



HAL
open science

Treatment of Idiopathic Pulmonary Fibrosis with Capsule or Tablet Formulations of Pirfenidone in the Real-Life French RaDiCo-ILD Cohort

Vincent Cottin, Sonia Guéguen, Hilario Nunes, Stéphane Jouneau, Bruno Crestani, Philippe Bonniaud, Lidwine Wemeau, Dominique Israël-Biet, Martine Reynaud-Gaubert, Anne Gondouin, et al.

► To cite this version:

Vincent Cottin, Sonia Guéguen, Hilario Nunes, Stéphane Jouneau, Bruno Crestani, et al.. Treatment of Idiopathic Pulmonary Fibrosis with Capsule or Tablet Formulations of Pirfenidone in the Real-Life French RaDiCo-ILD Cohort. *Advances in Therapy*, In press, 10.1007/s12325-021-01961-x . hal-03425736

HAL Id: hal-03425736

<https://hal.science/hal-03425736v1>

Submitted on 3 Jun 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Treatment of Idiopathic Pulmonary Fibrosis with Capsule or Tablet Formulations of Pirfenidone in the Real-Life French RaDiCo-ILD Cohort

Vincent Cottin · Sonia Guéguen · Hilario Nunes · Stéphane Jouneau · Bruno Crestani · Philippe Bonniaud · Lidwine Wemeau · Dominique Israël-Biet · Martine Reynaud-Gaubert · Anne Gondouin · Jacques Cadranel · Sylvain Marchand-Adam · Marie Chevereau · Isabelle Dufaure-Garé · Serge Amselem · Annick Clément

ABSTRACT

Introduction: Pirfenidone, an antifibrotic medication for idiopathic pulmonary fibrosis (IPF), is now available in France in two formulations: tablets since April 2018, and the initial capsules form. We conducted a cohort study to describe tolerance and acceptability of capsules

and/or tablets of pirfenidone in patients with IPF.

Methods: This study was nested within the French, non-randomized, multicenter RaDiCo-ILD (Rare Disease Cohort–Interstitial Lung Diseases). Included patients with IPF received at least one dose of pirfenidone tablets or capsules from July 2017 to June 2019 in three populations: the inclusion population (patients treated at least once with pirfenidone during the study period, $n = 288$); the potential switch population (patients treated with pirfenidone during the switch period starting April 2018, $n = 256$); the newly treated population (patients who initiated pirfenidone during the study period, $n = 162$). Each of those last two populations

Investigators of the RaDiCo study are listed in the Acknowledgments section.

V. Cottin (✉)
Pneumology Department, Center for Rare
Pulmonary Diseases, Lyon Civil Hospices–Claude
Bernard Lyon University–East Hospital Group–Louis
Pradel Hospital, 59 Boulevard Pinel, Lyon, 69677
BRON Cedex, France
e-mail: vincent.cottin@chu-lyon.fr

S. Guéguen · M. Chevereau · I. Dufaure-Garé ·
S. Amselem
Inserm-RaDiCo, Paris, France

H. Nunes
Pneumology Department, Avicenne University
Hospital, Bobigny, France

S. Jouneau
Pneumology Department, Rennes University
Hospital, Rennes, France

B. Crestani
Pneumology Department, Paris-Bichat University
Hospital, Paris, France

P. Bonniaud
Department of Pneumology and Thoracic
Endoscopy, Dijon University Hospital, Dijon, France

L. Wemeau
Pneumology Department, Lille University Hospital,
Lille, France

D. Israël-Biet
Department of Pneumology, Intensive Care and
Bronchial Endoscopies, Paris University Hospital-
Georges-Pompidou European Hospital, Paris, France

M. Reynaud-Gaubert
Department of Pneumology, Rare Respiratory

included three subgroups (tablets, capsules, and substitution).

Results: In 288 patients treated, 162 newly initiated pirfenidone during the study period: there were no meaningful differences in the baseline characteristics with the 256 patients treated during the potential switch period. In the newly treated population, 30.3% started pirfenidone treatment with tablet formulation. In the potential switch population, 44.9% of patients shifted from capsule to tablet. Half of the patients shifted to tablet formulation within the first 10 months. The mean treatment duration was 21.5 months with a mean dose of 2106.7 mg/day; 46.5% of patients discontinued treatment, mainly because of adverse events. There were fewer discontinuations in the tablets and substitution subgroups than in the capsules-only subgroup. The most reported adverse event was skin rash (11.5%). No new adverse event was identified.

Conclusions: This real-life cohort assessing the characteristics of the prescription of pirfenidone tablets and capsules suggests a good acceptability of the tablet formulation by patients with IPF.

Trial Registration: Clinical trial registered with www.clinicaltrials.gov (NCT04238871).

Keywords: Antifibrotic; Capsule; Idiopathic pulmonary fibrosis; Interstitial lung disease; Pirfenidone; Tablet

Diseases, Cystic Fibrosis, Marseille University Hospital, Marseilles, France

A. Gondouin
Pneumology Department, Besançon University Hospital, Besançon, France

J. Cadranel
Pneumology Department, Paris-Tenon University Hospital, Paris, France

S. Marchand-Adam
Pneumology Department, Tours University Hospital, Tours, France

A. Clément
Pediatric Pneumology Department, Paris-Trousseau University Hospital, Paris, France

Key Summary Points

Pirfenidone is indicated in the treatment of idiopathic pulmonary fibrosis (IPF) and is now available as tablets instead of capsules

A cohort study was conducted to describe real-life management of patients with IPF treated with pirfenidone tablets or capsules

The substitution between the two formulations (capsule or tablet) as well as the sociodemographic and medical characteristics of patients and safety were assessed in real life

A total of 44.9% (95% CI 38.8–51.0) patients shifted from capsule to tablet and 4.7% (95% CI 2.1; 7.3) from tablet to capsule

There were fewer discontinuations in the tablet-only and substitution subgroups than in the capsule-only subgroup

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic lung disease in which healthy tissue is replaced by altered extracellular matrix, leading to decreased lung compliance, respiratory failure, reduction in exercise capacity, deterioration in health-related quality of life (QoL), and ultimately death [1, 2].

IPF prevalence and incidence trends are on the rise [3]. Worldwide, the prevalence of IPF is estimated at 20/100,000 for male individuals and 13/100,000 for female individuals [4]. Available data in France showed a crude prevalence of 8.2 per 100,000 and an incidence of 2.8 per 100,000 per year [5]. The prevalence of IPF increases with age. Most patients are over 60 years of age at diagnosis and there is a higher proportion of men than women [6, 7]. The

average survival from the time of diagnosis is estimated as 3–5 years [8].

An international guideline for the diagnosis and the management of IPF has been used since 2011 [9]. The diagnosis of IPF is performed by a multidisciplinary team and is based on a diagnostic algorithm, combining the presence of clinical signs, radiological investigation, and biopsy in the appropriate clinical setting [10]. In France, patients with IPF can be diagnosed, treated, and followed in a network of expert centers for rare lung diseases [11, 12].

French practical treatment guidelines recommend two specific antifibrotic agents, pirfenidone and nintedanib, as well as symptomatic treatments [12–14]. Pirfenidone is a multifunctional, orally available small molecule with antifibrotic, anti-inflammatory, and antioxidative activities. Even if its mechanism of action has not been fully established, it is considered to exert inhibitory effects on multiple pathways, including inhibition of the transforming growth factor beta pathway, involved in the pathogenesis of IPF. Pirfenidone leads to attenuation of fibroblast proliferation, limiting the increased biosynthesis and accumulation of extracellular matrix [15–17].

The analysis of clinical efficacy of pirfenidone in patients with IPF was assessed in three pivotal phase III studies, resulting in clinically meaningful reductions in disease progression with an acceptable safety profile [18]. The long-term safety profile, following a 2-year follow-up of patients with IPF treated with pirfenidone evaluated in the prospective, observational PASSPORT study, was consistent with the known safety profile of pirfenidone [19, 20]. Pirfenidone has since been indicated in adults for the treatment of mild to moderate IPF [17].

Pirfenidone was approved for patients with IPF in 2011, and has been reimbursed in France since 2012 for patients with forced vital capacity of 50% or greater and a diffusion capacity for carbon monoxide of 30% or greater. Between 2012 and 2018, only a 267 mg capsule formulation of pirfenidone was available, requiring patients to take 3–9 capsules per day to reach the daily dosage of 2403 mg. A form of strongly dosed, small tablets was therefore developed,

allowing one to obtain a better compliance. Since April 2018, this tablet form with demonstrated bioequivalence [21] has been available with two dosages (267 mg and 801 mg) on the French market, together with the capsule formulation. It has been shown that both patients and healthcare professionals support the administration of the 801 mg tablet owing to its convenience of use, resultant patient quality of life, and treatment adherence [22].

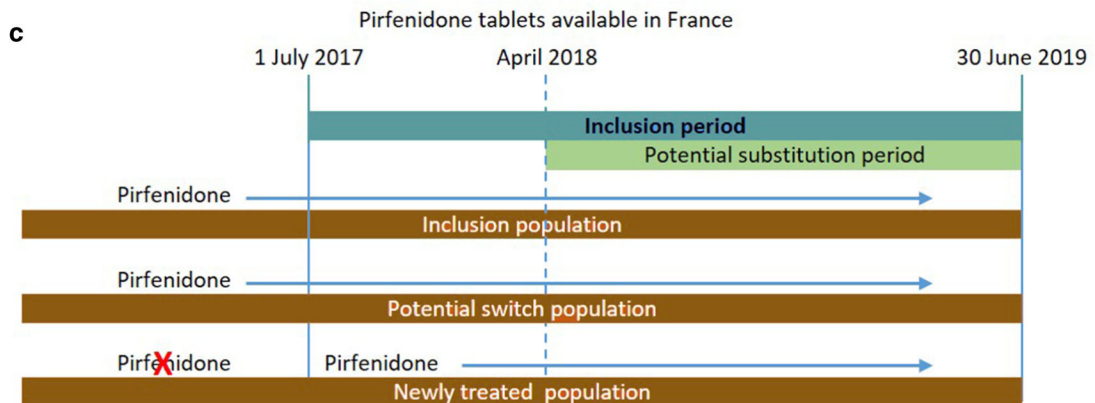
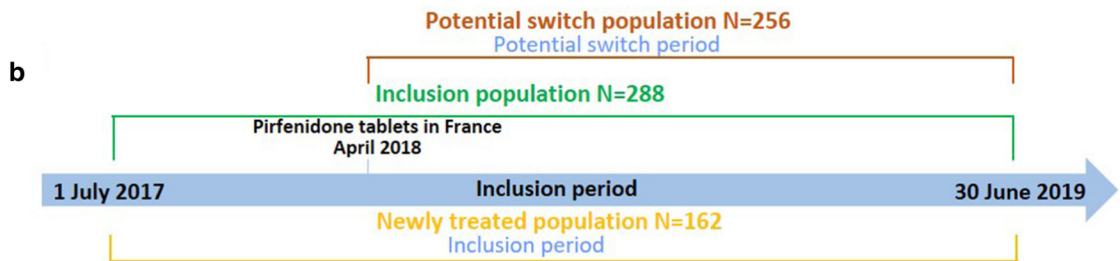
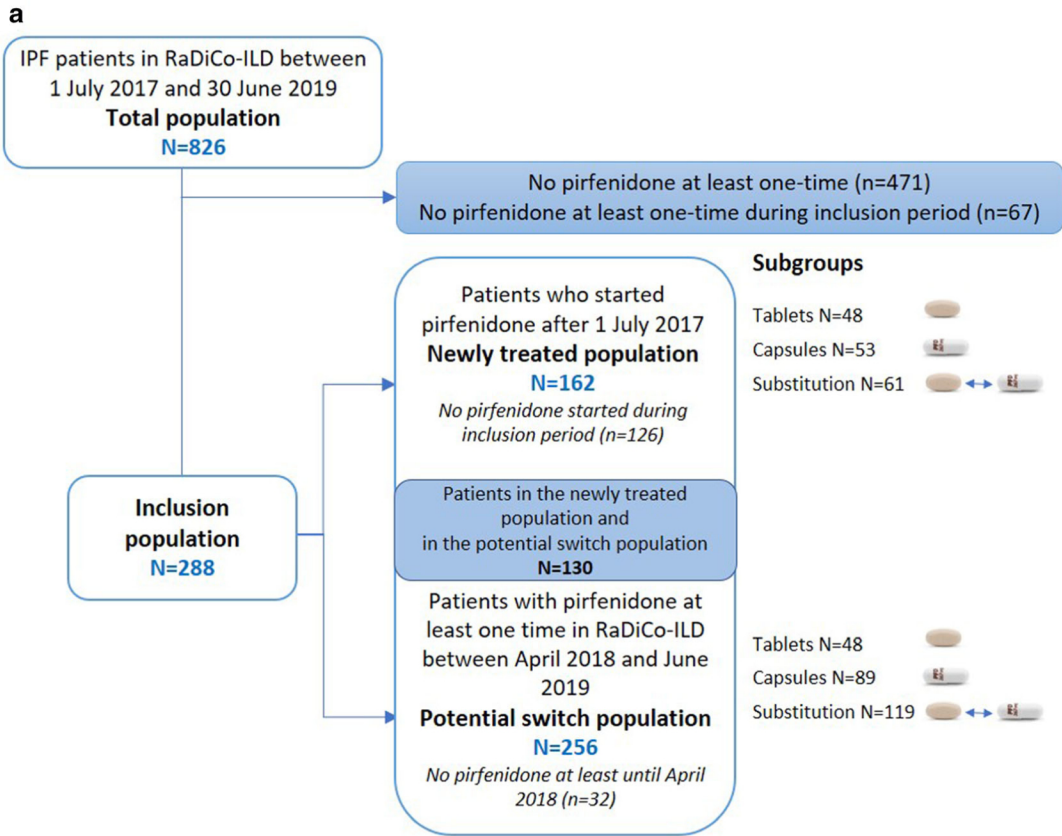
The present RaDiCo-ILD cohort study, conducted at the time of the launch on the French market of the tablet formulation (April 2018), was a nested study within the broader cohort French RaDiCo (Rare Disease Cohort)-ILD (Interstitial Lung Diseases) registry (NCT04238871), an ongoing observational study initiated in June 2017 [23].

This study aimed to describe real-life management of patients with IPF treated with pirfenidone, including prescription characteristics, and the course of treatment shift between the two dosage forms, capsules and tablets, in order to assess the level of suitability of the tablet formulation for patients and physicians.

METHODS

For enrollment in the present study, patients had to have been enrolled in the RaDiCo-ILD cohort with a diagnosis of IPF established in a multidisciplinary discussion according to international guidelines [10]. All patients diagnosed with IPF and treated at least once with pirfenidone between the start of the study (1 July 2017) and the end of the study (30 June 2019) were included (Fig. 1). Data were extracted from the RaDiCo-ILD cohort. This study followed patients for a maximum of 2 years (last follow-up visit of the last recruited patient).

Three populations were defined: the inclusion population with patients who were treated at least once with pirfenidone during the study period ($n = 288$); the potential switch population that included patients treated with pirfenidone, at least during the switch period starting April 2018 (availability of the tablet formulation) until study end ($n = 256$); the newly treated population including patients



◀**Fig. 1** Study flow chart (a), treatment period (b), and patient inclusion (c). Three populations were defined: the inclusion population included patients who were treated at least once with pirfenidone during the study period; the potential switch population that included patients treated with pirfenidone, at least during the switch period starting April 2018 (availability of the tablet formulation) until study end, 30 June 2019; the newly treated population including patients who initiated pirfenidone during the study period. The potential switch population and the newly treated population included three subgroups (tablets, capsules, and substitution)

who initiated pirfenidone during the study period ($n = 162$). The potential switch population and the newly treated population included three subgroups (tablets, capsules, and substitution). The term substitution was used only for subgroups of patients who could shift from tablets to capsules or capsules to tablets.

The treatment baseline was the reference period of treatment and was defined as the first day of the treatment period, even if the treatment had started before the study.

The primary objective was to assess the treatment acceptability by describing the treatment pattern of pirfenidone in patients with IPF and the switch between the two formulations (capsule or tablet) of pirfenidone. The main study outcomes were mostly assessed in the potential switch population and the newly treated population. They included the number of patients with capsules and tablets formulation, the switch rate between the formulations, the treatment duration, the daily dose, the dose modifications, the treatment discontinuation rate and the reasons, the time to patient switch to tablet formulation, and the time to treatment discontinuation.

The secondary objectives were the description of the sociodemographic and medical characteristics of patients in the potential switch and in the newly treated populations, and the description of the quality of life in the included population and in the newly treated populations. The quality of life (QoL) was assessed using the Saint George's respiratory questionnaire (SGRQ), specific to chronic respiratory diseases.

Safety was analyzed descriptively in the inclusion population ($n = 288$), the population with the largest number of patients. Adverse events (AEs) were those reported by patients to the physicians during the visit.

The usual administration schedule of pirfenidone is a dose escalation from 267 mg from days 1 to 7 administered three times a day (801 mg/day) to 534 mg from days 8 to 14 administered three times a day (1602 mg/day) until reaching the recommended dose of 801 mg administered three times a day (2403 mg/day).

Statistical Analysis Methodology

All statistical analyses were descriptive in nature. Time to treatment discontinuation was analyzed by the Kaplan–Meier method, using the date of treatment initiation as baseline, and censoring at the time of last study visit or lost to follow-up. Quantitative variables such as sociodemographic and medical characteristics as well as safety data and quality of life data were described by their means, standard deviation, 95% CI of the mean when required (primary objective), median, Q1, Q3, and minimum and maximum value. Qualitative variables were described by their count percentage and 95% CI of the percentage when required.

Patients who were lost to follow-up or patients that were without substitution at the end of follow-up or patients with competing event (e.g., lung graft) were considered as censored.

The different characteristics were assessed globally and in the three subgroups. Substitution in the subgroups from capsule to tablet and reverse substitution from tablet to capsule were assessed.

The analyses were performed with SAS® (version 9.4) and the REDCap® electronic data capture system was used. Data entry was performed by or on behalf of the principal investigators or sub-/co-investigators in the e-CRF provided by Institut National de la Santé et de la Recherche Médicale (Inserm)-UMR S 933-RaDiCo and saved in the associated

database. REDCap® is a secure, web-based application from the Vanderbilt University, TN, USA, designed to support data capture for research studies.

This trial was designed by representatives of the sponsor and academic advisors. The patients had signed a written informed consent before inclusion in the RaDiCo-ILD registry. The RaDiCo-ILD cohort protocol sponsored by Inserm was approved by the IRB CEEI (Institutional Review Board—Inserm Ethics Evaluation Committee) on 16 October 2015, and by the CCTIRS (Research Information Processing Advisory Committee) on 23 March 2016 and authorization was granted by the CNIL (Commission Nationale de l'Informatique et des Libertés) on 3 November 2016.

The RaDiCo-ILD cohort was implemented as part of the RaDiCo research program, funded under the “cohorts” program of the Investments for the Future (ANR-IO-COHO-03-01) and coordinated by the Inserm Unité UMR S933, Hôpital Trousseau, Paris, France.

RESULTS

The RaDiCo-ILD cohort registered 826 patients with IPF between 1 July 2017 and 30 June 2019. Patients treated with pirfenidone were grouped in the predefined inclusion population ($n = 288$), the potential switch population ($n = 256$), and the newly treated population ($n = 162$) (Fig. 1). Results are presented for the two main populations (potential switch population and the newly treated population).

In the potential switch population, men were predominant (85.9%) and age at inclusion was 72.3 ± 8.2 years old. Most patients were former smokers (71%). The mean duration between diagnosis and treatment initiation was 17.3 ± 23.8 months, with a median duration of 7.6 months (Q1, Q3; 2.2, 25.4). The most frequently reported first symptoms were dyspnea and cough, 91.5% and 71.4%, respectively. The mean FVC% was 77.5 ± 19.2 and the mean DLCO% was 44.3 ± 14.0 . The main comorbidity was arterial hypertension (46%) followed by sleep apnea, gastroesophageal reflux (30% each), and coronary disease (26%).

Demographic and disease characteristics in the tablet, capsule, and substitution subgroups of the potential switch population were globally equivalent (Table 1). Demography at inclusion for the included population and the newly treated population ($N = 288$) are presented in Supplementary Material.

The main study outcomes were as follows: the percentage of patients who started pirfenidone with the new tablet formulation accounted for 17.0% of the inclusion population and 30.3% of the newly treated population; in the potential switch population ($N = 256$), 44.9% (95% CI 38.8; 51.0) of patients shifted from capsules to tablets; in the newly treated population 36.4% (95% CI 29.0; 43.8) of patients shifted from capsules to tablets; the reverse switch rate was 4.7% (95% CI 2.1; 7.3) and 3.1% (95% CI 0.4; 5.8), respectively for the two considered populations (Table 2).

The mean pirfenidone treatment duration was 21.5 ± 18.7 months in the potential switch population, where 119 patients (46.5%) had discontinued treatment, and 10.3 ± 7.0 months in the newly treated population, where 83 patients (51.2%) had discontinued treatment (Table 2).

The median daily dose was 2348.4 mg (min; max 801.0; 2621.9), representing 97.7% of the target recommended daily dose (2403 mg/day) in the potential switch population, and 84.1% in the newly treated population. One identified patient received a maximal pirfenidone dose of 2621.9 mg. This misuse was notified according to the usual pharmacovigilance process (Table 2).

To reach the maximal dose, 65.8% of patients had an escalation schedule in the potential switch population and 88.2% in the newly treated population. The rates of patients with the recommended/usual schedule in both the potential switch and the newly treated populations were 54.3% and 77.0%, respectively. The rate of permanent dose decrease was 13.0% (95% CI 8.9; 17.1) in the potential switch population and 15.5% (95% CI 9.9; 21.1) in the newly treated population (Fig. 2).

Overall, treatment discontinuations reported in the capsule subgroup of both the potential switch population and the newly treated

Table 1 Demography at inclusion and disease characteristics in the potential switch population ($N = 256$) and the tablet, capsule, and substitution subgroups

	Potential switch population ($N = 256$)			Total ($N = 256$)
	Tablet ($N = 48$)	Capsule ($N = 89$)	Substitution ($N = 119$)	
Mean age at inclusion, years (SD)	71.2 (8.7)	72.1 (7.9)	72.8 (8.2)	72.3 (8.2)
Mean age at diagnosis, years (SD)	70.5 (8.6)	70.9 (8.0)	70.9 (8.2)	70.8 (8.2)
Male, n (%)	45 (93.8)	66 (74.2)	109 (91.6)	220 (85.9)
Tobacco status, n (%)				
No	8 (16.7)	25 (28.4)	26 (21.9)	59 (23.1)
Active	–	4 (4.6)	5 (4.2)	9 (3.5)
Quit	40 (83.3)	55 (62.5)	86 (72.3)	181 (71.0)
FVC				
Mean FEV/FVC (SD)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)
DLCO%	45.1 (12.1)	41.7 (13.5)	45.8 (14.9)	44.3 (14.0)
Mean duration between diagnosis and treatment, months (SD)	12.2 (33.1)	8.0 (11.2)	26.3 (23.3)	17.3 (23.8)
Concomitant treatments, n (%)				
Oxygen	16 (34.8)	40 (48.2)	44 (38.3)	100 (41.0)
Corticosteroids	15 (31.9)	44 (53.7)	40 (35.1)	99 (40.7)
First symptoms, n (%)				
Dyspnea	40 (90.9)	73 (89.0)	103 (93.6)	216 (91.5)
Cough	33 (76.7)	60 (74.1)	74 (67.3)	167 (71.4)
Fatigue	5 (10.6)	9 (10.8)	17 (14.7)	31 (12.6)
Chest pain	4 (9.3)	7 (9.1)	13 (12.3)	24 (10.6)
Comorbidities and risk factors, n (%)				
Cardiovascular disease	33 (70.2)	64 (75.3)	97 (82.9)	194 (77.9)
Gastrointestinal disease	16 (33.3)	45 (53.6)	57 (50.0)	118 (48.0)
Endocrine disease	16 (34.8)	24 (29.3)	34 (30.1)	74 (30.7)

The term substitution was used only for subgroups of patients who could shift from tablets to capsules or capsules to tablets
SD standard deviation, *FEV/FVC* forced expiratory volume/forced vital capacity, *DLCO* diffusing capacity of carbon monoxide

population were 60.7% and 67.9%, respectively, about 15% higher than in the tablets and the substitution subgroup (Tables 2 and 3). Within all the subgroups the main reason for treatment

discontinuation was related to adverse events with pirfenidone, in more than 60% of the cases (Fig. 3).

Table 2 Summary of main results in the potential switch population ($N = 256$) and the newly treated population ($N = 162$)

	Potential switch population ($N = 256$)	Newly treated population ($N = 162$)
Substitution from capsules to tablets, n (%) [95% CI]	115 (44.9) [38.8; 51.0]	59 (36.4) [29.0; 43.8]
Reverse substitution from tablets to capsules, n (%) [95% CI]	12 (4.7) [2.1; 7.3]	5 (3.1) [0.4; 5.8]
Duration of pirfenidone treatment in months, mean (SD)	21.5 (18.7)	10.3 (7.0)
Mean pirfenidone, mg a day (SD)	2106.7 (460.7)	2022.0 (491.1)
Median Pirfenidone, mg a day (min; max)	2348.4 (801.0; 2621.9)	2267.1 (801.0; 2621.9)
Treatment discontinuations, n (%)	119 (46.5)	83 (51.2)
Main reason for treatment discontinuation	$N = 119$	$N = 83$
Adverse events	81 (68.1)	61 (73.5)
Other	13 (10.9)	8 (9.6)
Lack of efficacy	12 (10.1)	6 (7.2)
Death	12 (10.1)	7 (8.4)
Poor compliance	1 (2.3)	1 (1.2)
Patients with adverse event, n (%) [95% CI]	87 (34.0) [28.2; 39.8]	65 (40.1) [32.6; 47.7]
Mean number of adverse event/patient, n (%) [95% CI]	2.0 (1.2) [1.8; 2.3]	2.1 (1.2) 1.7; 2.4
Serious adverse event (hospitalization), n (%) [95% CI]	3.0 (3.7) [0.0; 7.8]	3.0 (5.0) [0.0; 10.5]

SD standard deviation

The proportion of observations that were censored differed between the groups: 52.8% in the capsule group, 86.9% in the switch group, and 78.7% in the tablet group. The Kaplan–Meier analysis showed that there were fewer pirfenidone discontinuations in the tablets and substitution subgroups than in the capsule subgroup (Fig. 4). The capsule subgroup was the only one to cross the median duration, as 50%

of patients had a treatment discontinuation at 11.4 months.

The other treatments of fibrosis included oxygen therapy (41% of patients) and steroids (40.7%). Gastroesophageal reflux disease (GERD) treatments were the most prescribed ones other than pirfenidone (70.0%).

In the included population ($n = 256$), the mean total SGRQ score was 39.7 ± 19.5 at

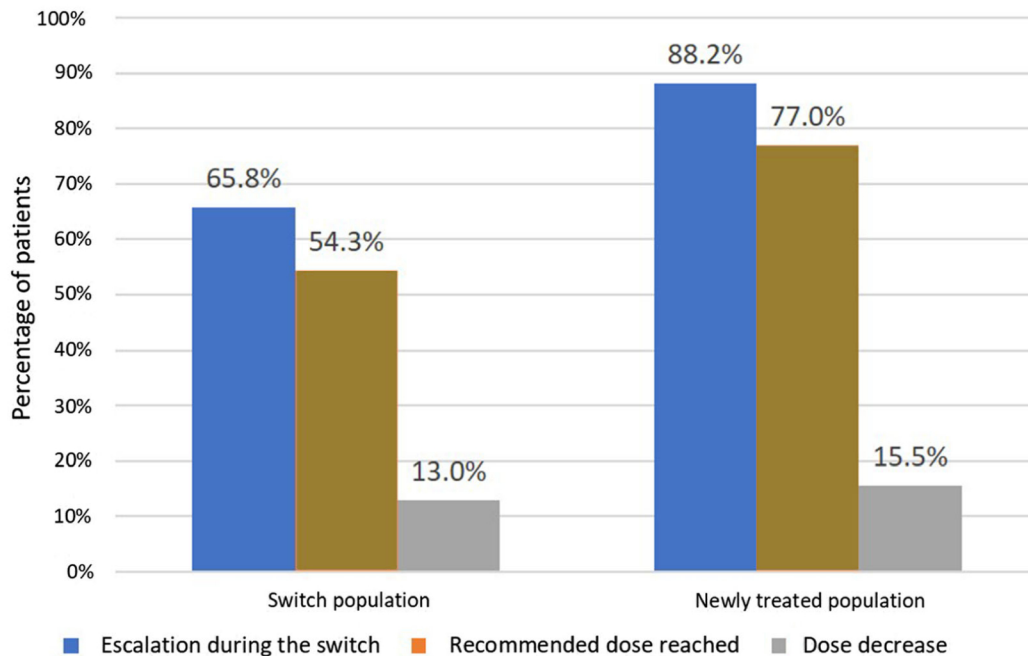


Fig. 2 Pirfenidone dose modifications in the potential switch population ($N = 256$) and the newly treated population ($N = 162$). Two patients missing in the

potential switch population and one patient missing in the newly treated population

Table 3 Treatment discontinuations according to the tablet, capsule, and substitution subgroups in the potential switch population ($N = 256$) and the newly treated population ($N = 162$)

Variable	Tablet	Capsule	Substitution	Total
Potential switch population	$N = 48$	$N = 89$	$N = 119$	$N = 256$
Treatment discontinuation, n (%) [95% CI]	22 (45.8) [36.9; 54.8]	54 (60.7) [51.9; 69.5]	43 (36.1) [27.5; 44.8]	119 (46.5) [37.5; 55.5]
Newly treated population	$N = 48^a$	$N = 53$	$N = 61$	$N = 162$
Treatment discontinuation, n (%) [95% CI]	22 (45.8) [33.3; 58.3]	36 (67.9) [56.2; 79.6]	25 (41.0) [28.6; 53.3]	83 (51.2) [38.7; 63.8]

CI confidence interval

^aThe tablet subgroup included 48 patients instead of the 49 patients who had tablet as a first prescription, because one of these patients shifted for capsule formulation and then was included in the potential switch population

inclusion in 186 patients evaluated, indicating a markedly deteriorated of QoL, with no noticeable difference between the different tablets, capsules, and substitution subgroups.

Safety Results

No differences in the percentage of patients with adverse events (AEs), in the mean number of AE/patient, and serious adverse events (SAEs) occurrences were noted whatever the populations. In the inclusion population, 112/288 patients (38.9%) experienced at least one AE.

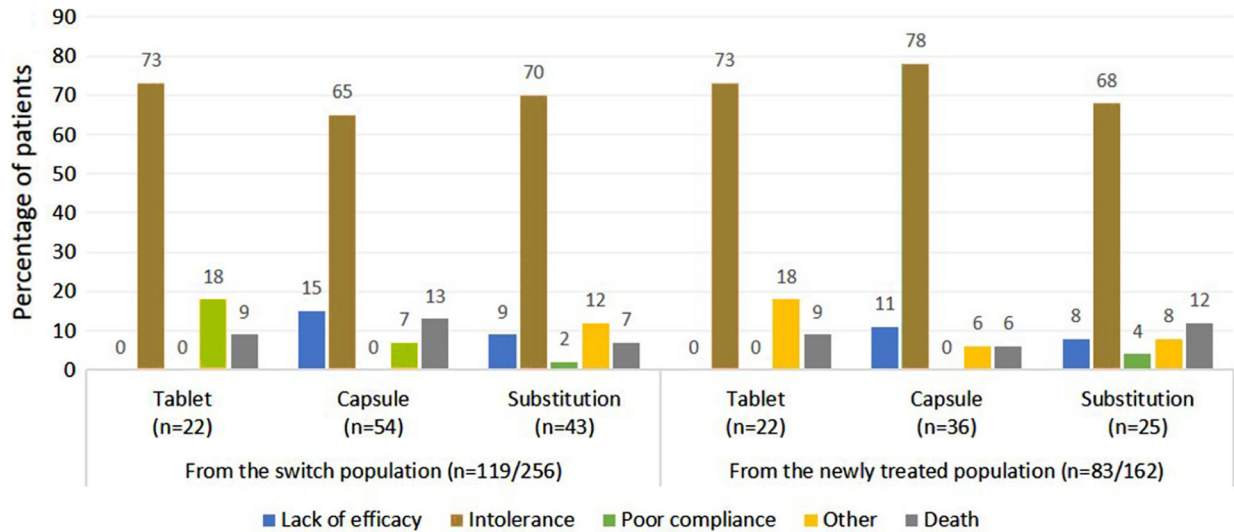


Fig. 3 Reasons for treatment discontinuation in the potential switch population ($N = 256$) and the newly treated population ($N = 162$)

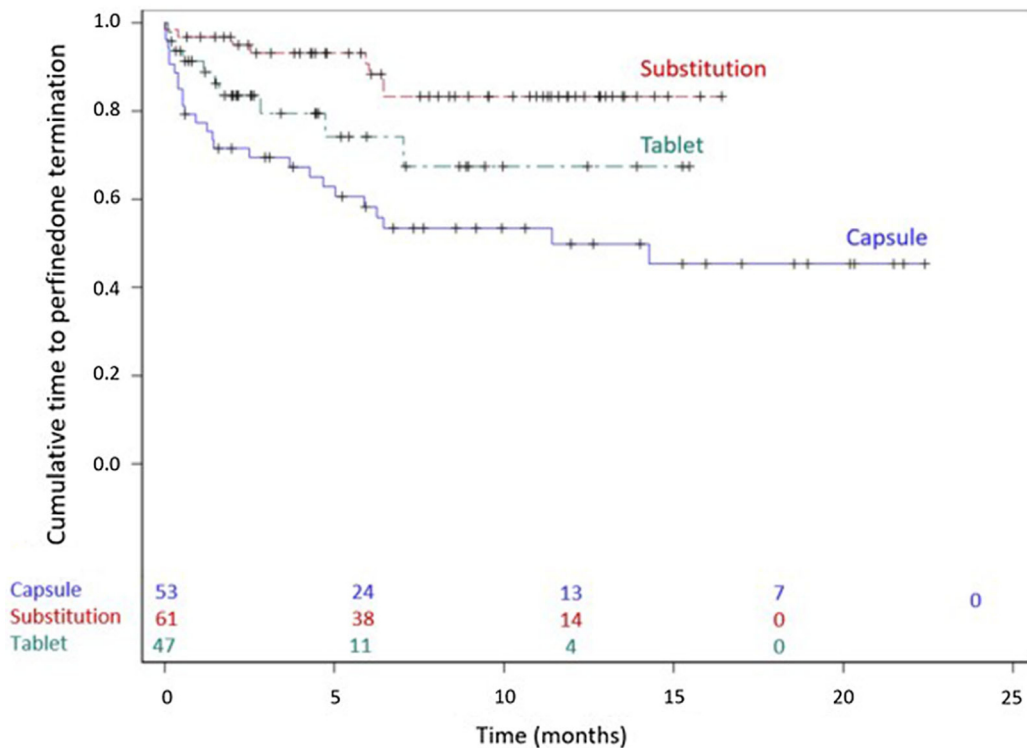


Fig. 4 Time to pirfenidone treatment discontinuation: Kaplan–Meier analysis in the newly treated population ($N = 162$). A total of 73.3% of patients were censored:

52.8% in the capsule group, 86.9% in the switch group, and 78.7% in the tablet group

The most reported AE was skin rash (33 patients, 11.5%), followed by asthenia (23 patients,

8.0%), weight loss (22 patients, 7.6%), and anorexia (20 patients, 6.9%) (Fig. 5).

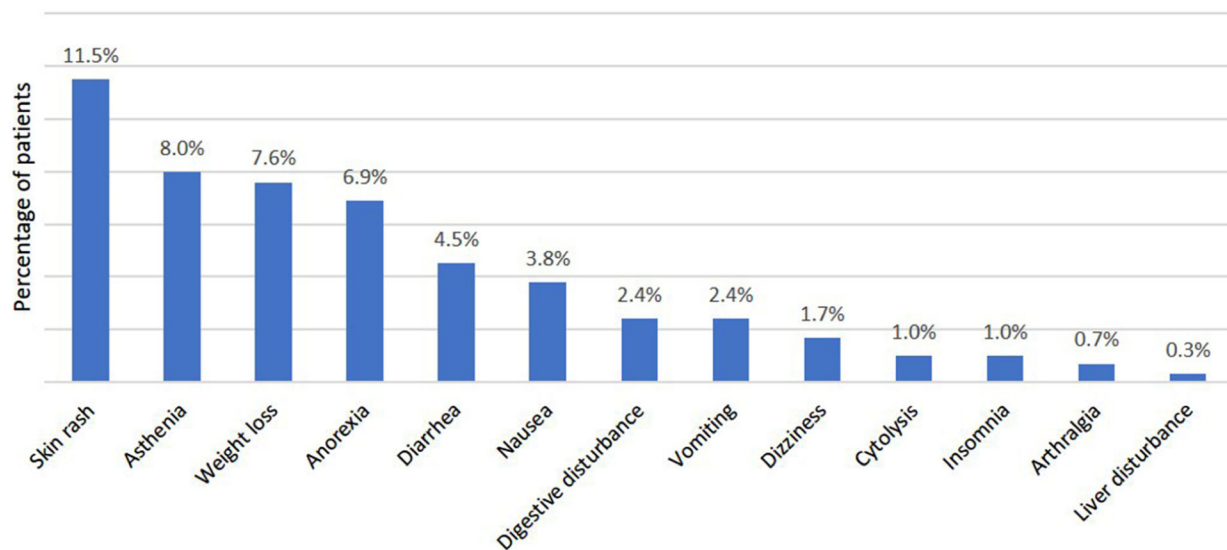


Fig. 5 Main reported adverse events in the inclusion population ($N = 288$)

SAEs requiring hospitalization and therefore qualified as SAE occurred in 5 (1.7%) patients. Deaths occurred in 12 (4.2%) patients; the reasons for deaths were not collected. No major differences in safety were noted between the inclusion population, the potential switch population, and the newly treated population.

DISCUSSION

This French retrospective descriptive secondary use cohort, conducted at the time of the launch on the French market of the tablet formulation (April 2018), provides information on the management of patients with IPF treated with pirfenidone and on the substitution from the capsule to the novel tablet formulation. Data was collected from an existing broader longitudinal, national, multicenter retrospective and prospective cohort, the RaDiCo-ILD cohort, and focused on patients who received at least one dose of pirfenidone during the study period.

With 826 patients with IPF included, the RaDiCo-ILD cohort is one of the largest described in Europe: more than 3500 patients were included in the EMPIRE registry (on 14 May 2020), 525 patients were included in the Eur-IPFreg, and 502 in the German INSIGHTS-IPF registry [8, 24, 25].

Regarding the demographic data, patients' characteristics were quite comparable to those of other European registries. Disease characteristics at inclusion were in accordance with an IPF diagnosis which is associated with a lower FVC% and a lower DLCO% and in accordance with the results published in Europe [8, 26, 27]. Regarding disease severity, the present study did not differ from other European IPF registries. The most important comorbidities (arterial hypertension, sleep apnea, gastroesophageal reflux, and coronary disease) appeared to be the same in this IPF cohort as those reported in the PROOF and EurIPFreg cohorts [8, 28].

The lower switch rate from capsules to tablets in our study may be due to the higher rate of patients treated from the start with the tablet formulation. The reverse switch rate (shift from tablet to capsule formulation) was low within the two considered populations.

In this cohort, the treatment duration was longer than that found in early studies such as the Swedish cohort in 2011 (treatment duration 9 months) [29], which may be because physicians currently educate their patients on potential adverse events and how to mitigate them. In addition, the two populations appear to differ in the gender distribution (60% men, 40% women) and the diagnosis was not clearly based on international recommendations.

Therefore, it is not clear whether the two populations are comparable.

More patients underwent a dose escalation within the newly treated population than in the potential switch population. This higher proportion was expected and may be due to the follow-up of the newly treated population which could have been better documented. However, the potential switch population had a probability of being on treatment for a longer period of time.

The lower rate of patients receiving the recommended standard schedule found in the potential switch population is in accordance with a population treated for a longer time that could have met several situations requiring temporary dosage adjustment followed by incomplete escalation.

Both in the potential switch population and in the newly treated population the mean daily dose was below the recommended daily dose, but the cumulated doses were globally as good as could be expected. These lower mean doses in the newly treated population highlight the occurrence of an escalation schedule captured during the study period. The mean daily dose is, along with dose intensity and the rate of dose decrease, one of the markers of compliance to prescription and treatment safety.

In a post hoc analysis of the patients included in the phase III clinical trials CAPACITY and ASCEND, the dose adaptation of pirfenidone was studied retrospectively over a 120-week follow-up [30]. The low mean daily dose described, 2054.0 mg/day, was fully attributable to dose decrease, related to probable safety issues, whereas the low mean daily dose described in the present cohort was mainly due to dose escalation, a marker of starting a treatment period, confirmed by the respective median dose intensity, 100% in the newly treated patients of this cohort, and 96% described by Nathan et al. [30].

In contrast to the phase III trials, the follow-up in this RaDiCo-ILD cohort took place in a context where there was the possibility to receive an alternative antifibrotic agent, and therefore the decision to take another medication may have been preferred to a dose decrease by some patients.

In the potential switch population, more pirfenidone treatment discontinuations were reported in the capsule subgroup than in the other subgroups. More treatment discontinuations were also reported in the capsule subgroup of the newly treated population. Among the various possible explanations, one of them could be that patients treated with pirfenidone capsules shifted to another treatment or stopped any treatment. Within all the subgroups, the main reason for treatment discontinuation was related to adverse events with pirfenidone, accounting for more than 60% of the reasons for treatment discontinuations.

Following the European Medicines Agency (EMA) approval of pirfenidone, the PASSPORT study, a safety registry, was set up to collect long-term data regarding patients with IPF treated with pirfenidone throughout Europe [19, 20]. In this registry, 20% of patients interrupted their treatment with pirfenidone because of adverse reactions, in accordance with other reports [31–33]. In the present cohort, 30% of the patients interrupted the pirfenidone treatment for adverse events. This higher proportion could be explained by the possibility to shift treatment with another antifibrotic agent since 2015. The patients treated before 2015 did not have this alternative and thus were surely less tempted to permanently discontinue their current treatment.

The safety results in this real-life cohort were in accordance with the known safety profile of pirfenidone. Reported AEs were already described in the Summary of Product Characteristics (SmPC) and no new AEs have been identified. Less than 5% of reported events were SAEs. The main adverse reactions reported in the inclusion population were skin rash, gastrointestinal disorders, and events linked to appetite disturbance (anorexia, weight loss). These results are coherent with the findings of other studies related to pirfenidone safety, which also reported skin and gastrointestinal disturbances [17, 20, 31, 32]. The mean score of the SGRQ in the potential switch population was lower than the scores reported in the Australian IPF registry and in the INSIGHTS-IPF registry [34].

The limitations of this cohort study include the retrospective collection of the data from a

prospective, observational study, which caused numerous missing data especially for laboratory tests. The information bias was limited by conducting the study within the network of the French expert centers that agreed in accordance with international guidelines to a common diagnosis algorithm that ensured the homogeneity of the patients' characteristics at inclusion [9, 10]. Furthermore, the fact that patients in the potential switch population had initiated pirfenidone prior to study entry creates potential prevalent user bias.

CONCLUSION

Our cohort study conducted in patients diagnosed with IPF aimed to describe the real-life management of pirfenidone tablets—as a new formulation—or capsules treatment, and substitution between those two formulations was assessed in real life. Almost 50% of patients switched from capsules to tablets and less than 5% switched from tablets to capsules, along with fewer discontinuations in the tablets-only and substitution subgroups than in the capsules-only subgroup. Although the retrospective collection of data resulted in missing data, we tried to limit bias through homogeneity of patient characteristics at inclusion. Globally, our real-life observations were consistent with the known safety profile of pirfenidone and suggest a good acceptance of the new tablet formulation by both patients and physicians.

ACKNOWLEDGEMENTS

The authors are grateful to the patients, their families, the physicians who participated in this study and the RaDiCo study project team.

Funding. This work was sponsored and funded by Roche – France. The sponsor is also funding the journal's Rapid Service Fees.

Medical Writing and/or Editorial Assistance. Medical writing support and editing was provided by Eltium (Dr Samia Rahal) under the

direction of the authors. This assistance was funded by Roche – France.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by the RaDiCo Team. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

List of Investigators. Pr. Emmanuel Bergot (Caen), Pr. Philippe Bonniaud (Dijon), Pr. Arnaud Bourdin (Montpellier), Pr. Jacques Cadranel (Paris), Pr. Cécile Chenivresse (Lille), Pr. Vincent Cottin (Lyon), Pr. Bruno Crestani (Paris), Pr. Jean-Charles Dalphin (Besançon), Dr. Claire Dromer (Bordeaux), Dr. Emmanuel Gomez (Nancy), Dr. Sandrine Hirschi (Strasbourg), Pr. Dominique Israël-Biet (Paris), Pr. Stéphane Jouneau (Rennes), Pr. Sylvain Marchand-Adam (Tours), Pr. David Montani (Kremlin-Bicêtre), Pr. Hilario Nunes (Paris), Dr. Grégoire Prévot (Toulouse), Dr. Sébastien Quantant (Grenoble), Pr. Martine Reynaud-Gaubert (Marseille), Pr. Dominique Valeyre (Paris), Dr. Lidwine Wemeau (Lille).

Disclosures. Vincent Cottin was consultant for Boehringer Ingelheim, Roche, Shionogi, Fibrogen, Galapagos, Celgene, Galecto; has received honoraria from Boehringer Ingelheim, Roche and subventions from Boehringer Ingelheim. Stéphane Jouneau has received fees, funding or reimbursement for national and international conferences, boards, expert or opinion groups, research projects over the past 5 years from Actelion, AIRB, AstraZeneca, Bellerophon Therapeutics, Biogen, BMS, Boehringer Ingelheim, Chiesi, Fibrogen, Galecto Biotech, Genzyme, Gilead, GSK, LVL, Mundipharma, Novartis, Olam Pharm, Pfizer, Pliant Therapeutics, Roche, Sanofi, Savara-Serendex.

Hilario Nunes has received subventions from Roche, Genentech, Boehringer Ingelheim. Stéphane Jouneau was consultant for AIRB, Boehringer, Roche, LVL, Novartis; has received honoraria from Actelion, AIRB, AstraZeneca, BMS, Boehringer, Chiesi, Gilead, GSK, LVL, Mundipharma, Novartis, Pfizer, Roche and Savara-Serendex. Bruno Crestani has received personal fees from Astrazeneca, Boehringer Ingelheim, Roche, Sanofi and Novartis. Philippe Bonniaud has received donations from GSK, AstraZeneca; honoraria from GSK, AstraZeneca, Sanofi, Roche, Boehringer; was consultant for GSK, AstraZeneca, Sanofi, Roche and Boehringer. Anne Gondouin has received honoraria from Roche and Boehringer Ingelheim; support for meeting from Boehringer Ingelheim and Roche. Jacques Cadranel has received personal fees for board of experts for Boehringer Ingelheim, and honoraria for presentations for Boehringer Ingelheim and Roche. Sylvain Marchand-Adam has received grants from Roche, presentations from Roche, AstraZeneca, Boehringer Ingelheim, Novartis; personal fees from Novartis and AstraZeneca; travel support from Boehringer Ingelheim; Advisory Board from Boehringer Ingelheim. Sonia Guéguen, Dominique Israel-Biet, Marie Chevereau, Isabelle Dufaure-Garé, Serge Amselem, Annick Clément, Martine Reynaud-Gaubert and Lidwine Wemeau have nothing to disclose.

Compliance with Ethics Guidelines. This trial was designed by representatives of the sponsor and academic advisors. The patients had signed a written informed consent before inclusion in the RaDiCo-ILD registry. The RaDiCo-ILD cohort protocol sponsored by Inserm was approved by the IRB CEEI (Institutional Review Board - Inserm Ethics Evaluation Committee) on 16 October 2015, and by the CCTIRS (Research Information Processing Advisory Committee) on 23 March 2016 and authorization was granted by the CNIL (Commission Nationale de l'Informatique et des Libertés) on 3 November 2016.

Data Availability. The datasets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

REFERENCES

1. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet*. 2017;389(10082):1941–52.
2. Wuyts WA, Wijsenbeek M, Bondue B, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. *Respiration*. 2020;99(1):73–82.
3. Sauleda J, Núñez B, Sala E, Soriano JB. Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. *Med Sci (Basel)*. 2018;6(4):110.
4. Kim DS, Collard HR, King TE Jr. Classification and natural history of the idiopathic interstitial pneumonias. *Proc Am Thorac Soc*. 2006;3(4):285–92.
5. Duchemann B, Annesi-Maesano I, de Jacobe NC, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *Eur Respir J*. 2017;50(2):1602419.
6. Cottin V, Crestani B, Valeyre D, et al. French national reference centre; network of competence centres for rare lung diseases. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. *Eur Respir Rev*. 2014;23(132):193–214.
7. Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. *Eur Respir Rev*. 2018;27(150):180077.
8. Guenther A, Krauss E, Tello S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respir Res*. 2018;19(1):141.
9. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192(2):e3-19.
10. Raghu G, Remy-Jardin M, Myers JL, et al. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT Clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44–68.

11. Centre de Référence des Maladies Pulmonaires Rares. Available from: <http://www.maladies-pulmonaires-rares.fr/>. Accessed 28 Oct 2021.
12. Cottin V, Crestani B, Cadranel J, et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis-2017 update. Full-length version. *Rev Mal Respir.* 2017;34(8):900–68.
13. George PM, Patterson CM, Reed AK, Thillai M. Lung transplantation for idiopathic pulmonary fibrosis. *Lancet Respir Med.* 2019;7(3):271–82.
14. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2071–82.
15. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study. *Am J Respir Crit Care Med.* 1999;159(4 Pt 1):1061–9.
16. Takeda Y, Tsujino K, Kijima T, Kumanogoh A. Efficacy and safety of pirfenidone for idiopathic pulmonary fibrosis. *Patient Prefer Adher.* 2014;21(8):361–70.
17. Summary of Product Characteristics (SmPC) Esbriet®. Available from: https://www.ema.europa.eu/en/documents/product-information/esbriet-epar-product-information_en.pdf. Accessed 28 Oct 2021.
18. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J.* 2016;47(1):243–53.
19. Cottin V, Koschel D, Günther A, et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. *ERJ Open Res.* 2018;4(4):00084–2018.
20. Jouneau S, Gamez AS, Tracllet J, et al. A 2-year observational study in patients suffering from idiopathic pulmonary fibrosis and treated with pirfenidone: a French ancillary study of PASSPORT. *Respiration.* 2019;98(1):19–28.
21. Pan L, Belloni P, Ding HT, Wang J, Rubino CM, Putnam WS. A pharmacokinetic bioequivalence study comparing pirfenidone tablet and capsule dosage forms in healthy adult volunteers. *Adv Ther.* 2017;34(9):2071–82.
22. Lancaster LH, Valenzuela C, Mason W, et al. Patients' and healthcare professionals' experiences of idiopathic pulmonary fibrosis treatment with the pirfenidone 801 mg tablet formulation: a multinational survey. *Pulm Ther.* 2020;6(1):93–105.
23. Cottin V, Jouneau S, Crestani B, et al. Demographics and baseline characteristics of patients with idiopathic pulmonary fibrosis (IPF) in a real-world setting: results of 847 patients enrolled in the Radico-ILD Cohort in France. *Am J Respir Crit Care Med.* 2020;201:A3349.
24. Behr J, Kreuter M, Hoepfer MM, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J.* 2015;46(1):186–96.
25. Tran T, Šterclová M, Mogulkoc N, et al. The European MultiPartner IPF registry (EMPIRE): validating long-term prognostic factors in idiopathic pulmonary fibrosis. *Respir Res.* 2020;21(1):11.
26. Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. *BMC Med Res Methodol.* 2012;12:96.
27. Ferrara G, Carlson L, Palm A, Einarsson J, Olivesten C, Sköld M. Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. *Eur Clin Respir J.* 2016;3:31090.
28. Wuyts WA, Dahlqvist C, Slabbynck H, et al. Baseline clinical characteristics, comorbidities and prescribed medication in a real-world population of patients with idiopathic pulmonary fibrosis: the PROOF registry. *BMJ Open Respir Res.* 2018;5(1):e000331.
29. Sköld CM, Arnheim-Dahlström L, Bartley K, et al. Patient journey and treatment patterns in adults with IPF based on health care data in Sweden from 2001 to 2015. *Respir Med.* 2019;155:72–8.
30. Nathan SD, Lancaster LH, Albera C, et al. Dose modification and dose intensity during treatment with pirfenidone: analysis of pooled data from three multinational phase III trials. *BMJ Open Respir Res.* 2018;5(1):e000323.
31. Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real world experiences: pirfenidone and nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. *J Clin Med.* 2016;5(9):78.
32. Galli JA, Pandya A, Vega-Olivo M, Dass C, Zhao H, Criner GJ. Pirfenidone and nintedanib for

pulmonary fibrosis in clinical practice: tolerability and adverse drug reactions. *Respirology*. 2017;22(6):1171–8.

33. Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment

of idiopathic pulmonary fibrosis. *Eur Respir Rev*. 2015;24(135):58–64.

34. Kreuter M, Swigris J, Pittrow D, et al. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. *J Respir Res*. 2017;18(1):139.