Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should pirfenidone versus nintedanib be used as therapy for post-COVID-19 pulmonary fibrosis?

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RECOMMENDATION

There is insufficient evidence to recommend the use of pirfenidone or nintedanib among patients with post-COVID-19 pulmonary fibrosis *(Very low certainty of evidence)*

Consensus Issues
Evidence to support this recommendation is indirect as the studies included do not involve patients with post-COVID-19 pulmonary fibrosis. This is due to the paucity of available data on the use of pirfenidone and nintedanib in this population. There is no strong evidence to favor one anti-fibrotic agent over the other except for less side effects with nintedanib. Both drugs are costly, with annual expenses amounting to approximately Php 4.3M and Php 2.4M for pirfenidone and nintedanib, respectively. This may increase the inequity of treatment among those who cannot afford these drugs.

Key Findings

Limited evidence is available on the use of pirfenidone or nintedanib among patients with post-COVID-19 fibrosis, most of which are from published case reports. There are no clinical trials or observational studies among this group of patients which directly compare both anti-fibrotic agents, nor are there studies comparing each drug individually to placebo. Hence, indirect evidence from [what type of studies and what PICO? Just describe the indirect evidence] showed no difference in mortality rate, respiratory-related hospitalizations, acute exacerbation of pulmonary fibrosis and percent predicted forced vital capacity (FVC%) at 6 and 12 months of treatment; higher frequency of diarrhea and transaminitis with nintedanib; and a higher rate of discontinuation due to adverse events with pirfenidone.

Introduction

Post-COVID-19 fibrosis is currently a recognized sequela of COVID-19 disease associated with fibrotic-like changes in the lung tissue with both viral and immune-mediated mechanisms involved.[8,9] The anti-fibrotic agents, pirfenidone and nintedanib, are well-tolerated and approved for use in idiopathic pulmonary fibrosis (IPF) and other progressive fibrosing lung disease regardless of underlying pathology.[10,11] A network meta-analysis comparing pirfenidone and nintedanib to placebo revealed that both drugs effectively reduce lung function decline in the first year of treatment as demonstrated by the change from baseline FVC [pirfenidone vs placebo: mean difference 0.12 L (95% CI 0.03 - 0.21 L); nintedanib vs placebo:

mean difference 0.11 L (95% CI 0.00 - 0.22 L). [12] The same network meta-analysis showed that treatment with pirfenidone was associated with a lower risk for decline in FVC% predicted by ≥10% over 1 year (OR 0.58, 95% CI 0.4 - 0.88) and reduced all-cause mortality (HR 0.52, 95% CrI 0.28 -0.93) when compared with placebo.[12] No difference was seen between nintedanib and placebo in terms of these parameters. The role of these drugs in the treatment of post-COVID-19 pulmonary fibrosis is still unknown.

Review Methods

An electronic search for published studies (PubMed, Cochrane Library, Herdin) and ongoing trials (Clinicaltrials.gov Registry, International Clinical Trials Registry Platform) was conducted using the free text and MeSH terms of the following key words: “pirfenidone,” “nintedanib,” “post-COVID-19 pulmonary fibrosis,” “COVID-19” and “pulmonary fibrosis” until September 19, 2021. Due to paucity of published studies on the use of these interventional drugs in COVID-19 patients, observational and controlled trials among non-COVID-19 patients with pulmonary fibrosis were included. Case reports, case series, reviews and letters were excluded.

Results

Summary of Characteristics of included studies

There were no randomized controlled trials nor observational studies found comparing pirfenidone to nintedanib, nor either drug with placebo, among patients with post-COVID-19 pulmonary fibrosis. However, indirect evidence from seven observational studies were found, screened, and included in the analysis.[1-7] One out of the seven studies had a prospective cohort design [4], while the rest were retrospective cohort studies. Five studies included patients with idiopathic pulmonary fibrosis (IPF) [1-4,6], while one study included those with IPF and pulmonary fibrosis from other etiologies such as nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis and connective tissue disease-associated interstitial lung disease.[5] The total number of participants across all studies was 2226 with an age range of 32-97 years old. Follow-up varied from 9-24 months. All studies did a head-to-head comparison between pirfenidone and nintedanib, with one study including in their analysis a control group that received neither drug.

Overall summary of methodological quality

Only two [3,4] out of the seven included studies adjusted their analysis for possible confounding bias inherent in observational studies. Additionally, these studies only indirectly address the research question because of the absence of COVID-19 infection among the participants. Hence, overall quality of evidence is very low.

Summary of results of included studies

Mortality Rate

Three studies reported mortality rate with follow-up range of 9 to 24 months.[2-4] A pooled analysis of mortality rate showed a trend favoring pirfenidone but results were not significant (RR 0.86, 95% CI 0.73-1.02; I^2 = 14%).

Rate of respiratory-related hospitalizations

Only the study by Belhassen et al. [3] reported respiratory-related hospitalizations as an outcome. It included 804 patients on pirfenidone and 509 on nintedanib with a follow-up of 3 years.

Unadjusted incidence rate was 27 per 100 person-years and 30.7 per 100 person-years for those on pirfenidone and nintedanib, respectively. The cumulative incidence of the event at one year was 22.85% vs 27.46%, and at 3 years was 48.26% vs 43.62% for pirfenidone and nintedanib, respectively. The adjusted HR was 1.3 (95% CI 1.0-1.7).

Acute exacerbations

Two studies reported the incidence of acute exacerbations of pulmonary fibrosis [5,6] with a follow-up of 10 months to 3 years. The study by Galli et al. included patients with IPF and pulmonary fibrosis of other etiologies. Their results showed that 16.3% and 10.5% of subjects experienced an acute exacerbation among those on pirfenidone and nintedanib, respectively (p=0.37). Mean time to first exacerbation was 294 days with pirfenidone and 247 days with nintedanib (p=0.72).[5] The study by Isshiki et al. included solely those with IPF. This study reported the cumulative incidence rate of acute exacerbations at 1-, 2- and 3-years in pirfenidone and nintedanib groups to be 5.1% vs 18.6%, 20.4% vs 25.3% and 22.6% vs 29.6%, respectively. The data on 1-year cumulative incidence rate was used in the pooled analysis of this review. The cumulative incidence rate of acute exacerbations was significantly lower in those on pirfenidone than nintedanib (p=0.035). A sub-group analysis on patients who started either drug as first-line therapy showed similar accumulated acute exacerbation of idiopathic pulmonary fibrosis incidence rates (p=0.136).[6] Pooled analysis showed no difference in the incidence of acute exacerbations of pulmonary fibrosis between both groups (RR 0.71, 95% CI 0.41-1.26; p=0.24) although there was note of significant heterogeneity (I^2=86%) probably due to the difference in populations.

Adverse events

Adverse events were reported by four studies.[2-5] Pooled analysis showed the following: there was no significant difference in risk for anorexia (RR 1.45, 95% CI 0.62-3.41; p=0.39), nausea or vomiting (RR 0.91, 95% CI 0.58-1.43; p=0.67), and rash (RR 2.87, 95% CI 0.97-8.56; p=0.06) between the two groups; whereas there was a significantly higher risk for diarrhea (RR 0.13, 95% CI 0.07-0.24; p<0.00001) and transaminitis (RR 0.25, 95% CI 0.08-0.79; p=0.02) among those taking nintedanib compared to pirfenidone. Discontinuation of the drug due to adverse events [2,3,5] was higher in the pirfenidone group (RR 1.18, 95% CI 1.05-1.31; p=0.004). Significant heterogeneity was observed in the data on diarrhea (I^2=65%) and discontinuation due to adverse events (I^2=70%) likely due to the differences in populations and study designs.

Ongoing Studies

There were 10 ongoing studies identified: 2 studies directly comparing pirfenidone vs nintedanib among COVID-19 patients [13-14]; 3 studies on nintedanib versus placebo among COVID-19 patients [15-17]; 4 studies on pirfenidone versus placebo among COVID-19 patients [18-21]; and 1 randomized controlled trial comparing pirfenidone vs nintedanib among patients with pulmonary fibrosis not associated with COVID-19.[22] Primary outcomes are change in FVC [13,15-20, 22], and the change in HRCT and arterial blood gas.[14,18,20,21]

Evidence to Decision

Cost	Mean duration of treatment in the abovementioned included studies is 12 months. Pirfenidone 267mg tablet costs Php 1323 per tablet and is given as three tablets three times a day (9 tablets/day) as maintenance dose [23]: Php 1323/tablet x 9 tablets/day x 30 days/month x 12 months = Php 4,286,520 Nintedanib 150mg tablet costs Php 3279 per tablet given as one tablet twice a day (2 tablets/day) [24]: Php 3279/tablet x 2 tablets/day x 30 days/month x 12 months = Php 2,360,880 A cost-effectiveness analysis study by Rinciog et al. [25] compared the two drugs (Pirfenidone 267mg three times a day vs Nintedanib 150mg twice a day) in the treatment of IPF in Belgium. There were similar survival and progression outcomes in both groups, as well as the total QALY (Pirfenidone 3.318 vs Nintedanib 3.353). Over a patient's lifetime, treatment with nintedanib accumulated lower overall costs than pirfenidone (€102,315 vs €113,313). This includes cost of the drug (Pirfenidone €88.32/day vs Nintedanib €79.21/day), patient monitoring of liver panel tests (€48.39 every 3 months), oxygen use (€775.82 every 3 months), cost related to acute exacerbations (€6,649.50) and adverse events, and palliative care costs (€3,783.61 for the last 30 days of life).
Availability	Both drugs are available at a private tertiary hospital in Metro Manila
Patient's Values or Preferences; Social Impact	No evidence
Factors to Impact Acceptability or Compliance	Higher rate of discontinuation of pirfenidone than nintedanib due to adverse events among patients with pulmonary fibrosis not related to COVID-19 (pooled RR 1.18, 95% CI 1.05-1.31; p=0.004) [2,3,5]

Recommendations from Other Groups

In the Swiss Recommendation for Long COVID, the committee settled on awaiting evidence from the ongoing RCTs that evaluate the efficacy and safety of pirfenidone and nintedanib among patients with post-COVID-19 fibrosis. However, they agreed that anti-fibrotic drugs may be given if an underlying progressive interstitial lung disease such as idiopathic pulmonary fibrosis is incidentally identified.

Research Gaps

There is still a paucity of data on the use of these anti-fibrotic agents in the setting of post-COVID-19 pulmonary fibrosis although many trials are underway.

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Appendix 1. Evidence to Decision

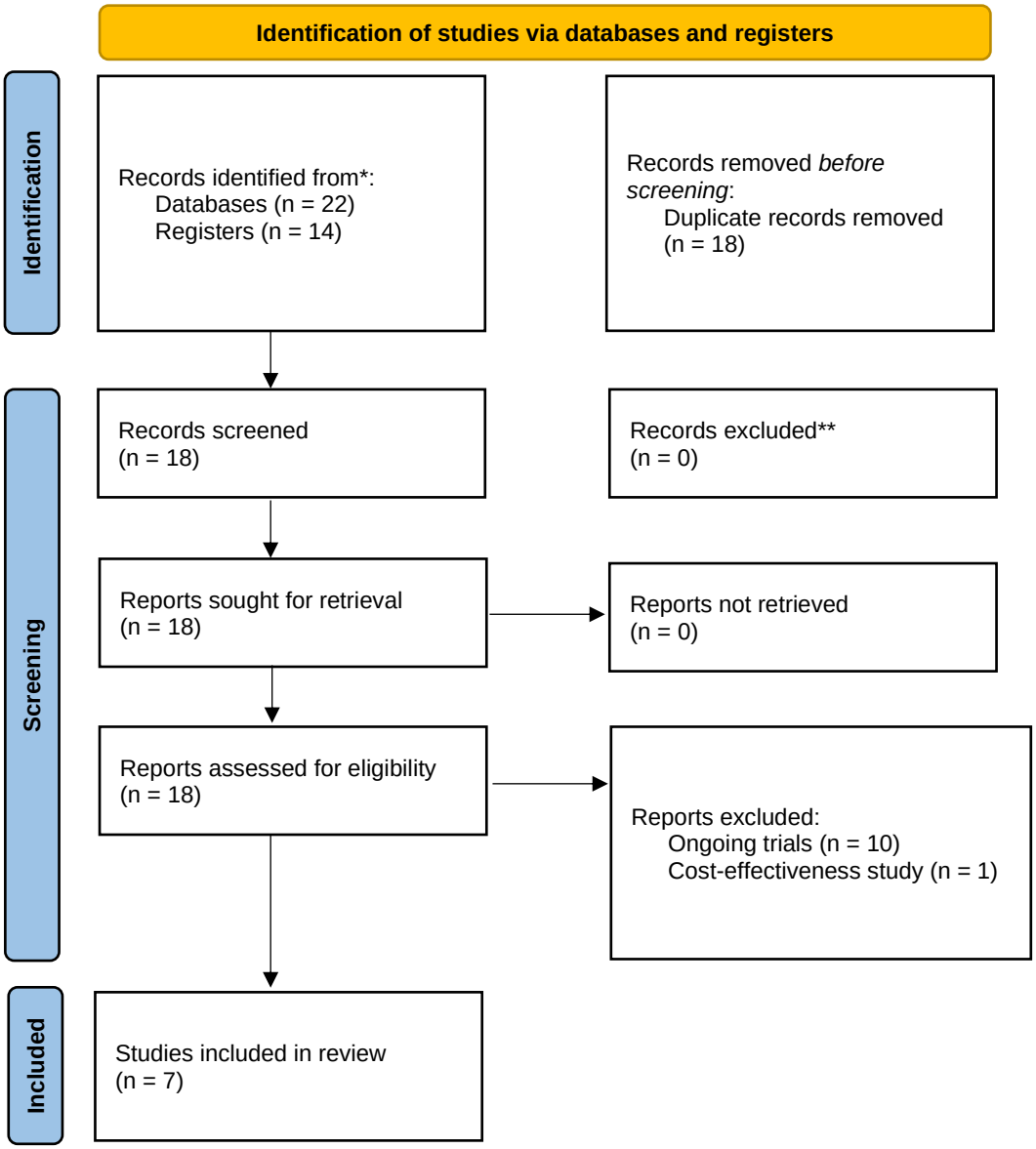
Table 1. Summary of initial judgements prior to the panel discussion: pirfenidone vs nintedanib (N = 9)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)				• There is paucity of evidence on the incidence and prognosis of post-COVID-19 pulmonary fibrosis. However, given the high prevalence of COVID-19 infection, this complication will likely have major health effects at the population level
Benefits	Large	Moderate	Small (3)	Uncertain (6)		No difference between the two drugs in terms of: • mortality rates (RR 0.86 [0.73, 1.02] p=0.08) • rate of respiratory-related hospitalizations (RR 1.11 [0.98, 1.25] p=0.10) • acute exacerbations (RR 0.71 [0.41, 1.26] p=0.24) • FVC% predicted at 6 (mean difference 3.19 [-3.38, 9.76] p=0.34) • 12 months of treatment (mean difference1.00 [-10.54, 12.54] p=0.87
Harm	Large (2)	Small (5)	Uncertain (2)	No response		• Slight increase in frequency of: (among those taking Nintedanib) • diarrhea (RR 0.13 [0.07, 0.24 p<0.00001])

							• transaminitis (RR 0.25 [0.08, 0.79] p=0.02) • Higher rate of discontinuation due to adverse events (RR 1.18 [1.05, 1.31] p=0.004) with pirfenidone. • No difference in rates of anorexia (RR 1.45 [0.62, 3.41 p=0.39]), nausea/vomiting (RR 0.91 [0.58, 1.43] p=0.67) and rashes (RR 2.87 [0.97, 8.56] p=0.06)
Certainty of Evidence	High (1)	Moderate	Low (4)	Very low (4)			• Observational and involved non-COVID patients with pulmonary fibrosis
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability (2)			
Resources Required	Uncertain (3)	Large cost (5)	Moderate Cost (1)	Negligible cost	Moderate savings	Large savings	• Pirfenidone 267mg tab: Php 1323/tab - Php 4,286,520 (12 mo) • Nintedanib 150mg tab: Php 3279/tab - Php 2,360,880 (12mo) • Similar survival and progression outcomes in both groups, total QALY (Pirfenidone 3.318 vs Nintedanib 3.353). • Over a patient's lifetime, treatment with nintedanib accumulated lower overall costs
Certainty of evidence of required resources	No included studies (6)	Very low	Low (2)	Moderate (1)	High		
Cost effectiveness	No included studies	Favors the comparison (5)	Does not favor either the intervention or the	Favors the intervention			

			comparison (4)			than pirfenidone (€102,315 vs €113,313).
Equity	Uncertain (5)	Reduced (2)	Probably no impact	Increased (2)		
Acceptability	Uncertain (7)	No (1)	Yes (1)			
Feasibility	Uncertain (4)	No (3)	Yes (2)			

Appendix 2. Search Yield and Results



PRISMA 2020 Flow Diagram

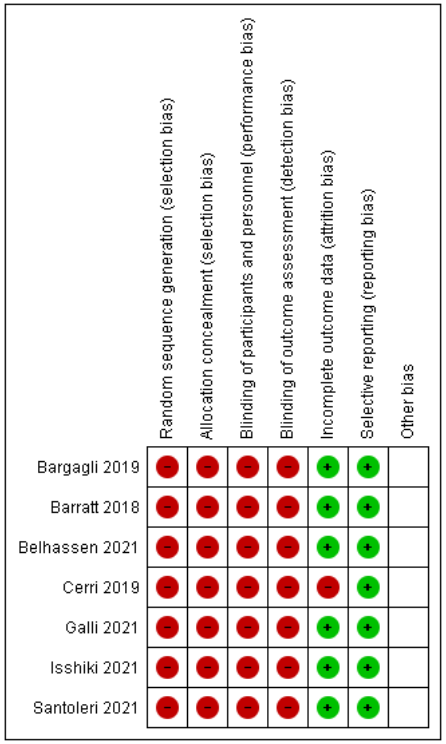
Appendix 3. Table of Included Studies (7)

Study ID	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Bargagli 2019	Retrospective cohort	Italy	82	Patients with IPF	Pirfenidone	Nintedanib	● FVC, FEV1, TLC, DLCO Percentages of predicted at time 0, after 6 months and 12 months
Barratt 2018	Retrospective cohort	England	164	Patients with IPF	Pirfenidone	Nintedanib	Treatment emergent adverse events: ● Adverse drug events ● Discontinuation of therapy due to disease progression (decline in percent predicted FVC of 10% or more within any 12-month period) ● Death
Belhassen 2021	Retrospective cohort	France	1313	Patients with IPF	Pirfenidone	Nintedanib	● All-cause mortality

							● Acute respiratory-related hospitalization ● Treatment discontinuation at 12 months
Cerri 2019	Prospective cohort	Italy	142	Patients with IPF	Pirfenidone or Nintedanib	No treatment	Primary outcomes: ● Changes in lung function parameters (FVC and DLCO) in 24 months ● Side effects Secondary outcomes: ● Rate of disease progression [Reduction in FVC ≥10% of predicted and/or diffusion capacity (DLCO) ≥15% of predicted] ● Mortality rate at 6, 12, 18 and 24 months
Galli 2021	Retrospective cohort	Philadelphia, USA	186	Patients with IPF and PF from other causes	Pirfenidone	Nintedanib	Primary outcome: ● Drug discontinuation as a result of an

							adverse drug event Secondary outcomes: ● Time to drug discontinuation ● Adverse events ● Clinical outcome ● Adverse event ● Severe bleeding events ● MI ● Acute exacerbation of pulmonary fibrosis
Isshiki 2021	Retrospective cohort	Japan	195	Patients with IPF	Pirfenidone	Nintedanib	● Acute exacerbation of idiopathic pulmonary fibrosis
Santoleri 2021	Retrospective cohort	Italy	144	Patients who picked up pirfenidone and nintedanib from hospital pharmacy at least twice	Pirfenidone	Nintedanib	● Adherence and persistence of treatment at 1 and 2 years ● FVC and DLCO at 6 and 12 months ● Gender-Age-Physiology (GAP) Index

Appendix 4. Study Appraisal



Risk of Bias Summary: review authors' judgements about each risk of bias item for each included study.

Appendix 5. GRADE Evidence Profile

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	P	N	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	observational studies	serious [a]	not serious	serious [b]	serious [d]	none	255/997 (25.6%)	174/586 (29.7%)	**RR 0.86** (0.73 to 1.02)	**42 fewer per 1,000** (from 80 fewer to 6 more)	⨁◯◯◯ VERY LOW	
Respiratory-related hospitalizations												
1	observational studies	not serious	not serious	serious [b]	serious [d]	none	388/804 (48.3%)	222/509 (43.6%)	**RR 1.21** (0.96 to 1.51)	**47 more per 1,000** (from 10 fewer to 103 more)	⨁◯◯◯ VERY LOW	
Acute exacerbation												
2	observational studies	serious [a]	serious [c]	serious [b]	serious [d]	none	28/260 (10.8%)	18/121 (14.9%)	**RR 0.71** (0.41 to 1.26)	**43 fewer per 1,000** (from 88 fewer to 39 more)	⨁◯◯◯ VERY LOW	
FVC % Predicted at 6 months of treatment												
2	observational studies	serious [a]	not serious	serious [b]	serious [e]	none	94	57	-	MD **3.19 higher** (3.38 lower to 9.76 higher)	⨁◯◯◯ VERY LOW	
FVC % Predicted at 12 months of treatment												
1	observational studies	serious [a]	not serious	serious [b]	serious [e]	none	42	27	-	MD **1 higher** (10.54 lower	⨁◯◯◯ VERY LOW	

										to 12.54 higher)		

Discontinuation due to Adverse event

3	observational studies	serious [a]	serious [c]	serious [b]	serious [d]	none	505/1048 (48.2%)	260/615 (42.3%)	**RR 1.18** (1.05 to 1.31)	**76 more per 1,000** (from 21 more to 131 more)	⨁◯◯◯ VERY LOW	

Anorexia

3	observational studies	serious [a]	not serious	serious [b]	serious [d]	none	22/322 (6.8%)	6/134 (4.5%)	**RR 1.45** (0.62 to 3.41)	**20 more per 1,000** (from 17 fewer to 108 more)	⨁◯◯◯ VERY LOW	

Nausea/Vomiting

3	observational studies	serious [a]	not serious	serious [b]	serious [d]	none	44/322 (13.7%)	21/134 (15.7%)	**RR 0.91** (0.58 to 1.43)	**14 fewer per 1,000** (from 66 fewer to 67 more)	⨁◯◯◯ VERY LOW	

Diarrhea

3	observational studies	serious [a]	serious [c]	serious [b]	not serious	none	12/322 (3.7%)	40/134 (29.9%)	**RR 0.13** (0.07 to 0.24)	**260 fewer per 1,000** (from 278 fewer to 227 fewer)	⨁◯◯◯ VERY LOW	

Transaminitis

3	observational studies	serious [a]	not serious	serious [b]	not serious	none	4/322 (1.2%)	7/134 (5.2%)	**RR 0.25** (0.08 to 0.79)	**39 fewer per 1,000** (from 48 fewer to 11 fewer)	⨁◯◯◯ VERY LOW	

Rash

2	observational studies	serious [a]	not serious	serious [b]	serious [d]	none	23/207 (11.1%)	3/85 (3.5%)	**RR 2.87** (0.97 to 8.56)	**66 more per 1,000** (from 1 fewer to 267 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. observational studies, did not adjust for confounding
b. patients included have pulmonary fibrosis not due to COVID-19
c. unexplained inconsistency and heterogeneity, with point estimates widely different (I^2 > 70%)
d. CI crosses null value (RR = 1)
e. Range from negative/lower to positive/higher

Appendix 6. Forest Plots

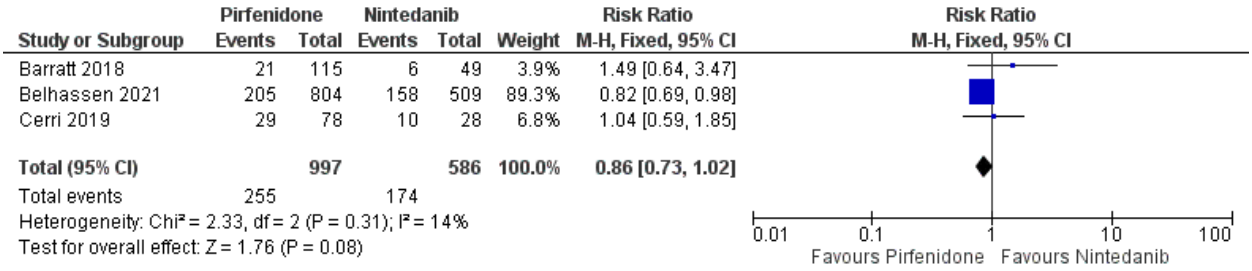


Figure 1. Mortality rate

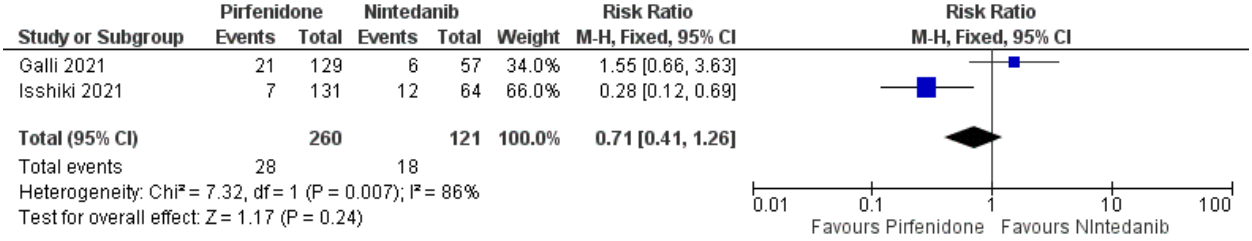


Figure 2. Acute exacerbations of pulmonary fibrosis

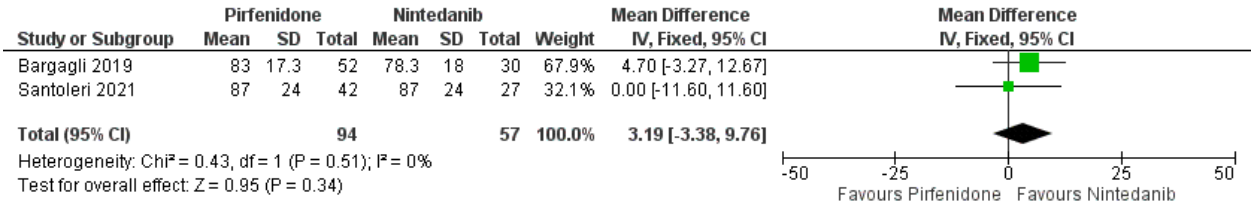


Figure 3. FVC% predicted at 6 months of treatment

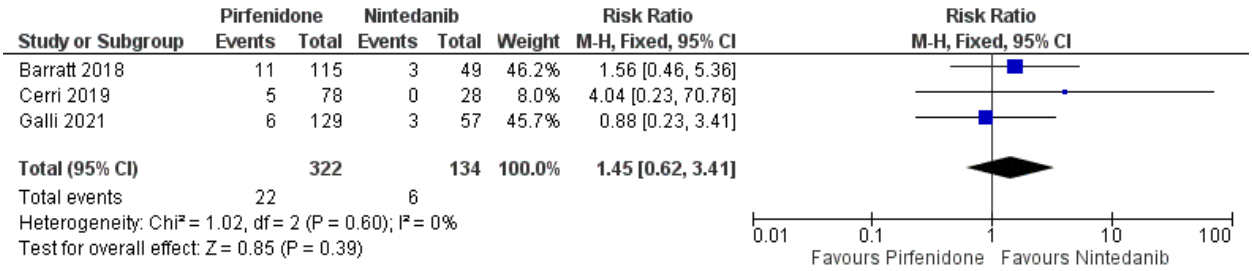


Figure 4. Adverse event: Anorexia

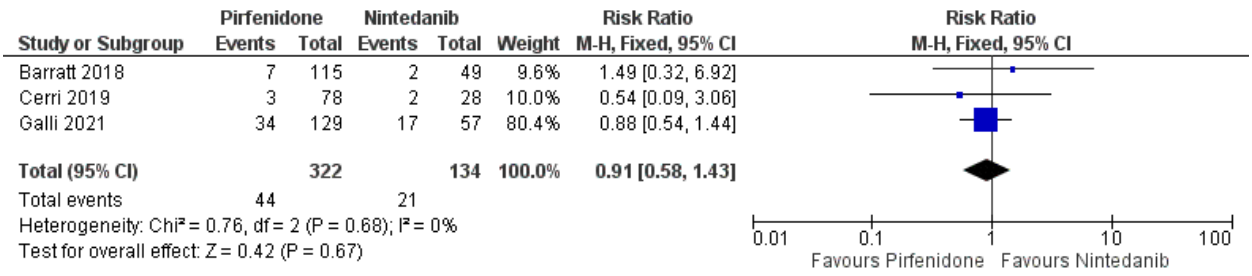


Figure 5. Adverse event: Nausea/Vomiting

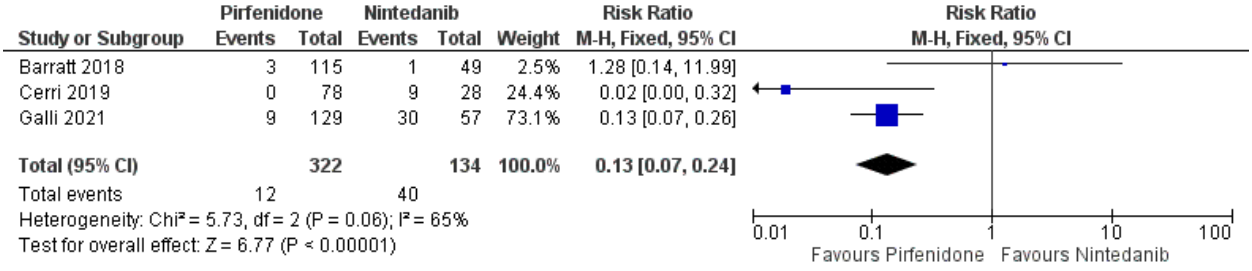


Figure 6. Adverse event: Diarrhea

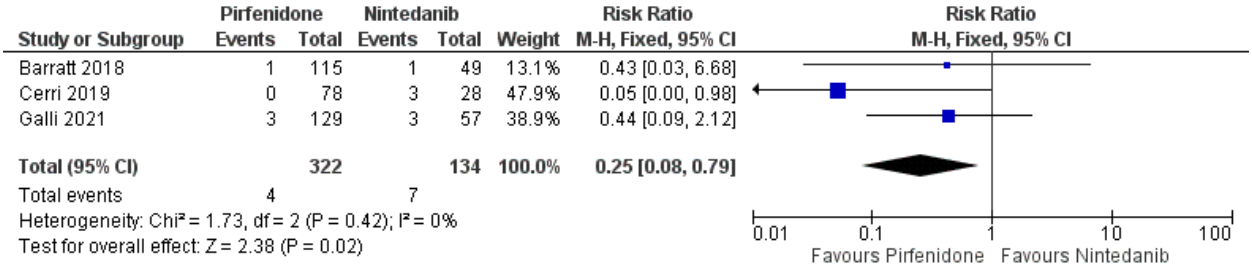


Figure 7. Adverse event: Transaminitis

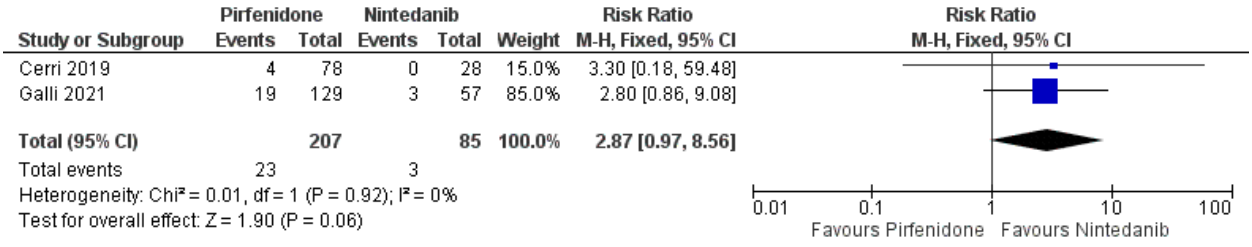


Figure 8. Adverse event: Rash

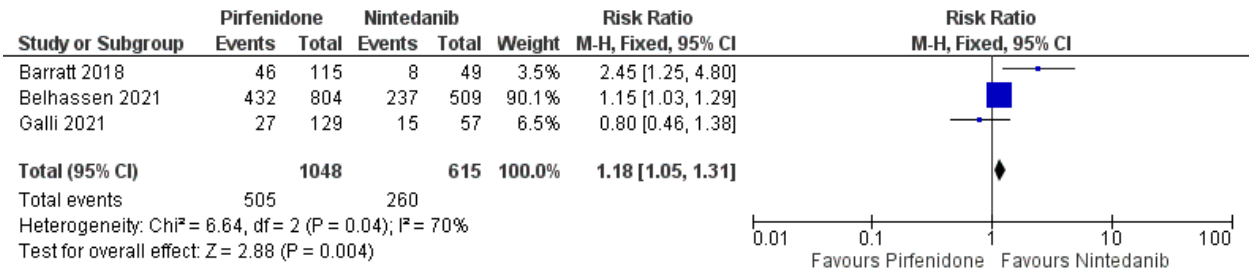


Figure 9. Discontinuation due to adverse events

Appendix 7. Characteristics of Ongoing Studies (10)

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/Population Recruited	Outcomes
A Study of the Efficacy and Safety of Pirfenidone vs. Nintedanib in the Treatment of Fibrotic Lung Disease After Coronavirus Disease-19 Pneumonia (PINCER) NCT04856111 December 31, 2021	Pirfenidone	Nintedanib	Inclusion Criteria: 1. Age above 18 years 2. Diagnosed to have COVID-19 by means of a real-time reverse transcription polymerase chain reaction (rRT-PCR) test performed on a respiratory (upper or lower respiratory) sample or positive IgM antibody test or a rapid antigen test with consistent clinicoradiologic findings within the previous 4 months 3. Persistent respiratory symptoms 4. Having post-COVID parenchymal involvement >10% of the lung parenchyma on visual inspection of the scans with the presence of radiologic signs of fibrosis, or having persistent reticulation or persistent consolidation despite a trial of glucocorticoids for a minimum period of 4 weeks after discharge for	Primary Outcome: 1. Change in the forced vital capacity (FVC) Secondary Outcome: 1. Proportion of subjects with improvement or stabilization (improvement or a <10% relative decline in FVC from the baseline value) 2. Proportion of subjects with a good composite response (< mMRC grade 2 breathlessness with ≥10% improvement in FVC with an O_2 saturation >92% during and after exertion) 3. Change in dyspnea score on modified Medical Research Council scale

			the acute COVID-19 illness Exclusion Criteria: 1. Pregnant or lactating women 2. Having absolute contraindication for pirfenidone or nintedanib 3. Known patient with diffuse lung disease prior to the diagnosis of COVID	4. Severity of dyspnea on the Functional Assessment of Chronic Illness Therapy - Dyspnea-10 item 5. Change in resting oxygen saturation 6. Proportion of subjects with oxygen desaturation on exercise testing 7. Percentage change in the six-minute walk distance 8. Proportion of participants who need rescue treatment 9. Change in health-related quality of life using the Short Form-36 questionnaire 10. Change in respiratory health status using the King's Brief ILD questionnaire 11. Changes in HRCT scores using the modified Salisbury system 12. Proportion of subjects who develop adverse effects due to either study drug 13. Predictors of response to antifibrotic agents, pirfenidone and nintedanib
Nintedanib Vs Pirfenidone in management of Covid19 related lung abnormality	Nintedanib	Pirfenidone	Inclusion criteria: 1. All cases of COVID-19 pneumonia who were diagnosed as COVID positive >15 days back or antibody positive and continue to be breathless	Primary outcome: 1. Improvement in CT-severity score 2. Improvement in Arterial Blood Gas. Secondary outcome:

CTRI/2020/12/029814 (Expected Completion Date not indicated)			symptomatically, have SPo2 <96%, CT-severity score >10 and CORADS-4/5/6 Exclusion criteria: 1. Patients having other interstitial lung diseases. 2. Patient having CKD or creatinine clearance <30 and CLD with deranged LFT will be excluded. 3. Not fulfilling the criteria for study 4. Not giving consent for study.	1. Improvement in 6-Minute Walk Distance
Efficacy and Safety of Nintedanib Ethanesulfonate Soft Capsule in the Treatment of Pulmonary Fibrosis in Patients With Moderate to Severe COVID-9(COVID 19) : a Single-center, Randomized, Placebo-controlled Study NCT04338802 ChiCTR2000031453 August 1, 2020	Nintedanib	Placebo	Inclusion Criteria: 1. 18-70 years old (including 18 and 70 years old), regardless of gender; 2. Infection with new coronavirus pneumonia confirmed by throat swab nucleic acid test. 3. CT examination of patients with multiple fibrotic shadows in both lungs; 4. Blood routine, liver, and kidney functions are within the controllable range: 5. Signed informed consent. Exclusion Criteria: 1. Previous history of chronic bronchitis, emphysema, interstitial lung disease or pulmonary heart disease; 2. Combining with other serious diseases 3. Active peptic ulcer 4. Pregnancy and lactation 5. Mental illness or cannot cooperate effectively 6. Researcher judges uncomfortable to participate in trial	Primary Outcomes: 1. Changes in forced vital capacity (FVC) Secondary Outcomes: 1. Changes in carbon monoxide dispersion (DLco%) 2. Changes in the six-minute walk test (6MWT) 3.Changes in High resolution CT score
Early Nintedanib Deployment in	Nintedanib 150 mg PO	Placebo equivalent	Inclusion Criteria:	Primary Outcome:

COVID-19 Interstitial Fibrosis (ENDCOV-I) NCT04619680 April 2024	twice a day, taken with food	given twice a day	1. Willing and able to provide written informed consent 2. Subjects Age > 18 3. Initial SARS-CoV-2 infection confirmed by PCR test or positive serologies 4. Fibrosis found on CT scan 5. Required one of the following after diagnosis with SARS-CoV-2: supplemental oxygen by nasal cannula, high flow oxygen, non invasive ventilation such as CPAP or BIPAP, or mechanical ventilation 6. Are 30 days from onset of initial SARS-CoV-2 symptoms 7. Forced Vital Capacity less than 80% predicted based on ATS/ERS criteria or DLCO<60% 8. Women of childbearing potential who agree to use of highly effective contraception during treatment and for three months following the last dose of nintedanib Exclusion Criteria: 1. Co-administration of other investigational agents against COVID-19 2. Active SARS-CoV-2 infection based on clinical judgment 3. Currently Pregnant or Breast Feeding 4. Current Use of Prednisone or equivalent > 10 mg/daily 5. Use of full dose anticoagulation therapy or high dose anti platelet	1. Change in Forced Vital Capacity (FVC) Secondary Outcome: 1. Deaths due to respiratory cause 2. Chest CT visual score 3. St. George's Respiratory Questionnaire (SGRQ) at 90 and 180 days 4. King's Brief Interstitial Lung Disease (KBILD) at 90 and 180 days 5. Leicester Cough Questionnaire (LCQ) at 90 and 180 days 6. Short Form (SF) 36 Health Survey at 90 and 180 days 7. Hospital Anxiety and Depression Scale (HADS) at 90 and 180 days 8. Number of participants with Increase in liver transaminases (AST and ALT) > 3 times the upper limit of normal at 90 and 180 days 9. Number of participants with Thrombotic events at 90 and 180 days 10. Number of participants with 10% weight loss over 90 and 180 days 19. Number of participants with GI events at 90 and 180 days

			drug therapy at screening (6. History of myocardial infarction within past 90 days 7. Life threatening bleed 8. Hemodynamic instability or shock 9. Superimposed pulmonary bacterial infection 10. Pre-existing interstitial lung disease 11. Active Hep A/B/C hepatitis as measured with PCR for viral load and/or serologies 12. Pre-existing liver disease: Including Abnormal Laboratory Liver Function: 13. Creatinine clearance <30 ml/min or currently on hemodialysis 14. Inability to tolerate orally administered medication	and anti-motility agents
Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis (NINTECOR) NCT04541680 EUCTR2020-002114-40-FR December 2021	Nintedanib	Placebo	Inclusion Criteria: 1. History of hospitalization for COVID-19 infection documented with positive PCR or positive serology in the previous 2 to 12 months 2. Lung opacities on HRCT involving more than 10% of the lung volume, with fibrotic features 3. DLCO≤ 70% of the predicted value Exclusion Criteria: 1. Pre-existing lung disorder with abnormal HRCT (including COPD, lung cancer, or pulmonary fibrosis) 2. Laboratory parameter thresholds:	Primary Outcome: 1. Decline in forced vital capacity (FVC) over 12 months Secondary Outcome: 1. Rate of decline of DLCO over 12 months 2. 6MWT at 12 months 3. Change in HRCT fibrosis score and HRCT fibrosis extension at inclusion and 12 months 4. Change in the total score on the St. George's Respiratory Questionnaire at 12 months

			● renal insufficiency (Creatinine clearance <30 ml/min) ● Total bilirubin > 1.5 above the upper limit of the normal range (ULN), ● Aspartate or alanine aminotransferase (AST or ALT) >3 × ULN 3. Recent surgery with wound healing in progress (<7days) 4. Underlying chronic liver disease 5. Significant pulmonary arterial hypertension (PAH) 6. History of cardiovascular diseases, any of the following: ● Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of Visit 1 ● Myocardial infarction within 6 months ● Unstable cardiac angina within 6 months 7. Bleeding risk 8. Alcohol or drug abuse 9. Ongoing or past antifibrotic treatment with pirfenidone or nintedanib 10. Hypersensitivity to nintedanib, peanut or soya or to any of the excipients of the specialty Ofev® 11. Patients not able to understand and follow study procedures	5. Change in the Dyspnea score (Multidimensional Dyspnea Profile and mMRC score) at 3, 6, 9 and 12 months 6. Change in Hospital Anxiety and Depression score at 3, 6, 9 and 12 months 7. Change in Biomarker assay (KL-6, NT-proBNP, CRP, D-dimers) at 12 months 8. Pulmonary hypertension prevalence 9. Association between genetic susceptibility (MUC5B polymorphism) and lung fibrosis in COVID-19 survivors 10. Incidence of clinical or biological adverse events with nintedanib versus placebo over 12 months

			12. No written informed consent from the patient 13. Absence of affiliation to the French social security 14. Participation in another interventional research	
A Randomized, Open-label Study to Evaluate the Efficacy and Safety of Pirfenidone in Patients With Severe and Critical Novel Coronavirus Infection NCT04282902 June 1, 2020	Pirfenidone	No Intervention	Inclusion Criteria: 1. Age ≥ 18 years. 2. Clinically diagnosed patients with new type of coronavirus pneumonia Exclusion Criteria: 1. AST and ALT> 1.5 x ULN 2. Bilirubin> 1.5 x ULN 3. Creatinine clearance rate calculated by Cockcroft-Gault formula at visit 1 <30 mL / min; 4. Patients with potential chronic liver disease 5. Previous treatment with nintedanib or pirfenidone 6. Received other research drug treatment within 1 month or 6 half-lives 7. IPF diagnosis based on ATS / ERS / JRS / ALAT 2011 guidelines (P11-07084); 8. Significant pulmonary hypertension (PAH) 9. Other clinically significant lung abnormalities considered by the investigator; 10. Major extrapulmonary physiological limitations 11. Cardiovascular diseases, any of the following diseases: Severe hypertension within 6 months, uncontrollable after treatment (≥160 / 100 mmHg); myocardial infarction within 6 months; unstable angina within 6 months;	Primary Outcome: 1. Lesion area of chest CT image at 4 weeks 2. Absolute change in pulse oxygen from baseline 3. Absolute change in blood gas from baseline 4. Absolute change in total score of King's brief questionnaire for interstitial Absolute change in total score of King's brief questionnaire for interstitial pulmonary disease (k-bild) from baseline at week 4 Secondary Outcome: 1. Time to death within 4 weeks due to respiratory problems 2. Time to disease progression or death within 4 weeks 3. Blood lymphocyte count 4. Absolute change in viral nucleic acid from baseline 5. Change in Dyspnea score 6. Changes in blood inflammatory indexes

			12. History of severe central nervous system (CNS) events; 13. Known trials Drug allergies; 14. Other diseases that may interfere with the testing process or as judged by the investigator 15. Women who are pregnant, breastfeeding, or planning pregnancy in this trial 16. Unable to understand or follow the trial procedures,	7. Absolute change in cough scores for pulmonary fibrosis survival symptoms from baseline
Phase-II Randomized Clinical Trial to Evaluate the Effect of Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis NCT04607928 August 1, 2021	Pirfenidone	Placebo	Inclusion Criteria: 1. Age > 18 years 2. Signed Informed Consent Form 3. Ability to comply with the study protocol in the opinion of the Investigator 4. Confirmation of SARS-COV2 infection in previous weeks which induced severe pneumonia and ARDS, with subsequent torpid recovery and/or incipient clinical-radiological signs of pulmonary fibrosis. 5. HRCT with fibrotic radiological changes of at least 5% after recovery from the acute process 6. Be able to understand the information given and sign the informed consent 7. For women or men of childbearing age who are not sterile, a commitment to use non-hormonal contraception during the 24-week treatment period will be required. Exclusion Criteria: 1. Use of systemic steroids) at doses greater than 15	Primary Outcome: 1. Change from Baseline in % in forced vital capacity (FVC) 2. Change in % fibrosis in high resolution computed tomography (HRCT) of the lung Secondary Outcome: 1. Maintenance of stability or functional improvement FVC . 2. Decreased oxygen requirement for physical activity 3. Improved exercise capacity (> 50 meter improvement or less decrease in% oxygen saturation) 4. Hospitalizations (general and due to respiratory problems) 5. Visits to the Emergency or Day Hospital for 6. Lung transplantation

			mg/day one month prior to randomization. 2. Severe or moderate myopathy that may associate a decrease of FVC. 3. Severe or life-limiting chronic disease prior to COVID19 infection 4. Treatment with pirfenidone or nintedanib prior to Covid19 5. Concomitant treatment with significant interactions with pirfenidone 6. Participation in any other investigational trial throughout the study 7. Active smoking. 8. Relevant blood alterations in the analysis made during the screening period: ● Total bilirubin > 2 ULN ● AST/SGOT or ALT/SGPT > 2.5 ULN ● Alkaline phosphatase >3.0 ULN ● Creatinine Clearance <40 mL/min, calculated by the Cockcroft-Gault formula 9. Pregnancy or lactation 10. Concomitant treatments that can cause severe digestive problems. 11. Gastric surgery in the last 3 months 12. Inability to complete required visits. 13. Previous intolerance or allergy to pirfenidone or hypersensitivity to any of its excipients. 14. History of angioedema	7. Death
Pirfenidone for coronavirus disease 2019 (COVID-19)	Pirfenidone	Placebo	Inclusion criteria: 1. History of COVID-19 illness diagnosed by RT-PCR/Rapid antigen/	Primary outcome: 1. The change in Forced Vital

related pulmonary fibrosis: A placebo-controlled randomized controlled trial CTRI/2021/03/032199 (Expected Completion Date not indicated)			Truenaat of throat or nasopharyngeal swab at least 8 weeks prior 2. Persistent respiratory symptoms or persistent hypoxemia (SpO2 <94% on room air) or oxygen desaturation on exercise AND Has evidence of pulmonary fibrosis on HRCT performed at least 8 weeks after COVID-19 diagnosis 3. Provides written informed consent for evaluation and treatment as per study protocol Exclusion criteria: 1. Patients not providing consent for participation in the study 2. FEV1/FVC ratio < 0.80 3. Active smokers 4. Any active malignancy/ malignancy within past 2 years 5. Severe hepatic impairment 6. Use of immunosuppressant drugs (except corticosteroids and tocilizumab) within last 6 weeks	Capacity (FVC) (% predicted) at 6 months Secondary outcomes: 1. Change in diffusion capacity for carbon mono-oxide (DLCO) at 3 and 6 months 2. Change in total lung capacity at 3 and 6 months 3. Adverse events during therapy 4. Change in high resolution computed tomography (HRCT) at 3 months 5. Change in Six-minute walk distance at 3 and 6 months 6. Change in dyspnea on modified borg dyspnea scale 7. Change in FVC at 3 months
A Randomized Phase-II Clinical Trial to Evaluate to Effect of Pirfenidone compared with Placebo in Pulmonary Fibrosis Post-COVID 19 (FIBRO-COVID) EUCTR2020-002518-42-ES (Expected Completion Date not indicated)	Pirfenidone	Placebo	Inclusion criteria: 1. Age > 18 years 2. Signed Informed Consent Form 3. Ability to comply with the study protocol in the opinion of the Investigator 4. Confirmation of SARS-COV2 infection in previous weeks which induced severe pneumonia and ARDS, with subsequent torpid recovery and/or incipient clinical-radiological signs of pulmonary fibrosis.	Primary Outcomes: 1. % change in FVC 2. Radiological change in % of pulmonary fibrosis (Chest HRCT) 3. Percentage of patients who improve functionally (=10% change in FVC) and radiologically (% of fibrotic signs in chest HRCT)

			5. HRCT with fibrotic radiological changes of at least 5% after recovery from the acute process 6. Be able to understand the information given and sign the informed consent 7. For women or men of childbearing age who are not sterile, a commitment to use non-hormonal contraception during the 24-week treatment period will be required. Exclusion criteria: 1. Use of systemic steroids (at doses greater than 15 mg/day one month prior to randomisation. 2. Severe or moderate myopathy that may associate a decrease of FVC. 3. Severe or life-limiting chronic disease prior to COVID19 infection 4. Treatment with pirfenidone or nintedanib prior to Covid19 5. Concomitant treatment with significant interactions with pirfenidone 6. Participation in any other investigational trial throughout the study 7. Active smoking. 8. Relevant blood alterations in the analysis made during the screening period: ● Total bilirubin > 2 ULN ● AST/SGOT or ALT/SGPT > 2.5 ULN ● Alkaline phosphatase >3.0 ULN ● Creatinine Clearance <40 mL/min, calculated by the	Secondary outcomes: 1. % of cases with progression of pulmonary fibrosis 2. Death or lung transplant (transplant free-survival time) 3. Improvement in quality of life 4. Hospitalizations or urgent visits of respiratory cause 5. Semi-annual rate of change in % FVC 6. HRCT Chest Fibrotic Score 7. Incidence of drug-associated adverse events (nature, seriousness, severity, frequency, causality, clinical consequence and time since drug onset) 8. Discontinuation of treatment. 9. % of cases with progression of pulmonary fibrosis 10. Exercise capacity 11. Decreased oxygen requirement for physical activity 12. Improvement in quality of life (difference in final K-BILD score greater than 5) 13. Lung transplant or death

			Cockcroft-Gault formula 9. Pregnancy or lactation 10. Concomitant treatments that can cause severe digestive problems. 11. Gastric surgery in the last 3 months. 12. Inability to complete required visits. 13. Previous intolerance or allergy to pirfenidone or hypersensitivity to any of its excipients. 14. History of angioedema	
The comparison of the efficacy and safety of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis JPRN-UMIN000020682 (Expected Completion Date not indicated)	Pirfenidone	Nintedanib	Inclusion criteria: 1. Idiopathic pulmonary fibrosis Exclusion criteria: 1. Coexisting lung cancer 2. Acute exacerbation of idiopathic pulmonary fibrosis 3. Severe cardiac or hepatic diseases 4. Pulmonary arterial hypertension 5. Sarcoidosis and respiratory infection, 6. Cannot perform pulmonary function test 7. Pregnant women 8. Use of prednisone greater than 20mg/day and immunosuppressives during the preceding 3 months 9. Patients who participated in other clinical trials in the last 3 months, the patients who are judged inappropriate for this study	Primary Outcome(s) 1. The change in vital capacity from baseline to months 12 Secondary Outcome(s) 1. Dyspnea 2. KL-6 3. SP-D 4. %DLCO 5. Changes in the lowest peripheral oxygen saturation during the 6-minute walk test 6. Arterial blood gas 7. The reduction of ground-glass and reticular opacities 8. Echocardiogram 9. Bronchoalveolar lavage 10. First occurrence of acute exacerbation 11. The development of lung cancer 12. Survival at 12 months