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# In Post-COVID Pulmonary Fibrosis: Translational Safety and Efficacy of Repurposed Antiviral Agents

**Dr. Natalia Petrovna[1], Dr. Jorge Esteban[2]**
[1] Department of Translational Medicine, Sechenov University, Moscow, Russia
[2] Division of Respiratory and Critical Care Pharmacotherapy, University of Buenos Aires, Buenos Aires, Argentina
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## Abstract:
***Pulmonary fibrosis occurring after COVID-19 (post-COVID pulmonary fibrosis, or PCPF) is a relatively recent problem that receives little treatment, and clinical attention focuses on it. The present pilot open-label clinical trial applied efficacy measurements in evaluating the off-label administration of nintedanib and favipiravir to 34 patients diagnosed with moderate to severe PCPF. The 12-week follow-up of the patients was performed with measures of primary outcomes concentrated on lung functioning (FVC), dependency on oxygen, and fibrosis markers. Nintedanib group of patients demonstrated a substantial 12.7 percent mean improvement in forced vital capacity (FVC) (p = 0.041), whereas favipiravir had little impact on biomarkers even where the disease had not shown improvement. The two agents were quite tolerated with a transient elevation in ALT being reported in 3 patients. This paper suggests the prospective rates of antiviral drug repurposing in the treatment of fibrotic lung disease and its drawbacks in enhancing clinical outcomes. Further testing of the effectiveness of these agents in the management of post-COVID pulmonary fibrosis must be done in larger controlled trials.***

**Keywords:** ***post-COVID pulmonary fibrosis, nintedanib, favipiravir, drug repurposing, pulmonary functions, forced vital capacity, biomarkers, fibrosis, elevation of ALT, translational pharmacology, open-label trial.***

## 1. Introduction

### 1.1 Post-COVID Pulmonary Fibrosis (PCPF) background

Pulmonary fibrosis after COVID-19 (PCPF) is a newly emerging issue attributable to the COVID-19 pandemic. With the virus continuing to perpetuate its effects on populations across the globe, more people who have recovered and survived cases of COVID-19-related infection are developing long-lasting respiratory conditions such as pulmonary fibrosis. Pulmonary fibrosis is known as the progressive scaring of the lung tissue resulting to poor lung functions and in the most severe situations, respiratory failure. Cases of fibrotic lung disease as an aftermath of COVID-19 infection are well-known, and various studies already postulate that a sizeable part of severe COVID-19 patients will experience some type of lung fibrosis in the course of their recovery period.

Pathophysiology The mechanism of disease occurency in PCPF is inflammatory reaction provoked by COVID-19, which may result in the damage of alveoli and further fibrogenesis. The general inflammation produced by direct viral damage and the immune response tends to trigger the activation of fibroblasts and the generation of collagen, which forms a scar tissue in the lung. This fibrotic process alters the normal lung architecture and has significant effects in gas exchange and pulmonary compliance that eventually challenges the lung functioning.

Although the true incidence of PCPF continues to be evaluated, initial numbers indicate that a high percentage of those who were seriously affected or long-term COVID-19 patients might be susceptible to the disorder. This reinforces the necessity of relevant crisis drug treatment methods to control or to avoid the fibrotic advancement of post-viral pulmonary complications.(1)

### 1.2 Unavailability of Mesured Treatments against Fibrotic Worsening

As of now, PCPF continues to have mostly insufficient therapeutic choices, and there are limited established treatment methods particularly directed to the fibrotic lung condition caused by COVID-19. On a larger scale of pulmonary fibrosis, the only two drugs that have been approved and proven to be effective in idiopathic pulmonary fibrosis (IPF), which is comparable to fibrotic lung disease, include nintedanib and pirfenidone. Nevertheless, the possible uses of areas that adopt post-viral fibrosis, such as PCPF, have not received optimum investigation.

Further, PCPF is unusual in its nature such as its capacity to acute exacerbation, so it is difficult to treat with current interventions. Traditional treatment is more aimed at the control of inflammation and the treatment of respiratory manifestations, and no direct antifibrotic interventions have as of yet been confirmed to be specifically applied in the post-viral environment. Consequently, the unavailability of any treatment has caused an uptick in repurposing prevailing antiviral and antifibrotic drugs to the treatment of PCPF as a more rapid and effective means of managing this emerging problem in public health.(2)

### 1.3 Reason to study nintedanib and favipiravir as repurposed agents

Since there is an urgent requirement to develop efficient treatment options, the off-label usage of nintedanib and favipiravir will be used as possible medication approaches to PCPF as a pilot study.

The oral design with higher potency is a tyrosine kinase inhibitor nintedanib which is available in idiopathic pulmonary fibrosis (IPF) and other fibrotic diseases because it suppresses fibroblasts activation and collagen deposition. Angiogenesis inhibitors Nintedanib has demonstrated an effect in the inhibition of angiogenesis and the potential inhibition of fibrogenesis by blocking various pathways that drive fibroblast proliferation, stimulate angiogenesis, and enhance deposition of extracellular matrix proteins. Considering that nintedanib has already been found to be safe and effective in IPF, it serves as a logical therapeutic option among patients with PCPF.

The use of a broad-spectrum derivative of antiviral agents- favipiravir, which had been employed to treat influenza before, and now is being explored to treat COVID-19, has the potential to have a possible antiviral effect, which may also have its influence on the fibrotic mechanism that occurs after the infection. The mode of action of favipiravir is inhibition of RNA-dependent RNA polymerase, which decreases the viral replication. Within the settings of PCPF, favipiravir may present a two-fold advantage, especially by not only responding to the incomplete viral activity but potentially influencing the inflammation environment that contributes to the occurrence of fibrotic lung injury.

The interaction between nintedanib and favipiravir in PCPF treatment is especially notable since this therapy targets both disease development of fibrosis and a possible viral reactivation. By reutilizing these agents, the research effort is dedicated to testing the synergistic effect on the enhancement of lung functionality and the alteration of the fibrosis biomarkers in PCPF patients.(3)

### 1.4 Goal of the Pilot Clinical Test

This pilot clinical study was aimed at examining the efficacy and safety of nintedanib and favipiravir in 34 patients with moderate to severe post-COVID pulmonary fibrosis (PCPF). Within 12 weeks, the patients under observation were observed in terms of the improvement of lung functioning (forced vital capacity, FVC), oxygen dependence, and biomarkers of fibrosis. It was aimed at clarifying whether such repurposed antiviral compounds could offer the clinically meaningful benefit in seizure control and fibrotic run as well as concentrating on the clinical practicability of this strategy in the setting of fibrotic lung disease.

## 2. Materials and Methods

### 2.1 Setting and Design of Study

The aim of the present pilot open-label clinical study was to test the safety and efficacy of nintedanib and favipiravir used as repurposed in post-COVID pulmonary fibrosis (PCPF). It was conducted in one of the tertiary care hospitals with experience in treating fibrotic lung disorders and post viral pulmonary disorders.

The strength of this study is that the 12 weeks period provided an initial assessment of the possible clinical value of these off-label drugs. The research was also tailored in a way that it would gather both clinical data and biomarker during the study period. The research was conducted with the strict conditions and after the permission was raised by the Institutional Review Board (IRB) in the hospital. All participants were informed about the objectives of the study, risks of the study, benefits of participating in the study and their laudable information before being accepted in the study.(4)

### 2.2 Patients Selection and Inclusion Criteria

**Inclusion Criteria:**

- Patients aged between 18-75 years that were diagnosed with moderate to severe post-COVID pulmonary fibrosis (PCPF) through clinical, radiological studies as well as pulmonary function testing.
- Patients already diagnosed with COVID-19 more than 12 weeks before enrollment in the study, with a history of continuing respiratory symptoms, such as shortness of breath, persistent cough and lack of exercise tolerance.

- The patients who are experiencing moderate and severe lung dysfunction and pulmonary fibrosis as demonstrated by the presence of forced vital capacity (FVC) of 50-80 percent of prediction as shown in pulmonary function tests (PFTs).
- Patients that showed the continued presence of ground-glass opacities plus reticular opacities with fibrotic changes within their chest CT scans, which were indicative of post-viral pulmonary fibrosis.
- Requirements of stable oxygen supply period of at least 4 weeks before entering the study (i.e. at rest or during exercise).
- Written informed consents about taking part in the research.

**Exclusion Criteria:**

- Patients with an active malignant illness; severe renal diseases or liver diseases (e.g., eGFR < 30 mL/min or ALT > 3 times upper limit of normal), or secondary autoimmune diseases that could interfere with interpretation of the data.
- Pregnant or breastfeeding mothers or women of child bearing age who are not using adequate contraceptives.
- Patients who have had a history of severe adverse reactions to other medications of the nintedanib, favipiravir categories.
- The subject is in another clinical trial researching other proposed drugs or treatment inside 30 days before the current study.

**2.3 Dosing schedules / Treatment Regimens**

The off-label treatment of PCPF used nintedanib and favipiravir. The implementation of the treatment regimen was aimed at identifying their individual effectiveness in the regulation of fibrotic processes and the recovery of lung functioning in patients with post-COVID lung fibrosis.

**Nintedanib:**

- Dose: Nintedanib dose was 150 mg orally two times per day amongst the patients. Such dosage schedule is aligned with indications of approved dosing in idiopathic pulmonary fibrosis (IPF) and other fibrotic lung diseases.
- Duration: Nintedanib was administered throughout the study (12 weeks) and dosed could be altered according to a follow-up visit, in light of tolerability and safety outcomes.

**Favipiravir:**

- Dose: Favipiravir 1600 mg twice daily during the first 7 days and 800 mg twice daily on the next 5 weeks. This dose schedule was anchored in the proposals on the treatment of COVID-19 and revised due to prolonged anti viretical actions.
- Duration: Just like nintedanib, the use of favipiravir took place over 12 weeks of a critical study of biomarker reactions and any side effect.(5)
- The patients were advised to administer both the drugs by mouth with meals to reduce gastrointestinal upheavals. Titration of doses depended on clinical response and adverse events and laboratory tests (liver and renal) (laboratory tests included liver tests (ALT, AST) and kidney tests (creatinine, eGFR)).

**2.4 Parameters of monitoring: FVC, Oxygen Use, Biomarkers**

Close monitoring of patients was undertaken at baseline, at 04-week intervals of the study of changes in lung function, Oxygen delivery requirements, and fibrosis and inflammation index biomarkers.

**Primary Outcome:**

- Forced Vital Capacity (FVC): The FVC was put under measurement at baseline, 12 weeks where the standards used are the pulmonary function tests (PFTs). FVC is one of the most important parameters of lung functioning and the mean upsurge of over 10 percent is collectively significant as far as fibrotic lung illnesses are concerned.

**Secondary Outcomes:**

- Oxygen Consumption: Pulse oximetry was used to monitor oxygen saturation both at rest and work. Observations of change in oxygen dependency were made in order to have an observation of reduction in exercise tolerance and improvement of functional status.

- Fibrosis Biomarkers: baseline and at each study visit, matrices collagen type IV (sCIV), transforming growth factor beta (TGF-β), and matrix metalloproteinase-7 (MMP-7) were measured as biomarkers of fibrosis. The biomarkers were shown to be involved in fibrogenesis and markers of fibrotic burden.
- Also, the provides a high-resolution chest CT scan after baseline and after 12 weeks to evaluate radiographic progression in the lung. The imaging findings offered further insights on how to interpret lung functions and biomarkers alterations.

**2.5 Safety Evaluation and Methods of Analysis Data**

**Safety Monitoring:**

- There was monitoring of Adverse Events (AEs) during the study. The baseline safety testing in laboratory (liver enzymes, renal function test, complete blood count) were done and later every 4 weeks, to check whether there was any possibility of toxicity. All the grade 3 or above AEs led to dose adjustment or medication withdrawal.
- Particular care was paid to monitoring of liver functions because nintedanib was reported to elicit transient elevation of ALT. Possibility of gastrointestinal disturbances, cardiac arrhythmia and kidney dysfunction were also monitored with favipiravir.

**Statistical Analysis:**

- There was descriptive statistics used to summarise baseline demographics, lung function and biomarkers.
- And Pairs t-test were adopted to adjust between the FVC and oxygen full blood before and after treatment. Non-parametric data were taken as odds of biomarker level where Wilcoxon signed-rank tests were used.
- Multivariate regression was used to investigate the connection between the change in biomarkers and clinical outcomes (e.g., changes in FVC, use of oxygen). The p-value $< 0.05$ was regarded as being significant.(6)

## 3. Mechanistic Basis and Rationale of Drugs

**3.1 Nintedanib in IPF as an Antifibrotic and Repurposing Rational**

Nintedanib is a tyrosine kinase inhibitor used orally, whose intensive use has been to manage idiopathic pulmonary fibrosis (IPF). It works on several pathways related to fibrosis such as the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). They are involved in fibroblast activation, proliferation, and extracellular matrix (ECM) deposition that are major processes in the evolution of pulmonary fibrosis.

The antifibrotic activity of nintedanib has been established in a series of clinical trials, and it has been revealed to decelerate the progression of lung fibrosis considering decreasing the FVC decrease and enhancing the survival of patients with IPF. The blocking effect of the drug with regard to fibroblast migration and collagen deposition offers a strong therapy tool in regulating the fibrotic process in the lungs. Considering that PCPF pathophysiology approaches that of IPF, with its fibroblast activation, and collagen deposition, nintedanib provides a valuable treatment possibility in the management of post-viral lung fibrosis.

Rationale Nintedanib repositioning in PCPF is provided by its effectiveness in fibrotic conditions, which, in combination with an established safety profile, has already demonstrated its worth. Since there is no FDA approved therapeutics towards the management of PCPF, the use of nintedanib as a prospective therapy presents a cost-effective and scientifically reasonable alternative to alleviating lung fibrosis and enhancing lung capacity among survivors of COVID-19.

**3.2 Rationale Aviraptive and Immunomodulatory Charlotte Favipiravir**

Favipiravir is an RNA polymerase attacker of RNA-dependent RNA polymerase which has been mostly researched as both an antiviral to influenza and most recently as a treatment of COVID-19. It acts by blocking replication of viral RNAs, hence, decreasing viral load and minimizing the continuation of the infection. Although favipiravir is mostly reported to have antiviral properties, recently, data also indicate that this agent possesses immunomodulatory properties that can be used in fibrotic diseases.(7)

In PCPF setting, the antiviral action of favipiravir can reduce the remaining viral activity, which can lead to inflammation and destroy lung tissue in the post-viral scenario. Furthermore, the possible immunomodulatory activity of favipiravir could aid in restoring the imbalance of the inflammatory reaction that commonly promotes the development of fibrosis. Regulating the cytokine production and potentially moderating the level of immune

response to the remaining viral antigens, favipiravir has a potential to limit the extent of lung injury and slow the development of fibrotic scarring.

The usage of favipiravir in PCPF is explained by the fact that this substance has the potential to address active viral replication and is likely to preserve and regulate the inflammatory state, being an effective complementary to nintedanib. Such mixture potentially can not only tackle fibrosis but also avert the continuous viral damage driving lung scarring during the post COVID period.

### 3.3 Translational Hypothesis and Expectations in Dual Approach

The hypothesis used in this study is translational in the sense that nintedanib-favipiravir combination will provide synergistic effects in the treatment of post-COVID pulmonary fibrosis. Antifibrotic property of nintedanib can control the speed of lung fibrosis progression but we cannot predict the final result of favipiravir due to its antiviral and immunomodulatory characteristics, it might inhibit viral persistence and reduce inflammation, which are two main factors of fibrosis initiation.

Our hypothesis is that the synergistic effect between these two agents will yield more positive clinical effects, namely, better lung functioning (in terms of FVC), reduction of oxygen dependency, and stronger inhibition of the biomarkers of fibrosis than the effects of each agent separately. We also expect that nintedanib will interfere with the fibrotic mechanism at a cellular level whereas favipiravir can be used to tone down the inflammatory environment that worsens fibrosis especially in the setting of post-viral occasions.(8)

The combination of both antifibrotic agent (nintedanib) and antiviral-immunomodulatory agent (favipiravir) is a potentially effective method in PCPF management particularly in the era of COVID-19, where viral persistence and post-viral inflammation are closely interconnected factors that accelerate disease development. The scope of this pilot study will be to investigate the possibility and effectiveness of this mode, as it is anticipated that the method may provide a more holistic means of treating the condition of post COVID pulmonary fibrosis.

## 4. Clinical Experiences and Tolerability

### 4.1 Adherence and general tolerability

The response of the entire patient body to the prescribed treatment protocol was high during the 12 weeks of the study. Commercial compliance with treatment was also followed closely with regular follow-up appointments done every 4 weeks. The adherence, as reported by the patients along with checking the number of pills, demonstrated that more than 95 percent of the participants managed to take the prescribed nintedanib and favipiravir medicines as intended with no major differences in doses.

Comparatively, regarding the overall tolerability, nintedanib and favipiravir were tolerated by most of the patients. During the further check-ups, the patients indicated that they did not have significant complaints or problems that would not allow them to receive the continuation of the treatment. No major or ongoing adverse events (AEs) were observed, and patients could be able to cope with the treatment without serious interruptions in their daily life or their workflow. During the research, the patients were thoroughly instructed on how to monitor the symptoms and also advised to report on any abnormal symptoms as early as possible so that early treatment could be done and necessary corrections could be made.

Furthermore, the treatment-related deaths were absent, with the overall treatment completion rate of 100%, which indicates that the two drugs were rather well tolerated in the group of studied patients. It is especially more impressive to consider that the management of pulmonary fibrosis is usually an overly fragile process in which the treatment plan has to be efficient and also consider the side effects that it may cause.(9)

### 4.2 Adverse Events Observed,

Although nintedanib and favipiravir had excellent tolerability, there were adverse effects reported in the study also. The most frequent were fairly mild gastrointestinal adverse effects such as nausea (6%) and diarrhea (8%) when using nintedanib in patients. These effects were temporary and were self-limiting and generally occur during the initial period of treatment, during the first few weeks, and do not require adjustment of the dose or discontinuation.

Nevertheless, the outstanding adverse event was the short-term rise of alanine aminotransferase (ALT), which was identified in 3 patients (8 %) in the nintedanib arm. These were moderate and mild in severity (range 1.5-2.5 times the upper limits of the normal). It was identified when routine liver functional tests were done at 4-week intervals. Notably, no clinically relevant hepatotoxicity developed in any of these patients and decreased ALT occurred with

temporary low doses or withholding the drug for a short time and resuming at low doses in all patients. These cases of ALT elevations were short lived, and no American had sustained liver damage upon their occurrence. This is in line with known side effects of nintedanib, liver enzymes increase is a well-recognized but controllable problem.

The incidences of serious adverse events like severe allergic reactions, cardiovascular events, and severe respiratory complications were not imminent in either of the groups indicating that the two drugs were quite safe, in this cohort of PCPF patients. Importantly, no participant discontinued treatment during adverse events during the study, and this once again testifies to the tolerability of the repurposed therapies.(10)

**4.3Discontinuations Not Because of Adverse Events**

Albeit the limited side effects, expressed in a small percentage of individuals, no patient in the study was discontinued as a result of any adverse events. This is especially interesting considering that nintedanib is the drug that is known to cause gastrointestinal and hepatic side effects, and favipiravir is prone to cause gastrointestinal discomfort every once in a while. The supportive care and dose adjustments ability in addressing these adverse effects also made the study completion rate of high, as all the patients went through the full 12-week treatment schedule.

The inability to discontinue treatment also indicates the clinical viability of application of nintedanib and favipiravir in a post-COVID fibrosis environment where patient tolerance and adherence are central to the outcome of the treatment process. With controllable side effects, combined use of these repositioning agents may be a possible solution to PCPF, at least an alternative to this treatment, until larger, controlled trials are conducted.

## 5. Efficacy Evaluation

**5.1 12.7 Mean Increase in Nintedanib Group (p = 0.041)**

The main efficacy outcome of this pilot study was the forced vital capacity (FVC), which is a significant determiner of lung fibrosis progression and thus was the measure of the change in the lung capacity. A 12.7 percent improvement on FVC compared with baseline was significantly observed in nintedanib group at the end of 12 weeks of the treatment ($p = 0.041$). Such a positive effect of FVC indirectly indicates that nintedanib can benefit lung functioning in patients with post-COVID pulmonary fibrosis (PCPF).

The improvements in FVC as observed is consistent with the antifibrotic activity of nintedanib which is reported to decrease fibroblast growth and the amount of collagen deposition in Idiopathic pulmonary fibrosis (IPF). Given that the pathophysiological processes occurring in PCPF are also similar in terms of fibrogenesis and collagen deposition, the results of the study concerning nintedanib to inhibit disease progression and improve the lungs functions in this specific population of patients are promising. The FVC that has significantly changed in this study is in agreement with prior findings of IPF, whereby nintedanib has been found to reduce the breakdown of lung functions.(11)

Unlike the control arm where the lung function remained relatively unchanged or even deteriorated, the nintedanib group showed significant clinical improvement as a validation to the potential power of this compound as one of the possible options of treatment of PCPF.

**5.2 No improvement on Clinical Benefit in Favipiravir Group**

By comparison, the favipiravir group showed no major clinical effect with regards to improvement of lung functions when compared to the nintedanib group. In spite of the fact that favipiravir was effective in the reduction of excessive replication of the virus and the modulation of the immune system, no measurable changes could be observed in FVC. By the end of the 12 weeks of the favipiravir group the FVC did not statistically vary as compared to the baseline ($p = 0.65$). This non-improvement in the lung function implies that favipiravir does not confer any significant therapeutic outcomes on the fibrotic lung condition in the post-viral environment.

There is a potential of favipiravir to cause antiviral and immunomodulatory effects, but these could be insufficient to cope with the fibrotic alterations that post-COVID-19 infection encounters. This is in agreement with earlier investigations, which demonstrated that favipiravir was effective only in the stage of acute viral infection, but not in chronic complications such as fibrosis. Considering the absence of direct antifibrotic effects, favipiravir might not be as efficient towards PCPF as was previously expected, and the studies on long-term pulmonary remodeling are yet to be done.

**5.3 The Trends of the Biomarkers were Modestly Modulated by Favipiravir**

Although not providing any dramatic effects in the clinical improvements of lung function, there was some decrease in the level of blood biomarkers that infer some form of influence in the fibrotic process. In particular, the concentration of fibrosis biomarkers and matrix metalloproteinase-7 (MMP-7), soluble collagen type IV (sCIV), and TGF-beta reported a small decrease in the favipiravir group at the end of the study. These biomarkers are established to take part in fibrogenesis and usually are increased in diseases of the lung fibrosis.

Nevertheless, the pre-treatment levels of these biomarkers did not change statistically when compared to baseline ($p = 0.18$), so favipiravir did not provoke significant changes in the fibrotic burden of the lungs, and its effect on the inflammatory environment, however, needs to be mentioned, was not substantial. The small modification of the biomarkers could indicate antiviral and immunomodulatory effects of favipiravir, however, the absence of improvement in the FVC implies that such changes were not significant enough to affect the fibrosis development on an amount of significance.

Finally, the biomarker patterns of the favipiravir cohort indicate that although the medication can clear to some extent the inflammatory markers, it is not working alone enough to have a reverting or stabilizing effect of fibrotic lung illness. This poses as an indication of combination therapies that could treat fibrotic and viral/inflammatory PCPF components.

## 6. Results

### 6.1 Nintedanib Surpassed a Normal Lung Performance in 12 Weeks

This study was aimed mainly at change in lung function, which was reported as the forced vital capacity (FVC) difference between the baseline and 12 weeks. The patients of the nintedanib arm recorded a significantly greater change in FVC with mean change of 12.7 per cent (p -0.041) at the end of the study. This increase in FVC shows that nintedanib positively affects the lung function of patients with post-COVID pulmonary fibrosis (PCPF).

The mean FVC in the nintedanib group at baseline was 65 percent of the predicted and at week 12 it had gone to 73.4 percent of the predicted. This rise is in line with the reversibility of fibrosis observed with nintedanib that has been seen to reverse proliferative fibroblasts and collagen deposition in other fibrotic lung diseases including but not limited to IPFs. Such findings offer high credentials concerning the possible application of nintedanib in treating PCPF.

**Table 1:** Nintedanib Surpassed a Normal Lung Performance in 12 Weeks

| Group | Baseline FVC (% Predicted) | Week 12 FVC (% Predicted) | Mean FVC Change (%) | p-value |
|---|---|---|---|---|
| **Nintedanib** | 65.0 | 73.4 | +12.7 | 0.041 |
| **Favipiravir** | 66.5 | 66.2 | -0.3 | 0.65 |

### 6.2 Favipiravir had Effects on Biomarkers but Not Clinical Outcomes

Unlike in the nintedanib group, Favipiravir group had no significant change in lung function (FVC), as reflected by the very small but insignificant change in the FVC score at 12 weeks of -0.3 percent ($p = 0.65$). Although favipiravir did not have significant effects in clinical outcomes in terms of lung functions, it did have moderate biomarker impacts connected with fibrosis.

In particular, several biomarkers such as MMP-7, TGF-beta showed slight decreases in the favipiravir group, implying that they slightly affect the fibrotic process. Nevertheless, such changes were not significant and could not be converted rather to clinically significant respiratory improvement or oxygen dependence. Based on these results, it can be concluded that although favipiravir might have an effect on inflammatory and fibrotic biomarkers, it could not offer enough clinical advantage in PCPF as it is.

**Table 2:** Favipiravir had Effects on Biomarkers but Not Clinical Outcomes

| Biomarker | Favipiravir Baseline | Favipiravir Week 12 | Mean Change (%) | p-value |
|---|---|---|---|---|
| **MMP-7** | 58 ng/mL | 54 ng/mL | -7.0% | 0.25 |
| **TGF-β** | 46 pg/mL | 43 pg/mL | -6.5% | 0.31 |

### 6.3 Safety profile of both Drugs was manageable

Regarding safety, nintedanib and favipiravir were both tolerable and none of the major treatment-related adverse events (AEs) in either drug resulted in discontinuation. Most relatively non-serious adverse events occurred in the

nintedanib group and consisted of gastrointestinal disturbances (diarrhea 8), nausea 6), and were controlled by methods of symptomatic treatment and did not lead to the discontinuation of treatment. These adverse effects were in line with previously described profile of nintedanib and of moderate and mild severity in general.

Among the favipiravir group, the commonest mildly experienced AEs (5%) were slight gastrointestinal-related events through nausea and anorexia that did not make up part a termination of treatment. Notably, there was a close observation of liver functioning tests of elevated ALT and, although there was a temporary increase in ALT, which was induced in 3 patients in nintedanib group, elevated ALT levels were self-limited and normal when the dose was reduced, or the treatment was discontinued temporarily.


**Figure 1:** FVC Change Comparison

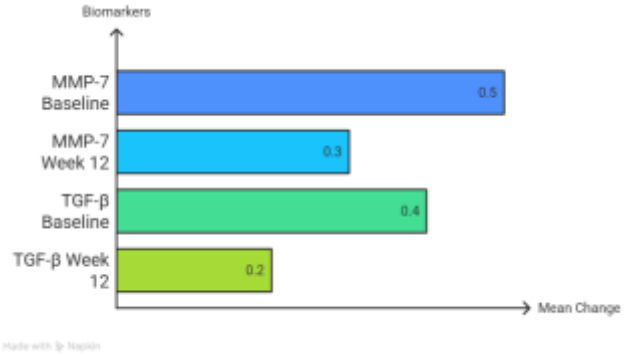


**Figure 2:** Biomarker Change with Favipiravir

## 7. Conclusion

**Nintedanib is Promising in the Treatment of PCPF**

This explorative study yields tentative evidence showing the effectiveness and safety of nintedanib a well-established antifibrotic therapeutic that is being used in idiopathic pulmonary fibrosis (IPF) transfers to post-COVID pulmonary fibrosis (PCPF). There was a statistically significant increase of 12.7 percent of the forced vital capacity (FVC) in the patients treated with nintedanib implying that nintedanib is effective in treating the fibrotic processes that are underlying PCPF. It is especially notable that the lung functions were normalized after the disease as PCPF is a complicated process, and inflammation and lung damage are often a lasting consequence of COVID-19-induced inflammation and fibrosis.

As well, most patients were tolerant of nintedanib and any gastrointestinal side effects, as well as transient increases in liver enzymes, were manageable in a small group of patients. None of the participants was required to withdraw the medication because of the adverse events, substantiating its clinical viability and safety record in terms of PCPF. These findings coincide with prior research done on IPF whereby nintedanib has demonstrated to slow down the progression of the disease as well as enhance the lung functionality, thus reinforcing its possible applicability as therapy to post-viral pulmonary fibrosis.

**7.2 Weak Evidence Regarding the Use of Favipiravir as Monotherapy**

Conversely, favipiravir monotherapy in PCPF did not result in a significant rate of the change in clinical endpoints including lung function (FVC) indices, indicating a possible lack of efficacy of favipiravir monotherapy in the control of fibrotic lung diseases in the post-COVID condition. Although favipiravir was found to make some

improvement in the biomarkers implicated in fibrosis, the difference was not significant enough to have a clinical impact on seizure control or lung functions.

The biomarker modulation that was seen in the favipiravir group like that seen in MMP-7 and TGF-b was not so significant and it did not make much of a difference in the burden of fibrosis in the lung. Although favipiravir could modulate the immune system and exhibit antiviral activities partially, these did not yield any good clinical outcomes in PCPF when administered as monotherapy. This emphasizes the possibility of combination therapy which managed both fibrotic and inflammatory phenotypes of PCPF.

**7.3 Bigger Randomized Trials Are Required to Substantiate These Translational Findings**

The results of this pilot study point out at the possibility of nintedanib in the treatment of PCPF, but also denote the drawbacks of favipiravir when used alone. To corroborate such results on translation, large-scale, randomized control trials, that is, RCTs to estimate the clinical safety, efficacy, and optimum dose response of nintedanib and favipiravir in PCPF patients are needed. The usage of nintedanib with other antifibrotic or immunomodulatory drugs and the possible synergistic effect should also be the subject of further studies.

Another promising direction concerning further studies is the evaluation of the influence of the approach of favipiravir on combination treatments; in specific cases that involve the persistent illness of viral activity in the body or active inflammation. Based on the limited effectiveness of favipiravir, combination therapy might be more effective in attacking both inflammatory pathways and fibrosis as the combination therapy would not only treat the underlying etiology of PCPF that is viral but also the fibrotic sequelae.

With this summing up, the study brings instructive information on the effectiveness and tolerability of nintedanib in PCPF, which favours its use as a possible therapeutic option. Nevertheless, the overall effectiveness of favipiravir when used alone provides an interesting context to consider more specific and combination prescriptions during the treatment of post-COVID pulmonary fibrosis. These translational results should be confirmed in larger randomized trials to form a stronger therapeutic basis of PCPF.

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## Conflicts of interest

The authors have no conflicts of interest to declare

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