.6 years; 78.1% male). Mean change from baseline in FVC and the percentage of patients with ≥ 10% absolute decline in % predicted FVC at Month 12 were −81.8 mL (SD, 419.6 mL; $P = 0.002$) and 16.0% (95% CI, 12.2–20.9%), respectively. Disease progression was similar across prespecified subgroups, including patients with definite vs possible UIP. Overall, 211 AEs occurred in 149 patients (39.3%), with serious AEs in 31 patients (8.2%) and 9 discontinuations due to AEs. Skin and gastrointestinal AEs were most frequent. Fifteen patients (4.0%) died.
Conclusions: The decline in FVC and the safety profile observed in this real-world IPF cohort were consistent with the findings of the Phase III pirfenidone trials.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, debilitating, irreversible, and fatal fibrotic lung disease that negatively impacts quality of life [1]. Patients with IPF without treatment in historical cohorts have a median survival of 2–5 years from the time of diagnosis [2].

Pirfenidone is an oral antifibrotic agent approved for the treatment of patients with IPF in Europe in 2011 and in the United States in 2014 and is conditionally recommended in international treatment guidelines [3]. In Phase III clinical trials, pirfenidone (2403 mg/day) reduced the rate of absolute decline in % predicted forced vital capacity (FVC) for up to 72 weeks with a manageable safety profile in patients with IPF [4,5]. In a pooled analysis of Phase III trial data, pirfenidone treatment

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over 52 weeks was associated with a reduced risk of all-cause mortality compared with placebo [6]. Long-term follow-up studies have confirmed the efficacy and safety of pirfenidone [7–9].

Real-world studies complement the tightly controlled clinical trial setting with broader inclusion criteria that are more representative of the entire population of patients with a given disease [10]. The efficacy of pirfenidone in patients with IPF has been well established in the clinical trial setting, but real-world studies of pirfenidone effectiveness have been mostly limited small, single-centre cohorts (≤ 100 patients) [8,11,12]. Italian Real-world Esbriet National Experience (IRENE) was an observational, retrospective, multicentre study to evaluate the effectiveness of pirfenidone over 12 months administered according to clinical practice in a large cohort of Italian patients with IPF who persisted with pirfenidone treatment for ≥ 6 months. This study also examined the effectiveness of pirfenidone in key patient subgroups in the real-world clinical setting.

2. Methods

2.1. Study design and population

This was an observational, retrospective, multicentre study of patients with IPF treated with pirfenidone in clinical practice in Italy. Patients were recruited from February 2017 to November 2017. Key inclusion criteria were age ≥ 40 years with a diagnosis of IPF (per the 2011 international guidelines); eligible for treatment in accordance with drug reimbursement criteria defined by the Italian regulatory authorities (% predicted FVC ≥ 50%, % predicted diffusing capacity for carbon monoxide [DLco] ≥ 35%); no treatment for IPF in the 30 days before enrolment (index date) and initiation of pirfenidone; initiation of pirfenidone after September 1, 2013, with ≥ 12 months of observation available from the time of treatment initiation through August 31, 2016 (shorter observation was permitted for deceased patients); and mandatory re-evaluation at Month 6 for continuation of treatment as defined by the Italian regulatory authorities [1]. Italian regulatory authorities' mandatory evaluation of absolute decline in % predicted FVC was performed at Month 6; only patients who had < 10% absolute decline in % predicted FVC at Month 6 continued pirfenidone (with reimbursement) and were included in the analysis population.

All alive patients provided informed written consent; consent was not required from patients who died before the date of enrolment in the study as per Italian law.

2.2. Outcomes

The primary outcomes for effectiveness were absolute change from baseline to Month 12 in FVC and the percentage of patients with ≥ 10% absolute decline in % predicted FVC at Month 12. Secondary effectiveness outcomes included absolute change in % predicted FVC, time to first ≥ 10% absolute decline in % predicted FVC over 12 months, time to death from any cause over 12 months, time to first respiratory-related hospitalisation over 12 months, time to first acute exacerbation of IPF over 12 months, and change from baseline to Month 12 in 6-min walk distance (6MWD). Effectiveness outcomes were also evaluated at Month 6; patients with ≥ 10% absolute decline in % predicted FVC at the mandatory re-evaluation were excluded from the Month 6 effectiveness outcomes. Safety was assessed by the occurrence of adverse events (AEs) over 12 months. AEs were categorised by Medical Dictionary for Regulatory Activities System Organ Class and preferred terms. Effectiveness outcomes were assessed in prespecified subgroups of patients. Patients were categorised by sex, age, presence or absence of emphysema, presence or absence of pulmonary hypertension, usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT), baseline Gender, Age, Physiology (GAP) Index, and baseline % predicted FVC [13]. Pulmonary hypertension was defined on clinical grounds (as recorded in patient charts).

Table 1
Demographics and baseline characteristics.

Characteristic[a]	All patients (N = 379)
Age, years	67.6 (7.1)
Male, n (%)	296 (78.1)
BMI, kg/m^2[b]	28.9 (4.1)
Smoking status, n (%)	
Former smoker	261 (68.9)
Nonsmoker	91 (24.0)
Time since first symptom onset, months	28.1 (30.3)
Time since diagnosis of IPF, months	5.9 (19.1)
HRCT pattern at diagnosis, n (%)[c]	
Definite UIP	259 (71.9)
Possible UIP	99 (27.5)
Inconsistent with UIP	2 (0.6)
Biopsy type, n (%)[d]	
Transbronchial cryobiopsy	29 (43.9)
Surgical lung biopsy	37 (56.1)
Bronchoalveolar lavage, n (%)[e]	143 (38.1)
FVC, % predicted	80.1 (16.4)
DLco, % predicted	53.5 (13.9)
FEV_1/FVC ratio, %	89.6 (13.0)
6MWD, m[f]	411.3 (114.2)

6MWD, 6-min walk distance; BMI, body mass index; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

[a] All values are mean (SD) unless otherwise noted.
[b] n = 284 patients with available data.
[c] n = 360 patients with available data.
[d] n = 66 patients with available data.
[e] n = 375 patients with available data.
[f] n = 271 patients with available data.

2.3. Statistical analyses

Baseline characteristics of the study population and safety were reported using descriptive statistics. Statistical significance in the absolute change from baseline in FVC and in % predicted FVC was evaluated using the paired *t*-test in both the total population and in prespecified subgroups. The percentage of patients who experienced ≥ 10% absolute decline in % predicted FVC was reported as point estimates with 95% CIs in both the total population and in prespecified subgroups. The Kaplan-Meier method was used to estimate time-to-event outcomes.

3. Results

3.1. Patients

The study population comprised 379 patients with IPF (Table 1). The mean age was 67.6 years (median age, 68 years), and most patients were male (78.1%) and former smokers (68.9%). Of 66 patients with available histological information, transbronchial cryobiopsy, and surgical lung biopsy had been performed in 29 and 37 patients, respectively. At baseline, mean % predicted FVC was 80.1% (SD, 16.4%), and the median was 79.0%. Mean baseline % predicted DLco was 53.5% (SD, 13.9%), and mean baseline 6MWD was 411.3 m (SD, 114.2 m). At baseline, 125 patients (33.0%) had GAP Index I, 94 (24.8%) had GAP Index II, and 7 (1.8%) had GAP Index III; GAP Index score was missing from the case report form for 153 patients (40.4%). A total of 259 patients (71.9%) had a definite UIP pattern on HRCT, and 99 (27.5%) had a possible UIP pattern. In subgroups of patients defined by UIP pattern on HRCT at baseline, mean % predicted FVC was 75.6% (SD, 15.7%) in patients with possible UIP and 81.3% (SD, 16.3%) in patients with definite UIP.

Table 2
Effectiveness outcomes in the total population.

Outcome	All patients (N = 379)[a]	
	Month 6	Month 12
Absolute change from baseline in FVC	(n = 359)	(n = 268)
Mean (SD), mL	−98.6 (484.3)	−81.8 (419.6)
P value (paired *t*-test)	< 0.001	0.002
Absolute change from baseline in % predicted FVC	(n = 372)	(n = 274)
Mean (SD)	0.20 (8.98)	−0.83 (10.64)
P value (paired *t*-test)	0.661	0.199
Patients with ≥ 10% absolute decline in % predicted FVC	(n = 372)	(n = 274)
Percentage (95% CI)	10.5 (7.8, 14.0)	16.0 (12.2, 20.9)

FVC, forced vital capacity.
[a] Number of patients in the total population at baseline. The number of patients with available data is noted; some data are missing due to incomplete capture of both FVC and % predicted FVC.

3.2. Effectiveness

The mean absolute change from baseline in FVC at Month 6 and Month 12 was −98.6 mL (SD, 484.3 mL) and −81.8 mL (SD, 419.6 mL), respectively; the change from baseline represented a statistically significant decline at both Month 6 ($P < 0.001$) and Month 12 ($P = 0.002$) (Table 2). The mean absolute change from baseline in % predicted FVC at Month 6 and Month 12 was 0.20% (SD, 8.98%) and −0.83% (SD, 10.64%), respectively; the change from baseline was not statistically significant at either Month 6 ($P = 0.661$) or Month 12 ($P = 0.199$). The proportion of patients with ≥ 10% absolute decline in % predicted FVC at Month 6 and Month 12 was 10.5% (95% CI, 7.8%–14.0%) and 16.0% (95% CI, 12.2%–20.9%), respectively.

Disease progression was generally similar across prespecified subgroups of patients, including patients with definite vs possible UIP pattern on HRCT, as measured by the absolute change from baseline in % predicted FVC (Fig. 1A) and the proportion of patients with ≥ 10% absolute decline in % predicted FVC (Fig. 1B). The subgroup of patients with pulmonary hypertension, prespecified in the study protocol, was too small (n = 12) to yield meaningful results therefore, and these data are not presented.

In time-to-event analyses, the median time was not reached over 12 months of observation in time to first ≥ 10% absolute decline in % predicted FVC (104 events, 27.4% of patients), time to death from any cause (15 events, 4.0%), time to first respiratory-related hospitalisation (21 events, 5.5%), and time to first acute exacerbation of IPF (22, 5.8%) (Fig. 2). At Month 12, the mean change in 6MWD was −15.2 m (SD, 115.1 m).

3.3. Safety

Overall, 211 total AEs were reported in 149 patients (39.3%); most AEs (68.7%) were mild in intensity (Table 3). Of these, 112 AEs in 95 patients (25.1%) were deemed related to pirfenidone by the investigator. Skin (14% of patients) and gastrointestinal AEs (12.4%) were the most frequent categories of reported AEs (Table 4). Photosensitivity reaction (5.0% of patients), rash (3.7%), and erythema (3.2%) were the most common skin-related AEs, and nausea (3.7%), diarrhoea (2.1%), and dyspepsia (2.1%) were the most frequently reported gastrointestinal AEs.

Serious AEs (SAEs; 33 events) were reported in 31 patients (8.2%). Nine SAEs in 9 patients (2.4%) were judged by the investigator to be related to pirfenidone, including 2 cases of erythema and 1 case each of pruritus, upper abdominal pain, gastro-oesophageal reflux disease, increased γ-glutamyltransferase levels, increased hepatic enzyme levels, decreased appetite, and headache. The most frequently reported types of SAEs were death (2.9% of patients) and respiratory, thoracic, and mediastinal disorders (2.1%) (Table 5). Nine patients (2.4%) discontinued pirfenidone due to AEs; these included 6 deaths and 1 case each of pneumonia, hepatic failure, and respiratory failure. None of the AEs leading to discontinuation were judged to be related to pirfenidone.

Fifteen patients (4.0%) died during the study. Among AEs leading to death were 1 case each reported as IPF, respiratory failure, pneumonia, and acute myeloid leukaemia; 11 deaths were reported in the general disorders and administration site conditions System Organ Class term without additional details. No deaths were deemed related to pirfenidone.

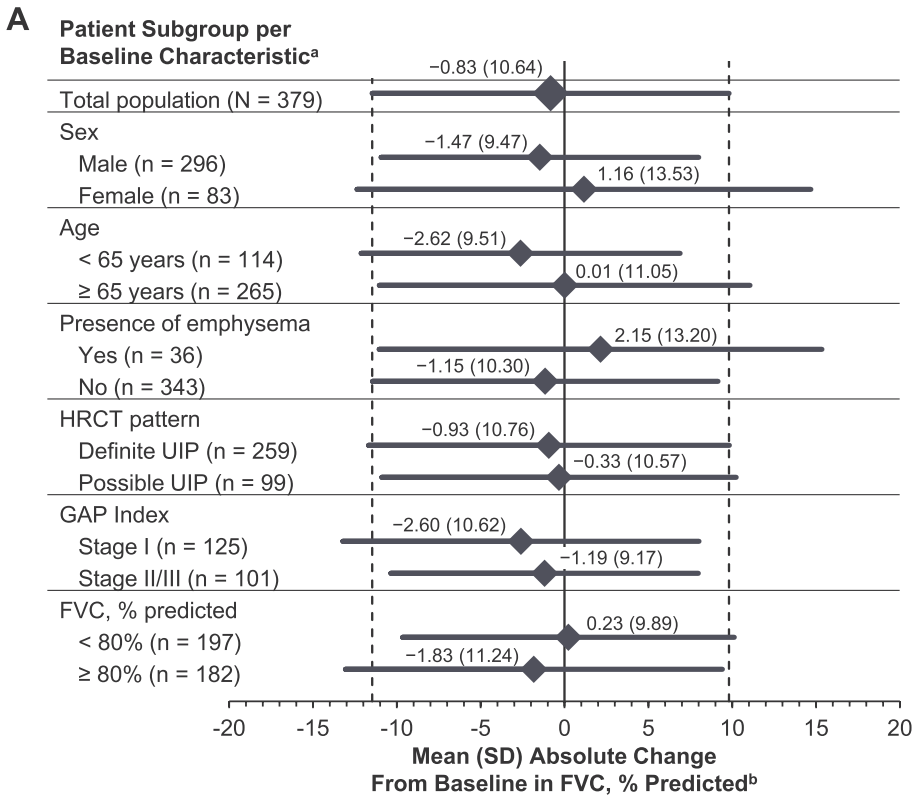
4. Discussion

IRENE was a multicentre, retrospective, observational study of Italian patients with IPF treated with pirfenidone in real-world clinical practice. Compared with the placebo cohorts of Phase III trials in IPF, disease progression was limited over 12 months of pirfenidone treatment as measured by the mean change from baseline in FVC and % predicted FVC and by the proportion of patients who experienced ≥ 10% absolute decline in % predicted FVC [4,5,14]. The effectiveness of pirfenidone was similar in subgroups of patients, including those with possible vs definite UIP pattern on HRCT. Over 12 months, 4.0% of patients died, 5.5% experienced a respiratory-related hospitalisation, and 5.8% experienced an acute exacerbation. Discontinuation of pirfenidone due to AEs was low in this cohort of patients; skin- and gastrointestinal-related AEs were the most frequently reported.

The demographic and baseline clinical characteristics of patients in the IRENE cohort were similar to those in pooled data from the Phase III ASCEND (Study 016; NCT01366209) and CAPACITY (Study 004; NCT00287716 and Study 006; NCT00287729) trials [15]. In both the Phase III trials and the IRENE cohort, patients had a median age of 68 years; however, the median baseline % predicted FVC was lower in the Phase III trials than in the IRENE cohort (71% vs. 79%) [15]. Eligibility criteria may have contributed to other differences in the patient populations: the Phase III clinical trial protocols excluded patients with key comorbid conditions, including obstructive airway disease, cardiovascular disease, active infections, and malignant tumours, whereas these were not exclusion criteria in the IRENE cohort [4,5].

Measures of absolute decline in FVC and % predicted FVC in the IRENE study were consistent with the efficacy findings of the Phase III trials in IPF; declines in FVC were similar to those observed in the pirfenidone groups and less than in the placebo groups [4,5,15]. In a previously reported retrospective multicentre study of 128 Italian patients with IPF treated with pirfenidone in the real-world setting, relative decline in % predicted FVC was greater in the 12 months before treatment initiation than in the 12 months after (−6.3% vs −1.3%) [16]. The mean absolute decline in % predicted FVC over 12 months of pirfenidone in the previously reported Italian cohort was consistent with the findings in the IRENE cohort (−1% vs −0.8%), despite somewhat lower mean baseline % predicted FVC in the previous study than in IRENE (75% vs 80%), reflecting the enrolment of patients in the previous study through the European Named Patient Access Program, which included patients with more advanced disease [16]. In a retrospective study of 92 Greek patients with IPF treated with pirfenidone in the real-world setting, a greater proportion of patients experienced ≥ 10% absolute decline in % predicted FVC over 12 months than in the IRENE study (35% vs 16.0%) [17]. Despite similarities in effectiveness findings, previously reported real-world studies analysed outcomes in patient populations that were more heterogeneous than the IRENE cohort, which included only patients who tolerated pirfenidone and had < 10% absolute decline in % predicted FVC at Month 6. Therefore, the IRENE cohort primarily comprised patients with less-advanced disease, in whom significant lung function decline had yet to occur.

Importantly, disease progression in pirfenidone-treated patients with possible UIP pattern on HRCT was similar to that in pirfenidone-treated patients with definite UIP pattern (i.e., honeycombing). In the



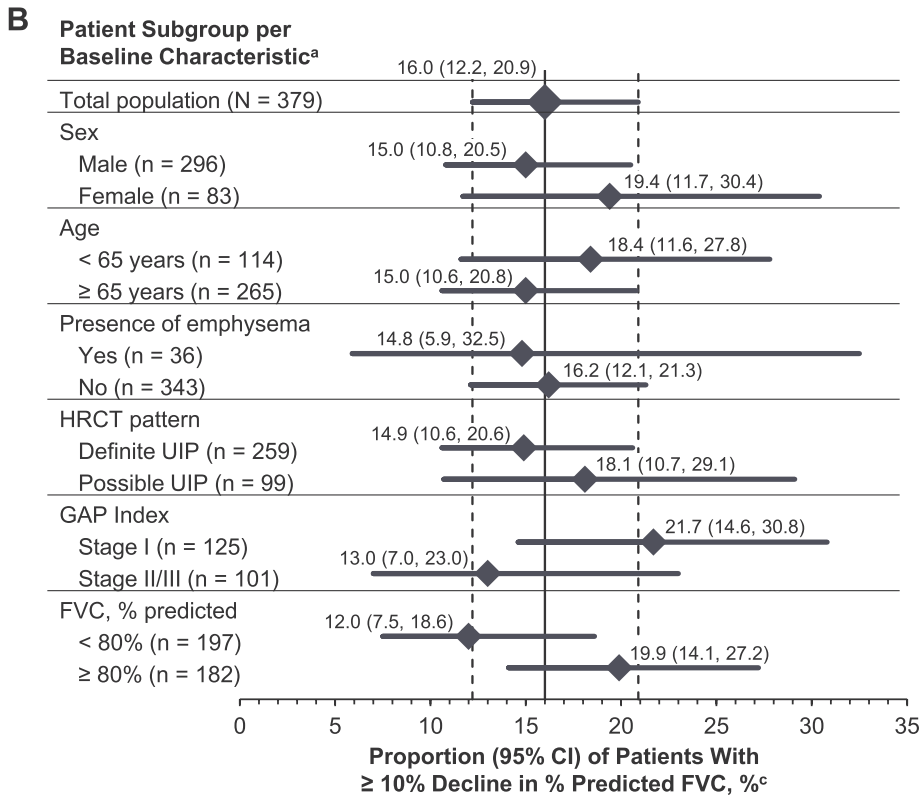


Fig. 1. Primary outcomes at Month 12 in prespecified subgroups of patients with idiopathic pulmonary fibrosis treated with pirfenidone. (**A**) Mean absolute change from baseline in % predicted FVC at Month 12. (**B**) Proportion of patients with ≥ 10% absolute decline in % predicted FVC at Month 12. FVC, forced vital capacity; GAP, Gender Age Physiology; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia.

[a] Numbers of patients in each subgroup refer to the numbers at baseline but do not necessarily reflect the numbers with available data at Month 12.

[b] Solid vertical line indicates no change from baseline in % predicted FVC at Month 12 in the total population; dashed lines indicate SD of the mean change.

[c] Solid vertical line indicates proportion of patients with ≥ 10% absolute decline in % predicted FVC in the total population; dashed lines indicate 95% CIs of this value.

IRENE cohort, patients were classified as definite UIP, possible UIP, and inconsistent with UIP according to the 2011 international guidelines because the study was completed before the recent publication of the Fleischner Society diagnostic criteria and the 2018 update to the international diagnostic guidelines were applicable [1,18,19]. The effectiveness data from the IRENE cohort support the use of pirfenidone in patients with a possible UIP pattern.

In the ASCEND and CAPACITY trials, pirfenidone treatment reduced the risk of all-cause mortality over 12 months [6]. In the European IPF Registry, the median survival of patients receiving antifibrotic therapy

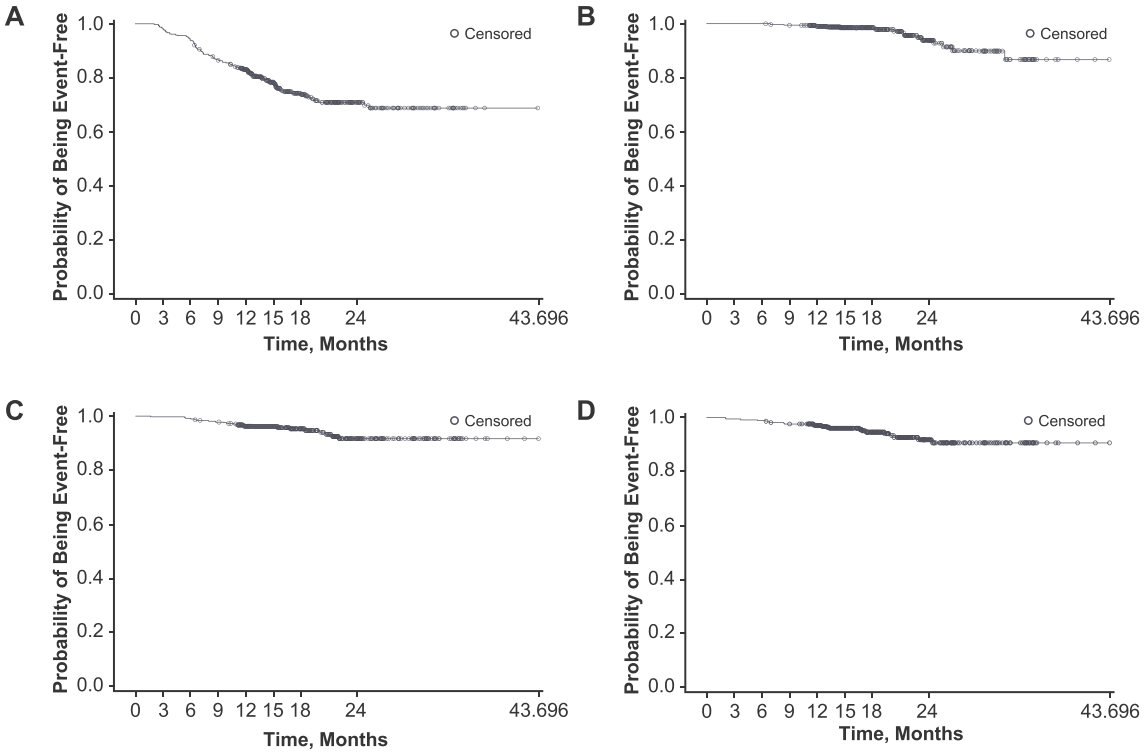


Fig. 2. Kaplan-Meier survival analysis of (**A**) time to first ≥ 10% absolute decline in % predicted FVC, (**B**) time to death from any cause, (**C**) time to first respiratory-related hospitalisation, and (**D**) time to first acute exacerbation of idiopathic pulmonary fibrosis. FVC, forced vital capacity.

Table 3
Summary of adverse events over 12 months.

Patients with ≥ 1 event, n (%)	All patients (N = 379)
≥ 1 AE	149 (39.3)
≥ 1 AE of mild intensity	107 (28.2)
≥ 1 AE of moderate intensity	32 (8.4)
≥ 1 AE of severe intensity	24 (6.3)
≥ 1 SAE	31 (8.2)
≥ 1 AE related to pirfenidone[a]	95 (25.1)
≥ 1 SAE related to pirfenidone[a]	9 (2.4)
AE leading to discontinuation of pirfenidone	9 (2.4)
AE leading to death	15 (4.0)

AE, adverse event; SAE, serious adverse event.
[a] Investigator judgment.

(83% were receiving pirfenidone) was recently reported to be 123 months [20]. In the IRENE cohort, low mortality was observed over 12 months of pirfenidone treatment (4% of patients died; median time to death was not reached), consistent with these previous findings.

The most commonly reported AEs in pirfenidone-treated patients in IRENE were skin- and gastrointestinal related, but discontinuations due to AEs in IRENE were much less frequent (2.5% of patients) than in clinical trials (34%–42%) and previous real-world studies (13%–29%) [9,21–24]. In RECAP (Study 012; NCT00662038), an open-label, long-term extension study of the ASCEND and CAPACITY trials, 34% of patients discontinued due to AEs over ≥ 5 years; of these, 39% of discontinuations due to AEs occurred in the first year of the study and most in patients who had newly initiated pirfenidone [25]. An analysis of pooled data from 5 clinical trials (including interim data from RECAP) found that 38% of patients discontinued pirfenidone over a median duration of exposure of 1.7 years (range, 1 week to 9.9 years); AEs requiring dose modification or discontinuation most often occurred in the first 6 months of treatment [22].

In an analysis of pooled data from the ASCEND and CAPACITY trials, the median time to the first gastrointestinal, rash, and photosensitivity AEs was 14, 82, and 90 days, respectively [26]. Several real-world studies have shown that tolerability issues, particularly gastrointestinal AEs, most frequently arise around the time immediately after initiation of pirfenidone [9,25–28]. In the European PASSPORT Registry, 29% of patients discontinued pirfenidone due to AEs, with a median time to discontinuation of 100 days [23]. In patients who received pirfenidone as part of an expanded access program in the United States, most gastrointestinal AEs occurred in the first month of treatment [24]. Unlike previously described pirfenidone safety populations, the IRENE cohort excluded patients who did not continue pirfenidone through Month 6, due to Italian regulatory authority requirements. These differences in study populations and in the observed rates of discontinuation highlight that management of AEs early during treatment is key to establishing and maintaining long-term treatment with pirfenidone.

The exclusion of patients who discontinued pirfenidone at or before Month 6 from the analysis population is an important difference when comparing the findings of the IRENE study with other real-world studies. No data were captured in these excluded patients, and the number of excluded patients was not recorded. Based on data from ASCEND and CAPACITY, PASSPORT, and Japanese postmarketing surveillance and the size of the IRENE cohort, a cautious estimate suggests that ≈ 80 to 140 patients were excluded from the IRENE cohort due to either disease progression by Month 6 (≈ 25 to 40 patients) or discontinuation of pirfenidone because of AEs during the first 6 months of treatment (≈ 55 to 100 patients) [8,15,29,30]. The low rate of discontinuation due to AEs observed from Month 6 to Month 12 in IRENE (2.4%) suggests that discontinuation due to AEs from treatment initiation to Month 6 could have been lower than estimates based on previous studies. No conclusions regarding IPF outcomes in this substantial minority of patients who discontinued pirfenidone ≤ 6 months after initiation can be drawn from the IRENE study. This group of patients could benefit from future research into optimizing adherence to pirfenidone, alternative disease management strategies, and the development of new therapies.

A key strength of this analysis is that the population comprised one

Table 4
Adverse events by SOC and Preferred Term over 12 months.

AEs by MedDRA SOC and Preferred Term, n (%)[a]	Patients with ≥ 1 event (N = 379)	Events, n
≥1 AE of any type	149 (39.3)	211
Skin and subcutaneous tissue disorders	53 (14.0)	54
Photosensitivity reaction	19 (5.0)	19
Rash	14 (3.7)	14
Erythema	12 (3.2)	12
Gastrointestinal disorders	47 (12.4)	51
Nausea	14 (3.7)	15
Diarrhoea	8 (2.1)	8
Dyspepsia	8 (2.1)	8
Infections and infestations[b]	20 (5.3)	21
Bronchitis	13 (3.4)	13
General disorders and administration site conditions	17 (4.5)	17
Death	11 (2.9)	11
Respiratory, thoracic, and mediastinal disorders[c]	16 (4.2)	19
Metabolism and nutrition disorders	14 (3.7)	14
Decreased appetite	12 (3.2)	12
Investigations[d]	12 (3.2)	13
Cardiac disorders[e]	4 (1.1)	4
Nervous system disorders	4 (1.1)	6
Musculoskeletal and connective tissue disorders	3 (0.8)	6
Neoplasms benign, malignant, and unspecified (including cysts and polyps)[f]	2 (0.5)	2
Hepatobiliary disorders	1 (0.3)	1
Renal and urinary disorders	1 (0.3)	1
Surgical and medical procedures	1 (0.3)	1
Vascular disorders	1 (0.3)	1

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.

[a] SOC terms in which ≥ 1 patient-reported event is listed; Preferred Terms in which ≥ 8 patients (≥ 2.1%) reported events are listed below the SOC.

[b] After bronchitis, the next most frequently reported infections and infestations were pneumonia (2 patients) and urinary tract infection (2).

[c] The most frequently reported respiratory thoracic and mediastinal disorders reported were IPF (5 patients), respiratory failure (4), dyspnoea (3), cough (2), and pulmonary hypertension (2).

[d] The most frequently reported investigation-related AEs were γ-glutamyltransferase increased (5 patients) and weight decreased (3).

[e] Cardiac disorders reported included myocardial ischaemia (2 patients), coronary artery disease (1), and myocardial infarction (1).

[f] Neoplasms benign, malignant, and unspecified (including cysts and polyps) reported included acute myeloid leukaemia (1 patient) and small cell lung cancer (1).

Table 5
SAEs by SOC and Preferred Term over 12 months.

SAEs by MedDRA SOC and Preferred Term, n (%)	Patients with ≥ 1 event (N = 379)	Events, n
≥1 SAE of any type	31 (8.2)	33
General disorders and administration site conditions	11 (2.9)	11
Death	11 (2.9)	11
Respiratory, thoracic, and mediastinal disorders	8 (2.1)	8
Idiopathic pulmonary fibrosis	3 (0.8)	3
Respiratory failure	3 (0.8)	3
Acute respiratory failure	1 (0.3)	1
Dyspnoea	1 (0.3)	1
Cardiac disorders	3 (0.8)	3
Coronary artery disease	1 (0.3)	1
Myocardial infarction	1 (0.3)	1
Myocardial ischaemia	1 (0.3)	1
Skin and subcutaneous tissue disorders	3 (0.8)	3
Erythema	2 (0.5)	2
Pruritus	1 (0.3)	1
Gastrointestinal disorders[a]	2 (0.5)	2
Investigations[b]	2 (0.5)	2
Infections and infestations[c]	1 (0.3)	1
Metabolism and nutrition disorders[d]	1 (0.3)	1
Neoplasms benign, malignant, and unspecified (including cysts and polyps)[e]	1 (0.3)	1
Nervous system disorders[f]	1 (0.3)	1

MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SOC, System Organ Class.

[a] Included 1 case of upper abdominal pain and 1 case of gastro-oesophageal reflux disease.

[b] Included 1 case of γ-glutamyltransferase increased and 1 case of hepatic enzyme increased.

[c] Included 1 case of pneumonia.

[d] Included 1 case of decreased appetite.

[e] Included 1 case of acute myeloid leukaemia.

[f] Included 1 case of headache.

of the largest cohorts of real-world patients with IPF treated with pirfenidone characterised to date. The sample size for the enrolment population was chosen to allow for analysis of prespecified subgroups of interest in the management of IPF. Patient selection was much less rigid than in clinical trials; therefore, the findings of this analysis may be more applicable to real-world patient management. The real-world nature of this study may capture a more complete picture of pirfenidone effectiveness than controlled clinical trials.

The interpretation of these findings is limited by the retrospective nature of the study and its single-arm design. The follow-up duration of 12 months was short in comparison with other real-world studies, but the study population was large. The analysis population selected against patients with tolerability issues and against those with ≥ 10% decline in % predicted FVC per Italian regulatory authority requirements; therefore, these results depict pirfenidone's effectiveness in patients with no major disease progression (> 10% absolute decline in % predicted FVC) or AEs leading to early discontinuation of pirfenidone. Participating sites were selected based on their experience in the management of patients with IPF, but pulmonary function test administration and data collection may have differed across sites. Patient subgroups were determined by baseline characteristics, which may not fully capture relevant subgroups for disease behaviour. For some patients, FVC was captured in either mL or % predicted but not both, yielding slightly different groups of patients with available data for each of these measures.

This retrospective analysis of a large observational cohort of Italian patients with IPF supported the previously known profile of pirfenidone in effectively delaying disease progression with manageable treatment-related AEs. The effectiveness of pirfenidone was similar in patients with possible UIP on HRCT and in those with definite UIP pattern. Adverse events were consistent with the known safety profile of pirfenidone.

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Author contribution statements

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; all authors contributed substantially to the study design, the data analysis and interpretation, and the writing of the manuscript.

Conflicts of interest

C Vancheri has served as a consultant for and received speakers bureau fees from Boehringer Ingelheim, Chiesi Farmaceutici, and Roche and has received research funding from Boehringer Ingelheim and

Roche.

A Sebastiani has served as a consultant for Boehringer Ingelheim and Roche.

S Tomassetti has served as a consultant for and received speakers bureau fees from Boehringer Ingelheim, and Roche and has received research funding from Roche.

A Pesci has served as a consultant for and received speakers bureau fees from Boehringer Ingelheim and Roche and has received research funding from Boehringer Ingelheim.

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P Rottoli has received personal fees for participation in scientific advisory boards and/or in educational meetings as a speaker and sponsorship for participation in international congresses from Menarini and Roche and a grant for a collaborator scholarship paid directly to the hospital.

A Ghirardini is an employee of Roche SpA.

K-U Kirchgaessler is an employee of F. Hoffmann-La Roche Ltd.

C Albera has served as a consultant and steering committee member for Roche; received speakers bureau fees from Roche, Boehringer Ingelheim, and Fibrogen; and received research funding from Boehringer Ingelheim.

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Appendix A. Supplementary data

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