# Phase 3 Trial (in Process) of the SYK Inhibitor Fostamatinib in Patients Hospitalized With COVID-19: Protocol and Study Implementation Updates

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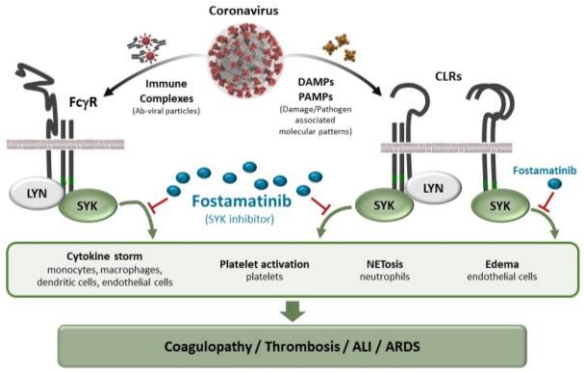
## Introduction

- Severe COVID-19 is characterized by a hyperinflammatory immune response associated with cytokine storm, release of neutrophil extracellular traps (NETosis), and platelet activation, resulting in coagulopathy, immunothrombosis, and organ injury.
- Spleen tyrosine kinase (SYK) is a crucial mediator of the signaling pathways leading to the hyperinflammatory response (**Figure 1,** ALI, acute lung injury; ARDS, acute respiratory distress syndrome).

**Figure 1. SYK Signaling Pathways in COVID-19**




- Fostamatinib is an oral SYK inhibitor approved for chronic immune thrombocytopenia that may downregulate SYK-mediated signaling pathways and the associated hyperinflammatory immune response in severe COVID-19.
- In *in vitro* studies, fostamatinib:
  - Abrogated the hyperimmune response triggered by anti-spike IgG.[1]
  - Inhibited hyperactivation in platelets.[2]
  - Blocked NETosis in neutrophils.[3]
- R406, the active metabolite of fostamatinib, was shown to protect against LPS-induced acute lung injury and thrombosis in mice.[4,5]
- We initiated a phase 3 clinical study (NCT04629703) to evaluate fostamatinib in patients hospitalized with COVID-19 in North and South America.

## Background: Phase 2 Study

- A phase 2 study (NCT04579393) evaluating fostamatinib vs. placebo with all patients on standard of care (SOC) in 59 hospitalized COVID-19 patients was recently completed and published.[6]
- The study met the primary endpoint of safety. The addition of fostamatinib decreased the incidence of serious adverse events (AEs) by 50% compared to placebo (10% vs. 21% of patients, respectively).
- Several secondary efficacy endpoints showed improvements in the fostamatinib group compared to placebo including:
  - Mortality
  - Median number of days on supplemental oxygen
  - Median number of days in ICU
  - Mean 8-point ordinal scale score at Day 15
- Three deaths occurred in the placebo group vs. 0 in the fostamatinib group by Day 29.
- The addition of fostamatinib to SOC in patients hospitalized with COVID-19 who required supplemental oxygen was well-tolerated.

## Phase 3 Study Update of Blinded Data

- As of 2 December 2021, 208 patients have been randomized, and 187 patients received at least 1 dose of study drug.
- Baseline clinical status score was 5 or 6 (Hospitalized, requiring supplemental oxygen) in 91.4% of patients and 8.7% of patients were < 5 (missing in 1 patient).
- Baseline median SpO2 (oxygen saturation) was 94% and ranged from 85-99%.
- The median duration of exposure was 12 days, and 187 patients (90%) remained in the study as of Day 29.
- One hundred thirty-two patients had 213 adverse events (AEs), and 33 had 25 serious AEs. Serious AEs occurring in ≥ 2 patients are shown in **Table 1**.
- Nine deaths were reported.

**Table 1. Patient Characteristics and Safety**

| Blinded Data | All Patients (n=208) |
|---|---|
| Mean age in years (range) | 50 (20-82) |
| Sex (male) | 152 (73%) |
| South America | 181 (87%) |
| Race, ethnicity (white, Hispanic or Latino) | 184 (89%) |
| Median BMI (interquartile range) | 32.6 (20-74) |
| Prior treatment: Dexamethasone/Remdesivir | 89%/10% |
| Serious Adverse Events in ≥ 1 patient | 33 (15%) |
| Pulmonary embolism | 6 (3%) |
| Respiratory failure | 6 (3%) |
| Septic Shock | 3 (1%) |
| Deep vein thrombosis | 2 (1%) |
| Transaminases increased | 3 (1%) |
| Dyspnea | 2 (1%) |
| Acute kidney injury | 2 (1%) |
| Pneumothorax | 2 (1%) |

## Methods: Phase 3 Study

- A Phase 3, randomized, double-blind, placebo-controlled, adaptive design, multi-center study (NCT04629703) is underway to evaluate fostamatinib in 308 adult patients hospitalized with COVID-19 on oxygen without intubation (**Figure 2**).
- The primary objective is to evaluate the safety and efficacy of fostamatinib in combination with SOC in patients hospitalized with COVID-19.
- The primary efficacy endpoint is the number of days on oxygen (Day 1 to 29) after randomization.
- Secondary endpoints include the change from baseline in the clinical status score on the 8-point ordinal scale, days in the ICU, time to sustained hospital discharge, all-cause mortality by day 29, and safety.

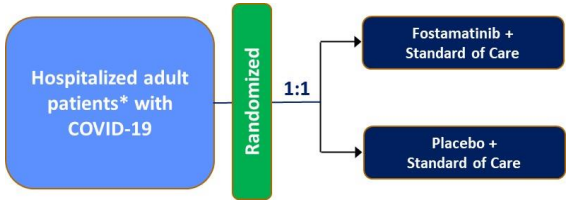



**Figure 2. Phase 3 Study Design**
*Patients provided written informed consent.

**Inclusion criteria**: Hospitalized COVID-19 patients who are receiving supplemental oxygen (as defined by a clinical status score of 5 or 6 on the 8-point ordinal scale).

**Exclusion criteria**: Patients using extracorporeal membrane oxygenation (ECMO), or with uncontrolled hypertension, history of myocardial infarction within 1 month prior to screening, liver or kidney function impairment, platelet count < 100,000/µL or neutrophil count < 1,000/µL.

## Discussion

- This phase 3 study has completed enrollment.
- One phase 2 study (NCT04579393) has been completed and met the primary endpoint of safety.[6]
- An additional phase 3 study (NCT04924660, ACTIV-4) led by Vanderbilt University Medical College and the NHLBI is currently enrolling patients.

## References

1. Hoepel W. *Sci Transl Med.* 2021
2. Apostolides S. *BioRxiv.* 2021
3. Strich J. *J Infect Dis.* 2020
4. Nadeem A. *Int Immunopharm.* 2019
5. Van Eeuwijk J. *Arterioscler Thromb Vasc Biol.* 2016
6. Strich JR. *Clin Infect Dis.* 2021

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