Pirfenidone in post-COVID-19 pulmonary fibrosis (FIBRO-COVID): a phase 2 randomised clinical trial

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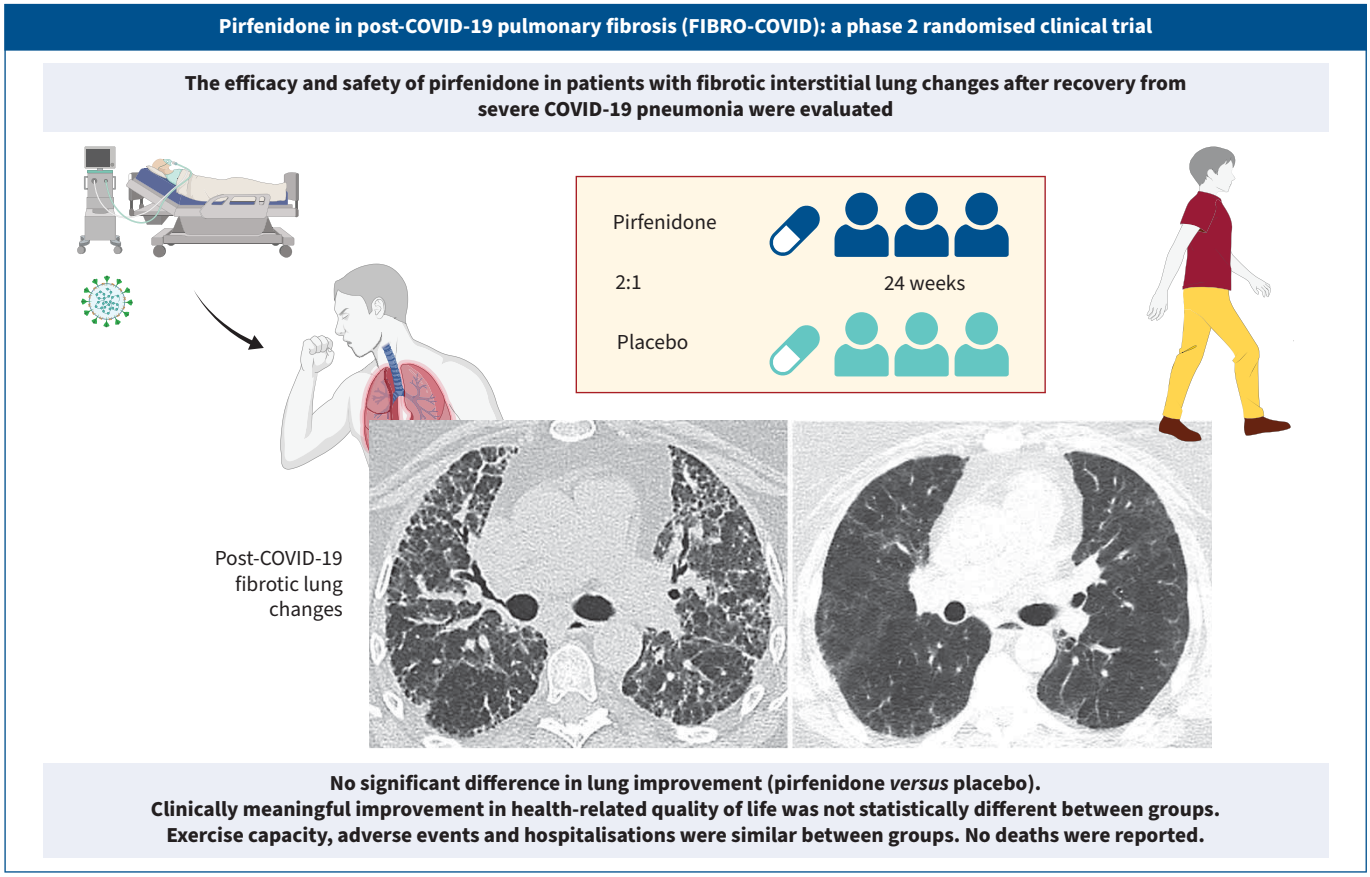

GRAPHICAL ABSTRACT Overview of the study.

https://doi.org/10.1183/13993003.02249-2024 Eur Respir J 2025; 65: 2402249

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Pirfenidone does not significantly reduce the proportion of patients with post-COVID-19 fibrotic changes after 6 months of treatment. FVC % improvement and % HRCT fibrotic reduction with pirfenidone were not statistically different from placebo. https://bit.ly/4alhGid

Cite this article as: Bermudo-Peloche G, Del Rio B, Vicens-Zygmunt V, *et al*. Pirfenidone in post-COVID-19 pulmonary fibrosis (FIBRO-COVID): a phase 2 randomised clinical trial. *Eur Respir J* 2025; 65: 2402249 [DOI: 10.1183/13993003.02249-2024].

Abstract

Background Patients with severe COVID-19 may develop lung fibrosis. Pirfenidone is an anti-fibrotic drug approved for idiopathic pulmonary fibrosis. The efficacy and safety of pirfenidone in patients with fibrotic interstitial lung changes after recovery from severe COVID-19 pneumonia were evaluated.

Methods This was a phase 2, double-blind, placebo-controlled, Spanish multicentre clinical trial. Patients were randomised to receive pirfenidone or placebo (2:1) for 24 weeks. The primary end-point was the proportion of patients that improved, considered when percentage change in forced vital capacity (FVC) was ⩾10% and/or any reduction in the fibrotic score on chest high-resolution computed tomography (HRCT). Secondary end-points included health-related quality of life (HRQoL), exercise capacity and drug safety profile.

This article has an editorial commentary: https://doi.org/10.1183/13993003.00331-2025

Received: 11 March 2024
Accepted: 9 Jan 2025

Results From 119 eligible patients, 113 were randomised and 103 were analysed (pirfenidone n=69 and placebo n=34). Most patients were male (73.5%) and were receiving low-dose prednisone; mean age was 63.7 years and mean body mass index was 29 $kg \cdot m^{-2}$. The percentage of patients that improved was similar in the pirfenidone and placebo groups (79.7% *versus* 82.3%, respectively). The mean predicted FVC increased by 12.74±20.6% with pirfenidone and 4.35±22.3% with placebo (p=0.071), and the HRCT (%) fibrotic score decreased by 5.44±3.69% with pirfenidone and 2.57±2.59% with placebo (p=0.52). Clinically meaningful improvement in HRQoL was not statistically different (55.2% in the pirfenidone group and 39.4% in the placebo group). Exercise capacity, adverse events and hospitalisations were similar between groups. No deaths were reported.

Conclusions The overall improvements in lung function and HRCT fibrotic score after 6 months with pirfenidone were not significantly different than with placebo.

Introduction

The severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) with acute respiratory distress syndrome (ARDS) in hospitalised patients is the main risk factor for mortality or developing post-acute interstitial persistent fibrotic changes [1–3]. Most patients with severe COVID-19 improve clinically and radiologically, but recovery is often slow, sometimes requiring supplemental oxygen upon returning home [4]. However, 25–35% of severe COVID-19 patients still show evidence of persistent structural and functional lung abnormalities 6–18 months after the acute phase of the disease [5–8]. A systematic review and meta-analysis of studies of hospitalised patients found that, after a median follow-up of 3 months, 50% of patients presented ground-glass persistent changes and 29% signs of fibrosis, with abnormal lung function in 38% of cases [9]. Similar to other forms of induced pulmonary fibrosis, once the scarring of the lung is established it may progress, especially in the aged population [10]. Therefore, early action to prevent the development and/or establishment of fibrosis as a result of severe COVID-19 ARDS could reduce the impact that the long-term fibrosis caused in the previous severe acute respiratory syndrome and Middle East respiratory syndrome epidemics [11].

Pulmonary fibrosis is a complex process of abnormal wound healing that involves many molecular pathways. In severe COVID-19 patients, the viral infection can induce a major inflammatory response and a cytokine release cascade whose components are also found in the pro-fibrotic response [12, 13]. For example, a decrease in the action of angiotensin-converting enzyme 2 leads to an increase in angiotensin II, which activates interleukin (IL)-6 and tumour necrosis factor (TNF)-α, and increases recruitment of neutrophils and macrophages, as well as direct endothelial cell injury [12]. Further, angiotensin II promotes collagen I gene activation through mitogen-activated protein kinases (MAPK/ERK) and transforming growth factor (TGF)-β1 release, both key factors in fibrosis development [14].

Pirfenidone is an anti-fibrotic pleiotropic drug approved for the treatment of patients with idiopathic pulmonary fibrosis (IPF) that acts on inflammatory and pro-fibrotic pathways, inhibiting TNF-α, TGF-β1, platelet-derived growth factor and collagen deposition [15, 16]. Pirfenidone has been shown to ameliorate early pulmonary fibrosis in lipopolysaccharide-induced ARDS by inhibiting endothelial-to-mesenchymal transition [17]. Furthermore, a preventive effect of bleomycin-induced lung fibrosis after lung damage has been demonstrated in the murine model [18–21]. Due to the inhibitory effects on inflammatory and fibrotic mediators induced by different triggers of lung damage, pirfenidone could be clinically beneficial for patients with severe COVID-19 ARDS and the consequent potential abnormal wound healing [13, 19, 20, 22–26]. Preliminary studies and case reports suggest some benefit of pirfenidone in COVID-19 infection [27–33] but, to date, no randomised clinical trial has assessed its potential preventive effect in reducing the lung fibrotic changes in patients after recovering from severe COVID-19. The present study formally evaluated the efficacy and safety of treatment with pirfenidone *versus* placebo over a period of 24 weeks in patients with fibrotic lung changes after recovery from the acute phase of severe COVID-19 pneumonia.

Materials and methods

Trial design

We conducted a multicentre, phase 2, randomised (2:1), double-blind, placebo-controlled clinical trial, with a two-arm parallel group design and 2:1 allocation, evaluating the effect of pirfenidone over 24 weeks in patients that survived from severe COVID-19 ARDS and presented persistent fibrotic interstitial lung changes after the acute phase. The study was conducted at 10 hospitals in Spain between July 2020 (first patient first visit) and January 2022 (last patient last visit). The study protocol was approved by the Ethics Committee of the University Hospital of Bellvitge (AC025/20). The study protocol was registered at ClinicalTrials.gov (NCT04607928) and EudraCT (2020-002518-42).

Study population

The study included adult patients (aged >18 years) with HRCT findings of lung interstitial fibrosis ⩾5% of lung volume after recovery from severe COVID-19 pneumonia that were evaluated at the outpatient clinic. The baseline chest HRCT was performed at least 1 month after the acute phase and <90 days after hospital discharge (30–90 days after recovery from severe pneumonia). Exclusion criteria included the use of high-dose systemic glucocorticosteroids (>15 mg·day^{-1} prednisone-equivalent at the time of screening); the presence of moderate-to-severe myopathy that could be associated with a decreased FVC; severe or life-limiting chronic illnesses prior to COVID-19 infection, including severe asthma, IPF, cancer, clinical dementia or uncontrolled ischaemic cardiomyopathy; active smoking habit; liver enzyme abnormalities; and receiving concomitant medications with significant interactions.

Study procedures

Patients followed a total of five visits (V): V0 (screening, −1 days to +42 days from signing the informed consent), V1 (randomisation), V2 (week 12), V3 (week 24 or end of treatment) and V4 (week 28 or follow-up). At V0, informed consent was first obtained, and then clinical variables, blood tests and baseline HRCT findings of interstitial changes were collected. At V1, all patients underwent pulmonary functional testing (PFT), including FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) measurement, and the 6-min walk test (6MWT). The King's Brief Interstitial Lung Disease (K-BILD) quality of life questionnaire was completed. After reviewing inclusion/exclusion criteria, randomisation was performed using an electronic centralised system (interactive voice response system) with hidden allocation.

Pirfenidone (Esbriet 267 mg capsules) and placebo were manufactured and provided by Roche Pharma AG, complying with Good Manufacturing Practice legal requirements. Placebo or pirfenidone was initiated at incremental doses, starting with 1602 mg·day^{-1} (divided into three doses every 8 h, 267 mg capsules with each meal) and, if there was no liver or associated serious events, was increased on day 7 to full doses of 2403 mg·day^{-1} or placebo (three capsules in each meal during the day). The dose increase could be extended for a further 1 week if the investigator considered it safe (slight elevation of liver enzymes, digestive discomfort or clear anorexia). Subsequently, three capsules in each meal during the day was maintained except if it was necessary to reduce the dose or suspend the drug due to adverse events. After 24 weeks of treatment (V3), chest HRCT, PFT and 6MWT were performed, clinical data were collected, and the K-BILD questionnaire was completed. The final V4 follow-up visit took place after 28 weeks (±7 days) of treatment.

The consumption of grapefruit juice, tobacco smoking and pharmacological therapies that interact with pirfenidone were prohibited during the study. Changes in medication and adverse events were collected and followed up.

Radiological evaluation

HRCTs were acquired with a multidetector CT scanner using a standardised protocol. Volumetric thin-section images were obtained and reconstructed using a high spatial resolution algorithm. HRCT images were obtained with the patient in the supine position and at sustained full inspiration and without contrast. A detailed description of the radiological analysis is included in the supplementary material.

The HRCT images were reviewed and scored at each visit (baseline and 24 weeks) by two chest radiologists, blinded to the clinical data, using a semiquantitative scoring scale that assesses the degree of ground-glass attenuation (ground-glass opacities (GGOs)), fibrotic-like changes (honeycombing, irregular reticulation, traction bronchiectasis, architectural distortion and reduction of lung volume) and emphysema. The lungs were evaluated in five different regions: aortic arch, carina, between the carina and the inferior pulmonary veins, inferior pulmonary veins, and 1 cm above the diaphragm [34]. The presence of bands and GGOs was identified but not considered for computation. The extent of fibrotic-like changes was visually quantified for each area and the overall percentage was calculated by averaging the fibrotic scores in the 10 areas. More details about this methodology are included in the supplementary material. A coefficient of agreement (κ) ⩾0.6 was considered acceptable and only patients with a fibrotic score >5% were randomised. The change in the percentage of fibrotic score was first assessed by side-by-side comparison of both radiological studies, followed by the calculation of the percentage change in the fibrotic scores that had been previously taken at the two time-points. Discrepancies were resolved by discussion, consensus and revision by central interstitial lung disease radiologists.

End-points and assessments

The primary end-point was the proportion of patients with post-COVID-19 fibrotic interstitial changes that improved, considering improvement an increase of absolute FVC ⩾10% and/or any reduction in the percentage of HRCT fibrotic changes after 24 weeks of treatment.

The secondary end-points included mean absolute percentage change of FVC and fibrotic HRCT score [35], the number of cases with absolute FVC percentage change ⩾10% and/or D_{LCO} percentage change ⩾15%, improvement in exercise capacity (increase in percentage oxygen saturation or metres walked >50 m), improvement of K-BILD score of at least 5 points (clinically significant), lung transplant or death, and the safety profile of pirfenidone. The frequency and severity of events, changes in medication, vital signs, and blood analytical values (mainly liver and kidney profile), as well as hospitalisations or emergency admissions for respiratory causes, were evaluated and described.

Statistical analysis

The clinical trial was designed with an experimental arm and a control arm, with two experimental subjects per control. Sample size calculation was based on the reported rate of subjects that recovered from lung fibrotic signs after surviving from severe infection during the SARS-CoV-1 pandemic (9–17%), with a type I error probability associated for the null hypothesis of 0.05 and considering a dropout rate of 5%. For a success rate in experimental subjects of 29%, 73 experimental subjects and 37 control subjects were required to reject the null hypothesis of an equal success rate for both experimental groups with a probability of 80%. Therefore, 110 subjects were included in the trial to achieve the main objective of the study. The analysis of the primary and secondary objectives was based on the modified intention-to-treat population (randomised population who completed the study without any major protocol violations). Clinical success was considered by examining the rate of improvement in FVC percentage (absolute) and the reduction of HRCT fibrotic score. Quantitative variables were described with measures of centralisation and dispersion (mean and standard deviation). Qualitative variables were described by absolute and relative frequencies.

Continuous variables were compared using the t-test or Mann–Whitney test, depending on whether the data distribution was normal or not. Categorical variables were compared using the Chi-squared test (or Fisher's exact test) depending on the application criteria. Cohen's κ was used to review the agreement between radiologists. Statistical significance was assumed at $p<0.05$. Data were analysed using R version 3.6.2 (www.r-project.org).

Results

Participants

Between 20 July 2020 and 30 July 2021, 119 eligible patients were screened (figure 1). From these, six subjects were excluded and 113 were randomised. Finally, 103 subjects completed the study and 10 patients prematurely discontinued due to drug toxicity (four patients in the pirfenidone group and three patients in the placebo group) or consent withdrawal (three patients in the pirfenidone arm) (figure 1). A total of 69 and 34 patients were evaluated in the pirfenidone and placebo groups, respectively. Most were male (73.5%), with a mean±SD age of 63.7±9.9 years and body mass index (BMI) of 29±4.1 $kg \cdot m^{-2}$. All patients had been hospitalised due to severe COVID-19 ARDS in the intensive care unit (ICU) and/or semi-ICU; none had been vaccinated for COVID-19 due to the lack of vaccines at that time, but all received systemic glucocorticosteroids and most of them received remdesivir (96 (93.2%)) or tocilizumab (52 (50.5%)). Respiratory support was required in most cases, including tracheal intubation and mechanical ventilation in 48.9%. Severity scores on ICU admission were only available in 45 patients. From them, mean±SD Acute Physiology and Chronic Health Evaluation II and Sequential Organ Assessment Failure scores were 13.4±4.7 and 6.1±2.1, respectively. The mean±SD time of hospitalisation for the acute phase was 49.6±36.2 days, with no differences between both groups (table 1). The time from hospital admission until the baseline HRCT scan ranged from 81.5 to 139.6 days. At inclusion, patients presented some type of limitation for daily activities, and the main symptoms were dyspnoea on exercise (97%), dry cough (26%) and fatigue (41%), with no differences between groups (table 1). Most patients (98%) were receiving a low dose of oral corticosteroids (prednisone or Dacortin) at baseline and the dose was similar in both groups (table 1). None received immunosuppressive drugs. Most patients presented a mild-to-moderate FVC decrease and moderate-to-severe decrease of D_{LCO}, with a mean±SD fibrotic score of 17.65±12.55%. Most fibrotic radiological signs were reticular septal thickening and traction bronchiectasis. The baseline characteristics of the patients in both arms are summarised in table 1.

Primary and secondary outcomes

After 24 weeks of treatment, the rate of patients with clinical improvement (increase of FVC ⩾10% absolute and/or any reduction in lung fibrotic HRCT score) was not statistically different between groups (79.7% of subjects in the pirfenidone group and 82.3% of subjects in the placebo group) (table 2). No differences in this primary end-point were found after adjusting by gender, age, use of oral glucocorticosteroids and smoking history. The mean±SD increase of absolute predicted FVC percentage was 12.74±20.6% with pirfenidone and 4.35±22.3% with placebo ($p=0.071$) (table 2 and figure 2). Most

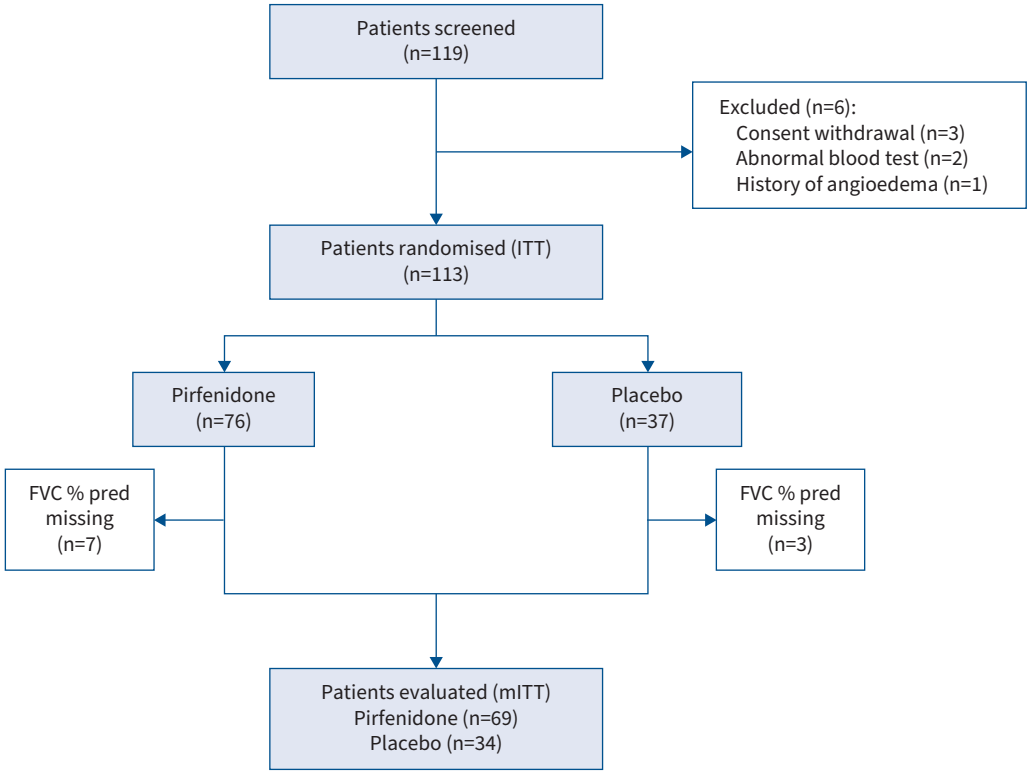

FIGURE 1 Patient flowchart. From 119 subjects initially screened, six subjects were excluded: withdrawal of consent (n=3), abnormal biochemical blood analysis (n=2) and history of angioedema (n=1). Finally, 113 subjects were randomised. Patients discontinued the study prematurely due to the following reasons: toxicity in four patients (3.5%) in the pirfenidone group and in three patients (2.7%) in the placebo group, and consent withdrawal in three patients (3.5%) in the pirfenidone group. FVC: forced vital capacity; ITT: intention-to-treat; mITT: modified intention-to-treat.

patients in both arms showed some reduction in the global interstitial findings (table 2). The mean±SD reduction in HRCT fibrotic score was −5.44±3.69% and −2.57±2.59% in the pirfenidone and placebo group, respectively (p=0.52). The type of fibrotic reduction was slightly different in the groups: patients receiving pirfenidone showed a similar decrease of fibrotic signs in the upper, middle and lower lobes, while subjects in the placebo arm showed non-significant higher improvement in the upper lobes. An increase of FVC ⩾10% (absolute) was observed in 27 (39.1%) patients in the pirfenidone group and nine (26.4%) patients in the placebo group (p=0.342).

Regarding the secondary outcomes, no statistical difference was observed in the number of cases that increased the predicted absolute FVC ⩾10% or D_{LCO} ⩾15% (p=0.831). A clinically meaningful improvement of HRQoL measured by K-BILD (score increase ⩾5 points) was observed in 32 (55.2%) patients in the pirfenidone group and 13 (39.4%) patients in the placebo group (p=0.191). The 6MWT did not show differences in metres walked or oxygen saturation between both arms (table 2). No patient died, or required lung transplantation or hospitalisation during the study. Nine patients visited the emergency department; six subjects were receiving pirfenidone (headache, perianal abscess, muscular pain and anaemia) and three subjects were from the placebo arm (respiratory infection, urine infection and ischaemic popliteal embolism) (p=0.71).

A total of 40 treatment-related adverse events (AEs) involving 25 patients were registered, mostly mild or moderate (table 3). The presence of AEs was not statistically different (25% pirfenidone *versus* 16% placebo; p=0.3421). Gastrointestinal and skin registered AEs were slightly higher in the pirfenidone group (table 3), but most of them improved after reducing the dose.

Discussion

We aimed to assess the effects of pirfenidone *versus* placebo in patients with persistent fibrotic changes on chest HRCT after surviving from severe COVID-19 pneumonia with ARDS. Most patients improved in

TABLE 1 Baseline patient characteristics

	Pirfenidone (n=69)	Placebo (n=34)
Male	46 (67)	29 (85)
Age (years)	65.0±9.4	63.4±9.9
BMI (kg·m^{-2})	28.9±4.2	29.3±4.4
Tobacco use		
Never smoked	37 (53)	13 (38)
Smoked previously	32 (47)	21 (62)
Prior disease	46 (66.7)	26 (76.4)
Respiratory disease	7 (15.2)	5 (14.7)
Cardiovascular disease	18 (39.1)	14 (41.1)
Gastric ulcer	1 (2.2)	0 (0)
Allergy	3 (6.5)	1 (3)
Autoimmune disease	4 (8.7)	3 (8.8)
Cancer	6 (13.0)	2 (6)
Bone fractures	1 (2.2)	1 (2.9)
Neurocognitive disease	1 (2.2)	0 (0)
Duration of hospitalisation (days)	52.8±42.1	46.4±32.6
Respiratory support during hospitalisation		
High flow (Optiflow)	27 (40)	10 (30)
Intubation	32 (47.8)	17 (50)
NIV	18 (26.9)	9 (26.4)
ECOG status		
0	0 (0)	1 (3)
1	60 (93.8)	30 (88.2)
2	4 (6.3)	2 (3.3)
3	0 (0)	1 (3.3)
Use of oral prednisolone	68 (98)	33 (97)
Dose of oral corticosteroids (mg)	6.8±5.1	6.4±4.8
HRCT total score (%)	32.1±14.8	24.81±17.6
HRCT fibrotic score (%)	20.4±15.4	14.9±9.7
PFT at randomisation		
FVC (mL)	2618±785	3021±854
FVC (% pred)	76.5±19.7	79.7±19.7
FEV_1 (mL)	2191±700	2448±616
FEV_1 (% pred)	80.4±21.6	83.1±18.2
D_{LCO} (mL)	13.7±7.20	14.3±7.79
D_{LCO} (% pred)	57.0±20.4	60.4±17.8

Data are presented as n (%) or mean±SD. BMI: body mass index; NIV: non-invasive mechanical ventilation; ECOG: Eastern Cooperative Oncology Group; HRCT: high-resolution computed tomography; PFT: pulmonary function testing; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

both arms after 24 weeks, with no significant differences. The degree of FVC percentage increase and reduction of HRCT fibrotic score was non-significantly higher in patients treated with pirfenidone. The safety profile of pirfenidone was consistent with previous clinical trials.

Together with nintedanib, pirfenidone is the most studied anti-fibrotic agent [36]. The mechanism of action is based on the inhibition of pro-fibrotic and pro-inflammatory signalling pathways [16, 19, 20]. Despite the potential, the use of pirfenidone in limiting the development of ARDS-induced fibrosis after COVID-19 was uncertain since its anti-fibrotic benefit slowing down FVC decline has been demonstrated once fibrosis is established and progressing [19, 20]. Therefore, our study tried to evaluate if pirfenidone would be useful to reduce the fibrotic establishment by enhancing wound healing after COVID-19 ARDS-induced lung damage. However, our study showed the rate of subjects that improved with pirfenidone was not different than in the placebo arm. The effect of pirfenidone in post-COVID-19 persistent interstitial lung changes has been previously evaluated in case reports and two clinical trials with no placebo arm [33]. The open-label study of Sansores *et al.* [32] evaluating 70 patients that presented post-acute lung sequelae of COVID-19 infection showed that pirfenidone was well tolerated and most cases improved after 12 weeks. Kerget *et al.* [33] randomised 30 patients with persistent respiratory symptoms after at least 3 months of COVID-19 infection to receive pirfenidone or nintedanib for 12 weeks,

TABLE 2 Evaluation of primary and secondary end-points

	Pirfenidone (n=69)	Placebo (n=34)	p-value
FVC			
FVC (% pred) V3	85.43±22.4	82.35±25.1	0.530
Change FVC (%) V3–V1	12.74±20.6	4.35±22.3	0.071
HRCT			
HRCT fibrotic score (%) V3	15.07±14.1	12.32±12.2	0.336
Change of fibrotic score (%) V3–baseline	−5.44±3.69	−2.57±2.59	0.522
Clinical success[#] (95% CI)	55 (79.7 (70.67–88.75))	28 (82.3 (70.7–94.64))	1.000
FVC change ⩾10%	27 (39.1)	9 (26.4)	0.342
Any reduction of fibrotic signs	42 (60.8)	22 (64.7)	0.829
HRCT ⩾+5 points	4 (5.8)	3 (8.8)	0.679
Total change of HRCT findings (%)	−13.5±5.2	−7.81±5.8	0.491
Change in FVC ⩾10% or D_{LCO} ⩾15%	29 (42)	13 (38.2)	0.831
Improvement of 6MWT[¶] (%)	39.2	43.3	0.447

Data are presented as mean±SD or n (%), unless otherwise stated. FVC: forced vital capacity; V: visit; HRCT: high-resolution computed tomography; K-BILD: King's Brief Interstitial Lung Disease quality of life questionnaire; 6MWT: 6-min walk test. [#]: improvement measured by FVC change and reduction in HRCT fibrotic score (modified intention-to-treat population). Clinical success defined as an improvement in FVC ⩾10% (between V1 and V3) and/or any reduction in the percentage of radiological fibrotic signs after 6 months of treatment (between baseline and V3). [¶]: defined as patients with an increase of >50 m in the 6MWT.

with no placebo arm. They concluded that the anti-fibrotic treatment was associated with an improvement of clinical and functional variables [33]. However, our placebo-control randomised trial demonstrates that most patients with persistent fibrotic lung changes after at least 1 month of hospital discharge also improve without anti-fibrotic treatment. Furthermore, KERGET *et al.* [33] showed that lower initial radiological score was associated with greater improvement after anti-fibrotic therapy. However, patients randomised to pirfenidone in our study had a higher baseline fibrotic HRCT score than the placebo arm and a greater reduction of fibrotic changes. Pirfenidone has also been evaluated in the acute phase of severe COVID-19 infection (ClinicalTrials.gov: NCT04282902), showing a strong effect on mitigating the cytokine storm, with a significant decrease of IL-2 receptor and TNF-α serum levels [37]. That study found no significant improvement in interstitial changes after 1 month of pirfenidone treatment [37]. In IPF and progressive pulmonary fibrosis, the anti-fibrotic treatment (pirfenidone or nintedanib) needs to last for at least 1–3 months to have a proven effect on lung function [38, 39]. Similarly, another recent randomised clinical trial in subjects admitted to the ICU due to severe COVID-19 infection found that pirfenidone, administered during the cytokine storm syndrome, tended to reduce the percentage of patients with fibrotic changes (from 35.8% to 29.8% of cases) but with higher liver toxicity [29]. Although pirfenidone could

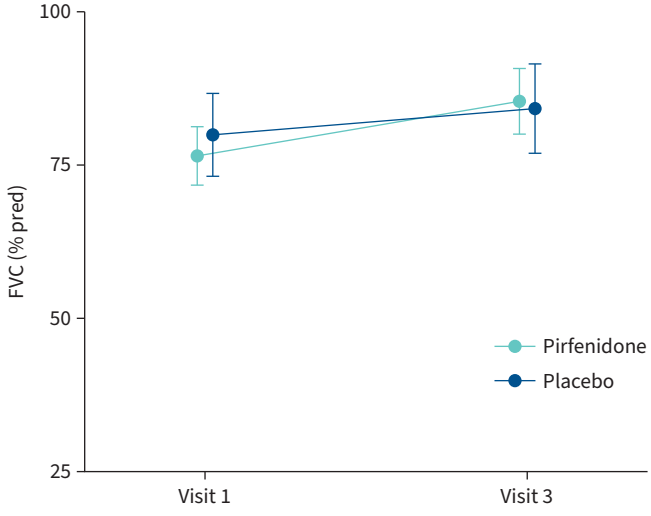

FIGURE 2 Mean difference in forced vital capacity (FVC) between visits 1 and 3. Error bars represent 95% confidence intervals.

TABLE 3 Treatment-related adverse events (AEs) in the study

	Pirfenidone (n=69)	Placebo (n=34)	p-value[#]
Patients reporting AEs			0.3421
Not treatment-related	57 (75)	31 (83.7)	
Treatment-related	19 (25)	6 (16.2)	
Treatment-related AEs per patient			0.8184
1	12 (63.2)	4 (66.7)	
2	3 (15.8)	0 (0)	
3	4 (21.1)	2 (33.3)	
Severity of AEs			0.1848
Mild	14 (73.7)	2 (33.3)	
Moderate	4 (21.1)	4 (66.7)	
Severe	1 (5.3)	0 (0)	
AEs[¶]			
Nausea and vomiting	6 (5.3)	3 (2.7)	
Skin lesions	6 (5.3)	1 (0.9)	
Gastro-oesophageal reflux	4 (3.5)	0 (0)	
Dyspepsia	3 (2.7)	0 (0)	
Asthenia	0 (0)	2 (1.8)	
Diarrhoea	2 (1.8)	0 (0)	
Epigastric pain	2 (1.8)	1 (0.9)	
Liver toxicity	2 (1.77)	0 (0)	
Dysphagia	1 (0.9)	0 (0)	
Abdominal distension and meteorism	1 (0.9)	0 (0)	
Pyrosis	1 (0.9)	0 (0)	
Constipation	0 (0)	1 (0)	
Headache	0 (0)	1 (0)	

Data are presented as n (%), unless otherwise stated. [#]: Fisher's exact test; [¶]: percentages calculated over the total number of patients.

act in the abnormal repair response after lung injury inhibiting the pro-fibrotic response, our study suggests that its addition to low-dose oral glucocorticosteroids did not show a significant benefit in recovering post-COVID-19 fibrotic lung damage.

Two other ongoing clinical trials have been established to evaluate the possible clinical benefit of pirfenidone in post-COVID-19 lung fibrosis, but with no results reported yet (ClinicalTrials.gov: NCT04856111 and NCT04652518). No safety concerns related to the use of pirfenidone in this type of frail patient after hospital discharge, usually receiving many other medications, have been reported. Our study shows that the number and grade of AEs observed in both groups did not significantly differ and pirfenidone-induced gastrointestinal events were reported less than in other clinical trials [15, 40, 41].

The present study has some limitations that should be considered. Only cases infected by the initial variants of SARS-CoV-2 and not previously vaccinated were included in the study. The potential limitation of evaluating this type of more severe case is at the same time a strength of the study since they were associated with more frequently persistent interstitial changes, which made it possible to analyse the effect of pirfenidone in the recovery of interstitial fibrotic changes induced by the combination of virus, ARDS and ventilator-induced lung damage. Another potential limitation was that the sample size was calculated for a primary end-point based on the results published from previous SARS-CoV-1 pandemics, and more severe SARS-CoV-2 patients than expected improved in the placebo arm, especially considering any type of fibrotic score reduction. Probably the early timeline for patient recruitment (30–90 days after the end of COVID-19 ARDS) could be part of the reason for a higher rate of lung improvement after 24 weeks. However, due to the main objective of the study (acting before lung fibrosis was established), patient recruitment had to occur after we identified relevant fibrotic signs during patient recovery.

In conclusion, the results show for the first time that the use of pirfenidone did not reduce the proportion of patients that showed post-COVID-19 fibrotic persistent changes after 6 months of treatment.

Acknowledgements: The authors thank Dynamics (currently Evidenze Group) and Francisco López de Saro (Trialance SCCL) for support with the writing of this manuscript. The authors thank the Barcelona Respiratory

Network (BRN) for engaging some of the participant sites to help in patient recruitment, and the Biobank of IDIBELL for processing and biobanking blood samples of these patients.

Data availability: Data will be available from the corresponding author upon reasonable request.

This clinical trial is prospectively registered at ClinicalTrials.gov with identifier number NCT04607928.

Ethics statement: The study protocol was approved by the Ethics Committee of the University Hospital of Bellvitge (AC025/20).

Conflicts of interest: M. Molina-Molina has received grants and fees for scientific advice from Boehringer Ingelheim, Roche, Ferrer and Veracyte, outside the submitted work. D. Castillo reports personal fees and non-financial support from Roche, grants, personal fees and non-financial support from Boehringer Ingelheim, grants from Fujirebio, and personal fees from Veracyte, outside the submitted work. J. Rigual Bobillo has received grants and fees for scientific advice from Boehringer Ingelheim, Roche, Daiichi Sankyo and AstraZeneca, outside the submitted work. The other authors have no conflicts of interest to declare.

Support statement: This study was supported by the Carlos III Health Institute (ISCIII), with grant PI21/01287, the CERCA programme and Roche through an investigator-initiated study programme, through which product supply was received. Roche did not participate in nor control the study design, development, data analysis or manuscript writing. The final document was reviewed by Roche before submission. Funding information for this article has been deposited with the Crossref Funder Registry.

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