Thieme

# Clinical course of mild-to-moderate idiopathic pulmonary fibrosis during therapy with pirfenidone: Results of the non-interventional study AERplus

## Klinischer Verlauf einer leichten bis mittelschweren idiopathischen Lungenfibrose unter Therapie mit Pirfenidon – Ergebnisse der nicht-interventionellen Studie AERplus

OPEN ACCESS

**Authors**

**Jens Schreiber[1], Wolfgang Schütte[2], Wolfgang Koerber[3], Bernd Seese[4], Dirk Koschel[5], Kathrin Neuland[6], Christian Grohé[7]**

**Institutions**

1 Pneumonology, Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany
2 Klinik für Innere Medizin II, Krankenhaus Martha-Maria Halle-Dölau, Halle, Germany
3 Abt. Pneumologie/Beatmungsmedizin und Schlaflabor, Evangelisches Krankenhaus Göttingen-Weende gGmbH, Bovenden-Lenglern, Germany
4 Abt. Pneumologie, Thoraxzentrum Bezirk Unterfranken, Münnerstadt, Germany
5 Innere Medizin und Pneumologie, Fachkrankenhaus Coswig, Coswig, Germany
6 Global Scientific Communications, Roche Pharma AG, Grenzach-Wyhlen, Germany
7 Klinik für Pneumologie, Evangelische Lungenklinik Berlin, Berlin, Germany

**Keywords**

idiopathic pulmonary fibrosis, pirfenidone, interstitial lung disease, pulmonary function, anti-fibrotic

**Schlüsselwörter**

idiopathische Lungenfibrose, Pirfenidon, interstitielle Lungenerkrankung, Lungenfunktion, antifibrotisch

**received** 8.11.2023
**accepted after revision** 11.1.2024

**Bibliography**

Pneumologie 2024; 78: 236–243
**DOI** 10.1055/a-2267-2074
**ISSN** 0934-8387
© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

**Corresponding author**

Prof. Jens Schreiber, Pneumonology, Otto-von-Guericke-Universität Magdeburg, 39106 Magdeburg, Germany
jens.schreiber@med.ovgu.de

## ABSTRACT

**Introduction** Pirfenidone was the first anti-fibrotic drug approved in Europe in 2011 for the treatment of mild-to-moderate idiopathic pulmonary fibrosis.

**Objectives** To investigate the clinical course of mild-to-moderate idiopathic pulmonary fibrosis in pirfenidone-treated patients in a real-world setting.

**Methods** The non-interventional study was conducted at 18 sites in Germany from 6/2014–12/2016. Adult patients with mild-to-moderate idiopathic pulmonary fibrosis were treated with pirfenidone (escalated from 3 × 1 to 3 × 3 capsules of 267 mg/day within 3 weeks) for 12 months. The observation period comprised 4 follow-up visits at months 3, 6, 9 and 12. Disease progression was defined as decrease of ≥ 10 % in vital capacity or ≥ 15 % in diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) and/or ≥ 50 m in 6-minute walking distance vs. baseline, or "lack of response/progression" as reason for therapy discontinuation.

**Results** A total of 51 patients (80.4 % male, mean age 70.6 years) were included in the full analysis set. Disease progression at any visit was reported for 23 (67.6 %) of 34 patients with available data. Over the course of the study, lung function parameters, physical resilience, impact of cough severity on quality of life, and the mean Gender, Age and Physiology Index (stage II) remained stable. In total, 29 patients

(56.9 %) experienced at least one adverse drug reaction (11 patients discontinued due to adverse drug reactions); serious adverse reactions were reported in 12 patients (23.5 %).

**Conclusions** The results of this study are in line with the established benefit-risk profile of pirfenidone. Therefore, pirfenidone can be considered a valuable treatment option to slow disease progression in mild-to-moderate idiopathic pulmonary fibrosis. NCT02622477

## ZUSAMMENFASSUNG

**Einleitung** Pirfenidon war das erste Antifibrotikum, das 2011 in Europa zur Behandlung leichter bis mittelschwerer idiopathischer Lungenfibrose zugelassen wurde.

**Ziel** Untersuchung des klinischen Verlaufs einer leichten bis mittelschweren idiopathischen Lungenfibrose bei Patient*innen, die unter Real-World-Bedingungen mit Pirfenidon behandelten wurden.

**Methoden** Die nicht-interventionelle Studie wurde im Zeitraum 6/2014–12/2016 an 18 Standorten in Deutschland durchgeführt. Erwachsene Patient*innen mit leichter bis mittelschwerer idiopathischer Lungenfibrose wurden über 12 Monate mit Pirfenidon (eskaliert von 3 × 1 auf 3 × 3 Kapseln à 267 mg/Tag innerhalb von 3 Wochen) behandelt. Der Beobachtungszeitraum umfasste 4 Nachuntersuchungen in den Monaten 3, 6, 9 und 12. Krankheitsprogression wurde definiert als Abnahme der Vitalkapazität um ≥ 10% oder der Diffusionskapazität der Lunge für Kohlenmonoxid ($DL_{CO}$) um ≥ 15 % und/oder um ≥ 50 m der 6-Minuten-Gehstrecke im Vergleich zum Ausgangswert oder „mangelndes Ansprechen/Progression" als Grund für den Therapieabbruch.

**Ergebnisse** 51 Patient*innen (80,4 % männlich, Durchschnittsalter 70,6 Jahre) wurden in das Full-Analysis-Set einbezogen. Für 23 (67,6 %) der 34 Patient*innen mit verfügbaren Daten wurde bei Follow-up-Visiten Krankheitsprogression gemeldet. Im Verlauf der Studie blieben die Lungenfunktionsparameter, die körperliche Belastbarkeit, der Einfluss der Hustenstärke auf die Lebensqualität und der mittlere Gender, Age and Physiology Index (Stadium II) stabil. Insgesamt kam es bei 29 Patient*innen (56,9%) zu mindestens einer unerwünschten Arzneimittelwirkung (11 Patient*innen brachen die Behandlung aufgrund unerwünschter Arzneimittelwirkungen ab); schwerwiegende unerwünschte Arzneimittelwirkungen wurden bei 12 Patient*innen (23,5 %) berichtet.

**Schlussfolgerung** Die Ergebnisse dieser Studie stimmen mit dem etablierten Nutzen-Risiko-Profil von Pirfenidon überein. Daher kann Pirfenidon als nützliche Behandlungsoption zur Verlangsamung des Krankheitsverlaufs bei leichter bis mittelschwerer idiopathischer Lungenfibrose angesehen werden.

## 1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease, characterized by scarring of the lung and worsening lung function [1]. As the most common form of idiopathic interstitial lung disease IPF primarily occurs in individuals aged 50 years and older [1]. If left untreated, IPF is associated with high morbidity and mortality with a mean life expectancy of 3 years after diagnosis [2]. Based on the definition of IPF unified in a consensus statement from 2000 [3], a review of epidemiological studies from around the world showed a huge variability in the prevalence and incidence of IPF due to different methodologies [4]. In Europe and North America the annual incidence ranges from 2.8 to 19 per 100,000 inhabitants [5] and the prevalence of 8.2 per 100,000 inhabitants marks IPF as an orphan disease [6]. Risk factors associated with development of IPF include genetic predisposition, environmental and occupational exposures, tobacco smoking, a family history of idiopathic lung disease, and comorbidities such as gastroesophageal reflux disease (GERD) and viral infections [7].

Diagnostic procedures have been updated several times since 2000, whereby high-resolution computed tomography (HRCT) remains crucial in the diagnostic work-up. IPF diagnosis is based on exclusion and is supported by the presence of a usual interstitial pneumonia (UIP) pattern in HRCT in patients without surgical lung biopsy or by certain pattern combinations in HRCT and biopsy. The multidisciplinary discussion of all findings represents the golden standard in the diagnostic process [7, 8].

At the time of diagnosis, the course of disease is unpredictable and may vary widely between individual IPF patients. Thus, the treatment course has to be tailored to each patient's individual requirements, taking the patient's medical history and comorbidities into consideration. Advances in understanding the pathology of IPF have shifted the focus of pharmacotherapy over the last two decades from anti-inflammatory approaches to anti-fibrotic treatment options [9]. Pirfenidone is an oral antifibrotic therapy that inhibits fibroblast proliferation and production of fibrosis-related proteins and cytokines [10]. Based on data from four randomized controlled trials demonstrating a clinically meaningful treatment effect and a favorable benefit-risk profile [11–13], pirfenidone was approved for the treatment of mild-to-moderate IPF in adults in the European Union in 2011. Following the additional randomized controlled trial ASCEND confirming the beneficial effect on disease progression [14], pirfenidone received marketing authorization in the United States in 2014. Treatment with pirfenidone for 1 year reduced the proportion of patients with a ≥ 10 % decline in percentage predicted forced vital capacity (FVC) or death by 44 % and improved progression-free survival by 38 % compared with placebo. A strong recommendation (based on systematic review of randomized controlled trials, post hoc analyses, and real-world evidence) was granted for pirfenidone in national guidelines [15] and a conditional recommendation (based on moderate confidence in estimates of effect) in international guidelines [16]. Long-term safety studies corroborated the safety profile of pirfenidone [17, 18]. In order to obtain additional prospective data on

the effectiveness of pirfenidone outside the tightly controlled conditions of a clinical trial, the non-interventional study AERplus was conducted to investigate the clinical course of mild-to-moderate IPF in pirfenidone-treated patients in a real-world setting.

## 2 Methods

### 2.1 Patients

Adult patients with a definite diagnosis of IPF and mild-to-moderate lung function impairment who were naïve to pirfenidone or had been treated with pirfenidone less than 30 days prior to enrolment, were eligible for inclusion. Exclusion criteria were: hypersensitivity against any ingredient of pirfenidone; concomitant use of fluvoxamine; severe hepatic impairment or end-stage liver failure; severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal failure requiring dialysis, or enrolment in interventional clinical trials. All patients were required to provide their written informed consent prior to enrolment.

### 2.2 Study design

AERplus was a prospective, open-label, single-arm, non-interventional multicenter post-marketing surveillance study, conducted at 18 sites (hospitals and outpatient centers) in Germany from June 2014 to December 2016 (NCT02622477). The study design and all relevant documents (e. g., protocol, informed consent, and questionnaires) were reviewed by the ethics committee of the Otto-von-Guericke-Universität Magdeburg (Ref. no. 161/13) and are consistent with the ethical standards included in the Declaration of Helsinki of 1964 and its later amendments. The planned duration of documentation for each patient was 12 months, consisting of an initial visit for enrolment, three follow-up visits at 3, 6, and 9 months, and an end-of-study visit at 12 months. Patients were treated with pirfenidone (week 1: 3 × 1 capsule of 267 mg per day; week 2: 3 × 2 capsules/day; from week 3: 3 × 3 capsules/day) up to 12 months. The decision to prescribe pirfenidone was made by the treating physician independently from the decision to enroll the patient and in accordance with the locally applicable Summary of Product Characteristics (SmPC).

### 2.3 Study assessments

Patient data were obtained during scheduled visits and entered into an electronic case report form (eCRF) by the investigator or study nurse. The composite endpoint disease progression was defined by the following four qualifying events: relative decrease of ≥ 10 % in vital capacity (VC) or ≥ 15 % in diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) and/or ≥ 50 m in 6-minute walking distance (6-MWD) vs. baseline assessment, or if the investigator stated “lack of response/progression” as reason for therapy discontinuation. Assessments of pulmonary function were performed at each visit and included FVC, Forced expiratory volume in 1 second ($FEV_1$), total lung capacity (TLC), VC, $DL_{CO}$, and Gender, Age and Physiology (GAP) Index [19]. Exercise capacity was assessed by 6-MWD. Exacerbations (assessed according to the discretion of the investigator) were recorded at each follow-up visit. Data on quality of life in chronic cough (Leicester Cough Questionnaire, LCQ [20]) and dyspnea severity (University of California San Diego Shortness of Breath Questionnaire, SOBQ [21]) were obtained by patient questionnaires (completed before each scheduled visit). Safety data collected throughout the study included the incidence of adverse drug reactions (ADR) and serious adverse reactions (SAR). ADRs were adverse events judged by the investigator as possibly or probably related to pirfenidone.

### 2.4 Statistical analyses

There were no predefined statistical hypotheses. A descriptive and exclusively explorative evaluation to obtain a statement on the clinical progression of mild-to-moderate IPF under therapy with pirfenidone was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). The analysis population consisted of all patients who were enrolled and received ≥ 1 dose of pirfenidone. For the effectiveness evaluation, changes in the following parameters were analyzed: disease progression, pulmonary function, exercise capacity, and LCQ and SOBQ scores. Due to the exploratory nature of the study, a formal sample size calculation was not performed. All patient data were anonymized.

## 3 Results

### 3.1 Baseline characteristics, patient disposition, and pirfenidone exposure

In total, 59 patients from 18 sites were enrolled in the study. Three patients did not have any documented data, two did not receive any pirfenidone, and three patients were excluded from the analysis set due to protocol violations (modified or unknown dosing on initial drug administration, n = 2; informed consent form missing, n = 1). Thus, the analysis population comprised 51 patients. Baseline demographics for the analysis population are summarized in ▶ **Table 1**. A heterogenous variety of comorbidities including emphysema was documented in 15 patients (29.4 %). After the initial 3-week dose adjustment phase all 51 patients received the full maintenance dose of 9 capsules pirfenidone/day. At each post-baseline visit, more than 50 % of the patients who were still in the study, reported to have taken the full maintenance dose. Dose adjustments were reported in 26 patients. One or more of the following reasons for dose adjustments were documented: ADRs (n = 15), patient wish (n = 4), other reason (not further specified, N = 8), and no information (N = 8). During the study, 5 patients (9.8 %) took IPF-related concomitant medication such as N-acetylcysteine (N = 2) and glucocorticoids (N = 3). The 12-month study period was completed by 17 patients (33.3 %), while 34 patients (66.7%) dropped out prematurely. The reasons for drop out are presented in ▶ **Table 2**.

### 3.2 Effectiveness

Data for the calculation of disease progression was available for 34 patients. Disease progression at any visit was reported for 23 (67.6 %) of these 34 patients. In detail, ≥ 10 % relative decrease of VC and ≥ 15 % relative decrease of $DL_{CO}$, respectively, were observed in 13 patients each (38.2 %), ≥ 50 m decrease of

▶ **Table 1** Patient demographics and baseline characteristics.

| Parameter | N = 51 |
|---|---|
| Gender, n (%) | |
| ▪ Male | 41 (80.4) |
| ▪ Female | 10 (19.6) |
| Age, mean ± SD (years) | 70.6 ± 8.8 |
| Time since IPF diagnosis, mean ± SD (weeks) | 44.2 ± 74.7 |
| Risk factors† | |
| ▪ Smoking status | |
| – Smokers | 2 (3.9) |
| – Former smokers | 23 (45.1) |
| – Non-smokers | 26 (51.0) |
| ▪ Exposure to asbestos | |
| – Yes | 5 (9.8) |
| – No | 29 (56.9) |
| – No information/unknown | 12 (23.5) |
| – Not assessed | 5 (9.8) |
| ▪ Exposure to stone dust | |
| – Yes | 5 (9.8) |
| – No | 27 (52.9) |
| – No information/unknown | 15 (29.4) |
| – Not assessed | 4 (7.8) |
| Methods used for initial IPF diagnosis‡, n (%) | |
| ▪ Total | 51 (100.0) |
| ▪ Imaging techniques | 41 (80.4) |
| ▪ Histopathology | 22 (43.1) |
| ▪ BAL | 24 (47.1) |
| ▪ Auscultation | 21 (41.2) |
| Additional examinations | |
| ▪ Imaging techniques | 10 (19.6) |
| IPF medication prior to study start‡, n (%) | |
| ▪ Patients with previous treatment | 13 (25.5) |
| – N-Acetylcysteine (NAC) | 4 (7.8) |
| – Azathioprine | 5 (9.8) |
| – Glucocorticoids | 6 (11.8) |
| – Cyclophosphamide | 1 (2.0) |
| – N-Acetylcysteine, pantoprazole, salbutamol | 1 (2.0) |
| – Ambrisetan (within the ARTEMIS trial) | 1 (2.0) |
| – Prednisolone | 1 (2.0) |
| Lung function, mean ± SD (% predicted) | |
| ▪ Forced vital capacity (%)§ | 70.2 ± 17.9 |
| ▪ Vital capacity (%)§ | 68.4 ± 16.5 |
| ▪ Forced expiratory volume in 1 second (%)§ | 78.6 ± 18.0 |
| ▪ Total lung capacity (%)§ | 71.3 ± 14.3 |
| ▪ Diffusing capacity of the lung for carbon monoxide (%)¶ | 45.2 ± 14.8 |
| 6-minute walking distance#, mean ± SD (m) | 378.0 ± 107.9 |
| GAP index§, mean ± SD | 4.5 ± 1.55 |

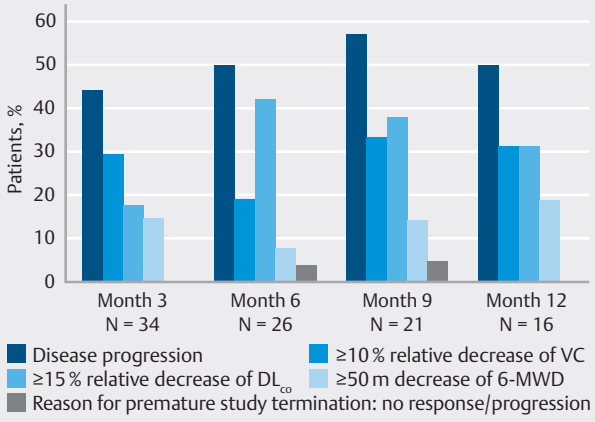
†No other risk factors were obtained than those listed here. ‡Multiple answers possible; §N = 43; ¶N = 36; #N = 30; BAL, bronchoalveolar lavage; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

6-MWD in 9 patients (26.5 %), and in 2 patients (5.9 %) the investigator stated "lack of response/progression" as the reason for therapy discontinuation. The proportion of patients with

▶ **Table 2** Reasons for drop-out (N = 34).

| Reason, N (%) | N = 34 |
|---|---|
| Lost to follow-up | 10 (29.4) |
| Adverse drug reaction | 8 (23.5) |
| Patient's wish | 8 (23.5) |
| "Lack of response/progression"† | 2 (5.9) |
| Death | 1 (2.9) |
| Other | 3 (8.8) |
| Death – not reason for therapy discontinuation‡ | 2 (5.9) |

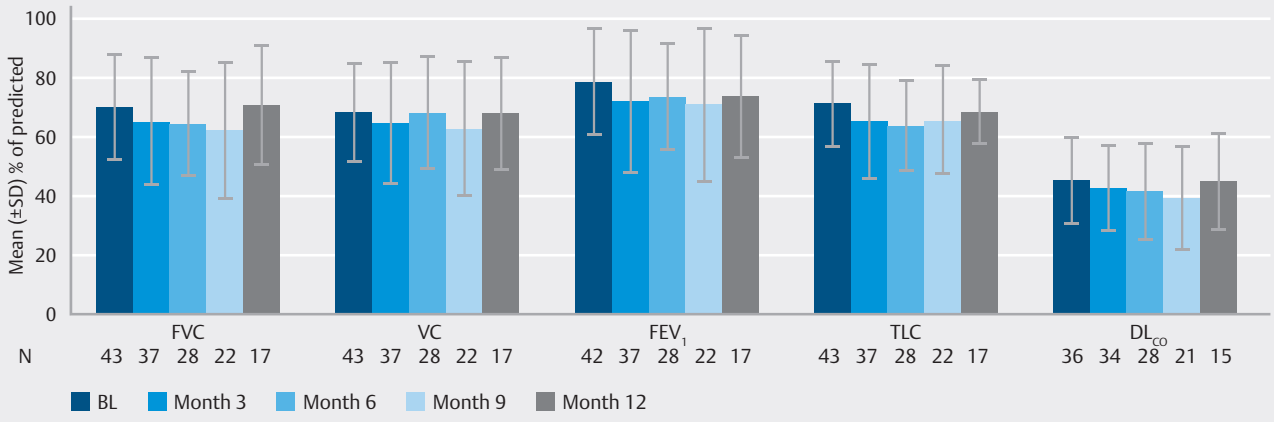
†The investigator stated "lack of response/progression" as reason for therapy discontinuation; ‡For these 2 patients, only the discontinuation was reported.



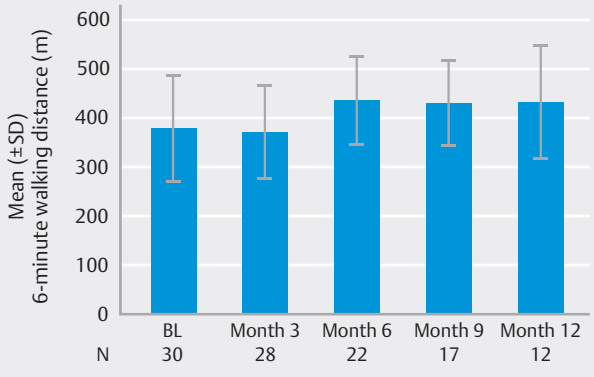

▶ **Fig. 1** Disease progression. Disease progression was defined as relative VC decrease of at least 10 % compared to baseline, or relative decrease of $DL_{CO}$ of at least 15 % compared to baseline, or decrease of the 6-minute walk distance (6-MWD) of at least 50 m compared to baseline, or if the investigator stated „lack of response/progression" as reason for therapy discontinuation. 6-MWD, 6-Minute walking distance; $DL_{CO}$, diffusing capacity of the lung for carbon monoxide; VC, vital capacity.

disease progression relative to baseline over the course of the study is shown in ▶ **Fig. 1**. The proportion of these patients was 44.1 % at month 3, 50.0 % at month 6, 57.1 % at month 9, and 50.0% at month 12.

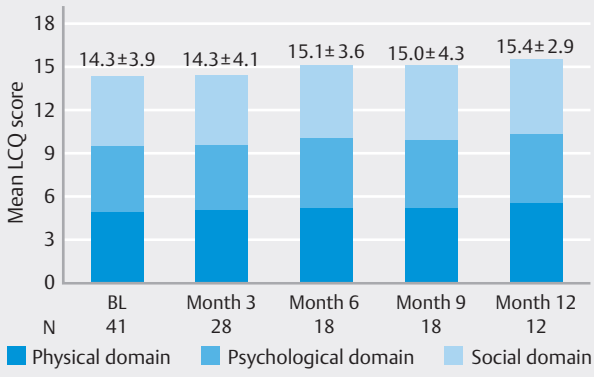
Overall, pulmonary function parameters remained stable over the course of the study (▶ **Fig. 2**). A mean GAP score of stage II was maintained over the course of the study (▶ **Table 3**). On treatment, 6-MWD values fluctuated between visits (mean changes relative to the previous visit: –15.3 ± 47.8 at month 3; 20.4 ± 20.4 ± 67.2 at month 6; –15.2 ± 34.2 at month 9; 8.2 ± 61.8 at month 12), but remained more or less steady from baseline (378.0 ± 107.9) to month 12 (432.9 ± 117.5) (▶ **Fig. 3**). Similarly, no substantial changes were observed in total LCQ scores (▶ **Fig. 4**) and mean total SOBQ scores (▶ **Table 3**).




▶ **Fig. 2** Pulmonary function. BL, baseline; $DL_{CO}$, diffusing capacity of the lung for carbon monoxide; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation; VC, vital capacity.




▶ **Fig. 3** 6-Minute Walking Distance. SD, standard deviation.




▶ **Fig. 4** Leicester Cough Questionnaire. Values denote total LCQ score ± standard deviation. The total score ranges from 3–21. Higher scores represent higher quality of life. LCQ, Leicester Cough Questionnaire.

▶ **Table 3** GAP and SOBQ score.

| | Baseline | Month 3 | Month 6 | Month 9 | Month 12 |
|---|---|---|---|---|---|
| GAP index | | | | | |
| N | 43 | 37 | 28 | 22 | 17 |
| GAP stage (mean GAP index score ± SD) | Stage II (4.5 ± 1.55) | Stage II (4.6 ± 1.48) | Stage II (4.8 ± 1.60) | Stage II (4.9 ± 1.75) | Stage II (4.6 ± 2.03) |
| Change vs. previous visit, Mean ± SD | – | 0.1 ± 0.74[†] | 0.2 ± 0.88 | 0.3 ± 0.72 | −0.1 ± 0.83 |
| SOBQ score | | | | | |
| N | 41 | 25 | 18 | 17 | 11 |
| Mean ± SD | 52.6 ± 29.3 | 55.8 ± 28.8 | 54.3 ± 28.3 | 58.0 ± 25.7 | 48.6 ± 29.5 |

[†]N = 34; The GAP index score was calculated based on the following variables: gender, age, FVC, and $DL_{CO}$. Higher GAP index scores correspond to a greater need for transplantation or treatment and a higher risk of mortality within the next 3 years. The total point score is used to classify patients as stage I (0–3 points), stage II (4–5 points), or stage III (6–8 points). Total SOBQ score values range between 0 and 120. Higher scores corresponded to more severe breathlessness. SOBQ, University of California San Diego Shortness of Breath Questionnaire.

Exacerbations as assessed at the discretion of the investigator were documented for 6 of 43 patients (14.0 %) with available observations during the course of study: for 3 patients at month 3, for 2 patients at month 6, and for 1 patient at month 9. All of these patients experienced one exacerbation each.

### 3.3 Safety

In total, 29 patients (56.9 %) experienced at least one ADR (▶ **Table 4**). The most common non-serious ADRs were nausea (9.8 %), decreased appetite (9.8 %), dizziness (9.8 %), and pruritus (7.8 %). Six patients discontinued pirfenidone due to non-serious ADRs. Twelve patients (23.5 %) experienced serious adverse reactions. SARs with a case frequency of ≥ 2 were pneumonia, pulmonary fibrosis, dyspnea, and syncope. SARs led to discontinuation of pirfenidone in 5 patients. In 4 patients, events of IPF exacerbation, pneumonia and subsequently renal failure, and dyspnea had fatal outcomes. No other fatal outcomes were reported in this study.

▶ **Table 4** Adverse drug reactions.

| Parameter | N = 51 |
|---|---|
| Any non-serious ADR | 29 (56.9) |
| Most common non-serious ADRs (incidence ≥ 5%)† | |
| ▪ Nausea | 5 (9.8) |
| ▪ Decreased appetite | 5 (9.8) |
| ▪ Dizziness | 5 (9.8) |
| ▪ Dyspnea | 3 (5.9) |
| ▪ Photosensitivity reaction | 3 (5.9) |
| ▪ Pruritus | 4 (7.8) |
| ▪ Rash | 3 (5.9) |
| Any serious adverse reaction† | 12 (23.5) |
| ▪ Pneumonia | 3 (5.9) |
| ▪ Dyspnea | 2 (3.9) |
| ▪ Pulmonary fibrosis‡ | 2 (3.9) |
| ▪ Syncope | 2 (3.9) |
| ▪ Acute cholecystitis | 1 (2.0) |
| ▪ Anemia | 1 (2.0) |
| ▪ Colon cancer | 1 (2.0) |
| ▪ Deep vein thrombosis | 1 (2.0) |
| ▪ Disease progression | 1 (2.0) |
| ▪ Dysphagia | 1 (2.0) |
| ▪ ECG ST segment depression | 1 (2.0) |
| ▪ Fall | 1 (2.0) |
| ▪ Hypoventilation | 1 (2.0) |
| ▪ Leukopenia | 1 (2.0) |
| ▪ Lumbal vertebral fraction | 1 (2.0) |
| ▪ Nausea | 1 (2.0) |
| ▪ Performance status decreased | 1 (2.0) |
| ▪ Pneumonia aspiration | 1 (2.0) |
| ▪ Renal failure | 1 (2.0) |
| ▪ Respiratory tract infection | 1 (2.0) |
| ▪ Sepsis | 1 (2.0) |
| ▪ Squamous cell carcinoma | 1 (2.0) |
| ▪ Tongue neoplasm | 1 (2.0) |
| SAR with fatal outcome§ | 4 (7.8) |

†Multiple answers possible. ‡Since idiopathic pulmonary fibrosis was a criterion for enrollment, this category of adverse events refers to worsening of disease. §The events of fatal IPF exacerbation, pneumonia, and dyspnea in 3 of these patients can be plausibly explained by the underlying condition of IPF, rather than being attributed to pirfenidone according to the discretion of the investigator. The fourth patient died due to community-acquired pneumonia requiring ventilation, ventilation insufficiency and kidney failure (assessed by the physician as unlikely related to pirfenidone). ADR, adverse drug reaction; SAR, serious adverse reaction.

## 4 Discussion

To the best of our knowledge this was the first prospective multicenter study to assess the effectiveness of pirfenidone on mild-to-moderate IPF in a real-world setting in Germany. Previous studies analyzed patient records from single centers retrospectively [22] or included patients who had participated in interventional clinical trials [23], which was an exclusion criterion in the present study. Our study results indicated a deceleration of decline in exercise capacity, lung parameters, shortness of breath, and cough severity-related quality of life. On the other hand, disease progression in 67.6% of patients with available data was also observed. Pirfenidone is not curative but able to slow disease progression, thus halting the deterioration of dyspnea and delaying the development of respiratory failure [24]. This is also reflected in the more or less stable GAP Index between 4–5 points, which pertains to Stage II of the three GAP stages with a 1-year mortality of 16.2% [19]. A decline in FVC of 10% or more over a 6-month period is associated with an increased risk of mortality [25, 26]. Therefore, the stable mean FVC values observed throughout our study might hint at deceleration of lung function decline. Yet, in light of the high drop-out rate, caution has to be observed with the interpretation of these results. Furthermore, it must be assumed that patients with more pronounced therapy responses were more likely to continue the study, while those with poor response tended to drop out.

The rate of disease progression was considerably lower in the German single-center studies (30 % [23] and 38 % [22]), which may be attributable to a less stringent definition, using only two qualifying events. The authors defined progression as a reduction of FVC ≥ 10 % predicted and/or $DL_{CO}$ ≥ 15 % predicted [22] or reduction of VC > 5 % predicted and/or $DL_{CO}$ > 10 % [23]. The present study applied a more stringent definition of the composite endpoint progression using four qualifying events (relative decrease of ≥ 10 % in VC or ≥ 15 % in $DL_{CO}$ and/or ≥ 50 m in 6-MWD vs. baseline assessment, or if the investigator stated "lack of response/progression" as reason for therapy discontinuation). The importance of taking measures other than FVC into account in the evaluation of disease progression in an individual patient has been emphasized in a consensus meeting [27]. Concomitant emphysema, a known confounder in interpreting measurements of FVC and $DL_{CO}$ [28], was reported in one patient only and should therefore not affect the overall results.

While the demographic and baseline characteristics, including gender distribution, age and most parameters of pulmonary function, of our study population were similar to the previous phase III clinical trials [12, 14], the German retrospective study [22], and the INSIGHTS IPF registry [29], fewer patients

were former smokers. The percentage of non-smokers comprised only one third in the previous studies and more than 50 % in the present study.

The incidence of adverse events was similar to that observed by Bonella and coworkers [23] and an Italian long-term safety study [30], and thus lower compared to the CAPACITY [12] and PASSPORT [18] studies as well as the German and Japanese retrospective studies [22, 31]. Compared to the pan-European 2-year PASSPORT study, a smaller proportion of patients discontinued treatment due to ADRs [18], which may be a consequence of the shorter follow-up period. The rate of treatment discontinuations due to adverse events was similar to the German retrospective study [22], but higher than the rate observed in clinical trials [12, 14] and other real-world studies [23, 31, 32], reinforcing the need for accompanying patient support programs. These could educate patients about potential symptoms they may expect, offer advice in preventing, mitigating and managing ADRs, and provide a helpline for questions and individual support. The decision to withdraw pirfenidone after occurrence of events such as skin reactions or gastrointestinal ADRs was consistent with the respective recommendations for risk minimization for these ADRs in the current pirfenidone SmPC [33]. Overall, the profile of adverse events reported as related to the study drug is within the range of what can be expected in this population of severely ill patients and is consistent with the current label [33].

This study is limited by its non-interventional single-arm design which allows the identification of associations, but excludes the conclusion of causal relationships. Yet, this study design has advantages in terms of patient heterogeneity and compliance assessment as it collects data in a real-world setting. Other limitations were the limited number of patients and missing values due to drop-outs. Our results should be interpreted with caution due to the declining numbers of patients over the course of the study. This is not uncommon in real-life and reflects the poor treatment persistence generally observed in IPF patients [34, 35]. The strength of this study is represented by objective measurements of pulmonary function and the use of validated scores to assess severity of dyspnea [21], quality of life in chronic cough [20], and staging of IPF [19]. Hence, the study provides a comprehensive view of the treatment effect with pirfenidone in Germany.

In conclusion, the results of this non-interventional study are in line with the established benefit-risk profile of pirfenidone. Therefore, pirfenidone can be considered a valuable treatment option to slow disease progression in patients with mild-to-moderate IPF.

## Acknowledgement

Writing assistance was provided by Dr. Petra Jöstingmeyer (medunit GmbH, Rheinbach, Germany). Roche Pharma AG provided funding for writing assistance in the development of this article.

## Funding Information

Roche Pharma AG
ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT02622477
Type of Study: Prospective, multi-center, non-interventional study

## Conflict of Interest

JS: grants, personal fees and research support from Roche, during the conduct of the study; WS: Research grants, investigator fees, honoraria, speakers fees from Lilly, Merck, AstraZeneca, Roche, Boehringer Ingelheim; WK: The author has no conflicts of interest to declare; BS: Speakers fees from Boehringer Ingelheim, Berlin Chemie, Roche, GSK; DK: consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, Grifols, Novartis, Roche/Intermune, Sanofi-Aventis and Teva; KN: Employee of Roche; CG: Boehringer Ingelheim, Novartis, Merck Sharp & Dome, Takeda, Boehringer Ingelheim, Roche. CG is editor-in-chief for the journal “Pneumologie”.

## References

[1] Raghu G, Remy-Jardin M, Richeldi L et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205: e18–e47 doi:10.1164/rccm.202202-0399ST

[2] Podolanczuk AJ, Thomson CC, Remy-Jardin M et al. Idiopathic pulmonary fibrosis: state of the art for 2023. Eur Respir J 2023; 61: doi:10.1183/13993003.00957-2022

[3] American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646–664 doi:10.1164/ajrccm.161.2.ats3-00

[4] Kaunisto J, Salomaa ER, Hodgson U et al. Idiopathic pulmonary fibrosis – a systematic review on methodology for the collection of epidemiological data. BMC Pulm Med 2013; 13: 53 doi:10.1186/1471-2466-13-53

[5] Olson AL, Gifford AH, Inase N et al. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. Eur Respir Rev 2018; 27: 180077 doi:10.1183/16000617.0077-2018

[6] Duchemann B, Annesi-Maesano I, Jacobe de Naurois C et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017; 50: 1602419 doi:10.1183/13993003.02419-2016

[7] Raghu G, Remy-Jardin M, Myers JL et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198: e44–e68 doi:10.1164/rccm.201807-1255ST

[8] Behr J, Günther A, Bonella F et al. S2K Guideline for Diagnosis of Idiopathic Pulmonary Fibrosis. Respiration 2021; 100: 238–271 doi:10.1159/000512315

[9] Behr J, Gunther A, Bonella F et al. German Guideline for Idiopathic Pulmonary Fibrosis - Update on Pharmacological Therapies 2017. Pneumologie 2018; 72: 155–168 doi:10.1055/s-0043-123035

[10] Kolb M, Bonella F, Wollin L. Therapeutic targets in idiopathic pulmonary fibrosis. Respir Med 2017; 131: 49–57 doi:10.1016/j.rmed.2017.07.062

[11] Azuma A, Nukiwa T, Tsuboi E et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am

J Respir Crit Care Med 2005; 171: 1040–1047 doi:10.1164/rccm.200404-571OC

[12] Noble PW, Albera C, Bradford WZ et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377: 1760–1769 doi:10.1016/s0140-6736(11)60405-4

[13] Taniguchi H, Ebina M, Kondoh Y et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821–829 doi:10.1183/09031936.00005209

[14] King TEJr, Bradford WZ, Castro-Bernardini S et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2083–2092 doi:10.1056/NEJMoa1402582

[15] Behr J, Bonella F, Frye BC et al. Pharmacological treatment of idiopathic pulmonary fibrosis (update) and progressive pulmonary fibrosis - S2k Guideline of the German Respiratory Society. Pneumologie 2023; 77: 94–119 doi:10.1055/a-1983-6796

[16] 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: e3–e19 doi:10.1164/rccm.201506-1063ST

[17] Costabel U, Albera C, Lancaster LH et al. An Open-Label Study of the Long-Term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (RECAP). Respiration 2017; 94: 408–415 doi:10.1159/000479976

[18] Cottin V, Koschel D, Gunther A et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. ERJ Open Res 2018; 4: 00084-2018 doi:10.1183/23120541.00084-2018

[19] Ley B, Ryerson CJ, Vittinghoff E et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012; 156: 684–691 doi:10.7326/0003-4819-156-10-201205150-00004

[20] Birring SS, Prudon B, Carr AJ et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003; 58: 339–343 doi:10.1136/thorax.58.4.339

[21] Eakin EG, Resnikoff PM, Prewitt LM et al. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. Chest 1998; 113: 619–624 doi:10.1378/chest.113.3.619

[22] Oltmanns U, Kahn N, Palmowski K et al. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration 2014; 88: 199–207 doi:10.1159/000363064

[23] Bonella F, Wessendorf TE, Costabel U. Clinical experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis. Dtsch Med Wochenschr 2013; 138: 518–523 doi:10.1055/s-0032-1332930

[24] 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: 58–64 doi:10.1183/09059180.00011514

[25] Paterniti MO, Bi Y, Rekić D et al. Acute Exacerbation and Decline in Forced Vital Capacity Are Associated with Increased Mortality in Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc 2017; 14: 1395–1402 doi:10.1513/AnnalsATS.201606-458OC

[26] Ley B, Bradford WZ, Vittinghoff E et al. Predictors of Mortality Poorly Predict Common Measures of Disease Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016; 194: 711–718 doi:10.1164/rccm.201508-1546OC

[27] Wuyts WA, Wijsenbeek M, Bondue B et al. Idiopathic Pulmonary Fibrosis: Best Practice in Monitoring and Managing a Relentless Fibrotic Disease. Respiration 2020; 99: 73–82 doi:10.1159/000504763

[28] Cottin V, Hansell DM, Sverzellati N et al. Effect of Emphysema Extent on Serial Lung Function in Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2017; 196: 1162–1171 doi:10.1164/rccm.201612-2492OC

[29] Behr J, Kreuter M, Hoeper MM et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J 2015; 46: 186–196 doi:10.1183/09031936.00217614

[30] Levra S, Guida G, Sprio AE et al. Long-Term Safety of Antifibrotic Drugs in IPF: A Real-World Experience. Biomedicines 2022; 10: 3229 doi:10.3390/biomedicines10123229

[31] Okuda R, Hagiwara E, Baba T et al. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. Respir Med 2013; 107: 1431–1437 doi:10.1016/j.rmed.2013.06.011

[32] Margaritopoulos GA, Trachalaki A, Wells AU et al. Pirfenidone improves survival in IPF: results from a real-life study. BMC Pulm Med 2018; 18: 177 doi:10.1186/s12890-018-0736-z

[33] EMA. Esbriet Summary of Product Characteristics. Accessed December 20, 2023: https://www.ema.europa.eu/en/documents/product-information/esbriet-epar-product-information_en.pdf

[34] 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: 72–78 doi:10.1016/j.rmed.2019.06.001

[35] Santoleri F, Auriemma L, Spacone A et al. Adherence, Persistence, and Effectiveness in Real Life. Multicenter Long-Term Study on the Use of Pirfenidone and Nintedanib in the Treatment of Idiopathic Pulmonary Fibrosis. J Pharm Pract 2022; 35: 853–858 doi:10.1177/08971900211008625